The chemistry of
organolithium compounds
Volume 2

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Edited by

ZVI RAPPOPORT

The Hebrew University, Jerusalem

and

ILAN MAREK

Technion-Israel Institute of Technology, Haifa

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Dedicated to

…**my parents Elie and Daniele** ***Ilan***

…**my fellow students Dudi, Maayan, Michal and Rami** ***Zvi***

Contributing authors

Per Ahlberg	Department of Chemistry, Göteborg University, SE-41296 Göteborg, Sweden. Fax: +46 31 772 2908; e-mail: Per.Ahlberg@chem.gu.se
Mohamed Amedjkouh	Department of Chemistry, Göteborg University, SE-41296 Göteborg, Sweden. Fax: +46 31 772 2908
Ivan Aprahamian	Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem, 91904, Israel. Fax: +972 2652 7547
Francisco J. Fañanás	Instituto Universitario de Química Organometálica "Enrique Moles", Unidad Asociada al CSIC, Universidad de Oviedo, C/Julián Clavería, 8, E-33006 Oviedo, Spain. Fax: +34 98 510 3446; e-mail: fjfv@uniovi.es
Gideon Fraenkel	Department of Chemistry, The Ohio State University, 100 W. 18th Avenue, Columbus, OH 43210, USA. Fax: +1 614 292 1685; e-mail: Fraenkel@mps.ohio-state.edu
Johan Granander	Department of Chemistry, Göteborg University, Kemivägen 10, SE-412 96, Göteborg, Sweden
Göran Hilmersson	Department of Chemistry, Göteborg University, Kemivägen 10, SE-412 96, Göteborg, Sweden. Fax: +46 31 772 3840; e-mail: hilmers@chem.gu.se
Jacques Maddaluno	Laboratoire des Fonctions Azotées & Oxygénées Complexes de l'IRCOF, UMR 6014 CNRS, Université de Rouen, F-76821 Mont St Aignan Cedex, France. Fax: +33 23 552 2971; e-mail: jmaddalu@crihan.fr
Carmen Najera	Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, E-03080 Alicante, Spain. Fax: +34 96 590 3549; e-mail: cnajera@ua.es
Hiroyuki Nakahira	Chemistry Research Laboratories, Research Division, Sumitomo Pharmaceuticals, Osaka 554-0022, Japan. Fax: +81 66 466 5483; e-mail: nakahira@sumitomopharm.co.jp

Norma Sbarbati Nudelman	Depto. Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pab. II, P 3 Ciudad Universitaria (1428), Buenos Aires, Argentina. Fax: +5411 4576 3346; e-mail: nudelman@qo.fcen.uba.ar
Daniel Pettersen	Department of Chemistry, Göteborg University, SE-41296 Göteborg, Sweden. Fax: +46 31 772 2908
Mordecai Rabinovitz	Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem, 91904, Israel. Fax: +972 2652 7547; e-mail: mordecai@vms.huji.ac.il
Ilhyong Ryu	Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599–8531, Japan. Fax: +81 72 254 9695; e-mail: ryu@c.s.osakafu-u.ac.jp
Roberto Sanz	Departamento de Química, Facultad de Ciencias, Universidad de Burgos, Plaza Missael Bañuelos s/n, E-09001 Burgos, Spain. e-mail: rsd@ubu.es
Jean-Yves Valnot	Laboratoire des Fonctions Azotées & Oxygénées Complexes de l'IRCOF, UMR 6014 CNRS, Université de Rouen, F-76821 Mont St Aignan Cedex, France. Fax: +33 23 552 2971; e-mail: jean-yves.valnot@univ-rouen.fr
Alvaro J. Vazquez	Depto. Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pab. II, P 3 Ciudad Universitaria (1428), Buenos Aires, Argentina. Fax: +5411 4576 3346
Raquel G. de Waisbaum	Depto. Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pab. II, P3 Ciudad Universitaria (14-28), Buenos Aires, Argentina. Fax: +5411 4576 3364
Miguel Yus	Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, E-03080 Alicante, Spain. Fax: +34 96 590 3549; e-mail: yus@ua.es

Foreword

A two-part volume on *The Chemistry of Organolithium Compounds* in the series 'The Chemistry of Functional Groups' (edited by Zvi Rappoport and Ilan Marek) was published in 2004 and included 18 chapters which are listed at the end of this volume following the indexes. Several chapters planned for the 2004 volume did not materialize, but now appear in the present volume together with other chapters, covering recent topics in Organolithium Chemistry.

This volume, which complements the earlier one, contains 9 chapters written by experts from 7 countries. These include a chapter on the dynamic behavior of organolithium compounds, written by one of the pioneers in the field, and a specific chapter on the structure and dynamics of chiral lithium amides in particular. The use of such amides in asymmetric synthesis is covered in another chapter, and other synthetic aspects are covered in chapters on acyllithium derivatives, on the carbolithiation reaction and on organolithiums as synthetic intermediates for tandem reactions. Other topics include the chemistry of ketone dilithio compounds, the chemistry of lithium enolates and homoenolates, and polycyclic and fullerene lithium carbanions.

We gratefully acknowledge the up-to-date contributions by all authors. Without their effort, this volume would not have been possible.

The literature coverage is up to 2004.

We would be grateful to readers who call our attention to any mistakes in the present volume.

Jerusalem and Haifa
July, 2005

ZVI RAPPOPORT
ILAN MAREK

The Chemistry of Functional Groups Preface to the series

The series 'The Chemistry of Functional Groups' was originally planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the preparation, properties and reactions of the functional group treated and on the effects which it exerts both in the immediate vicinity of the group in question and in the whole molecule.

A voluntary restriction on the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series and in textbooks (i.e. in books which are usually found in the chemical libraries of most universities and research institutes), should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the topic. Therefore each of the authors is asked not to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced postgraduate level.

It is realized that no plan can be devised for a volume that would give a complete coverage of the field with no overlap between chapters, while at the same time preserving the readability of the text. The Editors set themselves the goal of attaining reasonable coverage with moderate overlap, with a minimum of cross-references between the chapters. In this manner, sufficient freedom is given to the authors to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter deals with the general and theoretical aspects of the group.

(b) Chapters discuss the characterization and characteristics of the functional groups, i.e. qualitative and quantitative methods of determination including chemical and physical methods, MS, UV, IR, NMR, ESR and PES — as well as activating and directive effects exerted by the group, and its basicity, acidity and complex-forming ability.

(c) One or more chapters deal with the formation of the functional group in question, either from other groups already present in the molecule or by introducing the new group directly or indirectly. This is usually followed by a description of the synthetic uses of the group, including its reactions, transformations and rearrangements.

(d) Additional chapters deal with special topics such as electrochemistry, photochemistry, radiation chemistry, thermochemistry, syntheses and uses of isotopically labeled compounds, as well as with biochemistry, pharmacology and toxicology. Whenever applicable, unique chapters relevant only to single functional groups are also included (e.g. 'Polyethers', 'Tetraaminoethylenes' or 'Siloxanes').

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the authors and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, some volumes may be published without giving consideration to the originally planned logical order of the chapters.

Since the beginning of the Series in 1964, two main developments have occurred. The first of these is the publication of supplementary volumes which contain material relating to several kindred functional groups (Supplements A, B, C, D, E, F and S). The second ramification is the publication of a series of 'Updates', which contain in each volume selected and related chapters, reprinted in the original form in which they were published, together with an extensive updating of the subjects, if possible, by the authors of the original chapters. A complete list of all above mentioned volumes published to date will be found on the page opposite the inner title page of this book. Unfortunately, the publication of the 'Updates' has been discontinued for economic reasons.

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editors.

The publication of this series would never have been started, let alone continued, without the support of many persons in Israel and overseas, including colleagues, friends and family. The efficient and patient co-operation of staff-members of the publisher also rendered us invaluable aid. Our sincere thanks are due to all of them.

The Hebrew University
Jerusalem, Israel

SAUL PATAI
ZVI RAPPOPORT

Sadly, Saul Patai who founded 'The Chemistry of Functional Groups' series died in 1998, just after we started to work on the 100th volume of the series. As a long-term collaborator and co-editor of many volumes of the series, I undertook the editorship and I plan to continue editing the series along the same lines that served for the preceeding volumes. I hope that the continuing series will be a living memorial to its founder.

The Hebrew University
Jerusalem, Israel
May 2000

ZVI RAPPOPORT

Contents

List of abbreviations used

Ac	acetyl (MeCO)
acac	acetylacetone
Ad	adamantyl
AIBN	azoisobutyronitrile
Alk	alkyl
All	allyl
An	anisyl
Ar	aryl
Bn	benzyl
Bu	butyl (C_4H_9)
Bz	benzoyl (C_6H_5CO)
CD	circular dichroism
CI	chemical ionization
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
Cp	η^5-cyclopentadienyl
Cp*	η^5-pentamethylcyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAH	diisobutylaluminium hydride
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulphoxide
ee	enantiomeric excess
EI	electron impact
ESCA	electron spectroscopy for chemical analysis
ESR	electron spin resonance
Et	ethyl
eV	electron volt

Fc	ferrocenyl
FD	field desorption
FI	field ionization
FT	Fourier transform
Fu	furyl(OC_4H_3)
GLC	gas liquid chromatography
Hex	hexyl(C_6H_{13})
c-Hex	cyclohexyl(*c*-C_6H_{11})
HMPA	hexamethylphosphortriamide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
i-	iso
ICR	ion cyclotron resonance
Ip	ionization potential
IR	infrared
LAH	lithium aluminium hydride
LCAO	linear combination of atomic orbitals
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	metal
M	parent molecule
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
MNDO	modified neglect of diatomic overlap
MS	mass spectrum
n	normal
Naph	naphthyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Pen	pentyl(C_5H_{11})
Ph	phenyl
Pip	piperidyl($C_5H_{10}N$)
ppm	parts per million
Pr	propyl (C_3H_7)
PTC	phase transfer catalysis or phase transfer conditions
Py, Pyr	pyridyl (C_5H_4N)

R	any radical
RT	room temperature
s-	secondary
SET	single electron transfer
SOMO	singly occupied molecular orbital
t-	tertiary
TCNE	tetracyanoethylene
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thi	thienyl(SC_4H_3)
TLC	thin layer chromatography
TMEDA	tetramethylethylene diamine
TMS	trimethylsilyl or tetramethylsilane
Tol	tolyl(MeC_6H_4)
Tos or Ts	tosyl(*p*-toluenesulphonyl)
Trityl	triphenylmethyl(Ph_3C)
Xyl	xylyl($Me_2C_6H_3$)

In addition, entries in the 'List of Radical Names' in *IUPAC Nomenclature of Organic Chemistry*, 1979 Edition, Pergamon Press, Oxford, 1979, p. 305–322, will also be used in their unabbreviated forms, both in the text and in formulae instead of explicitly drawn structures.

CHAPTER 1

Dynamics of the reorganization behavior of organolithium compounds

GIDEON FRAENKEL

Department of Chemistry, The Ohio State University, 100 W. 18th Avenue, Columbus, Ohio 43210, USA
Fax: +1 614 292 1685; e-mail: Fraenkel@mps.ohio-state.edu

I. INTRODUCTION

Organolithium compounds[1] in solution consist of equilibrium mixtures of rapidly reorganizing species which differ by state of aggregation, degree of solvation and electronic structure. The first structures of organolithium compounds in the solid state came from X-ray crystallography[2]. More recently, NMR has been uniquely effective for identifying

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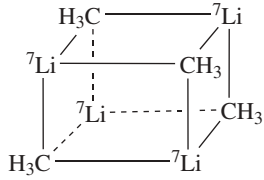
the structures of organolithium compounds in solution, including mixtures of different structures[3].

Our contribution to this field was inspired by the announcement of a group of chemists at the Dow Chemical Company that at −78 °C, ^{13}C NMR of $^{13}CH_3{}^7Li$ in diethyl ether solution exhibited splitting indicative of scalar coupling between ^{13}C and directly bonded ^7Li ($\mathbf{I} = \frac{3}{2}$)[4]. The multiplicity of the ^{13}C resonance was consistent with three nearest ^7Li neighbors directly bonded and equally coupled to the same ^{13}C in a cubic tetrameric aggregate **1**, drawn with solvation omitted.



(1)

These results became the basis of a widely used spin counting technique[5] which we initiated and has since[6] been widely used to identify the principal structures into which organolithium compounds assemble in solution[3]. These are unsolvated cubic tetramers, octahedral hexamers, octamers and nonamers as well as solvated monomers, bridged dimers and cubic tetramers. Several of these structures have also been obtained from X-ray crystallographic studies of organolithium compounds[2].

The Dow group also reported that with increasing temperature above −78 °C the multiplicity of the ^{13}C NMR of CH_3Li due to ^{13}C, ^7Li spin coupling is progressively averaged, so that by room temperature the methyl ^{13}C resonance consists of a single sharp line[4]. This phenomenon is necessarily the result of overall fast mutual exchange at equilibrium of lithium between organolithium aggregates. The rates of this exchange process are easily obtained using the methods of NMR line shape analysis as outlined below.

In fact using NMR studies, organolithium compounds have been found to reorganize rapidly at equilibrium via a variety of mechanisms which include inversion at lithium bound carbon, bond rotations, interconversion processes, mutual exchange of lithiums between organolithium species as well as different ligand lithium exchange processes. The dynamics of several of these processes have been elucidated using our density matrix theory for NMR of chemically reorganizing systems which takes account of any mechanism or combination of mechanisms as well as the principal modes of nuclear spin relaxation[7]. The actual procedures for handling these NMR line shape calculations are outlined in the next section. Approximations and underlying assumptions are included. However, derivations and explanations of the physics have been omitted. These are already well documented in the literature[7].

II. DYNAMIC NMR LINE SHAPE ANALYSIS[7]

Dynamics of typical reorganizing systems that have been investigated using NMR line shape analysis include first-order degenerate processes such as degenerate bond rotations (equation 1), first-order interconversions where A and B are different species (equation 2), bimolecular group transfer (equation 3) and mutual exchange (equation 4).

$$A \rightleftharpoons A' \tag{1}$$

$$A \rightleftharpoons B \tag{2}$$

$$AB + C \rightleftharpoons ABC \tag{3}$$

$$AB + CD \rightleftharpoons AD + CB \tag{4}$$

The parameters that are extricated from a line shape analysis are the reciprocal mean lifetimes, $1/\tau_{sp}$(sp = species), between successive exchanges via each particular step. In chemical usage $1/\tau_{sp}$ is preferably written as k^1_{sp}, the pseudo-first-order rate constant. The results of NMR line shape analysis provide kinetic information via the well-known relationship given in equation 5[7]. A term such as in equation 5 is used for each separate exchange step.

$$k^1_{sp} = \frac{\text{rate law}}{(sp)} \tag{5}$$

In these calculations it is mathematically convenient to use the spin product $\emptyset_\ell$,

$$\emptyset_\ell = \prod_s \varphi_s \tag{6}$$

(equation 6), where the φ_s's are individual spin functions and Π_s is the product over all of them. For example, for a two half-spin species (hydrogens in CH_2) the four spin products are $\alpha_A\alpha_B$, $\alpha\beta$, $\beta\alpha$ and $\beta\beta$, order of spins as in the first one. The four transitions of interest for the purpose of calculating NMR line shapes are $\alpha\alpha \rightarrow \alpha\beta$, $\alpha\alpha \rightarrow \beta\alpha$, $\alpha\beta \rightarrow \beta\beta$ and $\beta\alpha \rightarrow \beta\beta$.

All symbols used in the following derivation of the equations required to plot the NMR line shapes are listed below.

A	coefficient matrix of the density matrix equations
B	column of numbers on the right-hand side of the density matrix equations
h	Planck's constant
$\hbar$	$h/2\pi$
I, I^x, I^y, I^z	spin operators
I^+, I^-	raising and lowering spin operators
Im	Imaginary part of
I	general symbol for a spin operator
$j_\alpha(0)$	spectral density, extreme narrowing condition
$J_{s,t}$	scalar spin coupling constant
k_B	Boltzmann constant
k_1, k_2	rate constants
k^1	pseudo-first-order rate constant
m^z	eigenvalue of I^z
N	number of spin states
P	permutation matrix
Q	electric quadrupole moment
R	relaxation operator
s,t	labels for spins
T	all-purpose relaxation time, usually due to field inhomogeneity effects, including viscosity
T_1, T_2	longitudinal and transverse relaxation time
T_B	Kelvin temperature
α,β	spin states $I = \frac{1}{2}$
ν	frequency in Hz

ν_s	chemical shift frequency spin s, Hz
ν_o	average frequency Hz
e	density matrix rotating frame abbreviated as e
$\dot{e}$	time-dependence density
$e_{s,t}$	matrix element of density matrix
$\emptyset$	spin product function
φ	state of one spin
ω	frequency point, rad s^{-1}
$\overline{\omega}_o$	average frequency, see ω
ω_s,ω_t	shifts of nuclei s and t
$\overline{\phi}_1$	average RF field in rad s^{-1}
$\Delta\omega$	$\omega - \omega_s$

The derivation is also subject to the following conditions and assumption: 1) NMR is determined at low RF power. 2) A Boltzmann distribution of spin states obtains so that diagonal elements of the density matrix (e, see below) are given by equation 7,

$$e_{\ell,\ell} = \frac{1}{N} \tag{7}$$

where N is the number of spin states and their sum is unity (equation 8)

$$\sum_{\ell} e_{\ell,\ell} = 1 \tag{8}$$

3) The nuclear spin eigenvalues are small compared to the Boltzmann energies (equation 9)

$$\hbar\langle\emptyset_\ell|H|\emptyset_\ell\rangle \ll k_B T_B \tag{9}$$

4) The sample is homogeneous with respect to the RF field and the temperature. 5) All spins are subjected to the same RF field. 6) Chemical shift differences are small relative to the average shift frequency.

The NMR absorption, calculated as a function of frequency, is given by the sum in equation 10,

$$\text{Abs} = -\text{Im}\left(\sum_{\ell,n} e^{\text{sp}}_{\ell,n}\right) \tag{10}$$

where the $e_{\ell,n}$ are elements of the density matrix e (see below) and ℓ and n are two spin states connected by the flip of a single spin with $m_n^Z - m_\ell^Z = -1$.

With more than one species involved, the absorption (Abs) has to be summed over all molecular species each weighted by their relative concentrations, (sp) (equation 11).

$$\text{Abs} = -\text{Im}\sum_{\text{sp}}\sum_{\ell,n}(\text{sp})e^{\text{sp}}_{\ell,n} \tag{11}$$

The steady-state density matrix equation in the rotating frame, in operator form, is given in equation 12,

$$\dot{e} = 0 = i[\overline{e}, \overline{\mathbf{H}}_o + \overline{\mathbf{H}}_1] + \mathbf{R}\overline{e} + \mathbf{E}\overline{e} \tag{12}$$

where the $\overline{\mathbf{H}}$'s are Hamiltonians in the rotating frame while $\mathbf{R}$ and $\mathbf{E}$ are relaxation and exchange operators, respectively. In the many cases where line width is due to field inhomogeneities, $\overline{R}\overline{e}$ is replaced by $\overline{e}/T$ where $1/T$ is a phenomenological line width at

half height of a peak not observably perturbed by dynamic effects. The two Hamiltonians in equation 12 are given by equations 13 and 14,

$$\overline{\mathbf{H}}_u = \sum_s (\omega - \omega_s)\mathbf{I}_s^z + \sum_{s<t} J_{s,t}\left(\mathbf{I}_s^z\mathbf{I}_t^z + \frac{1}{2}(\mathbf{I}_s^+\mathbf{I}_t^- + \mathbf{I}_s^-\mathbf{I}_t^+)\right) \tag{13}$$

$$\overline{\mathbf{H}}_1 = \sum_s \overline{\phi}\,\mathbf{I}_s^x \tag{14}$$

where the **I**'s are spin operators and all frequencies are in rad s^{-1} with $J_{s,t}$ coupling constants, ω_s spin frequency, ω frequency point, ω_o average frequency and $\overline{\phi}$ the average RF power.

Using the above conditions and assumptions, it has been shown that the RF part of the commutator in equation 12 is given by equation 15,

$$\mathrm{i}[\boldsymbol{e}, \overline{\mathbf{H}}_1] = \frac{\hbar\overline{\omega}_o\overline{\phi}_1}{Nk_B T_B}\left(\sum_s \mathbf{I}_s^y\right) \tag{15}$$

so that the density matrix equation is more conveniently written as equation 16,

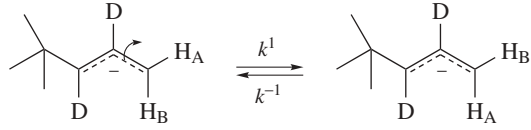
$$i[\mathbf{e}, \overline{\mathbf{H}}_o] - \frac{\mathbf{e}}{T} + Ee = -\frac{\hbar\overline{\omega}_o\overline{\phi}_1}{Nk_B T_B}\left(\sum_s \mathbf{I}_s^y\right) \tag{16}$$

To obtain the $e_{\ell,n}$ elements, we take all ℓ, n elements of both sides of equation 16 where $m_n^z - m_\ell^z = -1$. This generates a set of coupled inhomogeneous first-order equations in the $e_{\ell,n}$ elements which are called the **density matrix equations** and are solved for the required $e_{\ell,n}$ elements. For example, in the case of a two half-spin system we shall call AB, the required set of $\emptyset_\ell$, $\emptyset_n$ pairs are listed above. One of the density matrix equations obtained by taking the $\alpha\alpha$,$\alpha\beta$ element of equation 16 is given by equation 17,

$$\left(i(\omega - \omega_B) - i\frac{J}{2} - \frac{1}{T}\right)e_{\alpha\alpha,\alpha\beta} + \frac{iJ}{2}e_{\alpha\alpha,\beta\alpha} = \frac{\hbar\overline{\omega}_o\overline{\phi}_1}{Nk_B T_B}\left(\frac{1}{2}\right) \tag{17}$$

where exchange effects have been omitted for simplicity. There would be a set of equations analogous to equation 17 for each molecular species present in the reorganizing system. To appreciate how the mathematics is organized, we exhibit the set of coupled density matrix equations for a two half-spin system which includes provision for the dynamics of a mutual exchange of the two half-spins, as explained in the following section.

Such a system could be the indicated bond rotation in an allylic lithium compound **2** (equation 18).



$Li^+(OR_2)_3$ $\qquad$ $Li^+(OR_2)_3$

(2) (18)

Fast rotation around the 2,3-allyl bond would average the shift between the methylene hydrogens as well as the coupling constant between them.

$$\begin{bmatrix} i\left(\omega-\omega_{\mathrm{A}}-\frac{J}{2}\right)-\frac{1}{T}-k^1 & 0 & \frac{iJ}{2}+k^1 & 0 \\ 0 & i\left(\omega-\omega_{\mathrm{A}}+\frac{J}{2}\right)-\frac{1}{T}-k^1 & 0 & \frac{iJ}{2}+k^1 \\ \frac{iJ}{2}+k^1 & 0 & i\left(\omega-\omega_{\mathrm{B}}-\frac{J}{2}\right)-\frac{1}{T}-k^1 & 0 \\ 0 & \frac{iJ}{2}+k^1 & 0 & i\left(\omega-\omega_{\mathrm{B}}+\frac{J}{2}\right)-\frac{1}{T}-k^1 \end{bmatrix} \times \begin{bmatrix} e_{\alpha\alpha,\beta\alpha} \\ e_{\alpha\beta,\beta\beta} \\ e_{\alpha\alpha,\alpha\beta} \\ e_{\beta\alpha,\beta\beta} \end{bmatrix} = iC \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} \tag{19}$$

The set of coupled first-order density matrix equations in matrix form is exhibited in equation 19, where the proportionality constant C is given by equation 20; it simply weights the entire spectrum[8]. For calculational purposes we just set C equal to unity. Equation 20 does show that the signal/noise ratio for an NMR spectrum increases on cooling the sample.

$$C = \frac{i\hbar\overline{\omega}_{\mathrm{o}}\,\overline{\phi}_1}{2Nk_{\mathrm{B}}T_{\mathrm{B}}} \tag{20}$$

Equation 19 also illustrates features that are common to all sets of density matrix equations which are derived for NMR of reorganizing systems obtained under the conditions

listed above. Chemical shifts, ω_i, and frequency points, ω, are only found in the diagonal elements of the coefficient matrix, **A**. Coupling constants appear in both diagonal and off-diagonal elements of **A**, but only in the former in the case of first-order spectra. In the absence of effects due to reorganization dynamics the k's are all zero, so the calculated $e_{\ell,n}$ elements provide the NMR spectra. In such a case all the terms in equation 19 are known—ω_s's, ω points, $1/T$'s, and J's—except for the $e_{\ell,n}$ elements.

Where reorganization dynamics perturb the NMR spectra, the diagonal elements of the coefficient matrices include first-order rate constants with negative signs and rate constants in off-diagonal elements with positive signs. It is the rate constants in the off-diagonal elements which are responsible for averaging of transitions due to dynamic effects. Where the density matrix equations incorporate the NMR of a single molecular species, the coefficient matrix, **A**, is symmetrical about its diagonal. A word about units is now in order. Frequency terms are in rad s^{-1} and time is in seconds.

For calculating the $e_{\ell,n}$ elements for an NMR spectrum subject to dynamic effects, all the NMR parameters should be known together with a range of trial values for the rate constants. Then, via an iterative procedure, comparison of calculated and observed NMR line shapes provides the rate constants. As of this writing software for solving these density matrix equations is readily available and easily managed using any current PC.

NMR line shapes can be calculated for any reorganizing system undergoing any combination of reorganizing mechanisms given the appropriate NMR parameters and provided that the line shapes were obtained under the experimental conditions outlined above.

Each density matrix equation 16 is written for a single chemical species. The term responsible for dynamic effects is Ee given in equation 21 for the latter species undergoing a single reorganization process with pseudo-first-order rate constant k^1 and e(ae) denotes the density matrix after a particular reorganization process has taken place.

$$Ee = k^1(e(\mathrm{ae}) - e) \tag{21}$$

In the event that several reorganization processes (ex) obtain, then equation 21 is replaced by a sum over all of them (equation 22).

$$Ee = \sum_{\mathrm{ex}} k^1_{\mathrm{ex}}(e_{\mathrm{ex}}(\mathrm{ae}) - e) \tag{22}$$

It is the elements of e_{ex}(ae) which are responsible for the mixing of NMR transitions due to reorganization dynamics. The following paragraphs describe, without derivation or explanation, procedures for evaluating elements of e_{ex}(ae) for the principle types of reorganizing systems. Derivations and explanations of these procedures have already been excellently documented elsewhere[7]. Suffice it to say that operating in the spin product representation, the reorganization operators, which were formerly used in conjunction with other representations, become permutation matrices. This allows calculation of the $e(\mathrm{ae})_{\ell,n}$ elements in a simple manner with closed formulas, often by hand.

Throughout the following treatment, it is appropriate to assume that all nuclear spin relaxation times are long compared to the lifetimes of the transition states for reorganization. This has been called the *sudden approximation*[9].

Rotation around the CD−CHAHB bond of the allylic lithium compound in equation 18 is an example of a degenerate reorganization, which we abbreviate as in equation 23.

$$\begin{array}{ccc} & A & \longrightarrow & A^1 \\ \emptyset & ab & & ba \\ & a^1b^1 & & b^1a^1 \end{array} \tag{23}$$

We use the spin product representation, so that a spin product for the methylene hydrogens in the allylic lithium compound in equation 18 is written as ab, where the order of spins follows the numbering of the sites and ab, a^1b^1 are two spin states connected by a $\Delta m^z = -1$ transition. The effect of rotation around the C_2-C_3 bond is to exchange the environments of the methylene hydrogens and to permute the order of their spins in the spin products (equation 24).

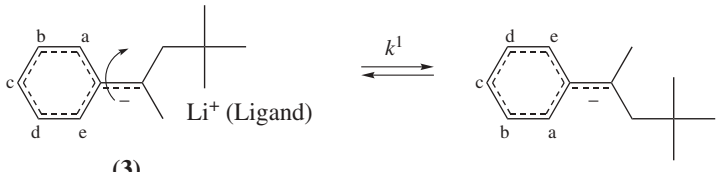
$$e_{ab,a^1b^1}(\text{ae}) = e_{ba,b^1a^1} \tag{24}$$

The resulting element of Ee is given by equation 25.

$$(Ee)_{ab,a^1b^1} = k^1(e_{ba,b^1a^1} - e_{ab,a^1b^1}) \tag{25}$$

The derivation of this Permutation of Indices procedure, PI, has been published elsewhere[7].

A more complicated first-order degenerate reorganization is illustrated by ring proton NMR of the rotating *t*-benzylic anion **3** in equation 26[10].



(**3**) (26)

The PI procedure gives the $(e(\text{ae}))_{\ell,\text{n}}$ elements shown in equation 27.

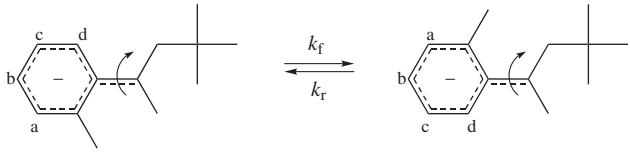
$$\langle abcde|e(\text{ae})|a^1b^1c^1d^1e^1\rangle = \langle edcba|e|e^1d^1c^1b^1a^1\rangle \tag{27}$$

Proton decoupled natural abundance dynamic ^{13}C NMR of the labeled ring carbons would be handled in a similar but simpler manner compared to the proton NMR. At low temperature, each ring carbon gives rise to a single line in the ^{13}C NMR. The 1:1 doublets for a and e and for b and d are well separated from each other and from resonance c. With increasing temperature there is progressive averaging of resonances a with e and b with d; resonance c is unchanged. The collapsing doublets can be treated independently as shown for the density matrix equation for the a/e system in equation 28.

$$\begin{bmatrix} i(\omega-\omega_a) & & & \\ -\dfrac{1}{T}-k & & k & \\ & i(\omega-\omega_e) & & \\ k & & -\dfrac{1}{T}-k & \end{bmatrix} \begin{bmatrix} e_{a,a^1} \\ \\ \\ e_{e,e^1} \end{bmatrix} = iC \begin{bmatrix} 1 \\ \\ \\ 1 \end{bmatrix} \tag{28}$$

Rotation around the ring-benzyl bond of **4** brings about the first-order interconversion of two benzylic lithium compounds, **4** and **5** (equation 29). Considering just the NMR of the ring protons, the conversion $e^{\mathbf{4}}_{\ell,n} \rightarrow (e^{\mathbf{4}}(\text{ae}))_{\ell,n}$ involves the two same pair of spin products but different Hamiltonians (equations 30 and 31).

$$A \rightleftharpoons B$$



(29)

Li^+ (Ligand) Li^+ (Ligand)

(4) **(5)**

$$\langle abcd \left| e^4(\text{ae}) \right| a^1b^1c^1d^1 \rangle = \langle abcd \left| e^5 \right| a^1b^1c^1d^1 \rangle \tag{30}$$

$$\langle abcd \left| e^5(\text{ae}) \right| a^1b^1c^1d^1 \rangle = \langle abcd \left| e^4 \right| a^1b^1c^1d^1 \rangle \tag{31}$$

Line shape analysis provides both rate constants as well as the equilibrium constants (equation 32), all as a function of temperature.

$$K = \frac{k_f}{k_r} \tag{32}$$

Extrapolating from the low-temperature integrated NMR spectra provides an independent measure of the equilibrium constant within the temperature range at which line shape analysis is carried out. This simplifies the line shape analysis to just one dynamic parameter, say k_r, since $k_f = Kk_r$.

Bimolecular mutual exchange of chemical species B with D between molecules AB and CD (equation 33) represents one of the more frequently encountered and more complicated NMR line shape cases.

$$\begin{array}{ccccccccc} & \text{AB} & + & \text{CD} & \overset{k_f}{\underset{k_r}{\rightleftharpoons}} & \text{AD} & + & \text{CB} \\ \text{Ø} & ab & & cd & & ad & & cb \end{array} \tag{33}$$

As before, the chemical species are named in terms of their exchanging parts and their spin products are factored in parallel fashion, as shown in equations 34–36.

$$\text{Ø}^{\text{AB}} = \text{Ø}^{\text{A}}\text{Ø}^{\text{B}} \tag{34}$$

$$\text{Ø}^{\text{A}} = a \tag{35}$$

$$\text{Ø}^{\text{B}} = b \tag{36}$$

To obtain elements of $e^{\text{AB}}_{(\text{ae})}$ we first multiply $e^{\text{AB}}_{\ell,n}$ by the trace of e^{CD}, which is unity (see equations 7 and 37).

$$\text{Tr}e^{\text{CD}} = \sum_{cd} e^{\text{CD}}_{cd,cd} = 1 \tag{37}$$

$$e^{\text{AB}}_{ab,a^1b^1} = e^{\text{AB}}_{ab,a^1b^1} \sum_{cd} e^{\text{CD}}_{cd,cd} \tag{38}$$

Note that CD is the second species on the AB side of the reaction (equation 33). The $e^{AB}_{(ae)}$ element is then found by permuting B with D in the superscripted chemical labels and b with d in the spin product subscripts in equation 38, right hand side giving equations 39 and 40. Notice the summation is over all terms that are diagonal in c and d (equations 39 and 40).

$$e^{AB}_{ab,a^1b^1}(ae) = \sum_{cd} e^{AD}_{ad,a^1d} e^{CB}_{cb,cb^1} \tag{39}$$

$$= \sum_{d} e^{AD}_{ad,a^1d} \sum_{c} e^{CB}_{cb,cb^1} \tag{40}$$

Note that the PI procedure is only appropriate when used in conjunction with the spin product representation. Not only is PI computationally convenient, but it also correlates so nicely with chemical intuition.

To show the form taken by these e(ae) elements, let AB, CD, AC and BD all be two half-spin systems. Then, a $(e^{AB}_{(ae)})_{\alpha\alpha,\alpha\beta}$ element is given by equations 41 and 42 and is incorporated into the $(Ee^{AB})_{\alpha\alpha,\alpha\beta}$ elements in equation 43.

$$\left(e^{AB}_{(ae)}\right)_{\alpha\alpha,\alpha\beta} = \sum_{\substack{d= \\ \alpha,\beta}} e^{AD}_{\alpha d,\alpha d} \sum_{\substack{c= \\ \alpha,\beta}} e^{CB}_{c\alpha,c\beta} \tag{41}$$

$$= \frac{1}{2}(e^{CB}_{\alpha\alpha,\alpha\beta} + e^{CB}_{\beta\alpha,\beta\beta}) \tag{42}$$

In the transformation of equation 41 to equation 43, and in equation 43, we have made use of equation 7 ($e_{ab,ab} = 1/4$) and that $k_{AB} = k_f(CD)$. The foregoing treatment shows that density matrix equations will almost always be first order in off-diagonal elements of the density matrix.

$$(Ee^{AB})_{\alpha\alpha,\alpha\beta} = k_f(CD)\left(\frac{1}{2}e^{CD}_{\alpha\alpha,\alpha\beta} + \frac{1}{2}e^{CB}_{\beta\alpha,\beta\beta} - e^{AB}_{\alpha\alpha,\alpha\beta}\right) \tag{43}$$

Using similar procedures to that for e^{AB}_{ab,a^1b^1}, the other e(ae) elements are listed in equations 44–46.

$$(e^{CD}_{(ae)})_{cd,c^1d^1} = \sum_{a} e^{AD}_{ad,ad^1} \sum_{b} e^{CB}_{cb,c^1b} \tag{44}$$

$$(e^{AD}_{(ae)})_{ad,a^1d^1} = \sum_{b} e^{AB}_{ab,a^1b} \sum_{c} e^{CD}_{cd,cd^1} \tag{45}$$

$$(e^{CB}_{(ae)})_{cb,c^1b^1} = \sum_{a} e^{AB}_{ab,ab^1} \sum_{d} e^{CD}_{cd,c^1d} \tag{46}$$

Needless to say, independent determination of the equilibrium constant simplifies the line shape analysis.

Reversible dissociation at equilibrium (equation 47) is mathematically a special case of mutual exchange.

$$\begin{array}{ccccccc} & AB & \underset{k_2}{\rightleftharpoons} & A & + & B \\ \emptyset & ab & k_2 & a & & b \end{array} \tag{47}$$

The $(e^{AB}_{(ae)})_{\ell,n}$ elements of the dissociating AB are picked out by dissecting the chemical label in parallel to factoring the spin product subscripts. The other elements are obtained via a reverse procedure to that in equation 48 (see equations 49 and 50). The Ee^{AB} element follows (eq. 51) together with an example where ab,a^1b^1 is $\alpha\alpha,\alpha\beta$, just to show the forms these elements take (equations 52 and 53).

$$(e^{AB}_{(ae)})_{ab,a^1b^1} = e^{A}_{a,a^1} e^{B}_{b,b^1} \tag{48}$$

$$e^{A}_{a,a^1} = e^{A}_{a,a^1} \sum_{b} e^{B}_{b,b} \tag{49}$$

$$(e^{A}(ae))_{a,a^1} = \sum_{b} e^{AB}_{ab,a^1b} \tag{50}$$

$$(Ee^{AB})_{ab,a^1b^1} = k_1(e^{A}_{a,a^1} e^{B}_{b,b^1} - e^{AB}_{ab,a^1b^1}) \tag{51}$$

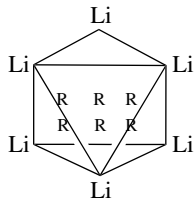
$$(Ee^{A})_{a,a^1} = k_2(B)\left(\sum_{b} e^{AB}_{ab,a^1b} - e^{A}_{a,a^1}\right) \tag{52}$$

$$(Ee^{AB})_{\alpha\alpha,\alpha\beta} = k_1\left(\frac{1}{2} e^{B}_{\alpha,\beta} - e^{AB}_{\alpha\alpha,\alpha\beta}\right) \tag{53}$$

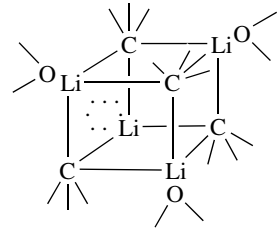
III. ORGANOLITHIUM COMPOUNDS[1–3]

A. Introduction

The principal structures into which organolithium compounds assemble are unsolvated octahedral hexamers **6**, and cubic tetramers, and solvated cubic tetramers **7**, bridged dimers **8** and monomers, **9**. In common among the solvated species, lithium is always tetracoordinate so that the dissociating direction is exothermic with negative entropy change due to the increase in coordination of lithium to a ligand ether or a tertiary amine.



(6)



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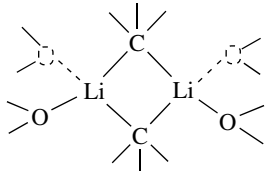

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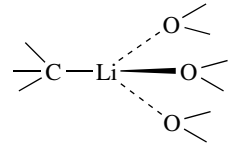
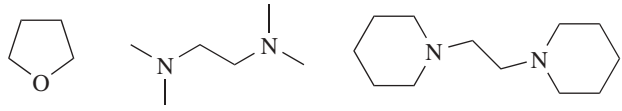


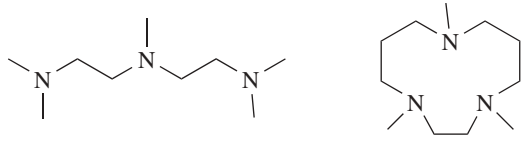
(9)

Here are some loose generalizations regarding the forms which different organolithiums assume[2,3].

Among unsolvated organolithium compounds only the alkyllithiums are soluble in noncoordinating solvents such as alkanes and arenes. Their states of aggregation depend on the structure close to lithium. Thus primary, tertiary and secondary alkyllithiums, all unsolvated, assemble into respectively hexamers, tetramers and equilibrium mixtures of hexamers and tetramers. Most organolithium compounds dissolve in and coordinate with donor compounds such as ethers and tertiary amines. The actual structures depend critically on the nature of the donor. Thus, diethyl ether solvates tend to be mainly cubic tetramers (with some dimers) while THF favors mixtures of monomers and dimers. Tertiary vicinal diamines such as TMEDA and 1,2-di-*N*-piperidinoethane, DPE, favor bidentated coordinated dimers. Finally, in the presence of triamines such as pentamethyl-triethylenediamine PMDTA and 1,4,7-trimethyl-1,4,7-triazacyclononane TMTAN, many organolithium compounds form tridentately complexed monomers.



THF TMEDA DPE



PMDTA TMTAN

Solution structures of organolithium compounds are now easily recognized by the multiplicity of the ^{13}C NMR of lithium bound carbon due to one bond $^{13}C-^{7}Li$ or $^{13}C-^{6}Li$ scalar coupling as well as by the magnitude of the coupling constants[3]. Table 1 lists the ^{13}C NMR multiplets due to one, two and three ^{6}Li's or ^{7}Li's equally one bond coupled to the same ^{13}C as in, respectively, monomers, dimers and tetramers.

The carbon–lithium coupling constants themselves are, for many examples, simply related to the states of aggregation n (equations 54a and 54b)[11].

$$^{1}J(^{13}C, ^{6}Li) = \frac{1}{n}(17.2 \pm 2) \tag{54a}$$

TABLE 1. ^{13}C NMR multiplets due to '$^{6}Li_n\,^{13}C$' and '$^{7}Li_n\,^{13}C$' [a] due to $^{6}Li-^{13}C$ or $^{7}Li-^{13}C$ coupling

Li species	n	Aggregation state	Multiplet [a]
^{6}Li	1	mon	1,1,1
^{6}Li	2	dim	1,2,3,2,1
^{6}Li	3	tet	1,3,6,7,6,3,1
^{7}Li	1	mon	1,1,1,1
^{7}Li	2	dim	1,2,3,4,3,2,1
^{7}Li	3	tet	1,3,6,10,12,12,10,6,3,1

[a] Equal coupling within each '$Li_n\,^{13}C$' site.

$$^{1}J(^{13}\mathrm{C},^{7}\mathrm{Li}) = \frac{1}{n}(45 \pm 5) \tag{54b}$$

Further, for reasons which can be rationalized but not explained, their values appear to be independent of the nature of the organic moiety. Based on the theoretical treatment of spin coupling due to Ramsey[12a], Grant and Lichtman[12b,c] and Karplus and Grant[12d], Fraenkel and Martin ascribed this phenomenon to an inverse relationship between 's' character associated with the $^{13}C-^{6}Li$ bond and its covalent character[13].

It is advisable to carry out the NMR studies of organolithium structure at low temperature in order to minimize averaging of the $Li-^{13}C$ coupling by fast intermolecular C−Li exchange and to prepare the $R^{6}Li$ compound in preference to using naturally abundant ^{7}Li. The nuclear electric quadrupole moment of ^{7}Li, $I = 3/2$, is large enough so that the ^{7}Li electric quadrupole induced relaxations rate may well be fast enough to average or partly average the $^{7}Li-^{13}C$ coupling constant[14]. This is not a problem with ^{13}C NMR of '$R^{6}Li$' species, since the quadrupole moment of ^{6}Li is smaller than that of ^{7}Li by a factor of 91[15].

Fast bimolecular C−Li exchange as in equation 55

$$^{13}C^{6}Li + {}^{13}C^{*6}Li^{*} \rightleftharpoons {}^{13}C^{6}Li^{*} + {}^{13}C^{*6}Li \tag{55}$$

averages the $^{13}C-^{6}Li$ coupling constant because the $^{6}Li^{*}$ has a 2/3 probability of being in a different spin state from the ^{6}Li it replaces. The observation, that a coupling constant $J(X,Y)$ within a molecule progressively averages to zero on warming the sample, is unambiguous evidence for fast intermolecular X−Y exchange. In principle, kinetic studies need not be undertaken except as a precaution.

Fast local reversible dissociation of a C−Li bond does not change the ^{13}C or ^{6}Li NMR line shape if the dissociating Li returns to its original site as in equation 56,

$$^{13}C^{6}Li \rightleftharpoons {}^{13}C^{-}\ {}^{6}Li^{+} \tag{56}$$

because the spin state of the ^{6}Li does not change during the lifetime of the exchange process.

If a nucleus in a molecule rapidly migrates among several sites *within* that molecule (but *not between molecules*) and is spin coupled to some of the sites, the resultant splitting is the weighted average (equation 57)

$$J_{\mathrm{av}} = \sum_{s} (\mathrm{r}_s) J_s \tag{57}$$

where s sums over sites and the r_s's are site fractional residence times.

As far as ^{13}C NMR of lithium bound carbon is concerned, averaging of $^{13}C-^{6}Li$ spin coupling between monomeric RLi species with ^{13}C in natural abundance is simulated as in equation 58,

$$\begin{array}{cccccccc} & ^{13}C^{6}Li & + & ^{12}C^{*6}Li^{*} & \rightleftharpoons & ^{13}C^{6}Li^{*} & + & ^{12}C^{6}Li \\ \emptyset & \alpha\ell & & m & & \alpha m & & \ell \\ & \beta\ell & & m & & \beta m & & \ell \end{array} \tag{58}$$

where ℓ and m are states of ^{6}Li ($I = \mathbf{1}$). The three required elements of the density matrix equation are $\langle\alpha(-1)|\dot{e}|\beta(-1)\rangle$, $\langle\alpha(0)|\dot{e}|\beta(0)\rangle$ and $\langle\alpha(-1)|\dot{e}|\beta(-1)\rangle$;(0), (−1) and (+1) are

abbreviations for states of ^{6}Li. The e(ae) elements are derived in equations 59 and 60

$$e^{\mathrm{CLi}}_{\alpha\ell,\beta\ell} = e^{\mathrm{CLi}}_{\alpha\ell,\beta\ell} \sum_m e^{\mathrm{Li}^*}_m \tag{59}$$

$$\begin{aligned}\left(e^{\mathrm{CLi}}_{(\mathrm{ae})}\right)_{\alpha\ell,\beta\ell} &= \sum_m e^{\mathrm{CLi}^*}_{\alpha m,\beta m} e^{\mathrm{Li}}_{\ell,\ell} \\ &= \frac{1}{3} e^{\mathrm{CLi}^*}_{\alpha m,\beta m}\end{aligned} \tag{60}$$

and the resulting density matrix equations in matrix form are exhibited in equation 61[13] by equation 62. The equations are solved for the $e^{\mathrm{CLi}}_{\alpha\ell,\beta\ell}$ elements, which are summed as in equation 10 to give the ^{13}C line shapes.

$$\begin{bmatrix} i(\Delta\omega - J) & \frac{1}{3}k^1 & \frac{1}{3}k^1 \\ -\frac{1}{T} - \frac{2}{3}k^1 & & \\ \frac{1}{3}k^1 & i(\Delta\omega) & \frac{1}{3}k^1 \\ & -\frac{1}{T} - \frac{2}{3}k^1 & \\ \frac{1}{3}k^1 & \frac{1}{3}k^1 & i(\Delta\omega + J) \\ & & -\frac{1}{T} - \frac{2}{3}k^1 \end{bmatrix} \begin{bmatrix} e^{\mathrm{CLi}}_{\alpha(-),\beta(-)} \\ e^{\mathrm{CLi}}_{\alpha(0),\beta(0)} \\ e^{\mathrm{CLi}}_{\alpha(+),\beta(+)} \end{bmatrix} = iC \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix} \tag{61}$$

$$\begin{aligned} k^1 &= \frac{k_2(^{13}\mathrm{C}^6\mathrm{Li})(^{12}\mathrm{C}^6\mathrm{Li})}{(^{13}\mathrm{C}^6\mathrm{Li})} \\ \mathrm{k}^1 &= k_2(^{12}\mathrm{C}^6\mathrm{Li}) \end{aligned} \tag{62}$$

In NMR studies of organolithium compounds, it often happens that ^{13}C$-^6$Li spin coupling is expected but not observed down to 150 K using, for example, a 0.1 M solution of an R^{6}Li compound with ^{13}C in natural abundance. Note that below 150 K many RLi compounds precipitate from solution. If the absence of ^{13}C$-^6$Li coupling is suspected to result from fast bimolecular C$-$Li exchange, even at 150 K, the rate can be dropped by use of a dilute sample, say 10^{-3} M in R^{6}Li enriched >95% in ^{13}C at lithium bound carbon. Under the same NMR instrumental conditions and temperature, ^{13}C resonances of ^{6}Li bound carbon in the two samples should exhibit the same signal/noise ratios. However, the intermolecular C$-$Li exchange rate in the dilute sample will be a factor of 100 slower than for the former sample above. An experiment of this type showed $^{13}\mathrm{C}_\alpha{}^6$Li spin coupling in a dilute sample of benzyllithium$-^{13}\mathrm{C}_\alpha-^6$Li complexed to TMEDA, but not in the more concentrated sample with ^{13}C in natural abundance[13].

In terms of ^{13}C NMR, the situation for R^{7}Li compounds is more complicated than for R^{6}Li since the one bond ^{13}C$-^7$Li coupling constant may be averaged or partially averaged by ^{7}Li nuclear electric quadrupole induced relaxation as well as fast intermolecular exchange. The latter rate increases with temperature whereas the quadrupole induced relaxation rate increases *on cooling* the sample. The rates of the two processes can overlap, so there may not be a temperature at which ^{13}C$-^7$Li coupling is well resolved. It may be greatly broadened or just appear as a broad line. In such a case, the resonance will narrow on both heating and cooling, for different reasons. Given an estimate of the ^{13}C^{7}Li

coupling constant, both C−Li bimolecular exchange and quadrupole induced ^{7}Li relaxation rates can be extracted from the ^{13}C NMR line shapes. Briefly, the procedure is as follows. ^{7}Li ($I = 3/2$) has four spin states abbreviated by their m^z values as (+3/2), (+1/2), (−1/2) and (−3/2). There are four required elements of the density matrix, $\langle \alpha\ell | \beta\ell \rangle$, ℓ being one of the spin states of ^{7}Li. Because we use the quadrupole relaxation operator at the extreme narrowing limit, just one composite relaxation parameter j_q suffices to account for the contribution of ^{7}Li quadrupolar relaxation to the ^{13}C NMR line shape in this system (see equation 63),

$$j_q = \frac{1}{30}\left(\frac{e^2 Q}{h}\right)^2 \tau_q \tag{63}$$

where Q, q and τ_q, are, respectively[14, 16], the ^{7}Li quadrupole moment, the electric field gradient and the quadrupolar correlation time. Note that equation 63 applies only at extreme narrowing and $I = 3/2$.

As before, for purposes of calculating the ^{13}C NMR line shapes of ^{7}Li bound carbon with ^{13}C in natural abundance, the exchanging system is simulated as in equation 64.

$$\begin{array}{cccccccc} & ^{13}C^7Li & + & ^{12}C^7Li^* & \underset{k_2}{\overset{k_2}{\rightleftharpoons}} & ^{13}C^7Li^* & + & ^{12}C^7Li \\ \emptyset & \alpha\ell & & m & & \alpha m & & \ell \\ & \beta\ell & & m & & \beta m & & \ell \end{array} \tag{64}$$

Then the elements of e(ae), derived as in equation 60, come out as in equation 65,

$$(e(\mathrm{ae}))_{\alpha\ell,\beta\ell} = \frac{1}{4}\sum_m e^{\mathrm{CLi}}_{\alpha m,\beta m} \tag{65}$$

since ^{7}Li has four nuclear spin states. Following the above-described procedures, the resulting matrix equations in matrix form are shown in equation 66. Given the solved $e^{\mathrm{CLi}}_{\alpha\ell,\beta\ell}$ elements, the absorption is obtained in the usual way (equation 67)[14].

$$\begin{bmatrix} i\left(\Delta\omega - \frac{3}{2}J\right) - \frac{1}{T} & 24j_q + \frac{1}{4}k^1 & 24j_q + \frac{1}{4}k^1 & \frac{1}{4}k^1 \\ -48j_q - \frac{3}{4}k^1 & & & \\ 24j_q + \frac{1}{4}k^1 & i\left(\Delta\omega - \frac{1}{2}J\right) - \frac{1}{T} & \frac{1}{4}k^1 & 24j_q + \frac{1}{4}k^1 \\ & -48j_q - \frac{3}{4}k^1 & & \\ 24j_q + \frac{1}{4}k^1 & \frac{1}{4}k^1 & i\left(\Delta\omega - \frac{1}{2}J\right) - \frac{1}{T} & 24j_q + \frac{1}{4}k^1 \\ & & -48j_q - \frac{3}{4}k^1 & \\ \frac{1}{4}k^1 & 24j_q + \frac{1}{4}k^1 & 24q + \frac{1}{4}k^1 & i\left(\Delta\omega + \frac{3}{2}J\right) - \frac{1}{T} \\ & & & -48j_q - \frac{3}{4}k^1 \end{bmatrix} \tag{66}$$

$$\times \begin{bmatrix} e_1 \\ e_2 \\ e_3 \\ e_4 \end{bmatrix} = iC \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} \tag{66}$$

$$\mathrm{Abs}(\omega) = -\mathrm{Im} \sum_m e^{CLi}_{\alpha m, \beta m} \tag{67}$$

B. Primary Alkyllithium Compounds

In 1968, a group of chemists at the Dow Chemical Company reported that the ^{13}C NMR spectra of solutions of methyllithium$-^{13}C-^{7}Li$ in THF at low temperature exhibited $^{13}C-^{7}Li$ spin coupling. With increasing temperature, the multiplicity of the ^{13}C resonance due to this spin coupling progressively averaged to a single line by 290 K. This was the first evidence that organolithium compounds undergo fast bimolecular C−Li bond exchange at equilibrium[4].

A careful study of proton NMR of 2-methylbutyllithium **10** in cyclopentane solution revealed intimate details on the dynamics of inversion as well as of bimolecular C−Li exchange[17]. At 252 K, proton NMR of the C_1 methylene hydrogens of (*R*)-**10** consists of the AB

$$(CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2Li)_n$$

(**10**)

part of an ABX system, due to the chirality at C_2. Actually, the X proton at C_2 is also coupled to CH_3 at C_2 and to the C_3H_2 protons. The AB resonance can be calculated independently of the X resonance because the X shift is well separated from those of A and B.

With increasing temperature above 251 K the shift between H_A and H_B in **10** (cf. 11a and 11b) is progressively averaged. Also, J_{AX} averages with J_{BX} (Figure 1). Ultimately, the AB resonance consists of an equal doublet of separation of $\frac{1}{2}(J_{AX} + J_{BX})$. This behavior is most reasonably the result of inversion at a lithium–carbon bond. As seen in a simplified example (equation 68), wherein R* is chiral, the result of an inversion is to exchange the environments of H_A with H_B.

Because the X resonance is well separated from that of AB, the latter line shape can be calculated separately for the inverting system depicted in equation 69.

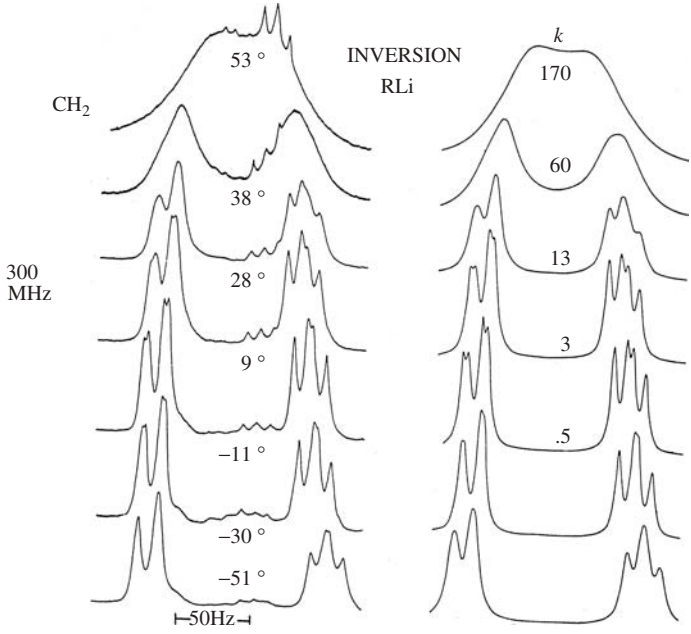
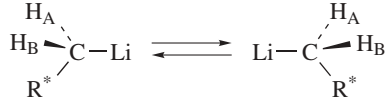


FIGURE 1. Left: proton NMR, 300 MHz, CH_2Li portion of (R)-2-methylbutyllithium, 1.5 M in pentane at different temperatures. Right: calculated NMR line shapes taking into account the dynamics of inversion. Reprinted with permission from Reference 17. Copyright (1976) American Chemical Society



(**11a**) (**11b**) (68)

$$R^* = CH_3CH_2CHCH_3$$

$$\begin{array}{lll} & ABX & BAX \\ Ø & abx & bax \\ & a^1b^1x & b^1a^1x^1 \end{array} \qquad (69)$$

Eight elements of the density matrix are required, $e_{abx,a^1b^1x^1}$ diagonal in x and involving a spin flip of a or b. The e(ae) elements come out in simple fashion (equation 70).

$$(e(\text{ae}))_{abx,a^1b^1x} = e_{bax,b^1a^1x} \qquad (70)$$

Taking the appropriate elements of the density matrix equation generates the eight coupled equations in the required e elements. Comparison of calculated with observed line shapes in Figure 1 yields the k^1 values and activation parameters (Table 2).

The AB proton resonance of racemic 2-methylbutyllithium in pentane is broadened (Figure 2) compared to that of the optically pure material due to the assumed presence of

TABLE 2. Activation parameters for exchange and inversion of 2-methylbutyllithium (RLi 1.5 M)[17]

Species, process	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (eu)	k^1 (281 K) (s^{-1})
(*R*-Li), inversion	15.6 ± 1	-0.6 ± 3	4.0
(*RS*)-RLi, inversion	14.8 ± 1	-3 ± 3	6.4
(*RS*)-RLi, exchange	3.3 ± 0.5	-39 ± 7	7.2

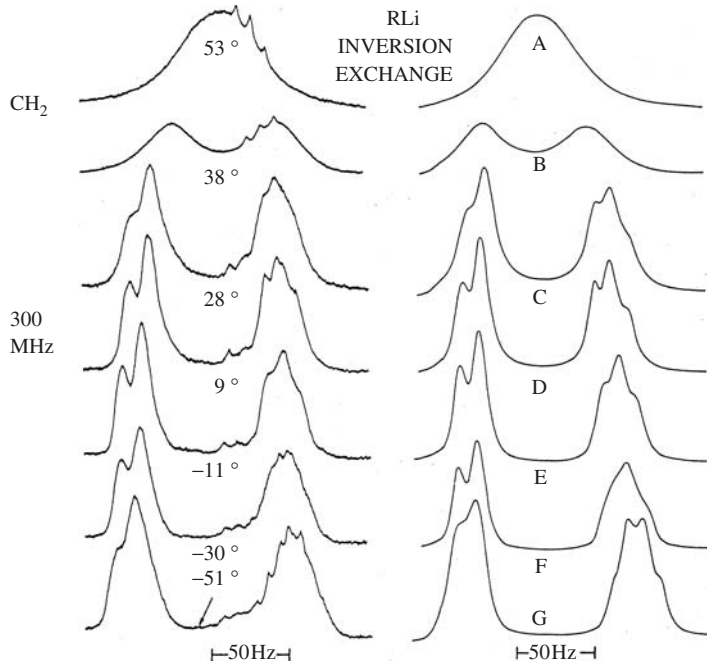


FIGURE 2. Left: proton NMR, 300 MHz, CH_2Li portion of racemic 2-methylbutyllithium, 1.5 M in pentane at different temperatures. Right: calculated NMR line shapes taking into account the dynamics of inversion and interaggregate exchange. Reprinted with permission from Reference 17. Copyright (1976) American Chemical Society

diastereomeric aggregates. The line shape changes with increasing temperature resemble those for (*R*)-**10**.

Differential vapor pressure measurements show (*RS*)-**10** to be a hexamer at 0 °C with *ca* 10% higher aggregates by −18 °C. We assume that (*RS*)-**10** takes the octahedral hexameric structure, that the diastereomeric aggregates have similar free energies and that one need not distinguish among the alkyl groups in any particular composition. Then, the relative abundances should follow a binomial distribution. Thus for $R_6 = S_6$, $R_5S = RS_5$, $R_4S_2 = R_2S_4$ and R_3S_3 the relative abundances should be 2:12:30:20, the last two amounting to 78% of the racemic material. A reasonable trial model for the NMR would be due mainly to overlapping spectra of the two more abundant diastereomeric octahedral hexamers which are designated T and U. Then changes of the line shapes on warming the compound would be due to a combination of inversion in T and U separately and interconversion

of T with U by exchange of alkyl groups. NMR line shape analysis for the AB parts of (*RS*)-**10** is handled in similar fashion to that for (*R*)-**10**, except now eight elements of the density matrix equation have to be derived for both U and T. The density matrix equations must take account of both reorganization processes via their e(ae) elements. Inversion in T and U is handled as in equation 71 (see equation 72), while for the T $\rightleftarrows$ U interconversion we just change the label as in equation 73

$$(e^{\mathrm{T}}_{(\mathrm{ae})})_{abx,a^1b^1x} = e^{\mathrm{T}}_{bax,b^1a^1x} \tag{71}$$

$$(e^{\mathrm{U}}_{(\mathrm{ae})})_{abx,a^1b^1x} = e^{\mathrm{U}}_{bax,b^1a^1x} \tag{72}$$

$$(e^{\mathrm{T}}_{(\mathrm{ae})})_{abx,a^1b^1x} = e^{\mathrm{U}}_{abx,a^1b^1x} \tag{73}$$

The solution for the e^{T} and e^{U} elements followed by the usual summation process (equation 11) provides the calculated line shapes in Figure 2. Their comparison with the experimental spectra yields the pseudo-first-order rate constants and Eyring activation parameters given in Table 2.

Seebach and coworkers[18] have reported that a combination of integration and NMR line shape fitting establishes that in THF-d_8, n-butyllithium$-{}^6$Li, **12**, consists of an equilibrium between interconverting dimers D and tetramers T (equation 74) with $K = (D)^2/(T)$ being 2.6×10^{-2} M at 185 K.

$CH_3CH_2CH_2CH_2{}^6Li$

(**12**)

$$(n\text{-Bu})_4(\mathrm{THF})_4 + 4\mathrm{THF} \rightleftarrows 2n\text{-Bu}_2(\mathrm{THF})_4 \tag{74}$$

The temperature dependence of the equilibrium yielded $\Delta H^\circ = -2.06$ kcal mol^{-1} and $\Delta S^\circ = 1.8$ eu.

The dimer was recognized by the multiplicity of the ^{13}C NMR due to lithium bound carbon. Given ^1J (^{13}C, ^{6}Li) in dimer provided an estimate of the value for tetramer (cf. equation 54a).

With increasing temperature above 185 K and with increasing concentration of the n-butyllithium, the authors reported progressive averaging of the ^{13}C$-^6$Li coupling constant of dimers as well as of the resonances of dimer with tetramer. A line shape analysis of the ^{13}C NMR of lithium bound carbon, using our PI method, best took account of the interconversion of tetramers with dimers via a degenerate process (equation 75),

$$\mathrm{D} + \mathrm{T} \rightleftarrows \mathrm{D}^1 + \mathrm{T}^1 \tag{75}$$

involving possibly a hexameric intermediate, rather than a dissociative exchange (equation 76).

$$2\mathrm{D} \rightleftarrows \mathrm{T} \tag{76}$$

The PI analysis was also used to estimate parameters not directly accessible from the NMR spectra, such as the one bond ^{13}C$-^6$Li coupling constant in the tetramer. Interestingly, to fit the data between 163 K and 204 K it was necessary to systematically reduce the value of ^1J(^{13}C, ^{6}Li) in dimer from 8.93 Hz to 6.93 Hz. This analysis resulted in the activation parameters of $\Delta H^\ddagger = 3.8$ kcal mol^{-1} and $\Delta S^\ddagger = -31$ eu for the process given in equation 75.[18]

Carbon-13 NMR of 1-propyllithium$-{}^{13}C_1-{}^6$Li, **13**, in cyclopentane at 200 K, showed resonances for five species assigned from the multiplicities and splittings of their ^{13}C

$CH_3CH_2{}^{13}CH_2{}^{6}Li$
(**13**)

resonances, due to ^{6}Li bound carbon, to be hexamer (major), octamer and three different nonamers, all fluxional, that is undergoing fast intra-aggregate C–Li exchange (Figure 3)[19]. For example, in octahedral hexamers one would expect just coupling of ^{13}C to its three nearest neighbors, with a coupling constant of 5 Hz to 6 Hz and a multiplicity of 1:3:6:7:3:6:1. Instead, 9 to 11 lines were observed with a splitting of *ca* 3 Hz. That was more consistent with a coupling of 6 Hz to the three nearest ^{6}Li neighbors averaged with very small couplings to the other three ^{6}Li's in a fluxional aggregate giving rise to thirteen lines 1:6:21:90:126:140:126:90:21:6:1 of which 9 to 11 were observed. The other resonances were analyzed in a similar manner. Lithium-6 NMR of a solution in cyclopentane of 1-propyllithium–^{6}Li with ^{13}C in natural abundance gave five sharp

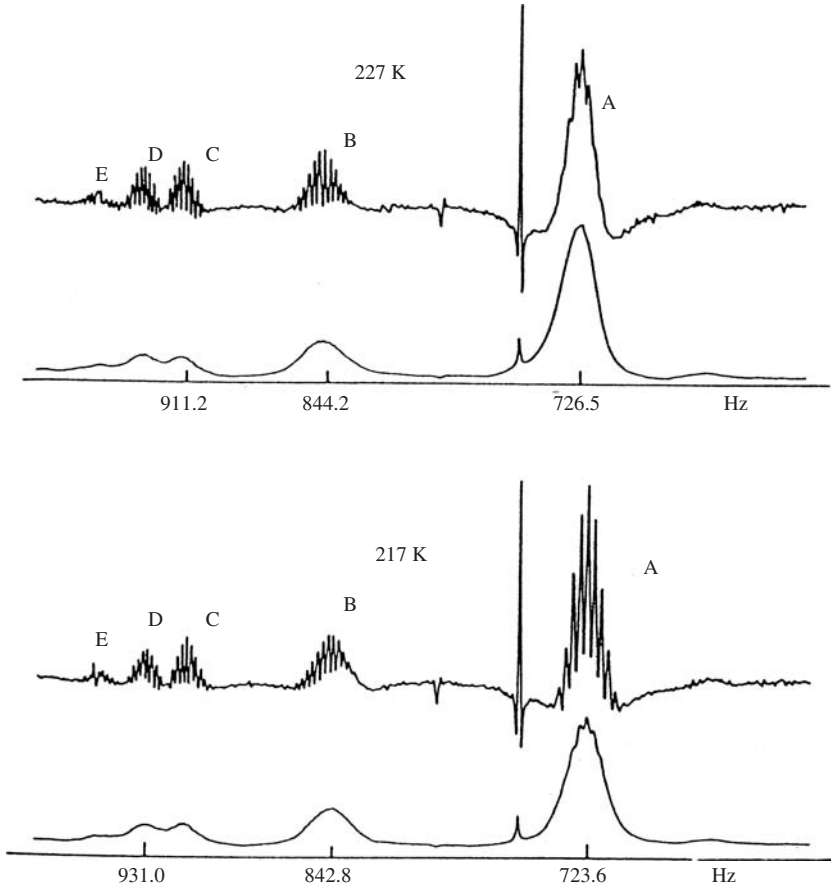


FIGURE 3. NMR (^{13}C 67.89 MHz), C_1 of *n*-propyllithium–$^{13}C_1$–^{6}Li, 0.5 M in cyclopentane at two temperatures; upper: line shapes with resolution enhancement. Reprinted with permission from Reference 19. Copyright (1980) American Chemical Society

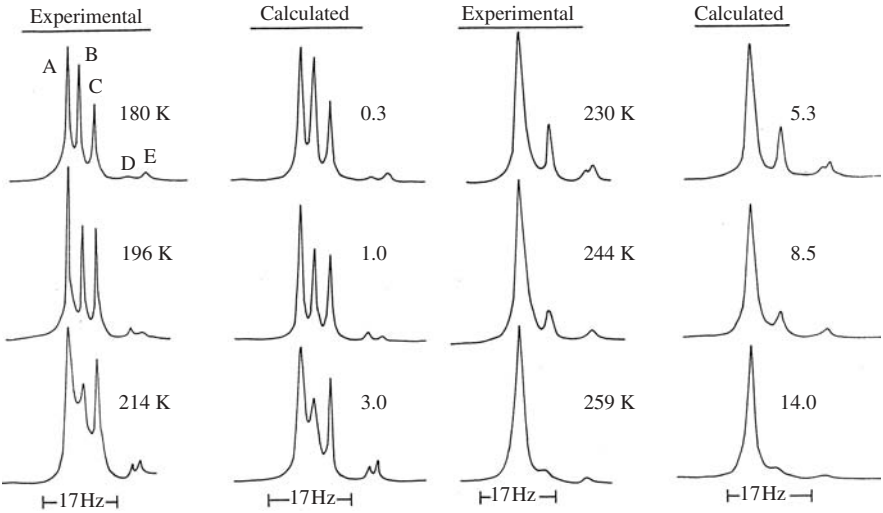


FIGURE 4. NMR ^{6}Li, 39.73 MHz, of *n*-propyllithium–^{6}Li, 0.6 M in cyclopentane. Left: observed at different temperatures. Right: calculated line shapes which take into account the dynamics of intermolecular C–Li exchange, with rate constants. Reprinted with permission from Reference 19. Copyright (1980) American Chemical Society

lines at low temperature with relative intensities similar to the ^{13}C NMR data (Figure 4). Thermodynamic parameters were derived from the relative intensities of the ^{13}C NMR and the ^{6}Li resonances.

Below 200 K the $^{13}C_1$ resonances broaden differentially with decreasing temperature, indicating a slowing down of the intra-aggregate C–Li exchange at different rates for different species.

With increasing temperature above 200 K the resonances for the different species in both the ^{13}C and ^{6}Li spectra undergo averaging, as do also the splittings due to ^{13}C–^{6}Li coupling. These changes are clearly the result of intermolecular C–Li exchange. Also note that by room temperature the equilibria have all shifted to hexamer.

NMR line shape analysis of the intermolecular exchanging system was handled in two ways, which gave very similar results, by use of the ^{6}Li resonances of 1-propyllithium–^{6}Li and by calculating the ^{13}C NMR of lithium bound carbon in hexamer under conditions when hexamer prevailed in the equilibrium.

In the ^{6}Li NMR of $CH_3CH_2CH_2{}^{6}Li$ with ^{13}C in natural abundance, ^{6}Li is uncoupled and the lines are sharp at low temperature. So the ^{6}Li NMR can be simulated as due to pseudo-half-spin transitions and each element of the density matrix is just labeled by site, A, B etc. Lithiums can undergo mutual exchange between any pair of aggregates as indicated by equation 77.

$$\mathrm{ALi} + \mathrm{BLi}^{*} \underset{}{\overset{k_2}{\rightleftharpoons}} \mathrm{ALi}^{*} + \mathrm{BLi} \tag{77}$$

The e(ae) elements are given by equation 78

$$e^{\mathrm{B}}(\mathrm{ae}) = e^{\mathrm{A}} \tag{78}$$

and the Ee elements have to include all exchanges of one species (equation 79).

$$Ee^{\mathrm{A}} = \sum_{\mathrm{N}\neq\mathrm{A}} k_1(e^{\mathrm{N}} - e^{\mathrm{A}}) \tag{79}$$

For simplicity, the k_2's were taken to be the same at any particular temperature. There are five density matrix equations. They are solved for the e elements and absorption is summed as before. It was important to carefully estimate the relative concentrations of the different aggregates.

The ^{13}C line shapes for lithium bound carbon were analyzed under conditions when hexamer predominated. The exchanging system was simulated as in equation 80.

$$\mathrm{CLi_6} + \mathrm{C^*Li_6^*} \rightleftharpoons \mathrm{CLi_6^*} + \mathrm{C^*Li_6} \tag{80}$$

Altogether, 728 elements of the density matrix are required. All are off-diagonal in ^{13}C and diagonal in the states of ^{6}Li, ℓ (equation 81), where ℓ's are the spin products for the six ^{6}Li's (equation 82).

$$\langle \alpha\ell | e | \beta\ell \rangle \tag{81}$$

$$\ell = \prod_{s=1}^{s=6} \varphi_{s\ell} \tag{82}$$

The e(ae) elements are obtained as outlined in Section I for a bimolecular exchanging system (equation 83).

$$(e(\mathrm{ae}))_{\alpha\ell,\beta\ell} = \frac{1}{364} \sum_m e_{\alpha m,\beta m} \tag{83}$$

The 728 elements of the density matrix are simplified to just 13 unknowns by summing the elements into groups where the ℓ's have the same associated $\sum_i \mathrm{m}_{\ell i}^z = M$ value (equation 84).

$$e^M = \sum_\ell \langle \alpha\ell_M | e | \beta\ell_M \rangle \tag{84}$$

This results in 13 density matrix equations, which are solved to give the ^{13}C NMR line shapes.

The resulting first-order rate constants using both the ^{13}C and ^{6}Li NMR line shapes are listed in Table 3; $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ from both sets of line shapes are, respectively, 5.5 ± 0.25 kcal mol^{-1} and -42 eu.

TABLE 3. First-order rate constants for C−Li exchange in propyllithium−^{13}C$_1$−^{6}Li in cyclopentane, from ^{13}C and ^{6}Li line shapes[19]

T(K)	k_1 (^{13}C NMR)	T(K)	k_1' (^{6}Li NMR)
205	1.0	180	0.3
226	4.0	196	0.9
235	10.0	214	2.9
252	15.0	230	5.1
298	40.0	244	6.0
		259	9.5

Neopentyllithium–^{6}Li, (NpLi) **14**, in methylcyclohexane at 240 K showed ^{13}C NMR resonances, as yet unidentified, for four species, most likely higher aggregates as for **12**[20]. In the presence of potential ligands, monomers, dimers and tetramers were identified. These were recognized by their one bond ^{13}C–^{6}Li coupling constants, multiplicities of the C_1H_2 ^{13}C NMR and their $^{13}C_1$ chemical shifts. In diethyl ether-d_{10} dimers were observed, in THF monomers and dimers, and when complexed to triamines such as PMDTA and TMTAN only monomers are formed. Where equilibria between solvated species were observed, the smaller aggregate accumulated with decreasing temperature. Thus, the thermodynamics for the equilibrium in THF, proposed in equation 85,

$(CH_3)_3CCH_2{}^6Li$
(**14**)

$$2\ \mathrm{THF} + (\mathrm{NpLi})_2(\mathrm{THF})_4 \rightleftharpoons 2\ \mathrm{NpLi(THF)_3} \tag{85}$$

gave $\Delta H^\circ = 1.4$ kcal mol^{-1} with $\Delta S^\circ = 11$ eu.

Tertiary triamines, such as pentamethyldiethylene triamine PMDTA and 1,4,7-trimethyl-1,4,7-triazacyclononane TMTAN, form tridentate monomeric complexes, exclusively, with neopentyllithium. Carbon-13 NMR of these complexes show unusual intimate details of structure and dynamic behavior. Carbon-13 NMR of a solution 0.59 M in **14** and 0.34 M in PMDTA in diethyl ether-d_{10} showed all the PMDTA to be complexed to monomeric neopentyllithium–^{6}Li. The remaining 0.25 M **14** was dimer complexed to the ether. At 166 K, all but two carbons, CH_2's at 57.34 δ, of the complexed PMDTA are magnetically nonequivalent (Figure 5). With increasing temperature above 166 K, the pairs of ^{13}C resonances due to $N(CH_3)_2$ at 43.85 δ and 47.09 δ and at 44.82 δ and 50.06 δ each progressively average to broad lines at their respective centers, by 206 K; see the dotted lines in Figure 5. Likewise, the doublet at 51.86 δ and 54.68 δ due to two CH_2's averages to a single line by 210 K. Above 200 K, with increasing temperature, the broadened $N(CH_3)_2$ doublet just described averages to a single line by 246 K. Throughout the temperature range 166 K to 246 K the NCH_3 resonance is sharp and unchanged.

It was proposed that the *t*-butyl group of **14**•PMDTA is unsymmetrically sited with respect to the coordinated PMDTA (Figure 6). The partial averaging of $N(CH_3)_2$ resonances and the averaging of CH_2 resonances all at lower temperatures was ascribed to fast rotation of coordinated PMDTA around the C–Li bond. Then, above 206 K, averaging of the broadened $N(CH_3)_2$ doublet would be due to fast local reversible dissociation of N–Li coordination accompanied by inversion at nitrogen and rotation around the C–N bond prior to N–Li recombination. NMR line shapes were calculated to take account of both processes (Figure 5). The resulting activating parameters were found to be $\Delta H_r^\ddagger = 7.7 \pm 0.5$kcal mol^{-1} and $\Delta S_r^\ddagger = -9 \pm 2$ eu for rotation and $\Delta H_i^\ddagger$ 8.7 kcal mol^{-1} and $\Delta S_i^\ddagger = -3$ eu for inversion at nitrogen.

As noted, the sample of neopentyllithium in diethyl ether-d_{10}, described above, contained neopentyllithium dimer solvated by diethyl ether-d_{10}, 0.125 M, in addition to the **14**•PMDTA monomer 0.34 M. Averaging of the ^{6}Li NMR for these two species indicated a fast mutual exchange of lithiums between PMDTA coordinated monomer and ether solvated dimer. NMR line shape analysis of the ^{6}Li resonance gave $\Delta H^\ddagger = 12$ kcal mol^{-1} and $\Delta S^\ddagger = +10$ eu for this exchange process. It is interesting that at 230 K the pseudo-first-order rate constants for inversion in **14**•PMDTA and exchange between the latter monomer and dimeric etherate are, respectively, 5.06 s^{-1} and 2.57 s^{-1}. This implies that the two processes may be mechanistically linked and that nitrogen inversion in **14**•PMDTA alone must be a much slower process.

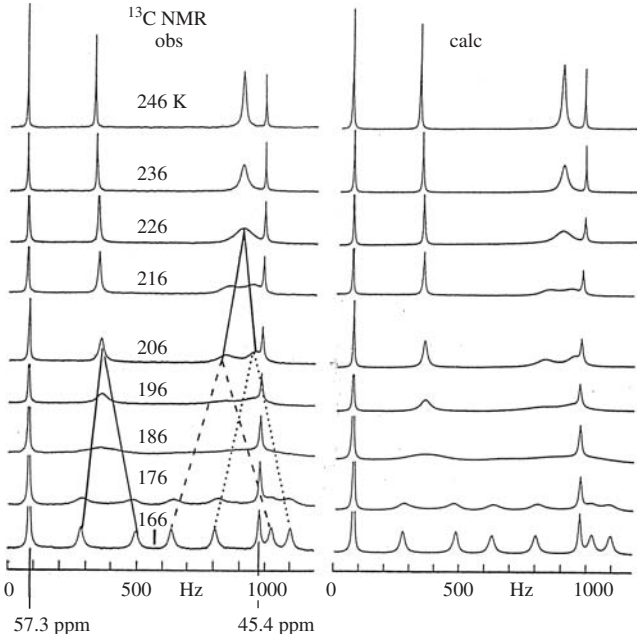


FIGURE 5. Left: ^{13}C NMR PMDTA resonance of a solution of neopentyllithium–^{6}Li, 0.59 M, with PMDTA, 0.34 M, in diethyl ether-d_{10}, at different temperatures. Dotted lines connect averaging resonances. Peak assignments counting from the left at 166 K are 1, 2, 3 ($\mathbf{C}H_2N$), 4, 5, 7, 8 (($\mathbf{C}H_3)_2N$) and 6 (CH_3N). Right: calculated line shapes which result from rotation around the C−Li axis and inversion at nitrogen. Reprinted with permission from Reference 20. Copyright (1990) American Chemical Society

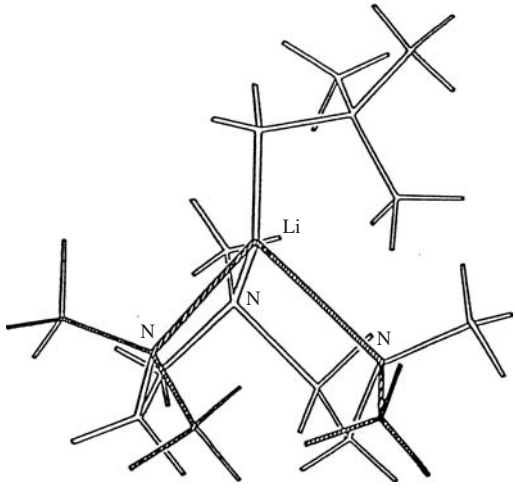


FIGURE 6. Proposed conformer of the *neope*ntyllithium complexed to PMDTA. Reprinted with permission from Reference 20. Copyright (1990) American Chemical Society

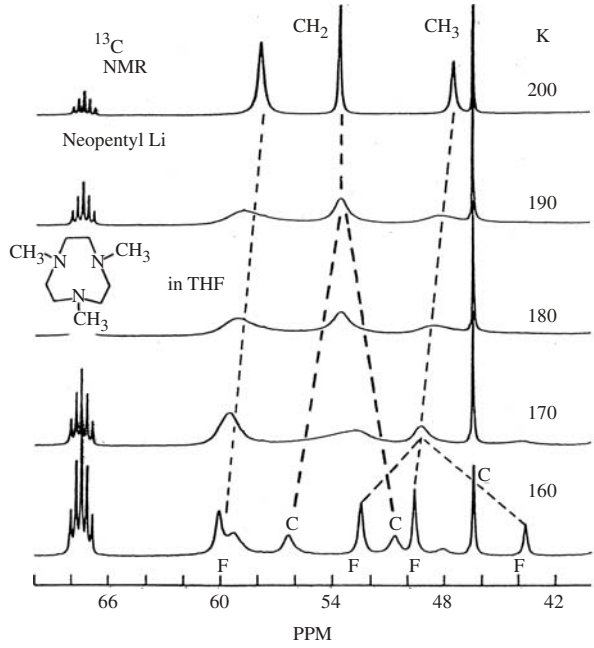
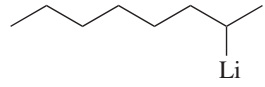


FIGURE 7. ^{13}C NMR of *neope*ntyllithium–^{6}Li, 0.7 M, with TMTAN, 1.4 M, at different temperatures, triamine part only. Resonances of complex labeled **C**, those of free amine labeled **F**. Reprinted with permission from Reference 20. Copyright (1990) American Chemical Society

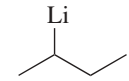
The triamine 1,4,7-trimethyl-1,4,7-triazacyclononane TMTAN also formed a tridentate complex with monomeric **14**. Carbon-13 NMR of a mixture of **14**, 0.7 M, with TMTAN (1.4 M) in THF-d_8 revealed the presence of the complex **14**•TMTAN together with the remaining free triamine (Figure 7). Exchange of TMTAN between the complex and its free state in solution was found to be slow relative to the NMR time scale up to 260 K. The free triamine showed ^{13}C resonances for several conformers ('C' in Figure 7) whose resonances averaged with increasing temperature due to fast interconversions among them. Complexed **14** appeared to be a single species with two nonequivalent methylenes in the complexed triamine part. This supports a proposed crown structure for the complexed triamine wherein the distances between Li and CH_2 carbon alternate, proceeding around the ligand ring. This structure has a C_3 axis and is chiral. Above 160 K, with increasing temperature, these two resonances progressively average. This was proposed to be due to inversion of the ring without decoordination or C−Li bond exchange[20].

C. Secondary Alkyllithium Compounds

In 1950, Letsinger reported that carbonation of 2-lithiooctane, **15**, prepared by exchange of (−)-2-iodooctane with *s*-butyllithium in petroleum ether at −70 °C, gave (−)-2-methylheptanoic acid[21]. However, after first warming the 2-lithiooctane solution to 0 °C over 20 minutes the resulting carboxylic acid was racemic. This was the first observation that a secondary alkyllithium compound inverts much more slowly than does a primary RLi compound.



(15)

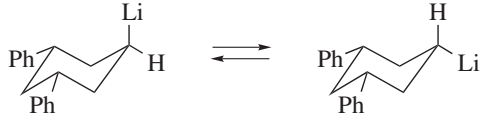


(16)

Solutions of racemic *s*-butyllithium–^{6}Li **16** in cyclopentane at 232 K show ^{13}C NMR spectra, indicating the presence of two major species in equilibrium[22]. The ^{13}C resonance at 16.89 δ of multiplicity 1:3:6:7:6:3:1 and with separation of 6.1 Hz due to one bond C–Li coupling clearly indicates a tetramer. At 20.9 δ, there is a poorly resolved resonance whose shape is consistent with that expected for ^{6}Li bound carbon of a fast fluxional octahedral hexamer. This proposed hexamer shows fine structure in ^{13}C NMR around 31 δ and 19 δ, indicative of at least three diastereomeric hexamers within which inversion at lithium bound carbon is slow relative to the NMR time scale as well as interconversion of the different diastereomers. As the hexamers appear to be fluxional, the order of **R** and **S** alkyls within the aggregates was neglected. For simplicity, the hexameric diastereomers were assumed to have similar free energies. Then the relative distributions in the order of the different diastereomers $\mathbf{R}_1\mathbf{S}_5 = \mathbf{R}_5\mathbf{S}_1$, $\mathbf{R}_4\mathbf{S}_2 = \mathbf{R}_2\mathbf{S}_4$ and $\mathbf{R}_3\mathbf{S}_3$ would be 12:30:20, respectively, which do correlate with the NMR data.

Between 232 K and 272 K, the ^{13}C multiplet due to lithium bound carbon, with splitting 6.1 Hz, in tetramer broadens and resolves again into a multiplet of 9 lines, splitting 4.1 Hz, indicating fast intramolecular reorganization of the C–Li bonds. On warming the compound above 272 K, the latter resonance broadens again and averages with the resonance for hexamer, showing now fast intermolecular C–Li exchange.

In the presence of coordinating ligands, *s*-butyllithium tends to deaggregate, forming monomers and dimers in THF and just monomers when complexed with PMDTA.



(86)

(17a) **(17e)**

Cyclic alkyllithiums also appear to invert slowly at lithium bound carbon. Reich and coworkers[23] reported that 3,5-diphenylcyclohexyllithium formed in THF at −78 °C with lithium axial isomerizes to an equilibrium mixture of the axial-Li **17a** and equatorial-Li compounds **17c**, the eq/ax ratio being 92/8 at −78 °C (equation 86). Under the latter conditions the half-life for equilibration was 9 minutes. Actually, the rates varied with ligand and appear to proceed through a transition structure of higher aggregation than the ground state lithiocyclohexane.

D. Tertiary Alkyllithium Compounds

Thomas and coworkers showed that *t*-butyllithium in pentane consists exclusively of cubic tetramers. Below 251 K, the ^{13}C NMR of ^{6}Li bound carbon consists of a 1:3:6:7:6:3:1 multiplet with $^{1}J(^{13}\mathrm{C},^{6}\mathrm{Li}) = 5.1$ Hz, the familiar signature of a cubic tetramer[24]. On increasing the temperature above 251 K, this resonance broadens and resolves again by 268 K into a nonet with splitting of 4.1 Hz due to fast intra-aggregate C–Li exchange. Carbon-13 NMR line shape analysis established $\Delta H^{\ddagger} = 25 \pm 1$ kcal mol^{-1} and $\Delta S^{\ddagger} = 44$ eu.

For purposes of calculating the ^{13}C NMR line shape, we need only consider the spin states of one ^{13}C and the four ^{6}Li's in the tetramer. The 31 required elements of the density matrix take the form shown in equation 87,

$$\langle \alpha \ell | e | \beta \ell \rangle \tag{87}$$

where the ℓ's are the product spin states of four lithiums (equation 88).

$$\ell = defg \tag{88}$$

The Hamiltonian (equation 89)

$$\mathbf{H} = (\omega_c - \omega) I_c^z I_1^z + I_c^z I_2^z + I_c^z I_3^z) \tag{89}$$

includes the shift of the ^{13}C and couplings, J, all the same, to three of the four lithiums which are labeled as '1, 2, 3 and 4'. To obtain the e(ae) elements, one permutes the spins in the spin products, each of d, e and f with g. The first of these terms is shown in equation 90.

$$\langle \alpha defg | e(\text{ae}) | \beta defg \rangle = \langle \alpha gefd | e | \beta gefd \rangle \tag{90}$$

The resulting 81 equations in the unknown elements may be simplified by summing the elements in which the ℓ's have the same associated M value (equations 91 and 92).

$$e^M = \sum_{\ell} \langle \alpha \ell_M | e | \beta \ell_M \rangle \tag{91}$$

$$M = \sum_{s} m_{s\ell}^z \tag{92}$$

The resulting matrix equation is solved and absorption obtained as shown above.

Kinetically, the fluxional process is first order in tetramer. Thomas and coworkers discussed three mechanisms: 1) a dissociation–recombination of dimers, 2) unfolding of the tetramer into an eight-membered ring with alternating α-carbons and lithiums and 3) a 'concerted center to edge rotation' of three of the alkyl groups. For different reasons, many authors have preferred the dissociation–recombination mechanism in which the transition structure is a very loose tetramer.

In the presence of potential ligands for lithium, *t*-butyllithium was found to be a dimer in diethyl ether-d_{10}, a mixture of dimers and monomers in THF-d_{10} and entirely monomeric when complexed to PMDTA. All these results are derived from one bond $^{13}C-^{6}Li$ coupling patterns in ^{13}C NMR spectra, needless to say with NMR determined at low temperature, >160 K, since the reagent rapidly deprotonates all these ligands at higher temperatures.

E. Aryllithium Compounds

Using low-temperature ^{13}C NMR spectra, Reich and coworkers found that phenyllithium–^{6}Li (**18**) in diethyl ether-d_{10} consists of an equilibrium between dimers and tetramers[25]. The spectra of these species were well resolved and identified by their one bond $^{13}C-^{6}Li$ coupling constants and multiplicities of their ^{13}C resonances for lithium bound carbon, 7.6 Hz and 1:2:3:2:1 for dimers and 5.1 Hz and 1:3:6:7:6:3:1 for tetramers. On increasing the temperature above 170 K, the coupling constants and shifts between the species progressively average out. Line shape analysis provides the

TABLE 4. Thermodynamic (○) and Eyring activation (‡) parameters for the interconversion of dimers, D, and tetramers, T, of phenyllithium in diethyl ether-d_{10} [a]

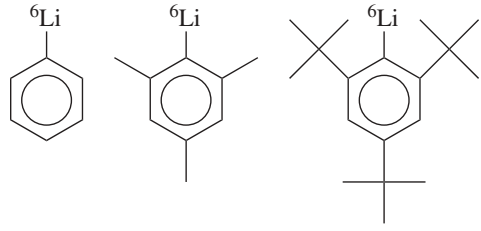
$$2D \underset{k_r}{\overset{k_f}{\rightleftharpoons}} T$$

*	ΔH^* (kcal mol^{-1})	ΔS^* (eu)
‡f	9.1 ± 0.6	6 ± 4
‡r	9.3 ± 0.6	0 ± 4
o	0.0 ± 2	7 ± 2

[a] Data taken from Reference 25.

activation parameters as well as the thermodynamics for the interconversion of dimers with tetramers (equation 93), listed in Table 4[25]. A proposed dissociation–recombination scheme is shown in Figure 8.

$$2\ D \rightleftharpoons T \tag{93}$$



(18) **(19)** **(20)**

Phenyllithium in THF, originally reported to form only dimers, has since been recognized by Reich and coworkers to give rise to an equilibrium mixture of monomers, $^1J(^{13}C, ^6Li) = 15.3$ Hz, and dimers, $^1J(^{13}C, ^6Li) = 7.9$ Hz[25]. With increasing temperature, the resonances for the two species average as do the splittings due to the $^{13}C-^6Li$ spin coupling. The dynamics and thermodynamics for this system are summarized in Table 5.

Here again, the mechanism is proposed to follow the description of the overall process. The dissociation of a dimer (**22**) in one of two modes (equation 94) will scramble the

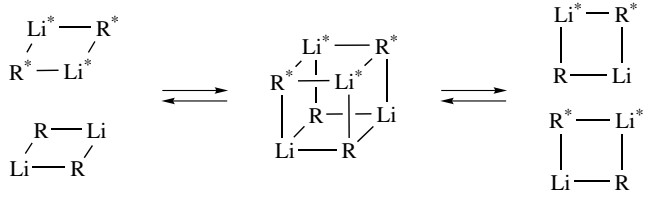


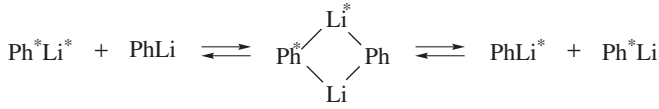
FIGURE 8. Intermolecular C−Li exchange between dimeric organolithium compounds via a cubic tetramer

TABLE 5. Thermodynamic (○) and Eyring activation (‡) parameters for the interconversion of dimers, D, and monomers, M, of phenyllithium in THF-d_8[25]

$$2M \underset{k_r}{\overset{k_f}{\rightleftharpoons}} D$$

*	ΔH^* (kcal mol^{-1})	ΔS^*, (eu)
‡f	7.5 ± 0.1	$+2.5 \pm 1$
‡r	7.0 ± 0.1	-7.4 ± 1
o	0.5 ± 0.2	10.0 ± 2

$^{13}C-^{6}Li$ bonds in monomer, (**21**) thus averaging the $^{13}C-^{6}Li$ coupling constants.



(94)

(**21**) (**22**)

Note that the averaging of a coupling constant to zero in the absence of relaxation effects is diagnostic for bimolecular exchange kinetics.

X-ray crystallography has demonstrated that in the solid state TMEDA is bidentately complexed with Li bridged dimeric phenyllithium[26]. The first example that similar structures obtain in solution came from an NMR study of phenyllithium$-^{6}Li$ with TMEDA in diethyl ether-d_{10}[27]. At 198 K, the ^{13}C resonance at 187.5 δ of ^{6}Li bound carbon consisted of the familiar 1:2:3:2:1 multiplet with $^{1}J(^{13}C, ^{6}Li)$ being 7.6 Hz[27]. The origin of this coupling constant was confirmed by repeating the experiment using phenyllithium$-^{7}Li$[27]. This time, $^{1}J(^{13}C, ^{7}Li)$ was 20 Hz with the expected 1:2:3:4:3:2:1 multiplicity. Since phenyllithium was known to form largely tetramers with diethyl ether, it was concluded that the TMEDA was complexed to dimeric phenyllithium. In addition, there was a weak broad resonance at 184 δ. It was apparently due to ^{6}Li bound carbon of another unidentified phenyllithium species. On warming the sample, the two resonances broadened and averaged to a single line by 300 K, clearly again the result of fast intermolecular C−Li exchange.

It is now well known that in diethyl ether or THF several organolithium compounds form monomeric tridentate complexes with PMDTA. Schleyer and coworkers described such complexes with aryllithium compounds[11]. As expected, ^{13}C NMR spectra of ^{6}Li bound carbon in these monomers consists of a 1:1:1 triplet with $^{1}J(^{13}C, ^{6}Li)$ of *ca* 15 Hz. NMR spectra of these complexes show remarkable details of structure and dynamic behavior. For example, in a ^{13}C NMR study of the system mesityllithium$-^{6}Li$ (**19**) with PMDTA in THF, Fraenkel and coworkers reported that at 179 K, all but two of the PMDTA carbons were found to be magnetically nonequivalent[14]. The areas, but for one, are all very similar. This indicates that only complexed ligand could be detected in this sample (Figure 9). In addition, the *ortho* methyls and *ortho* carbons each gave rise to a 1:1 doublet. Numbering the ^{13}C NMR peaks in the spectrum at 179 K in Figure 9 from the left, the first four are due to methylenes, the seventh peak is for NCH_3 and the remaining ones are due to $N(CH_3)_2$. The last resonance, number 8, is for two dimethylamino methyls. With increasing temperature between 179 K and 230 K, the first two pairs of methylene peaks

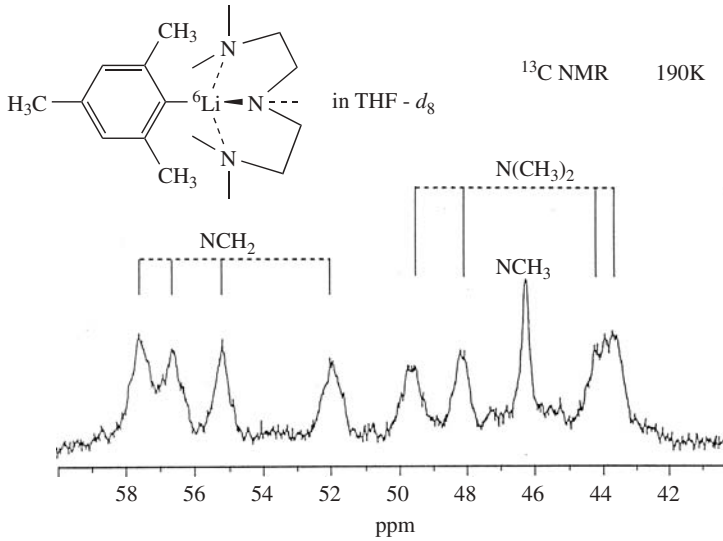


FIGURE 9. NMR, ^{13}C, mesityllithium•PMDTA complex in THF-d_8, triamine part, 190 K. Reprinted with permission from Reference 14. Copyright (1995) American Chemical Society

average to single lines at their respective centers and all the N-methyl resonances end up as a single broad line at δ 46. Apparently, the averaged dimethylamino absorption overlaps with that for N-methyl. In addition, there is averaging of the nonequivalent aromatic *ortho* carbon and *ortho* methyl resonances, respectively (Figure 10). Clearly, the aromatic plane in this complex is unsymmetrically sited with respect to the coordinated PMDTA. The averaging of resonances must be associated with the dynamics of rotation around the C−Li bond. This is supported by the results of line shape analysis which yield essentially the same activation parameters for each pair of collapsing doublets, those for ligand methylenes, aromatic *ortho* and *ortho* methyl carbons (Table 6). The spectrum of the complexed PMDTA and the pattern of line shape changes described above are very similar to results obtained in a study of neopentyllithium also complexed to PMDTA. In that investigation, the changes in the dimethylamino ^{13}C line shape could be resolved into rotation around the C−Li bond at lower temperatures and the dynamics of inversion at higher temperatures. In the case of **19**•PMDTA the rates of these two processes must overlap, hence they could not be resolved.

The authors pointed out that rotation around the C−Li bond would be subject to strong steric repulsions in the transition structure between the *ortho* mesityl methyls and dimethylamino methyls on the PMDTA. Instead, they proposed a less hindered transition structure in which the bond between Li and the central nitrogen had been replaced by coordination to THF-d_8. This would be more consistent with the large negative $\Delta S^{\ddagger}$ reported.

Monomeric 2,4,6-tri-*t*-butylphenyllithium **20** provided unusual insights into the nature of ^{7}Li relaxation. Schleyer and coworkers reported NMR data on **20** in THF with PMDTA. At 193 K, the ^{13}C NMR spectrum of Li bound carbon consisted of two resonances, a broad doublet, separation 70 Hz due to $^{13}\mathbf{C}-^{7}Li$ overlaid by a cleanly resolved triplet due to the **20**•^{6}Li isotopomer (^{6}Li in natural abundance) with $^{1}J(^{13}C, ^{6}Li)$ of 16 Hz, the signature for

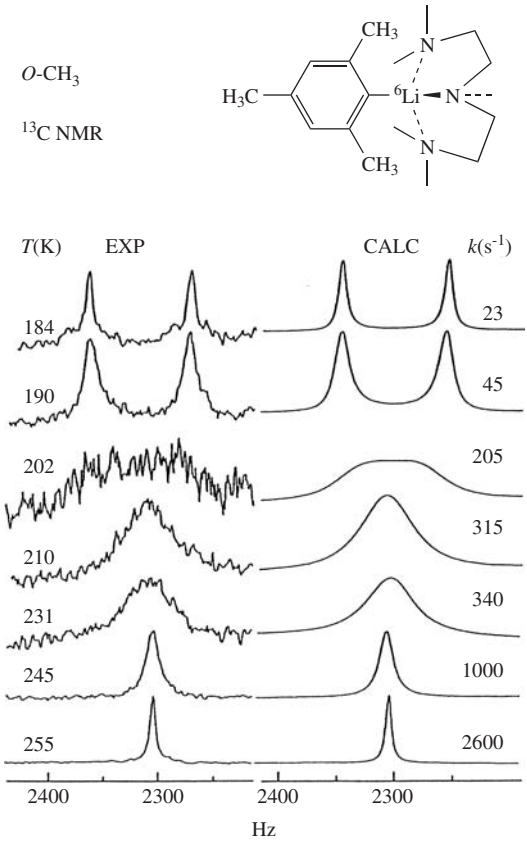


FIGURE 10. ^{13}C NMR, *o*-methyl resonance of the mesityllithium•PMDTA complex in THF-d_8. Left: observed different temperatures. Right: calculated line shapes with rate constants. Reprinted with permission from Reference 14. Copyright (1995) American Chemical Society

TABLE 6. Activation parameters for rotation around the C−Li bond in mesityllithium•PMDTA[14]

^{13}C resonance	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (eu)
ortho ring carbons	5.1 ± 0.3	-22 ± 3
ortho mesityl methyls	5.3 ± 0.3	-21 ± 3
methylenes of PMDTA	4.7 ± 0.5	-24 ± 2

a monomer, (Figure 11)[11]. Clearly, under these conditions intermolecular C−Li exchange is slow relative to the NMR time scale. Given that the latter exchange rate is slow and that the ^{13}C resonance for ^{7}Li bound carbon is not the expected equal quartet with $^{1}J(^{13}C, ^{7}Li)$ of 42.5 Hz, the broad $^{13}\mathbf{C}-^{7}Li$ resonance described above had to result from some

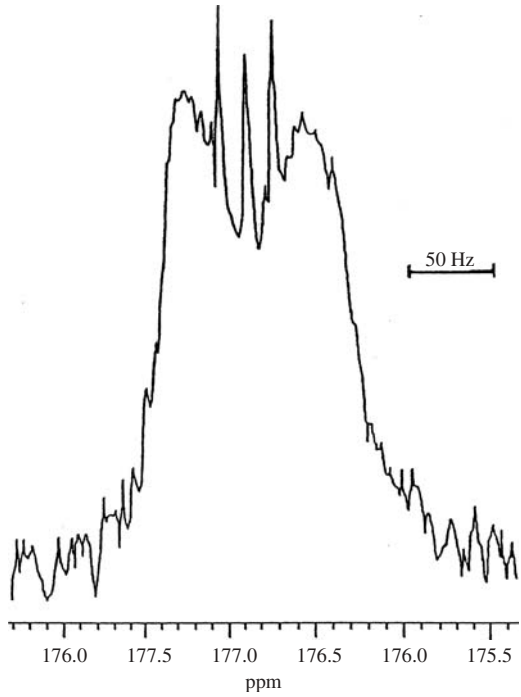


FIGURE 11. ^{13}C NMR, C_1 of 2,4,6-tri-*tert*-butylphenyllithium in THF-d_8 at 200 K. Reprinted with permission from Reference 11. Copyright (1987) American Chemical Society

mode of ^{7}Li relaxation. Fraenkel and coworkers calculated ^{13}C NMR line shapes for pseudospecies $^{13}C-^{7}Li$ perturbed by different mechanisms of ^{7}Li relaxation as a function of the relaxation rates[14]. Two examples are shown in Figures 12 and 13. The nature of these line shape changes is highly dependent on the mode of ^{7}Li relaxation; those for ^{7}Li quadrupole induced relaxation closely match the Schleyer spectrum. This calculation is described in Section II (see equations 66 and 67) for the density matrix equations in matrix form and the relaxation parameter, respectively. Actually, given the well-resolved $^{13}C-^{6}Li$ triplet, both dipolar and chemical shift anisotropy relaxation, respectively, can be qualitatively eliminated as responsible for the shape of the $^{13}C-^{7}Li$ resonance seen in Figure 11.

Compound **20** was also prepared enriched in ^{6}Li in THF-d_8 with PMDTA. Since the ^{13}C resonances of the PMDTA were no different from those of free PMDTA, it was concluded that PMDTA was not complexed to **20** in this sample[14]. Examination of the ^{13}C resonance of ^{6}Li bound carbon confirmed the monomeric structure for the compound. Above 240 K, the equal triplet $^{13}C-^{6}Li$ resonance progressively averages to a single line by 271 K due to fast bimolecular C−Li exchange, with $\Delta H^{\ddagger} = 14.4$ kcal mol^{-1} and $\Delta S^{\ddagger} = 7$ eu. It is interesting that the latter process is much slower than the reorganization within complexed PMDTA in **19**•PMDTA[14].

Reich and coworkers have extended their studies of aryllithium compounds by use of pendant potential ligands[28]. They have identified equilibria between monomers and three kinds of internally solvated bridged dimers using a combination of ^{13}C, ^{6}Li and ^{15}N NMR

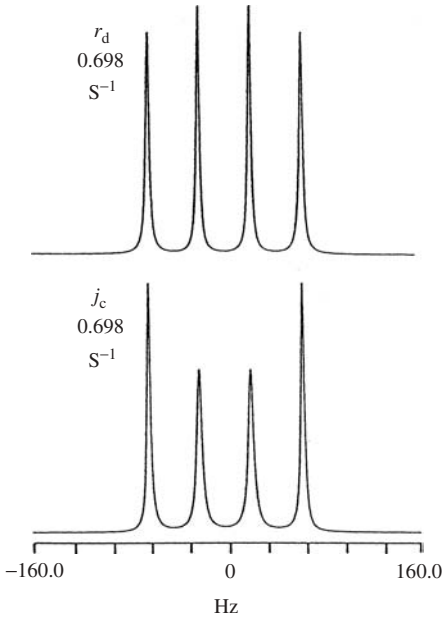


FIGURE 12. Bottom: ^{13}C NMR line shapes of ^{7}Li bound ^{13}C, $^{1}J(^{13}C,^{7}Li) = 43.3$ Hz, subject to relaxation via anisotropy of the chemical shift, csa, at different rates, j_c; Top: as above, but calculated as a function of the dipole–dipole (dd) relaxation rate, r_d. Reprinted with permission from Reference 14. Copyright (1995) American Chemical Society

spectra. States of aggregation were identified by the multiplicities of ^{13}C resonances due to ^{6}Li bound carbon. In addition, $\Delta G^{\ddagger}$ values due to the interconversion of monomers to dimers were determined at different coalescence temperatures.

F. Allyllithium and Alkylallyllithium Compounds, Rotation Behavior[29]

With few exceptions most allylic lithium compounds dissolve in and coordinate with ethers and tertiary amines[29]. As of this writing there have been no reports of $^{13}C-^{7}Li$ or $^{13}C-^{6}Li$ spin coupling in any allylic lithium compounds aside from some internally solvated species described below.

Neopentylallyllithium, prepared by carefully adding *t*-butyllithium to 1,3-butadiene in hydrocarbon solution, is one of the few alkane soluble allylic lithium species[30]. Unsolvated, it consists of an equilibrium mixture of slowly interconverting *trans* and *cis* isomers (see **23t** $\rightleftarrows$ **23c**) whose ^{13}C and proton chemical shifts closely resemble those of alkenes. These species are regarded essentially as localized. Adding different potential lithium ligands (L) gives, in addition, equilibrium mixtures of slowly interconverting *endo* and *exo* delocalized ion-paired salts, **24ex** $\rightleftarrows$ **24en** (equation 95). While the interconversions between the localized species and between the delocalized species are both slow, those between *cis* localized and *endo* delocalized and between *trans* localized and *exo* delocalized are too fast to measure even at 180 K. In the presence of 11 equivalents of THF-d_8 or one equivalent of 1,3-bis(2-tetrahydrofuranyl)-2,2-dimethylpropane **25** (mixture of diastereomers), the spectra are identical to those for *exo* and *endo*

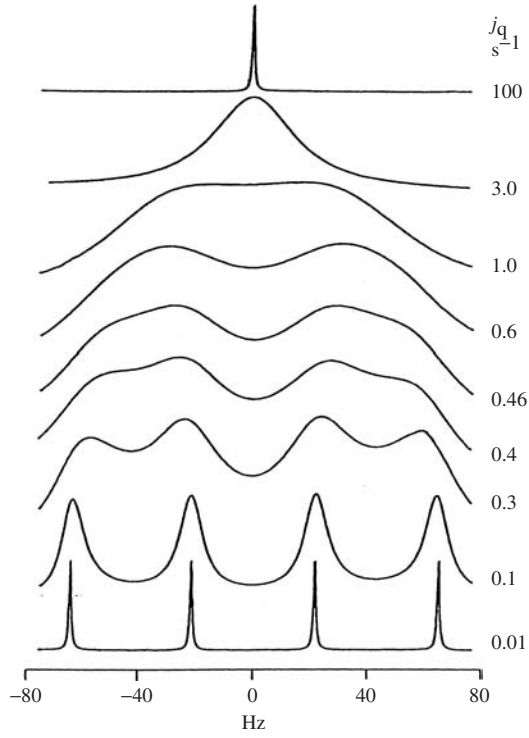
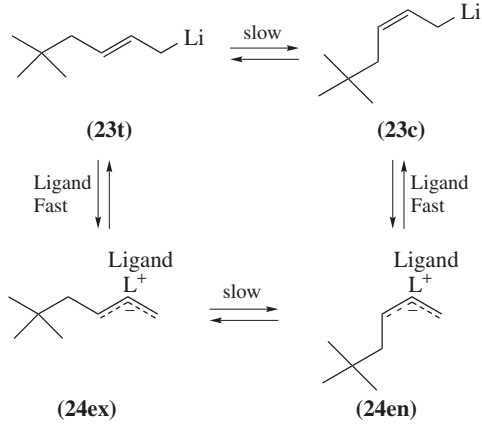


FIGURE 13. Calculated ^{13}C NMR line shapes ^{7}Li bound ^{13}C, $^{1}J(^{13}C,^{7}Li) = 43.3$ Hz as a function of the ^{7}Li quadrupole induced relaxation rate j_q. Reprinted with permission from Reference 14. Copyright (1995) American Chemical Society

1-neopetylallylcesium[30]. From its NMR shifts this compound is regarded as a delocalized carbanide contact ion-pair.



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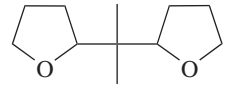
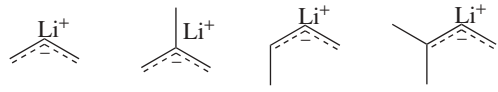
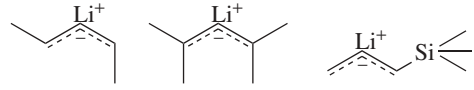


(25)

Other allylic lithium compounds which have been investigated include **26** to **32** omitting solvation around lithium.



(26) **(27)** **(28)** **(29)**



(30) **(31)** **(32)**

Interesting insights into dynamics of interconversion of species and rotation is provided by the behavior of 2-methylallyllithium **27** in diethyl ether-d_{10}[31]. The low-temperature NMR spectrum of the methylene protons, diagrammed in Figure 14, revealed evidence for an equilibrium mixture of two interconverting species as represented by the a/s and a^1/s^1 doublets, respectively. NOE experiments established that the s and s^1 resonances, degenerate at 1.98 δ, represent hydrogens *syn* to CH_3 in both species. Experiments with superior ligands for lithium result in just two lines of equal intensity, 1.98 δ and 2.14 δ. These are assigned to the more dissociated of the two species. With increasing temperature there is averaging of resonances a with a^1 due to interconversion of species and, due to rotation around the allyl bonds, resonances a with s and a^1 with s^1. Proton line shape analysis, which took account of both processes, gave for rotation (r) $\Delta H_r^{\ddagger} = 9.6$ kcal mol^{-1} and $\Delta S_r^{\ddagger} = -7$ eu while for interconversion (in) of species the parameters were $\Delta H_{in}^{\ddagger} = 7.3$ kcal mol^{-1} and $\Delta S_{in}^{\ddagger} = -3$ eu. The structures of the two species could not be identified from these experiments; both contain delocalized allyl anions. Further, their states of aggregation are different.

Some examples which show the dynamic effects of alkyl and silyl substituents on barriers to rotation in allyllithium compounds **26** to **32** are listed in Table 7. These results were obtained from proton NMR line shape data. The procedure for compounds **26**, **28**, **29** and **32**, which exhibited rotation around their $C{=}CH_2$ bonds, is diagrammed by structure **33** in which hydrogens A, B and X are all nonequivalent and each couples to the others. Rotation averages the A and B shifts as well as the coupling constant between them and $^3J(H_A,H_X)$ averages with $^3J(H_B,H_X)$, (Figure 15). At the same time, the H_X resonance

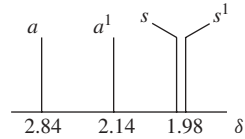
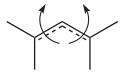
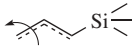
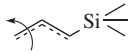
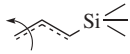
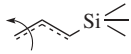
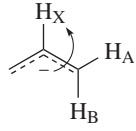


FIGURE 14. Assignment of the $\mathbf{C}H_2$ proton NMR of 2-methylallyllithium in diethyl ether-d_{10}

TABLE 7. Barriers to rotation in allylic lithium compounds

Compounds [a]	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (eu)	Medium	Resonance	Reference
26 	10		THF-d_8	^{1}H, CH	35
27 	9.6	+7.3	Et_2O-d_{10}	^{1}H, CH_2	31
28 	19	+28	THF-d_8	^{1}H, CH_2	33
29 	18	+33	THF-d_8	^{1}H, CH_2	33
30 	21	+30	THF-d_8	^{1}H, C_2H	33
31 	15	+9	Et_2O-d_{10}/TMEDA	^{13}C, CH_3	32
32 	14	+4	Et_2O-d_{10}	^{1}H, CH_2	34
32 	11	−12	THF-d_8/Et_2O-d_{10}	^{1}H, CH_2	34
32 	17	+2	THF-d_8/PMDT, 1 eq	^{1}H, CH_2	34
32 	14	+9	THF-d_8/TMEDA, 1 eq	^{1}H, CH_2	34
32 	16	+10	THF-d_8/PMDTA	^{1}H, CH_2	34

[a] Arrows indicate mode of rotation.



(33)

exhibits the averaging of J_{AX} with J_{BX} (Figure 15) appropriately labeled. Note that only the inside resonances are averaged.

A special situation applies to compound **30**. The *exo–endo* structure was identified from the two allyl vicinal proton coupling constants[33]. Only one stereoisomer could be detected. With increasing temperature above 210 K the latter two coupling constants average, the result of presumably sequential rotations around both allyl carbon–carbon

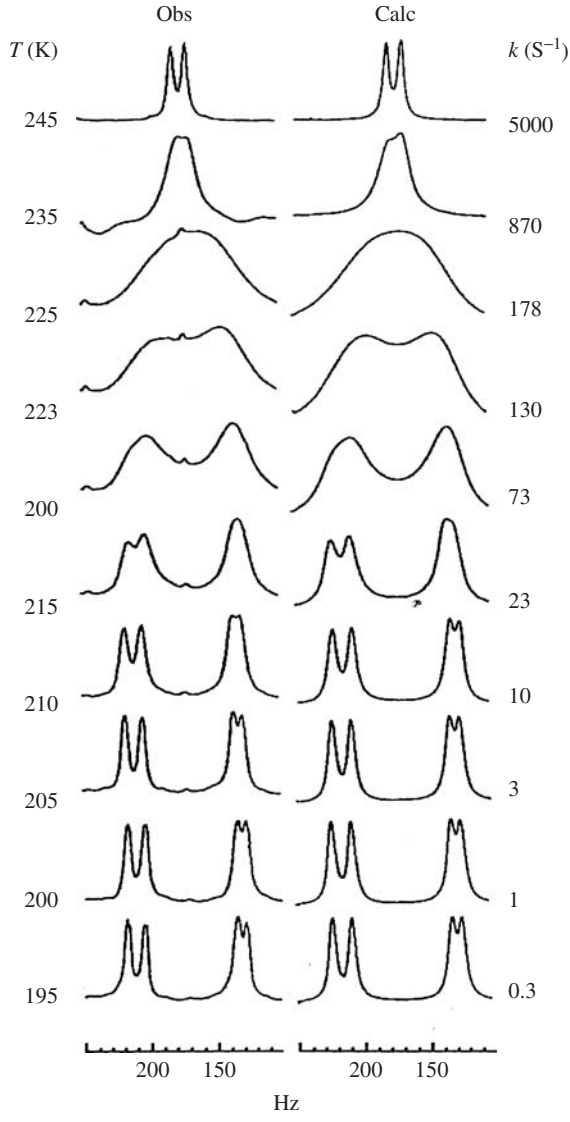


FIGURE 15. Proton NMR of 1,1-dimethylallyllithium•TMEDA complex in THF-d_8. (a) Left: observed methylene resonance, different temperatures; right: calculated line shapes with first-order rate constants for rotation around the C_2-C_3 bond. (b) Left: observed $C_2\mathbf{H}$ resonance, different temperatures; right: calculated line shapes with first-order rate constants for C_2-C_3 rotation. Reprinted with permission from Reference 33. Copyright (2000) American Chemical Society

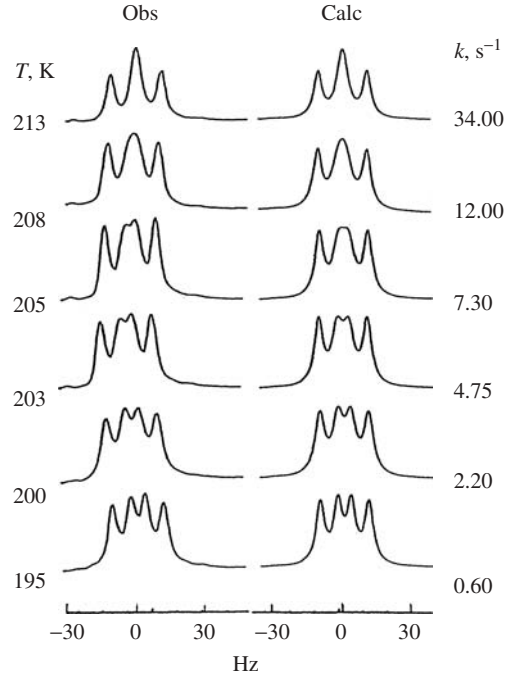


FIGURE 15. (*continued*)

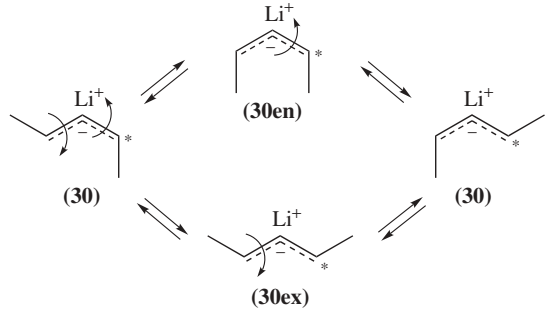


FIGURE 16. Proposed sequence of bond rotations for *endo,exo*-1,3-dimethylallyllithium•TMEDA in THF-d_8

bonds. A scheme for the rotation mechanism (Figure 16) was proposed which involved two undetected intermediates.

Regarding unsymmetrically substituted compounds **28** and **32**, only one stereoisomer could be detected in each preparation. Barriers could only be determined for the less substituted allyl bond, $C{=}{=}CH_2$ which applies also to **29**. This suggests also that the larger

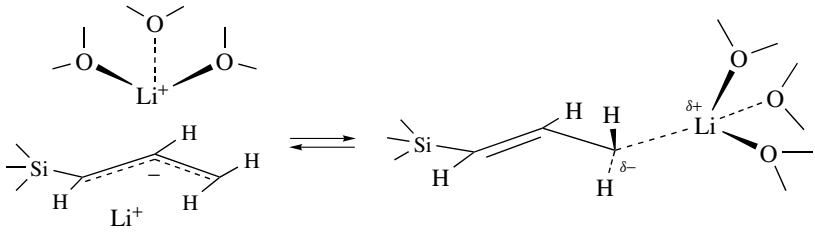


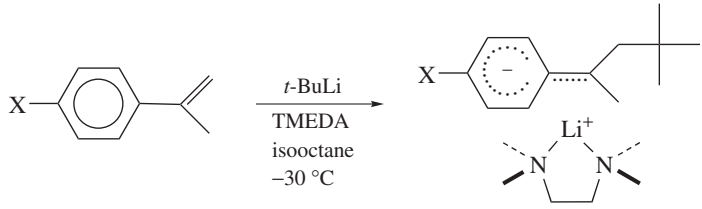
FIGURE 17. Proposed mechanism for allyl bond rotation in allylic lithium compounds, demonstrated for **32**

of the π allyl bond orders is to the more substituted terminus consistent with the widely accepted view that alkyl substitution stabilizes π structure.

Inspection of Table 7 shows that rates of rotation in allyllithium compound **32** and the associated barriers depend strongly on the nature of lithium solvation[34]. Thus the rotational process cannot involve a free allylic anion alone. Rather, the process must be driven by a chemical mechanism. This has been proposed by calculations to involve the development of a degree of Li−C (terminal) covalence in the transition state accompanied by some change in the solvation around lithium. It is demonstrated for compound **32** in Figure 17.

G. Tertiary Benzylic Lithium Compounds

A variety of tertiary benzylic lithium compounds have been prepared by addition of *t*-butyllithium in isooctane with TMEDA to substituted styrenes **34** at 243 K[10] (equation 96).



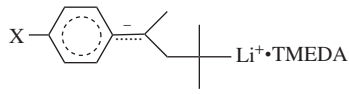
(96)

(34) **(35)**

Carbon-13 chemical shifts are typically 75, 106, 128.5 and 86 for, respectively, α, *o*, *m* and *p* carbons indicating delocalized anions within contact ion-pairs. At low temperature, all the ring hydrogens are nonequivalent and, with increasing temperature, the resonances for the two *ortho* protons average as do those for the *meta* protons due to increasingly faster rotation around the C_a-C_i bonds. The ϵ(ae) elements which account for the changes in the proton NMR line shape analysis are described in equation 27.

Inspection of the barriers to rotation in Table 8 shows that substituents such as *p*-2-propyl, *p*-*t*-butyl and *p*-Me_3Ge have much the same influence on the barrier as *p*-H. In contrast, *p*-Me_3Si raises the barrier by 4 kcal mol^{-1} and with *p*-Ph, *p*-PhS and *p*-$PhMe_2Si$ the rate of rotation is too slow to measure. It was proposed that the last four substituents stabilized the ground state by conjugation with the benzylic anion. In

TABLE 8. Activation Parameters for rotation in tertiary benzylic lithiums•TMEDA in isooctane[10]



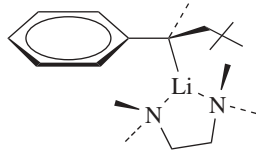
(35)

#	X	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (eu)
35a	H	18.7 ± 0.4	0.3 ± 1
35b	$(CH_3)_2CH$	18.5 ± 0.4	4.6 ± 1.3
35c	$(CH_3)_3C$	18.5 ± 0.5	5.2 ± 1.3
35d	$(CH_3)_3Ge$	18.2 ± 0.7	4.7 ± 0.7
35e	Cyclopropyl	11.8 ± 0.5	-15.5 ± 5
35f	$(CH_3)_3Si$	22.0 ± 1.5	3.4 ± 1.5
35g	$Ph(CH_3)_2Si$ [a]	>26	
35h	PhS [a]	>26	

[a] Too slow to measure.

contrast, with *p*-cyclopropyl the barrier is lower due to ground state destabilization. This system is a vinylogous cyclopropylcarbinyl carbanion. Note the well-known instability of cyclopropylcarbinyl carbanion with respect to rearrangement.

Barriers to rotation in conjugated organolithium compounds are strongly dependent on the nature of coordination to lithium. These barriers clearly are not the result of rotation in a carbanion alone. Instead, it was proposed that rotation proceeds through a transition structure **36** in which some α-carbon–lithium covalency had developed.

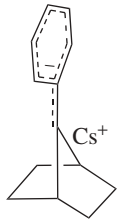


(36)

Among benzylic lithium compounds which exhibit tetrahedral structure at lithium bound C_α, experiments have been undertaken to investigate the dynamics of inversion at the latter carbanionic carbon. For example, Peoples and Grutzner[36] reported NMR data for 7-phenyl-7-metallonorbornanes. With M = K or Cs, all methylene carbons were magnetically equivalent.

Selected shifts for C_7, C_o, C_m and C_p were found to be 91.8, 108, 131 and 90.4 δ units, respectively. These results supported structure **37**, which is a conjugated benzylic anion that bisected the bicycloheptane.

By contrast, in the case of the Li derivative the benzylic shifts for C_7, C_o, C_m and C_p were, respectively, at δ 64, 118, 128 and 107. Further, at 163 K the ethylenic units had different shifts, δ 32.2 and δ 28.8. These results are consistent with an unconjugated benzylic system and with tetrahedral structure at C_7 (assigned to the carbon bound lithium), **38**. With increasing temperature the shifts between the ethylenic units progressively averaged out. Line shape analysis of this collapsing doublet resulted in $\Delta H_i^{\ddagger} = 6.7$ kcal mol^{-1}



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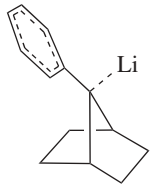
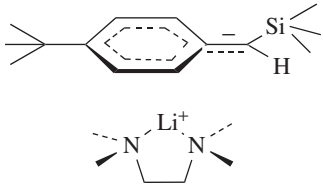


(38)

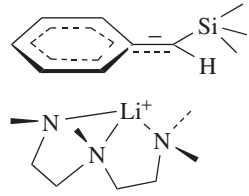
and $\Delta S_i^{\ddagger} = -14$ eu. These parameters were assigned to carbanionic inversion at the benzylic carbon.

H. Secondary Benzylic Lithium Compounds[13,37]

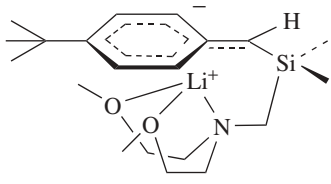
In further studies of ion-pairing, a variety of *sec*-α-silyl benzylic lithium compounds **39**, **40**, **41** and **42**, were prepared, both externally and internally solvated, the latter by means of a potential ligand attached to the carbanionic moiety. Ion-paired carbanide salts tend to assemble into several arrangements which differ in aggregation, solvation and in the proximity of anion to cation. Many of these species interconvert rapidly relative to the NMR time scale even at quite low temperatures. An internally solvated ion-pair carbanide salt is more likely to assume a single molecular structure, to undergo the latter exchange processes more slowly and thus be more amenable to NMR spectroscopic studies of structure and dynamic behavior.



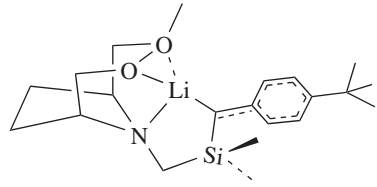
(39)



(40)



(41)



(42)

Compounds **39**-**42** display an array of aryl ^{13}C chemical shifts together with one bond $^{13}C-^{6}Li$ coupling constants seen at low temperature of 3 to 4 Hz, which is suggestive of more localized benzyllithium compounds compared to the clearly delocalized *t*-benzyllithiums described above. The 1:1:1 multiplicity of the ^{6}Li bonded ^{13}C NMR

reflects monomeric structures. These are chiral compounds, since the geminal silyl methyl ^{13}C resonances in **39**, **41** and **42** are all equal doublets at low temperature. In addition, at low temperature the *ortho* carbons are magnetically nonequivalent. These results show that at low temperature, intermolecular C−Li exchange, inversion at carbanionic carbon and rotation around the benzyl ring bond are all slow relative to the NMR time scale. With increasing temperature there are interesting changes in the NMR line shapes, which provide dynamic information on these latter processes.

Some comments on NMR parameters are now in order. These compounds show very similar arrays of ^{13}C ring shifts, typically, in δ units, C_α 40, C_i 156 to 158, C_o120, C_m126, C_p (*t*-butyl) 128, C_p (H) 109, which implies that they have similar electronic structures. HOESY experiments, ^6Li {^1H}, place lithium near C_α**H** and ligand hydrogens but far from the aromatic hydrogens.

Ordinarily, intermolecular C−Li bond exchange among benzylic lithium compounds tends to be very fast. This averages out the $^{13}C-^6Li$ coupling constants and explains why they have been rarely reported, as of this writing. However, at low temperature the exchange rates among **40** and **41** are slow enough to reveal the values of 3 Hz to 4 Hz for such coupling constants, mentioned above.

These $^{13}C-^6Li$ coupling constants are much smaller than the many examples commonly found for a wide variety of monomeric organolithium compounds, which all lie within the range 16 ± 2 Hz, quite independently as to the nature of the organic moiety[11]. It has been proposed that the '$C^{\delta-}-Li^{\delta+}$' bonds in benzylic lithium compounds are more ionic than the C−Li bonds among the former 'common pattern' species[13]. Further, X-ray crystallography places lithium normal to the benzyl plane at C_α among benzylic lithium compounds, which reduces the 's' character associated with the '$C^{\delta-}-Li^{\delta+}$' bonds[38]. Both effects may contribute to the low $^{13}C-^6Li$ coupling constants found among benzylic lithium compounds[12, 13].

Dynamics of C−Li exchange. Above 270 K, with increasing temperature there is averaging of the one bond $^{13}C-^6Li$ coupling constants in **40** and **41** due to fast bimolecular C−Li exchange. NMR line shape analysis of these collapsing triplets using equation 58 above gives $\Delta H^\ddagger$ values typically between 9 kcal mol^{-1} and 11 kcal mol^{-1} (Table 9).

Carbanionic inversion. With increasing temperature above 180 K, diastereotopic shifts between the geminal silyl methyl resonances in **39**, **41** and **42** average to single lines by 280 K, which is clearly the result of overall inversion at C_α. Similar effects were seen among the ^{13}C ligand resonances of **41** and **42**. In **41**, O**C**H$_2$, O**C**H$_3$ and N**C**H$_2$ and in **42**, O**C**H$_3$, O**C**H$_2$ and N**C**H all gave rise to equal doublets which averaged into single lines at their respective centers on warming the samples above 180 K. The $\Delta H^\ddagger$ values for inversion are typically 5 to 6 kcal mol^{-1}. In the case of each compound, line shape analysis of the latter collapsing doublets gave very similar results to those obtained from the *gem* methyl silyl resonances (Table 9). Thus any contribution from nitrogen inversion to these ligand line shapes must be too slow to detect.

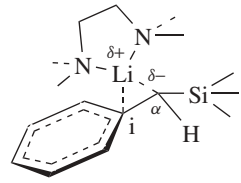
Rotation around $C_\alpha-C_i$. The third reorganization process which has been investigated is rotation around the $C_\alpha-C_i$(Ar) bond. The *ortho* carbons are nonequivalent at 245 K in **39**, **41** and **42**. With increasing temperature these doublets average. Dynamic parameters obtained from the NMR line shapes are listed in Table 9.

These results provide some interesting insights into the nature of the three reorganization processes.

The similarities among the ring ^{13}C shifts of **39**–**42** imply similar electronic structures. Since X-ray crystallography shows that the arrangement around C_α in **43** is slightly out of plane with a $C_o^*-C_i-C_\alpha-Si$ angle of $+13^o$ [38], we can assume that **39**–**42** have similar structural features to **43**.

TABLE 9. Reorganization dynamics of α-silylbenzylic lithium compounds in THF-d_8 solution

	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (eu)
Resonance	Inversion at C_α	
39[13] $Si(\mathbf{C}H_3)_2$	5.1	-21 ± 4
41[13] $Si(\mathbf{C}H_3)_2$	6.4	-14 ± 3
$O\mathbf{C}H_3$	7.2	-10 ± 2
$N\mathbf{C}H_2$	6.1	-15 ± 9
42[37] $Si(\mathbf{C}H_3)_2$	4.8	-24 ± 4
$O\mathbf{C}H_3$	4.3	-26 ± 4
$O\mathbf{C}H_2$	4.6	-24 ± 4
	C–Li Intermolecular Exchange	
40[37] $\mathbf{C}_\alpha$	9.4	-15 ± 3
41[13] $\mathbf{C}_\alpha$	10.8	-21 ± 4
	Rotation Around $C_\alpha - C_i(Ar)$	
39[13] $\mathbf{C}_{ortho}$	14.2	$+5.6 \pm 0.5$
41[13] $\mathbf{C}_{ortho}$	14	$+6.6 \pm 0.5$
42[37] $\mathbf{C}_{ortho}$	8.5	-14 ± 3



(43)

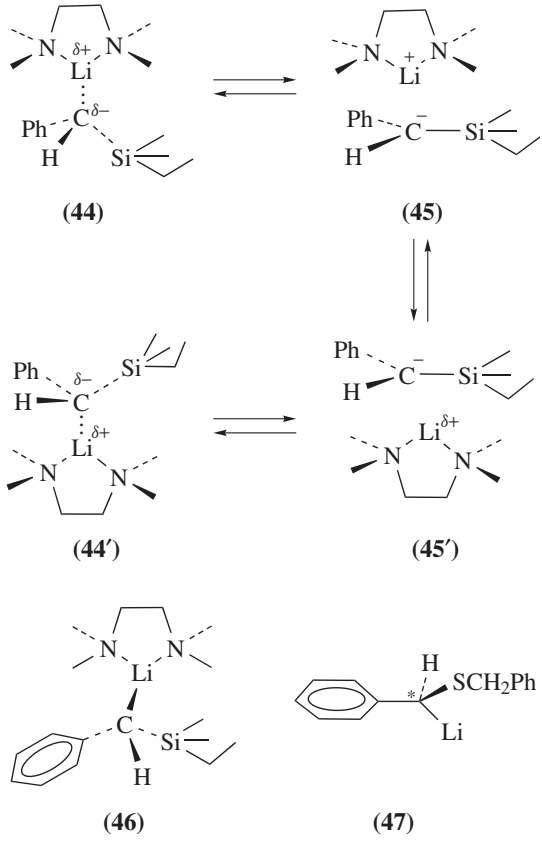
The reorganization processes described above proceed at very different rates and are unlikely to be concerted. At 250 K, the k''s for inversion, aryl rotation and C–Li exchange in the case of **41** are 2832, 76 and 0.04 s^{-1}, respectively. Kinetically, inversion and aryl rotation are first order, while C–Li exchange necessarily is second order.

The activation parameters for exchange and inversion lie within definite ranges and appear to be more determined by the reorganization process rather than by the particular compound undergoing inversion. Thus, one could say that the decoordination of lithium to ligand is the major contribution to the activation parameters for C–Li exchange.

In the case of inversion, the similarity of activation parameters for internally and externally solvated species implies that the passage which coordinated Li takes between the two sides of the benzylic plane involves much the same changes in the free energies of both systems.

Activation for inversion and rotation requires very different changes in the torsional angle $C_o^*-C_i-C_\alpha-Si$. For inversion this change is small, just enough to planarize the structure around C_α with concomitant increase in the ionic character of the 'C$\cdots$ Li' bond (see **44** $\rightleftarrows$ **45** and **44′** $\rightleftarrows$ **45′** in equation 97). This is also consistent with the large negative $\Delta S_i^{\ddagger}$ values. By contrast, the transition structure for rotation should be close to

tetrahedral with a substantial increase in C−Li covalence, thus seriously disrupting the benzylic conjugation, as shown in **46**.



(97)

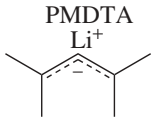
An α-sulfur-substituted benzylic lithium compound, **47**, also exhibited NMR behavior indicative of the dynamics of carbanionic inversion[39]. At 173 K in THF solution, the methylene protons were magnetically nonequivalent giving rise to a typical AB NMR spectrum indicating chirality at the (labeled*) carbon bonded to lithium. With increasing temperature the AB shift and coupling constant progressively average out to a single line by 253 K. Line shape analysis gave $\Delta H^{\ddagger} = 7.5 \pm 0.4$ kcal mol^{-1} and $\Delta S^{\ddagger} = -12 \pm 2$ eu for the inversion process. Similar effects have been reported, qualitatively, in the cases of benzylic lithium compounds with amino, seleno and sulfone substituents at C_{α}. However, only $\Delta G^{\ddagger}$ values were reported and these were obtained from coalescence methods[39].

I. Reorganization Behavior of Ion-paired Organolithium Compounds

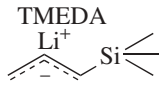
Not long before this writing the concept that ion-pairs might assemble into favored structures was not considered seriously. Ultraviolet spectroscopy had revealed some broad

categories of ion-pairing[40]. These included contact ion-pairs (CIP), $A^-M^+(LIG)_n$, solvent separated ion-pairs (SSIP), $A^-||M^+(LIG)_n$, aggregated and solvated to different degrees, as well as dimers which incorporate a triple-ion, $(A^-M^+A^-)M^+(LIG)_n$, where LIG = ligand.

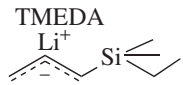
In the past, NMR spectroscopy has not been a useful technique to investigate structure and dynamic behavior of ion-pairs. Results of such studies indicated that interconversion of the different ion-paired species present was fast enough to average the spectra for the different species present[41]. However, recently NOE experiments, pioneered by Pochapsky and coworkers[42], have been successfully applied to map some ion-paired salts. Further, it has been found that at sufficiently low temperatures, interconversion and reorganization processes within and between ion-paired salts become slow enough to reveal NMR spectra of the ion-pairs not perturbed by dynamic effects.



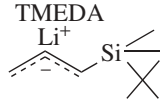
(31a)



(32a)



(48)



(49)

(50)

(51)

(52)

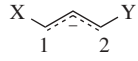
(53)

Consider the results of some low-temperature ^{13}C NMR studies of allylic lithium compounds **31a**[32], **32a**[34], **48**[43a], **49**[43a], **50**[43b], **51**[43a], **52**[43a] and **53**[43a]. At 170 K the terminal allyl carbons of nominally symmetrical **50** and **53** are magnetically nonequivalent. Under the same conditions the dimethylamino resonances of both complexes give rise to equal doublets. These results showed that complexed ligand is unsymmetrically disposed with respect to the allyl moieties in **50** and **53**. Their NMR spectra are considered to be unperturbed by dynamic effects related to molecular reorganization. In similar fashion the $N(CH_3)_2$ ^{13}C resonances of the complexes **31b**, **32a**, **49**, **50** and **53** were also 1:1 doublets below 170 K.

With increasing temperature above 170 K, averaging was observed of the terminal allyl resonances of **50** and **51** as well as of the $N(CH_3)_2$ doublets. In similar fashion the $N(CH_3)_2$ doublets described above also progressively averaged to single lines at their respective centers. The results of NMR lineshape analysis of these spectral changes are listed in Table 10.

The line shape changes described above were ascribed to reorientation of the complexed ligand with respect to the allyl moiety. Reorientation could take place via several routes. One of these, face transfer of a coordinated TMEDA (equation 98), was investigated

TABLE 10. Dynamics of reorganization of allylic lithium TMEDA complexes, 0.3 M in diethyl ether-d_{10} from ^{13}C NMR line shape analysis

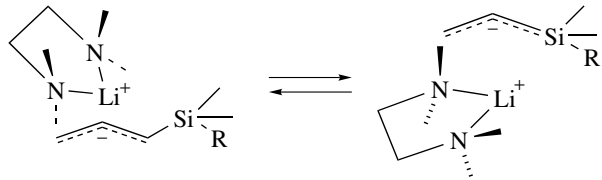


$Li^+ \bullet$ TMEDA, $\Delta H^{\ddagger}$ kcal mol^{-1} ($\Delta S^{\ddagger}$ eu)

#	X	Y	NCH_3	^{13}C NMR used $Si(CH_3)_2$	C_1, C_3	Reference
32a	H		7.2(2)[a] 8.7(7)[b]			34
48	H			4.9 (−21)		43a
49	H		6.5 (−10)	5.6 (−19)		43a
50			7.1 (−20)		7.3 (−21)	43b
51			5.4	7.0 (−20)		43a
52				6.9 (−12) 7.1 (−22)		43a
53			8.7 (−5)		6.6 (−15)	43a
31b			4.9(−29)[c] 7.8(−5)[d]			32

[a] PMDTA complex $N(\mathbf{C}H_3)_2$ resonance.
[b] PMDTA complex $\mathbf{C}H_2N(CH_3)_2$ resonance.
[c] Internal reorganization.
[d] Exchange of free with complexed TMEDA.

independently by use of the geminal silyl methyl substituent in **48**, **49** and **51**, exemplified by **54a** and **54b**.



(98)

(54a) **(54b)**

At low temperature the ^{13}C NMR spectra of these geminal methyls consisted of clean 1:1 doublets for each of the compounds. Diastereotopic methyls established the chiral characters of these three compounds. Above 170 K, with increasing temperature there was progressive averaging of these doublets. Phenomenologically, this implied the operation of transfer of coordinated TMEDA between faces of the allyl plane which is, overall, inversion. The process is first order in the allylic lithium compound. The activation parameters are typically $\Delta H^{\ddagger}$ of 5 to 7 kcal mol^{-1} with a large negative $\Delta S^{\ddagger}$ of *ca* -25 ± 5 eu

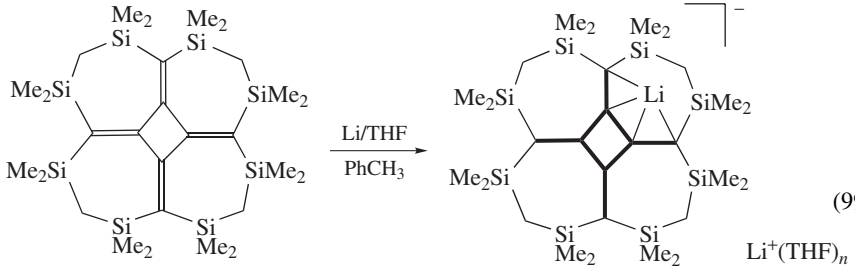
(Table 10). Dynamic effects observed in the cases of **31b**, **38**, **51** and **53** are most likely largely also due to this inversion process, even though averaging effects seen in the $N(CH_3)_2$ resonances may have slower contributions from other processes such as fast reversible N−Li dissociation accompanied by inversion of nitrogen.

Further details of ion-pair reorganization dynamics ensued from NMR studies of **52**. The low temperature, 160 K, ^{13}C NMR of the geminal silyl methyls consists of three singlets in a 2:1:1 ratio. These were ascribed to two overlapping doublets, the larger peak being due to one line from each doublet; see Figure 14.

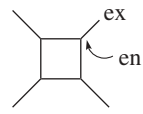
With increasing temperature the two doublets, proposed above, average to a single doublet. Then, on further warming, the latter averages to a single line. NMR line shape analysis established the dynamics of two different processes. The low-temperature averaging was ascribed to reorientation of coordinated TMEDA *on one side* of the allyl plane while at high temperature the final averaging was considered most likely to result from the face transfer process described above. Notice that while both processes have similar $\Delta H^{\ddagger}$ values, the entropies of activation are quite different, −12 eu for rotation of coordinated ligand on one side of the allyl plane and −22 eu for the slower inversion process, in similar fashion to the inversion $\Delta S^{\ddagger}$ values of **48**, **49** and **51** (Table 10).

These results, described above, showed for the first time that selected ion-pairs organize into well-defined structures and how mechanisms of reorganization within and between ion-pairs have been revealed with the methods of dynamic NMR.

Dynamic reorganization of ion-pairs has also been investigated by Sekiguchi and coworkers, who reduced **55** with lithium to produce the dilithium ion-paired compound, **56** (equation 99)[44]. Lithium-6 NMR consisted of two lines of equal intensity at δ − 0.38 and −0.66 (referenced to LiCl in methanol). The former resonance was assigned to externally solvated $^6Li^+$ while the latter was more consistent with $^6Li^+$ tightly bound to one face of the conjugated dianion. At low temperature the exocyclic and endocyclic ^{13}C resonances of **56** (cf. **57**) each consist of a 1:1 doublet, which shows that the contact bound lithium is unsymmetrically sited with respect to the plane of the dianion.



(55) (56) (99)



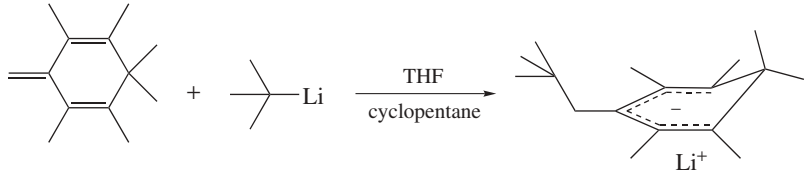
(57)

With increasing temperature, these two doublets progressively average to single lines at their respective centers by 298 K. This behavior was ascribed to a lithium 'walk' around one face of the plane of the dianion. NMR line shape analysis of these data gave rise to $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for the lithium 'walk' of 12.6 kcal mol^{-1} and +4.5 eu, respectively.

Throughout the temperature range investigated the ^{6}Li NMR did not change. Further, the proton resonance of CH_2 also remained unchanged as a clean AB multiplet. This showed that both transfer of Li^+ between faces of the dianion plane and mutual exchange of lithiums between their external and contact sites were both slow relative to the NMR time scale.

By contrast to the solution structure, **56**, in the solid state, the two lithiums are sited on opposite sides of the dianion plane.

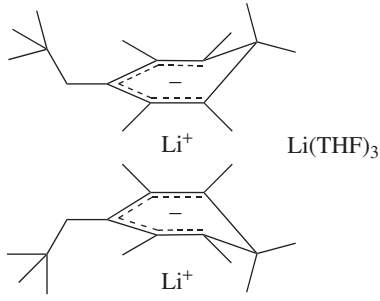
Reaction of triene **58** with *t*-butyllithium (equation 100) gives an equilibrium mixture of two dimers (equation 101), one contact ion-paired **59** and the other a triple ion sandwich with external solvated Li^+ **60**[45], recognized by two widely separated ^{7}Li resonances. These results were the first to unambiguously authenticate the existence of such triple ions.



(100)

(58) **(59)**

$$(A^-Li^+THF)_2 + THF \rightleftharpoons (A^-Li^+A^-) \cdot Li^+(THF)_3 \qquad (101)$$



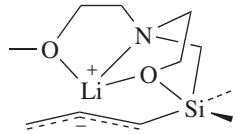
(60)

The triple ion species **60** is favored at low temperatures with THF as ligand, in the presence of HMPT and with glymes. Using ^{7}Li NMR, the equilibrium of equation 101 was characterized with $\Delta H^\circ = -4 \pm 0.3$ kcal mol^{-1} and $\Delta S^\circ = -10 \pm 2$ eu. While exchange of contact-ion paired Li^+ with sandwiched Li^+ is quite slow, the resonances of externally solvated Li^+ in **60** and contact ion-paired lithium in **59** average with increasing temperature. Lithium-7 NMR line shape analysis gave $\Delta H^\ddagger = 7.3 \pm 0.4$ kcal mol^{-1} and $\Delta S^\ddagger = -18 \pm 3$ eu for this exchange process.

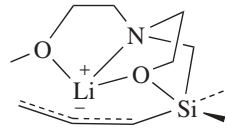
Paquette, Schleyer and coworkers reported that lithium isodicyclopentadienide adopted structures similar to **59** and **60**[46]. An equilibrium was proposed between externally solvated triple ion containing dimer, $(A^-\ Li^+\ A^-)\ Li^+\ (THF)_n$, and a monomeric contact ion-paired species $(A^-\ Li^+)\ (THF)_n$. Lithium-7 NMR obtained as a function of temperature revealed the operation of two exchange processes: 1) exchange of Li^+ between its sandwiched and contact sites with $\Delta H^\ddagger = 8.6 \pm 0.5$ kcal mol^{-1} and $\Delta S^\ddagger = +3.2 \pm 2.7$ eu

and 2) lithium exchange between its externally solvated and contact ion-paired sites with $\Delta H^{\ddagger} = 6.5 \pm 0.2$ kcal mol^{-1} and $\Delta S^{\ddagger} = -8.4 \pm 0.9$ eu.

In experiments designed to slow down the exchange of ions among ion-pairs and thus reduce the perturbation of NOE mapping experiments by dynamic phenomena, Fraenkel and Cabral investigated a potentially internally solvated allylic lithium compound, **61**[47].



(61ex)



(61en)

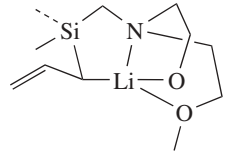
Carbon-13 and proton NMR spectra established that the compound was indeed monomeric and internally solvated as shown in **61ex**. At low temperature two stereoisomers were observed, one *exo* and the other *endo*, the ratio *exo/endo* being 88/12 in toluene and 33/67 in THF. At low temperature, 200 K, the ligand carbons are magnetically nonequivalent. With increasing temperature, the ^{13}C NMR doublets due to OCH_2, NCH_2 and OCH_3 of **61** in toluene-d_8 solution each progressively average to single lines at their respective centers. NMR line shape analysis gave the same dynamic parameters for each set of collapsing doublets. The authors ascribed these effects to the dynamics of transfer of the pendant complexed ligand between faces of the allyl plane[47]. The *exo* → *exo* and *endo* → *endo* listings in Table 11 both refer to the face transfer, net inversion process. In addition, the analysis of the NMR line shapes provides dynamic information on rotation around the C_1-C_2 allyl bonds in **61ex** and **61en**, (see the *endo* → *exo* listings in Table 11). For the latter process $\Delta H^{\ddagger}$ is typically *ca* 16 kcal mol^{-1} while inversion is much faster with $\Delta H^{\ddagger} = ca$ 8 kcal mol^{-1}. Interestingly, the former value is a little larger than those observed for face transfer of externally coordinated lithium compounds where the $\Delta H^{\ddagger}$ values lie within the range 5 to 7 kcal mol^{-1}. Throughout the temperature range of 245 K to 313 K investigated, rotation around the C_2-C_3 bond of **61en** was too slow to measure using dynamic NMR methods.

That rotation around the C_1-C_2 bond of **61en** is faster than that around the C_2-C_3 bond is consistent with the proposal that the transition state for rotation in allyllithium involves some increase in C_1-Li covalence, see **62**, compared to the delocalized state.

TABLE 11. Activation parameters for inversion **i** and rotation **r** in the system **61ex** and **61en**[47]

	Resonance	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (eu)
		In THF-d_8	
endo → *exo*, **r**	OCH_2	16.4 ± 1	11.7 ± 2
endo → *exo*, **r**	$\mathbf{C}_2$H	15.4 ± 1	9.2 ± 2
endo → *exo*, **r**	$C_2\mathbf{H}$	16.4 ± 1	12 ± 2
endo → *endo*, **i**	OCH_2	7.0 ± 0.4	-15 ± 3
		In toluene-d_8	
exo → *exo*, **i**		7.6 ± 0.4	-15 ± 3
exo → *exo*, **i**		8.1 ± 0.4	-12 ± 2

Modeling shows that the pendant ligand in **61en** places lithium in the proximity of C_1 and not C_3. This would facilitate development of some degree of C_1-Li covalence. Further, any charge localized at C_1 by development of the transition state would be stabilized by the silicon substituent.

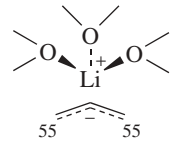


(62)

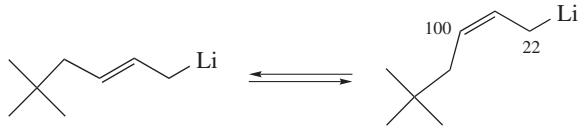
As noted above, the exchange rate of ions between ion-pairs in solution is frequently very fast, even at low temperatures[48]. As a result, the NMR spectrum of a mixture of ion-paired species of the same organolithium compound consists of the weighted average of the spectra of all the species present[41]. In experiments to facilitate NMR NOE studies of ion-pair structure, several allylic lithium compounds were prepared with potential ligands for lithium tethered to the allyl carbanionic moiety. It was proposed that encapsulation of Li^+ by internal solvation would inhibit the exchange of Li^+ among the different ion-pairs present[47,49]. The data obtained in studies of **61** represent the first successful example of such an experiment[47]. Compound **61** is indeed an internally solvated delocalized ion-paired organolithium compound and dynamics of several of its reorganization processes were investigated, as described above[47].

J. Internally Solvated Organolithium Compounds

Ordinarily, allylic lithium compounds assume just two main types of structures. Externally solvated allylic lithium compounds are fully delocalized contact ion-pairs with coordinated Li^+ sited on the axis normal to the center of the allyl planes as demonstrated in **63**, and shown by ^{13}C NMR shifts of the allyl termini[50] and by X-ray crystallography[51]. By contrast the ^{13}C and proton NMR spectra of unsolvated allylic lithium compounds, for example exchanging **64ex** and **64en** (equation 102), also with selected ^{13}C shifts (see **64en**), so closely resemble those of alkenes that such compounds must be regarded as localized[51].

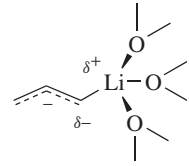


(63)



(102)

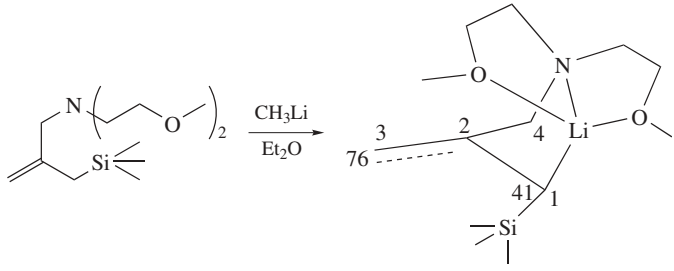
(64ex) **(64en)**



(65)

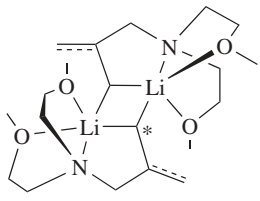
Not long before this writing, partially delocalized structures **65**, which lie on a continuum between **63** and **64ex/64en**, had not been reported.

The first evidence for a partially localized allylic lithium compound came from metalation studies of **66** using CH_3Li in diethyl ether. The product of this reaction (equation 103) is best described as **67** on the basis of X-ray crystallographic and solution NMR data[49a, b]. Thus, while **54** is delocalized, just moving the ligand tether to the central carbon induces major changes in electronic structure, as described below. Similar results to those reported for **67** were also observed in the cases of **68**[49b, d], **69**[49c], **70**[49b], **71**[49d], **72**[49d], **73**[49d], **74**[49d], **75**[49d], **76**[49d] and **77**[49d].

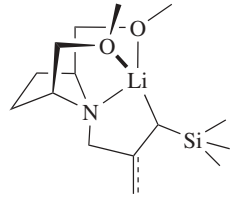


(103)

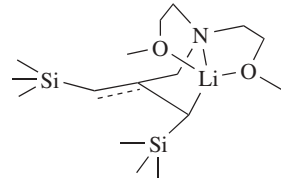
(66) **(67)**



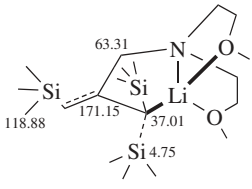
(68)[49d]



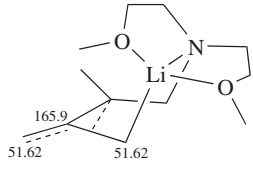
(69)[49c]



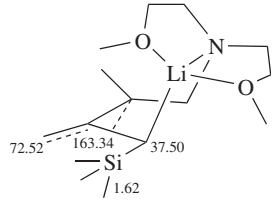
(70)[49b]



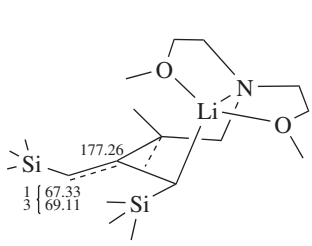
(71)[49d]



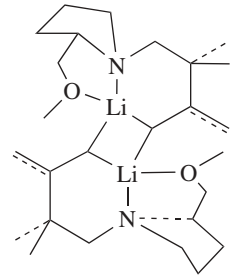
(72)[49d]



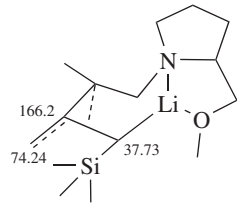
(73)[49d]



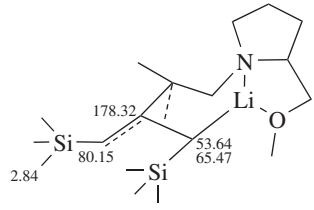
(74)[49d]



(75)[49d]



(76)[49d]



(77)[49d]

These compounds **63**–**77** share numerous structural features. X-ray crystallography and/or solution ^{13}C NMR show the pendant ligands to be fully coordinated to lithium. X-ray crystallography of **68** to **72** and **74** and **75** shows that in each of these compounds the allyl C−C bonds have different lengths (Table 12[49d]) which lie between those for solvated delocalized **63** and proposed, from its ^{13}C shifts, localized unsolvated **64ex** and **64en**. In every case, lithium is closest to one of the terminal allyl carbons.

The terminal allyl ^{13}C NMR shifts also lie between those for solvated delocalized **63** and unsolvated proposed localized **64** (Table 12). In several cases there is spin coupling between ^{6}Li or ^{7}Li and the more ^{13}C NMR shielded of the terminal allyl carbons. The latter were matched to the terminal carbons of the longer allyl C−C bonds, labeled as C_1; see **67** for numbering.

Finally, all carbons of the pendant ligands in compounds **67** to **77** are nonequivalent in the X-ray structure and/or by their solution ^{13}C NMR chemical shifts[49].

It was proposed that the tethers of the pendant ligands were too short to place lithium on the axis normal to the center of the allyl plane but instead put coordinated lithium off the axis normal to the allyl plane at C_1[49d]. As a result what would ordinarily be a delocalized allyl anion becomes a polarized and partially localized anion, building up negative charge at C_1 due to the proximity of coordinated Li^+[49d]. The possible contribution of a small degree of covalence to the C−Li bond could not be evaluated.

The authors commented that perturbation of conjugation due to stereochemical control of lithium coordination among compounds **67**–**77** appears to be a continuously variable effect[49d]. Thus, as the differences between the C_1-C_2 and C_2-C_3 bond lengths, respectively, and ^{13}C chemical shifts $\delta_3 - \delta_1$ both increase, the angle the C−Li^+ bond makes with the allyl plane decreases systematically (Table 12)[49d].

Internally solvated allylic lithium compounds undergo three fast equilibrium reorganization processes—inversion at lithium bound carbon, bimolecular C−Li exchange and lithium 1,3-sigmatropic shifts[49].

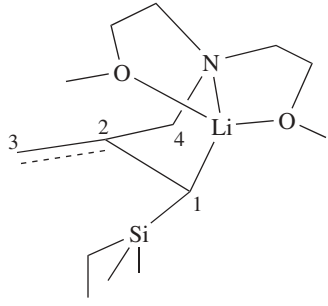
TABLE 12. Selected X-ray structural and NMR parameters of internally solvated allylic lithium compounds (M = monomer, D = dimer, P = polymer). For numbering see structure **67**[49d]

	Solid solution		J $^{13}C-Li$ (Hz)	Bond lengths (Å) C_1-C_2	Bond lengths (Å) C_2-C_3	^{13}C shifts δ C_1	^{13}C shifts δ C_3	Torsional angles[a] $Li-C_1-C_2-C_4^0$	Torsional angles[a] $Si_1-C_1-C_2-C_4^0$	Torsional angles[a] $Si_3-C_3-C_2-C_4^0$
68	D	D	—[b]	1.436(4)[c]	1.349(1)[c]	58.55[b]	58.55[b]	−50.12(0.03)[c]	—	—
67	P	M	3.0 ^{6}Li	1.397(4)	1.361(4)	41.10	76.30	−55.27(0.25)	173.59(0.19)	—
69	P	M	7.0 ^{7}Li	1.415(7)	1.351(8)	42.81	72.95	47.8(5)	179.6(4)	—
70	M	M	6.1 ^{7}Li	1.431(3)	1.351(3)	54.12	78.10	52.97(0.2)	176.7(0.16)	−5.32(0.34)
71	M	M	15.9 ^{7}Li	1.494(7)	1.306(8)	37.01	118.88	−30.3(0.61)	82.03(0.58)[d] −142.37(0.48)[d]	−9.13(1.12)
72	M	M	—[b]	1.426(2)	1.366(2)	51.62[b]	51.62[b]	73.46(0.14)	—	—
73	—[e]	M	8.1 ^{7}Li	—[e]	—[e]	37.50	72.52	—[e]	—[e]	—
74	M	M	4.6 ^{7}Li[f] 4.1 ^{7}Li[f]	1.415(8)	1.368(20)	67.33[b]	69.11[b]	−90.9(3)	171.3(3)	15.1(7)
75[f]	D	—[g]	—[g]	1.415(8)[c]	1.368(20)[c]	—[g]	—[g]	−103.58(3)[c]	—	—
76	—[c]	M	8.7 ^{7}Li	—[e]	—[e]	37.73	74.24	—[e]	—[e]	
77	—[e]	M[g]	5.1 ^{7}Li	—[e]	—[e]	53.64[h] 65.47[h]	80.15[h] 80.15[h]	—[e]	—[e]	—[e]

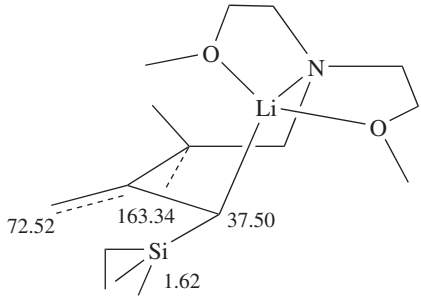
[a] Torsional angle with respect to allyl plane at C_2-C_4.
[b] Exchange averaged.
[c] Weighted average over two dimers.
[d] Refers to 1,1-bis(TMS).
[e] Did not crystallize.
[f] Averaged values (see text).
[g] Insoluble.
[h] Two stereoisomers.

At low temperature, all carbons of the pendant ligands of compounds **67**–**69**, **73** and **74** are magnetically nonequivalent. For example, in the ^{13}C NMR spectrum at 160 K of **67** due to $\mathbf{C}H_3O$, $\mathbf{C}H_2O$ and $N\mathbf{C}H_2C$, each of the latter gives rise to an equal doublet[49b]. With increasing temperature, all the latter doublets average progressively to single lines at their respective centers. NMR line shape analysis of each of the doublets yields the same rate constants, implying that a common mechanism is responsible for all these line shape changes. Similar results were obtained with compounds **69**[49c], **73**[49d] and **74**[49d].

Compounds **78**[49c] and **79**[49c] are analogs of **67** and **69**, respectively, with dimethylethylsilyl instead of TMS. At low temperature, 170 K, the geminal methyl silyl ^{13}C NMR signals of **78** and **79** consist of equal doublets, diagnostic of chiral environments in both compounds. With increasing temperature above 170 K, these diastereotopic doublets average progressively to single lines at their respective centers. This behavior is necessarily indicative of the dynamics of molecular inversion at lithium bound carbon. Line shape analysis of the latter collapsing doublets gives the same results as those obtained from changes in the ^{13}C NMR signals of the ligand carbons. One can conclude that inversion is also mainly responsible for averaging of the ligand ^{13}C resonances of **67**, **69**, **73** and **74**.

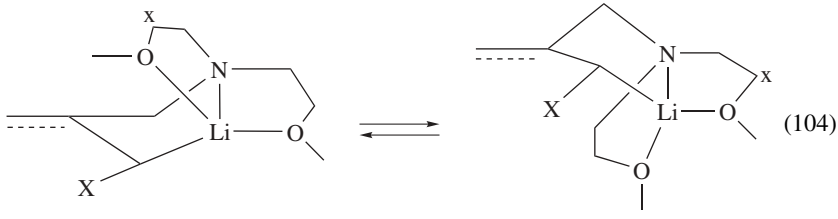


(78)



(79)

Inversion of **67**, **69**, **73**, **74**, **78** and **79** most likely takes place by transfer of coordinated lithium between faces of the allyl plane (cf. **80** $\rightleftarrows$ **80a**, equation 104). It is a first-order process. Activation parameters are listed in Table 13.



(104)

(80) **(80a)**

The second dynamic process involves C–Li exchange. Around and below 230 K, most of the internally solvated allylic lithium compounds exhibit one bond spin coupling between ^{13}C and ^{7}Li ($I = 3/2$) and to ^{6}Li ($I = 1$). The ^{13}C NMR of lithium bound carbon consists of equally spaced equal multiplets, an equal triplet for coupling to ^{6}Li and an equal quartet for coupling to ^{7}Li. The separation between adjacent lines are the coupling constants.

TABLE 13. Quantitative and qualitative dynamic behavior of internally solvated allylic lithium compounds in diethyl ether-d_{10} solution

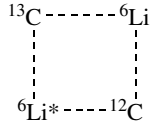
	C−Li exchange		Inversion		1,3 Li sigmatropic	
Compound	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (eu)	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (eu)	shift, 250 K k_1 (s^{-1})	Reference
67	11[a] ± 0.5	−6[a] ± 2	8[a] ± 0.5	−10[a] ± 3	—	49a,b
68	(fast)[b]		(fast)[b]		8.8×10^{6}[c,d]	49a
69	12[e]	−5[e] ± 2	9[e] ± 0.5	−7[e] ± 2	—	49c
70					1.0	49b
71	(slow)[f]		—		—	49d
72	(fast)[b]		(fast)[b]		1.4×10^{5}[c,g]	49d
73	11 ± 0.5	−15 ± 4	15 ± 1	+2 ± 0.5	—	49d
74	(slow)[f]		(slow)[e]		$>10^{8}$	49d
76	6 ± 0.3	−27 ± 5	—		—	49d
77	(slow)[f]		—		$<10^{-2}$	49d
78	12 ± 1	−6 ± 2	6 ± 0.5	−18 ± 3	—	49c
79	—	—	12 ± 0.7	−2 ± 0.5	—	49c

[a] Reference 49b.
[b] Too fast to measure.
[c] Estimated from line broadening.
[d] $\pm 2 \times 10^{5}$ s^{-1}.
[e] Reference 49c.
[f] Too slow to measure.
[g] $\pm 2 \times 10^{4}$ s^{-1}.

With increasing temperature, the ^{13}C NMR multiplets of **67**, **69**, **73**, **78** and **79** due to carbon−lithium coupling average progressively to single lines at their respective centers. This is diagnostic of mutual exchange of lithium between two organolithium species. It is not even necessary to carry out kinetic studies. As far as ^{13}C NMR of lithium-6 bound carbon is concerned, the system is simulated for ^{13}C in natural abundance as in equation (58a).

$$^{13}C^{6}Li + {}^{12}C^{6}Li^{*} \rightleftharpoons {}^{13}C^{6}Li^{*} + {}^{12}C^{6}Li \qquad (58a)$$

The resulting three coupled density matrix equations 61 are solved for the required density matrix elements which are summed (equation 10) to give the ^{13}C NMR line shapes. A similar procedure provides the ^{13}C NMR line shapes for carbon bound ^{7}Li. Comparison of observed and calculated NMR line shapes provides the Eyring activation parameters for bimolecular C−Li exchange listed in Table 13.



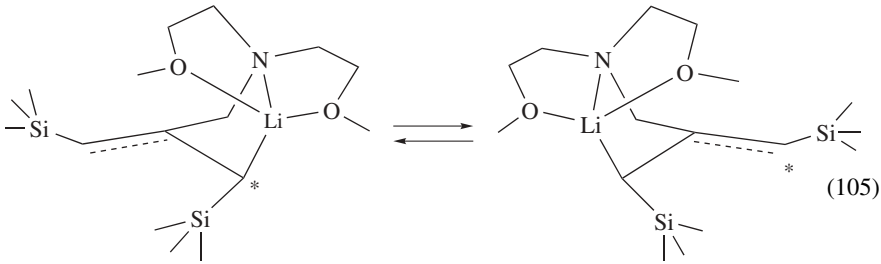
(81)

Bimolecular exchange implies a dimeric transition state shown in partial form as **81**, most likely preceded by a dimeric intermediate. Note that compounds **68** and **75** are dimers in the ground state. Thus, dimeric structures may be energetically accessible from ground state monomeric internally solvated allylic lithium compounds. Further, it is interesting

that if the pendant ligand is $-N(CH_2CH_2OCH_3)_2$, the $\Delta H^{\ddagger}$ values for C−Li exchange are uniformly around 11 to 12 kcal mol^{-1}, respectively, for both one and two carbon tethers. This suggests that the primary activation for this exchange process involves decoordination of lithium from the pendant ligand.

Internally solvated allylic lithium compounds also exhibited fast lithium sigmatropic shifts in the case of unsubstituted compounds **68** and **72** and symmetrically 1,3-disubstituted compounds **70** and **74**. For example, between 270 K and 330 K the two methylsilyl ^{13}C resonances of **70** average progressively to a single line as do their two corresponding methylsilyl proton resonances[49b]. NMR line shape analysis of this change gives $\Delta H^{\ddagger} = 18$ kcal mol^{-1}. Interestingly, within the above temperature range the two terminal allyl ^{13}C resonances broaden and disappear into the base line. These terminal resonances are too far apart to average by 330 K the highest temperatures at which satisfactory NMR spectra could be obtained.

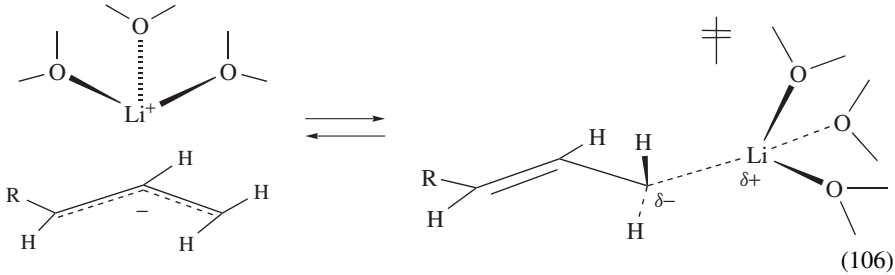
The NMR data for **70** described above indicated the presence of only one species. Thus the sigmatropic shift **70a/70b** (equation 105) had to be accompanied by rotations around both allyl C−C bonds.



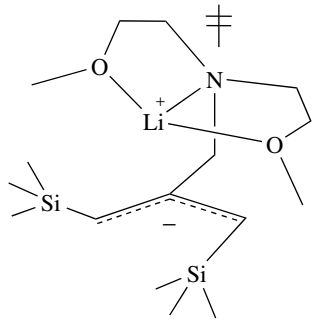
(105)

(70a) **(70b)**

There is an interesting qualitative relationship in the dynamic behavior of **70** with rotation around allyl C−C bonds in delocalized allylic lithium compounds. Because these rates of rotation depend on the nature of the lithium ligand, it was proposed that the rotational process is chemically driven by lithium and does not just involve rotation within the delocalized anion alone[34]. In this proposed model (equation 106), coordinated Li^+ moves from normal to the center of the allyl plane to a site *exo* to C_1 within the allyl plane. This partially localizes the allyl moiety, develops tetrahedral structure and builds up some negative charge at C_1. By contrast, the ground state of **70** is partially localized while the transition structure for the sigmatropic shift should be regarded as more delocalized relative to the ground state, **82**. Clearly, the stereochemistry of lithium coordination must be responsible for the relative energies of these localized and delocalized states.



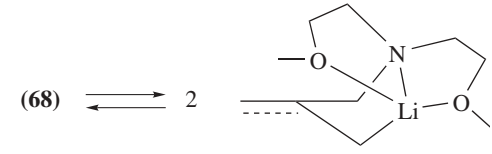
(106)



(82)

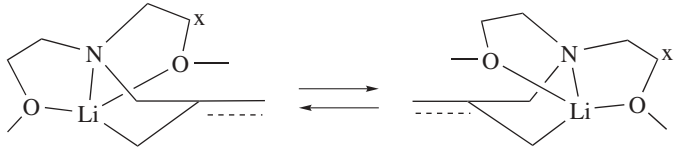
The Li sigmatropic shifts in **68**, **72** and **74** are much faster than in **70**. X-ray crystallography shows all four compounds to be internally solvated. Only **68** is a dimer both in the solid and in solution as determined from freezing point measurements; the other three are monomers in the solid as well as in solution. Neither **68** nor **72** exhibited $^{13}C-^{6}Li$ (or ^{7}Li) spin coupling down to 150 K.

At room temperature, the terminal allyl ^{13}C resonances of **68** and **72** each consist of a single sharp peak. On cooling the samples, these lines broaden and disappear into the base line indicating a fast Li 1,3-sigmatropic shift in both cases, too fast to allow resolution of the C_1 and C_3 resonances by 150 K. On the basis of these observations it was proposed that **68** is in rapid equilibrium with a low concentration of monomer **83**, which undergoes a very rapid Li sigmatropic shift (equations 107 and 108). The "x" clarifies the stereochemistry of the shift. The fast monomer dimer equilibrium would be responsible for averaging $^{13}C-Li$ spin coupling. A similar situation applies in monomeric **72** in equilibrium with a low concentration of dimer.



(107)

(83)

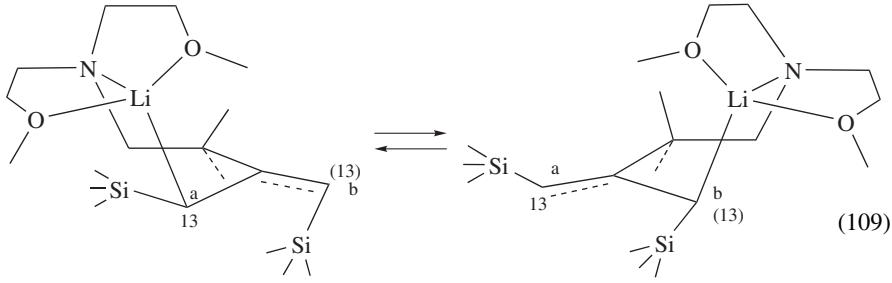


(108)

(83′) **(83)**

From the broadening of the terminal allyl ^{13}C resonances, estimates were made of the sigmatropic shift rates. Since the terminal allyl ^{13}C shifts could not be measured, they were estimated via a combination of *ab initio*, DFT and GIAO calculations using the crystallographic structural parameters as initial input in the calculations. As listed in Table 13, these rates are very fast at 250 K, with values of k_1 within the range 10^5 s^{-1} to 10^7 s^{-1} [49d].

In contrast to compounds **68**, **70** and **72**, the Li 1,3-sigmatropic shift in **74** is too fast to measure at all temperatures investigated, down to 150 K. The data indicated that while **74** describes the X-ray crystallographic structure, in solution the material consists of two stereoisomers **74** and **84** in roughly equal concentrations, rapidly interconverting by means of a very fast Li 1,3-sigmatropic shift (equation 109).



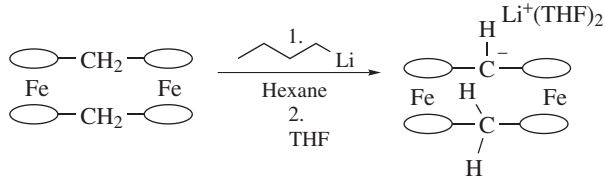
(109)

(84) **(74)**

While the sigmatropic shift is fast, intermolecular C−Li exchange and rotation around the C−C allylic bonds in the two compounds are both *slow* relative to the NMR time scale. As a result, the terminal allyl ^{13}C resonances consist of two equal quartets due to $^{13}C-^{7}Li$ coupling. One quartet is the average of the *a* shifts in the two stereoisomers while the other is the average of the *b* shifts (equation 109). Further, because ^{13}C is in natural abundance and the solution is approximately equimolar in **84** and **74**, the splitting of 4.6 Hz of the $^{13}C_a$ resonance is the average of that in **84** of *ca* 9.1 Hz with *ca* zero in **74**. An analogous rationale applies to the $^{13}C_b$ averaged resonances due to the isotopomers of **84** and **74** with ^{13}C at C_b.

K. Proton Transfer Within a Carbanionic Species

The Ahlberg group reported on the unusual structure and dynamic behavior of a hydrogen-bridged organolithium compound which undergoes a rapid intramolecular proton transfer[52]. This compound, **86** (equation 110), was prepared by metalation at the methylene bridge of **85** using butyllithium in hexane. X-ray crystallography and solution ^{13}C and proton NMR established the structure shown as **86**. Lithium is near and external to the carbanionic carbon. Of the hydrogens associated with the two carbon bridge, two, (C**H**Li) and one methylene hydrogen, are *exo* while the other methylene hydrogen is *endo*, i.e. between the bridging carbons. There is geminal proton−proton coupling between the methylene hydrogens (18 Hz), but it is not observed between either methylene hydrogen and $C^{-}\mathbf{H}Li^{+}$. At 166 K in THF solution, the compound exhibited one bond ^{13}C, ^{6}Li spin coupling of 4 Hz ($^{13}\mathbf{C}Li$, δ 31.7). The authors concluded that interaction between the bridging hydrogen and the carbanionic carbon to be minimal and not consistent with their results.

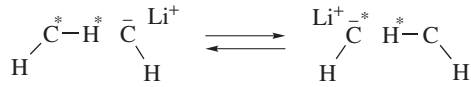


(110)

(85) **(86)**

Above 166 K with increasing temperature, the ^{13}C NMR triplet due to ^{6}Li bound carbon in **86** averaged progressively as a result of fast intermolecular C−Li bond exchange; however, a line shape analysis of these spectra was not reported.

Of special interest, with increasing temperature above 166 K, the *endo* proton doublet, due to geminal coupling, averages progressively to a 1:2:1 triplet by 288 K, splitting 9 Hz. This is the result of fast degenerate transfer of the *endo* methylene proton between the two bridged carbons, the latter proton remaining *endo* between the latter carbons at all times as shown by the partial structure given in equation 111.



(111)

Line shape analysis of the proton transfer in THF gave $\Delta H^{\ddagger} = 4.5$ kcal mol^{-1} and $\Delta S^{\ddagger} = -21$ eu. Actually, the proton transfer rate depends critically on solvent. It is slow in diethyl ether-d_{10}. Adding up to 2 mol% THF-d_8 to the ether solution, the rate is first order in THF-d_8. However, above the latter THF-d_8 concentration the kinetic order in THF-d_8 increases. Faster transfer in the presence of superior ligands for lithium in conjunction with the large negative entropy of activation implies that development of the transition state involves increased solvation around Li^+. In principle, that should facilitate transfer of lithium between two ends of the bridge.

L. Concluding Remarks

We have shown how organolithium compounds adopt a variety of structures which differ in state of aggregation and degree of solvation. These species interconvert rapidly at equilibrium by different mechanisms, such as intermolecular C−Li exchange ligand transfer and dissociation–recombination processes as well as first-order reorganizations such as inversion and rotation. Dynamics of many of these processes have been determined by our methods of NMR line shape analysis.

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CHAPTER 2

Organolithiums as useful synthetic intermediates for tandem reactions

ALVARO J. VÁZQUEZ, RAQUEL G. DE WAISBAUM and NORMA SBARBATI NUDELMAN

Depto. Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pab. II, P 3 Ciudad Universitaria (1428), Buenos Aires, Argentina
Fax: +5411 4576 3346; e-mail: nudelman@qo.fcen.uba.ar

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I. INTRODUCTION

The development of cleaner and more economic processes[1,2] is one of the most fruitful challenges for synthetic chemists in the present decade. The field is receiving much attention from scientific as well as industrial sectors. Some recent examples have been reported, where chemists learned from nature to develop 'green alternatives'[3–5]. In other cases, they apply their creativity designing synthetic strategies for building complex molecular structures from rather simple ones in a minimum number of operations. In this sense, tandem reactions are considered among the most efficient and economical strategies, and are often viewed as 'spectacular and aesthetically pleasing events'[6]. Since they combine several transformations of the same molecule and often incorporate added components without isolating the intermediates or changing the reaction conditions[7], a spectacular decrease in the amounts of solvents, reagents, adsorbents and energy is obtained, compared with stepwise reactions[8].

Organolithium compounds are among the most popular organometallics due to their excellent nucleophilic reactivity, and their importance in organic synthesis is very well known[9]. Therefore, tandem reactions using organolithium compounds constitute nowadays one of the most powerful synthetic strategies, since they combine the versatility of organolithiums with the minimization of waste, energy, solvents etc. of the tandem reactions.

These reactions are usually designed on the basis of rational mechanistic considerations and they proceed rapidly upon initiation, leading to the final product through a number of intermediates. Thus, once the reaction sequence is triggered, a reactive intermediate may be formed and it proceeds to the next stage via an intramolecular or intermolecular reaction leading to a new compound. The new compound, in turn, may itself be in a favorable situation to undergo further reactions, thus generating a product of greater complexity. For this reason, the strategy is also called 'cascade' or 'domino' reactions. Following the common usage, the three terms will be used indistinctively throughout this review.

This chapter is not intended to be a general and comprehensive overview, and since several reviews have been published in the last few years on tandem reactions[7,8,10,11] and also on organolithium compounds[9,12,13], we have mainly concentrated on the literature of the last 10 years and focused only on tandem reactions that use organolithiums. The reactions have been classified taking into account the main kind of chemical transformations involved in giving rise to the construction of different kinds of chains and/or rings. Although in some cases the classification is not very straightforward, the chapter illustrates the roads to achieve molecular complexity with a number of typical examples. It is noteworthy that in many cases the process results in the construction of rather complex products, each containing chiral centers from non-chiral precursors through cascade reactions.

The organolithium intermediates formed in the tandem reactions, are usually treated with different reagents to produce a variety of products. The way that these kind of reactions are written in Schemes differs from an author to author. Therefore, to be consistent through the chapter, the following convention was adopted: "E" means any reagent that, on reaction with an organolithium compound, delivers an electrophilic moiety, E,

TABLE 1. Electrophilic reagents, "E", and organic moieties present in the product, E

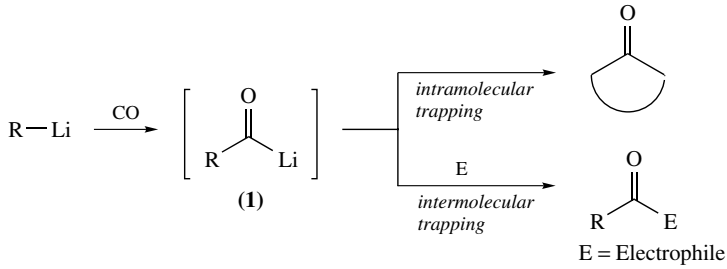
"E"	E	"E"	E
MeOH	H	Me_3SiCl	Me_3Si = TMS
CO_2	CO_2H	XR	R(alkyl or allyl)
H_2O	H	Me_2NCHO	CHO
RCHO	RCH(OH)	Bu_3SnCl	Bu_3Sn
R^1R^2CHO	$R^1R^2C(OH)$	$ClCO_2Et$	CO_2Et

rendering a product in which that moiety replaces the lithium atom. Table 1 shows the reagent, "E", and the corresponding organic moiety that appears in the product, E.

II. FUNCTIONALIZED CHAINS

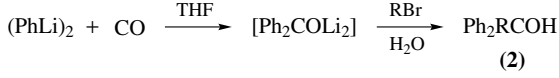
A. Reaction with CO

The reaction of organolithium reagents with CO has long been considered to be an important approach to introduce carbonyl groups into organic molecules and it has been recently applied in interesting tandem reactions[14]. Due to the high reactivity of the initial intermediate (the carbonyllithium species **1**) the reaction was early considered to be synthetically unappealing[15]. Nevertheless, useful synthetic methods were then developed from the primary carbonylation of organolithium reagents by '*in situ*' intra- or inter-molecular trapping of intermediate **1** (Scheme 1)[16, 17]. In addition to being strong nucleophiles, these species are also electrophiles, since the carbonyl function is susceptible to nucleophilic attack[18].



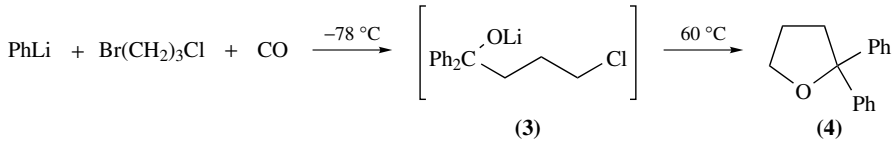
SCHEME 1

This tandem sequence reaction of organolithium compounds with carbon monoxide followed by reaction with suitable electrophiles E[16, 17, 19] provides a useful tool for the preparation of a wide diversity of molecules containing one or more carbonyl functionalities; the synthetic usefulness of the carbonylation of numerous organolithiums has been demonstrated[20]. Acyl anions of the main row elements are of prime interest since they are expected to be potent nucleophilic reagents. The high reactivity of these reagents can be constructively used to perform tandem sequences of reactions that lead to useful intermediates. We have earlier reported a procedure which combines nucleophilic acylation of an alkyl halide with organolithium addition to produce diarylalkylcarbinols, some of which are of industrial interest. Diphenylalkylcarbinols, **2**, were easily prepared by carbonylation of phenyllithium in THF in the presence of the appropriate alkyl bromide (Scheme 2)[21].



SCHEME 2

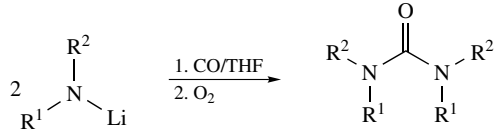
This reaction was easily extended to produce substituted cyclic ethers in a one-pot synthesis (Scheme 3). Thus, by carrying out the carbonylation of phenyllithium in the presence of 1-bromo-3-chloropropane at −78 °C, the lithium enolate intermediate **3** was obtained which cyclizes to **4** by warming up the reaction mixture.



(3) **(4)**

SCHEME 3

The utility of carbonylation of lithium amides for the synthesis of complex molecules has been also demonstrated. *N*,*N*,*N*′,*N*′-Tetrasubstituted ureas **5** were obtained in good yields by reaction of lithium alkyl amides in THF solution with carbon monoxide under mild conditions (0 °C, 1013 mbar), followed by treatment with oxygen prior to work-up (Scheme 4)[22].



(5)

SCHEME 4

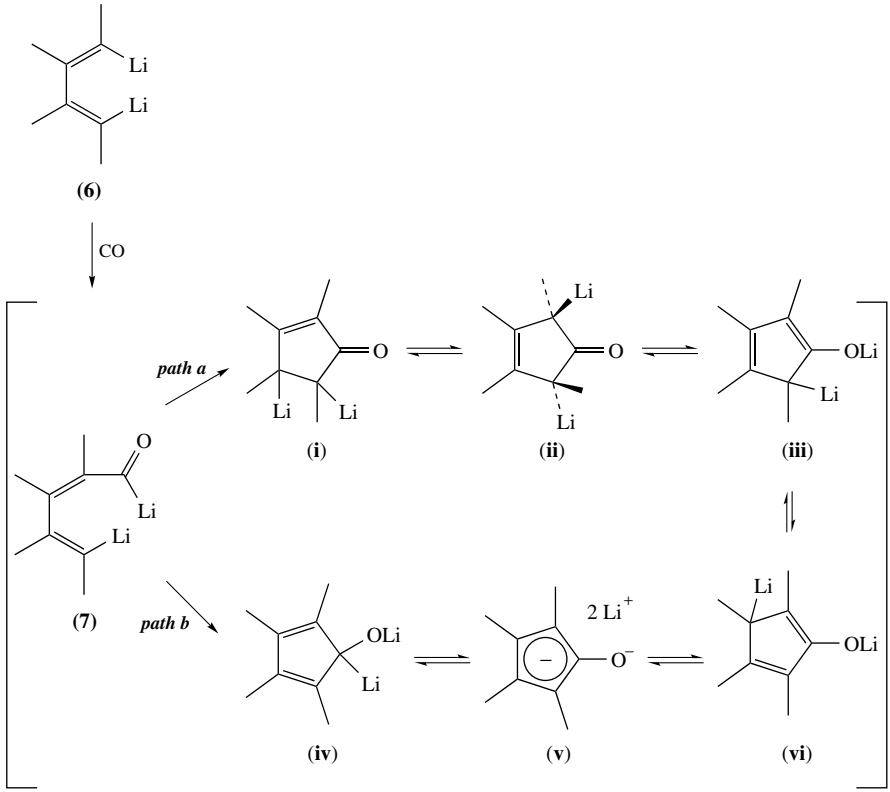
It has been recently reported that the reactions of 1,4-dilithio-1,3 dienes with carbon monoxide provides a useful tandem methodology for the synthesis of cyclopentenones[14]. The reaction constitutes an unprecedented pattern of highly selective efficient carbonylation, since in 1 h at −78 °C it affords, after hydrolysis, *trans*-3-cyclopenten-1-one in an excellent isolated yield and with perfect *trans* selectivity.

Although it is not yet clear as to why the cyclopentanone derivatives are formed in highly regio- and stereo-selective patterns, it is obvious that one or more new dilithio oxygenated intermediates are generated in the carbonylation reaction of **6**. An acyclic carbonyllithium species **7** is proposed to be the first reaction intermediate, which immediately undergoes intramolecular acyl-lithiation of the lithiated C=C double bond (***path a*** in Scheme 5), or intramolecular nucleophilic attack of the carbonyl group by the remaining alkenyllithium moiety (***path b*** in Scheme 5), followed by sequential rearrangement to afford cyclic dilithium compounds, such as **i–vi** (Scheme 5)[23].

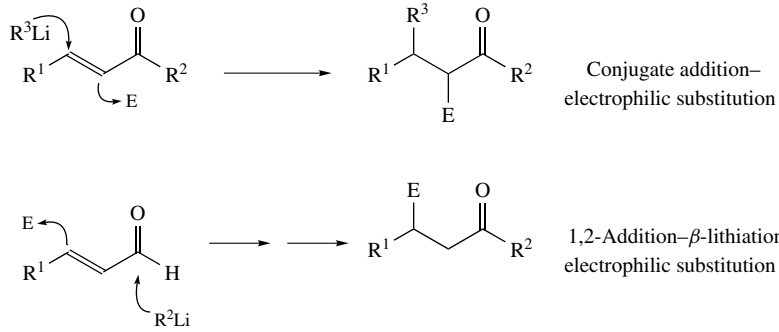
B. Carbon–Carbon Bonds

Several studies with organolithiums bridge inorganic, physical, organic and theoretical chemistry[24]. These reagents are the most widely used organometallics in contemporary organic chemistry[25] and they can generate enolates, ylides and dipole-stabilized sp^2 or *sp* or delocalized carbanions[19], which are useful intermediates in diverse applications.

Addition of organolithiums to α,β-unsaturated carbonyl compounds is one of the most widely used reactions for the construction of carbon–carbon bonds[26,27]. The versatility of this reaction is such that it can lead to the formation of a broad variety of compounds depending upon the transformation applied. In particular, the conjugate addition followed by electrophilic trapping can give rise to a large number of α,β-disubstituted carbonyl compounds (Scheme 6). Nevertheless, we have observed that the addition of aryllithiums to (*E*)-cinnamaldehyde is strongly dependent on the reaction conditions; these conditions



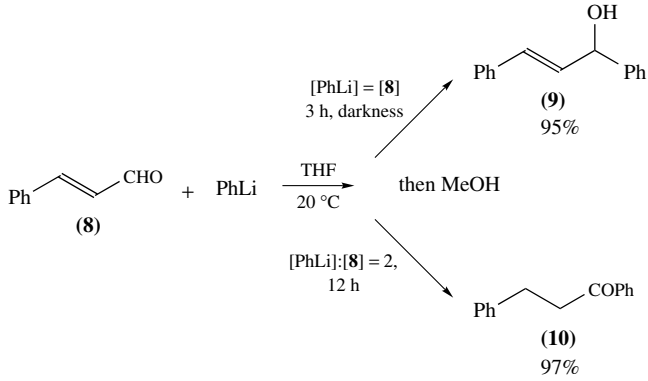
SCHEME 5



SCHEME 6

can be modified, leading to a new tandem strategy in which the organolithium adds to the carbonyl group, giving an intermediate which can be trapped by electrophilic attack at the β-position, thus affording carbonyl compounds alkylated at the β-position (Scheme 6).

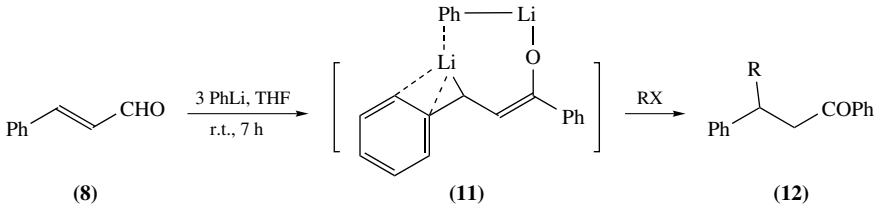
As is shown in Scheme 7, the addition of an equimolar amount of phenyllithium to (*E*)-cinnamaldehyde, **8**, in THF affords the 1,3-diphenyl-2-propen-1-ol, **9**, as the main product, while the (*E*)-chalcone and 1,3-diphenyl-1-propanone **10** were found in trace amounts. Nevertheless, by a careful choice of reaction conditions, the product distribution in the reaction mixture can be changed to give a high yield of **10**, the optimum conditions being [PhLi] : [**8**] = 2 and 12 h reaction time. Under these conditions, a brilliant deep violet solution is formed and **10** is obtained in 97% yield, after quenching with MeOH[28].



SCHEME 7

This new tandem addition–β-lithiation–substitution constitutes a 'one-pot' methodology for the synthesis of β-substituted dihydrochalcones in high yields[28,29]. NMR spectroscopic studies of the reaction mixture as well as isotopic exchange reactions and trapping of intermediates have shown that the precursor of **10** is a β-lithiated intermediate **11**[29].

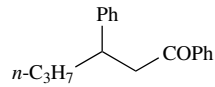
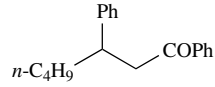
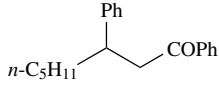
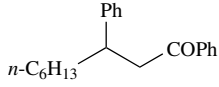
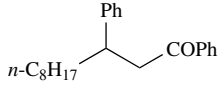
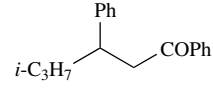
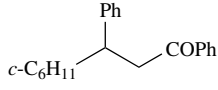
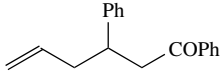
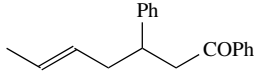
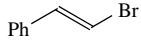
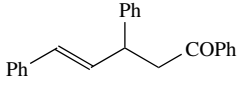
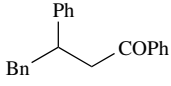
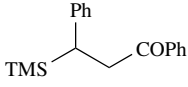
Addition of an electrophile to the reaction mixture, followed by allowing the reaction to stand at 20 °C until decoloration of the solution was observed (2–8 h, depending on RX), gave the β-substituted dihydrochalcone **12** in yields ranging from 77% to 100% (Scheme 8). The tandem reaction works well with alkyl chlorides as well as with bromides; primary halides gave high yields of the substituted products even for relatively long normal chains (e.g. $C_8H_{17}Br$). Hindered alkyl bromides, such as isopropyl and cyclohexyl, also gave good results (80 and 100%, respectively) and allyl, vinyl and TMS β-substituted dihydrochalcones could be easily obtained in 77–100% yields (Table 2).



SCHEME 8

As part of an ongoing effort to extend the scope of this methodology, we investigated the influence of both the α,β-unsaturated aldehyde structure and the organolithium structure on the formation of the tandem product. Aliphatic α,β-unsaturated aldehydes as well as aliphatic lithium reagents failed to afford the tandem reaction,

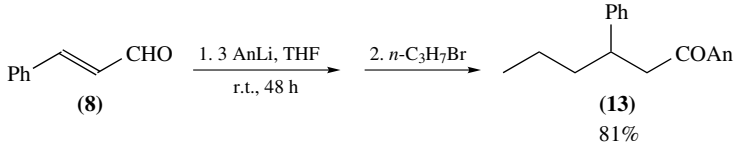
TABLE 2. Tandem addition–β-lithiation–electrophilic substitution

RX	β-Substituted dihydrochalcone	% Yield [a]
n-C_3H_7Br		91
n-C_4H_9Br (Cl)		83 (100)
n-$C_5H_{11}Br$		92
n-$C_6H_{13}Br$		88
n-$C_8H_{17}Br$		99
i-C_3H_7Br		100
c-$C_6H_{11}Br$		80
CH_2=$CHCH_2Br$ (Cl)		95 (80)
CH_3CH=$CHCH_2Cl$		77
		100
BnBr (Cl)		81 (80)
TMSCl		98

[a] Determined by quantitative GC using decalin as internal standard.

giving mostly the regular adduct, while aromatic lithium reagents, such as o-anisyllithium (AnLi = 2-methoxyphenyllithium), gave good yields of product **13** (Scheme 9).

This one-pot sequence readily creates a wide variety of β-substituted dihydrochalcones besides a new carbon–carbon bond, opening up a new methodology in organic synthesis. As far as we know, this is the only report of this kind of tandem methodology found

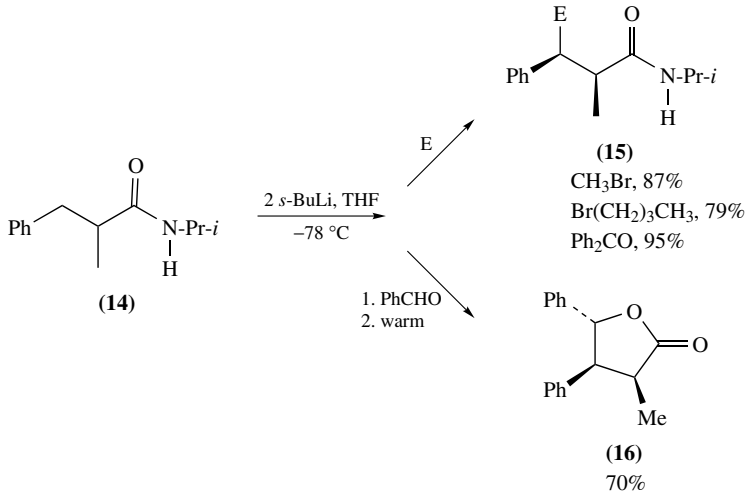


SCHEME 9

in the literature. Further work is under way to obtain enantiomerically enriched β-alkyl substituted dihydrochalcones by this approach.

A different approach to tandem sequences of lithiation–substitution are those reactions involving deprotonation–substitutions, which are usually governed by the formation of a complex between an organolithium reagent and a functional group prior to a deprotonative directed lithiation. This effect has been termed the complex induced proximity effect (CIPE)[30,31]. The CIPE rationalizes the regio- and stereo-chemistry of reactions of organolithiums with organic precursors involving functionalities such as C=O or P=O and has been advocated to promote β-substitution[32,33]. Several coordination complexes were structurally characterized using different techniques such as X-ray diffraction[34] and NMR[35,36] spectroscopy, among others. The proximity between the organolithium reactant and the reactive group induces, in several cases, a favorable transition structure for the formation of an unexpected product[37].

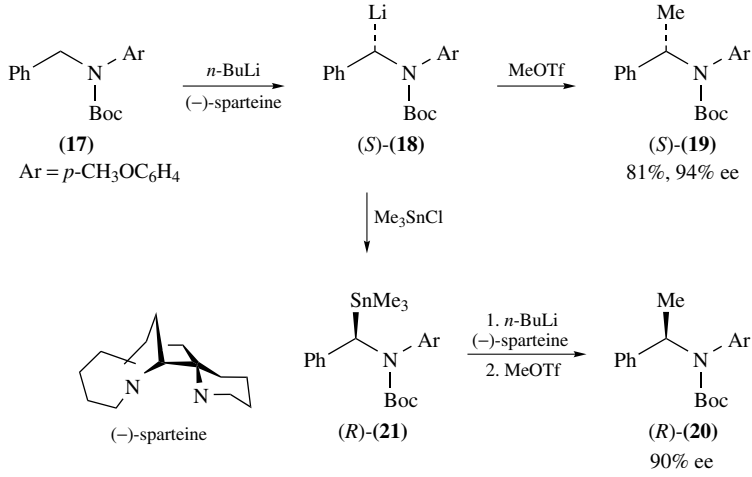
When the lithiation–substitution methodology was applied to α-methyl-β-aryl secondary amides, the lithiation occurred regioselectively at the β-position, and the resulting lithiated intermediate reacted with a range of electrophiles to give substituted products with excellent diastereoselectivity (Scheme 10)[38]. It was reported that the regioselective β-lithiation of *N*-isopropyl-3-phenylpropionamide, **14**, followed by reaction with an electrophile E provided **15** as a single diastereomer. The reaction of **14** with benzaldehyde to give **16** illustrates the potential of this tandem reaction for the synthesis of three contiguous stereogenic centers in a single transformation.



SCHEME 10

Chiral ligand-mediated lithiation–substitution sequences to promote stereoselectivity in pro-chiral compounds have been exploited widely over the past decade[25]. An asymmetric deprotonation carried out by the organolithium can be the enantio-determining step, or an asymmetric substitution as a postdeprotonation step. (−)-Sparteine, a readily available alkaloid, has been extensively used in this type of stereoselective transformation, giving high yields of enantiomeric excess.

As an example, it is worth mentioning the excellent enantioselectivity observed in the lithiation–substitution of *N*-Boc-*N*-benzylamine, **17** (Boc = *tert*-butoxycarbonyl), which was attributed to an asymmetric deprotonation. It was reported that the reaction of **17** with *n*-BuLi in the presence of (−)-sparteine, followed by reaction with methyl triflate, gave (*S*)-**19** with high enantiomeric excess. On the contrary, stannylation of the intermediate **18** gives (*R*)-**21** with inversion of configuration, which by treatment with *n*-BuLi/(−)-sparteine, followed by methyl triflate, produces the opposite enantiomer of **19**, (*R*)-**20** (Scheme 11)[39].

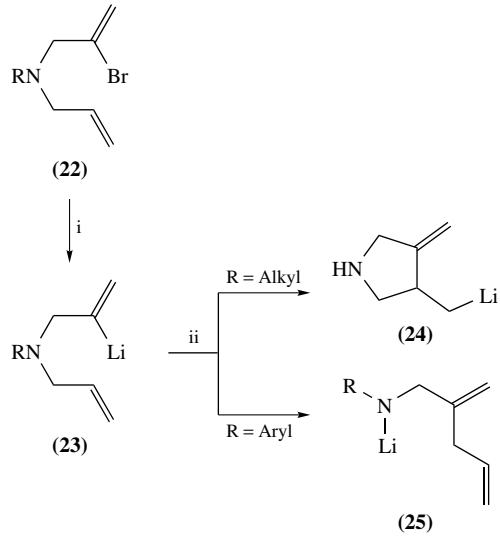


SCHEME 11

The carbolithiation of alkenes and alkynes is a useful transformation for the generation of a new carbon–carbon bond, specially when the alkenes and alkynes are activated by conjugation to carbonyl and related electron-withdrawing groups. Similarly to the intramolecular carbolithiation, it is possible to carry out this reaction with high diastereoselectivity.

Organolithium reagents usually react as nucleophiles toward polarized multiple bonds, the addition to carbonyl compounds being a classical example of this process[40]. As a consequence of that, the addition to a non-polarized carbon–carbon double bond, the so-called carbolithiation[41], is not a simple reaction. However, from a synthetic point of view, the carbolithiation is an interesting process because a new organolithium reagent is formed, which can react with a typical electrophile to introduce an electrophilic fragment in the new backbone. It means that through the mentioned tandem process it is possible to modify both the carbon chain and the functionality in one tandem operation.

Barluenga and coworkers[42] studied in recent years the behavior of 2-lithioallyl and 2-lithioaryl amines, as well as of 2-lithioaryl ethers[43], in their anionic cyclizations onto unactivated double bonds. They reported the effect of different substituents at the terminal

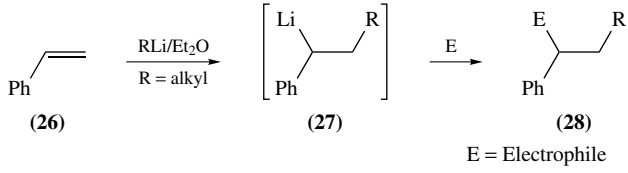


Reagent and conditions: (i) *t*-BuLi (2 eq.), Et_2O, −78 °C; (ii) TMEDA, −78 to 20 °C

SCHEME 12

position of the allyl moiety in the intramolecular carbolithiation reaction of *N*-allyl-*N*-2-lithioallylamine derivatives **23** (obtained from **22**) affording products such as **24** and **25** (Scheme 12).

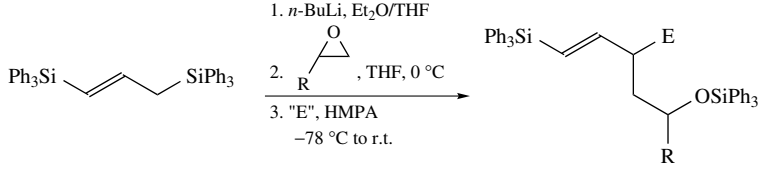
The synthetic potential of the carbolithiation reaction of unactivated alkenes lies in the fact that both a new carbon−carbon bond and organolithium compound are generated in tandem[44]. The newly generated organolithium species may then be exploited for further *in situ* transformations. An inconvenient side reaction of this methodology is the anionic polymerization process, which could propagate if the generated organolithium reacts with another molecule of alkene. However, it has been reported[45] that with diethyl ether as solvent, at low temperature, the anionic polymerization is avoided, and the organolithium is synthetically available for further transformations. Employing these conditions, addition of alkyllithiums at styrene **26** terminal carbon and subsequent trapping of the intermediate **27** with several electrophiles result in the formation of alkyl-substituted benzenes **28**[44] (Scheme 13).



SCHEME 13

The tandem carbolithiation−rearrangement of silyl derivatives constitutes also a useful synthetic methodology. The carbon−carbon bond formation is triggered by anionic rearrangement of a silyl group from carbon to oxygen and constitutes a new methodology for

the construction of complex organic molecules[46,47]. Accordingly, Oshima and coworkers[48] have recently reported that in the reaction of 1,3-bis(triphenylsilyl)propene **29** with butyllithium, followed by ethylene oxide, an HMPA-induced anionic 1,4-rearrangement of a silyl group from carbon to oxygen took place, giving rise to an allylic lithium intermediate. The intermediate could be trapped in a one-pot reaction by various electrophiles to provide the corresponding adducts **30** and **31** as regioisomeric mixtures (Scheme 14).

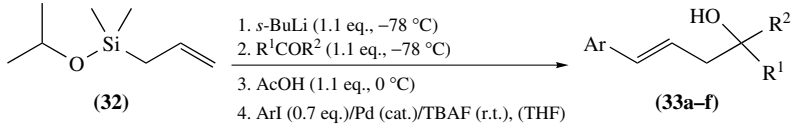


(29) **(30)** + **(31)**

R = H	E: PhCH(OH),	50%
	E: *n*-C_6H_{13}(OH),	39%
	E: CH_3,	50%
	E: $CH_2{=}CH_2$,	51%
R = CH_3	E: PhCH(OH),	52%
R = Ph	E: PhCH(OH),	52%
R = *n*-C_4H_9	E: PhCH(OH),	35%

SCHEME 14

Li and Navasero[49] reported a two-step method that involves the synthesis of vinylsilane from allyl(isopropoxy)dimethylsilane, **32**, and the subsequent Pd-catalyzed cross-coupling of the resulting vinylsilane. The strategy was applied to the synthesis of disubstituted homoallylic alcohols, **33a–f. 32** was treated with *s*-BuLi, followed by reaction with the corresponding aldehyde or ketone, subsequent neutralization with AcOH and treatment with ArI/I_2/$Pd_2(dba)_3$. When iodobenzene was used with $Pd_2(dba)_3$ as catalyst, disubstituted homoallylic alcohols **33a–c** were obtained in 62 to 87% yields. In the case of 2-iodoanisole, with $(allylPdCl)_2$ as catalyst, the alcohols **33d–f** were obtained in 41 to 71% yields (Scheme 15).



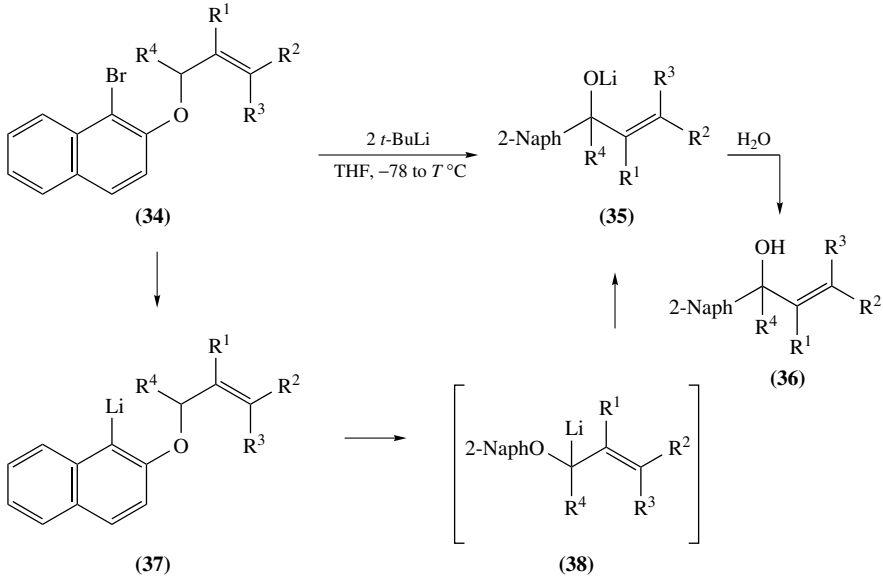
(32) **(33a–f)**

Pd(cat) = $Pad_2(dba)_3$, allylPdCl

(a) $R^1 = R^2 = CH_3$, Ar = Ph
(b) $R^1 = R^2$ = *c*-Hex, Ar = Ph
(c) $R^1 = CH_2CH_2Ph$, R^2 = H, Ar = Ph
(d) $R^1 = R^2 = CH_3$, Ar = 2-$MeOC_6H_4$
(e) $R^1 = R^2$ = *c*-Hex, Ar = 2-$MeOC_6H_4$
(f) $R^1 = CH_2CH_2Ph$, R^2 = H, Ar = 2-$MeOC_6H_4$

SCHEME 15

Barluenga and coworkers[50] have recently reported the transformation of 2-lithioaryl allyl and benzyl ethers into allyl and benzyl alcohol derivatives through a tandem anion translocation-[1,2]-Wittig rearrangement. The initial organolithium compounds, **37**, generated by treatment of the allyl and benzyl 1-bromo-2-naphthyl ethers, **34**, with *t*-BuLi, underwent an anion translocation process generating new lithium derivatives, **38** (Scheme 16).



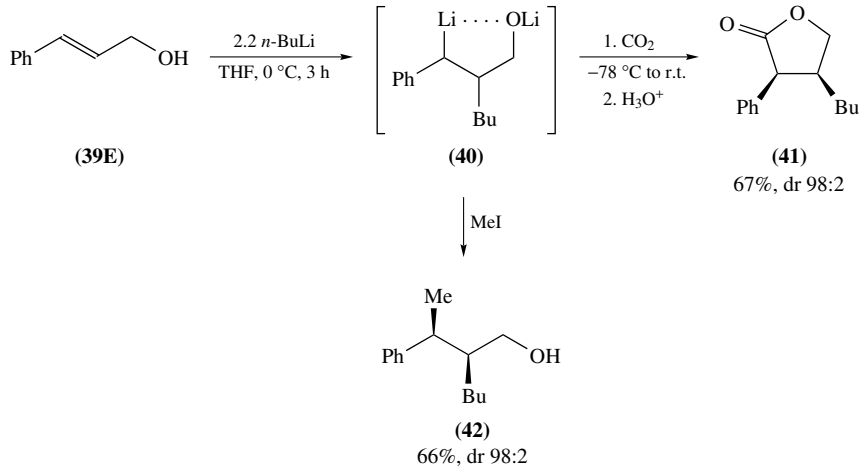
SCHEME 16

The Wittig rearrangement of these anions afforded the alkoxides **35**, which upon hydrolysis produced the alcohols **36**. This type of reaction constitutes an alternative to new organolithium compounds that are difficult to obtain by traditional methods.

The addition of organolithiums to allylic alcohols followed by trapping of the intermediates by electrophiles is a good example of the usefulness of this type of carbolithiation. The sequence leads, generally, to the formation of diastereomeric alcohols, but the use of chiral ligands confers enantioselectivity to the tandem reaction.

The addition of alkyllithiums to allylic alcohols has been of a great deal of interest in recent years[51]. The products **41** or **42** could be obtained via **40** in a diastereomeric ratio of 98:2 by treatment of the (*E*)-cinnamyl alcohol, **39E**, with *n*-BuLi and quenching of the resulting solution with CO_2 or MeI, respectively (Scheme 17)[52].

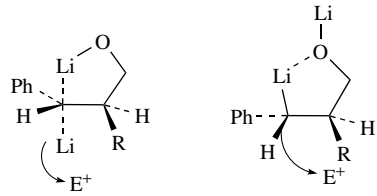
The high *syn*-selectivity seems to be independent of the stereochemistry of the starting material, since the use of **39Z** also resulted in the preferential formation of the *syn*-isomer in a similar ratio. To explain this, the authors proposed 5-membered cyclic benzyllithium species having a sp^2-like carbon to which two lithium atoms coordinate from both upper and lower sites as shown in **43** (Scheme 18). Such a dilithiated species would selectively react with electrophiles from the opposite site of the O−Li substituent. Another intermediate, **44**, in which the benzylic lithium is coordinated with the heteroatom, may also be considered[53]. Both intermediates are likely, since in each of them the steric hindrance between the phenyl group and the alkyl group is minimal. Assuming that the reaction with



(39E) **(40)** **(41)**
67%, dr 98:2

(42)
66%, dr 98:2

SCHEME 17



(43) **(44)**

SCHEME 18

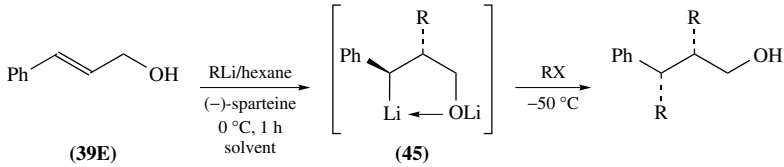
an electrophile takes place under retention of the configuration at the benzylic carbon, then the product should be formed through the hetero-chelated diastereomer **44**. From the theoretical point of view the activation barriers for retentive and inverse attack at the benzylic carbon will not differ very much[54].

It was observed that when chiral ligands are used, the sterochemistry of the olefin is crucial for the enantioselectivity of the carbolithiation. Thus, asymmetric carbolithiation of **39E** with *n*-BuLi in the presence of (−)-sparteine gives the carbometallated product (*S*)-**46** and compounds **47–49** in *ca* 80%ee (Scheme 19)[55].

Primary as well as secondary alkyllithiums lead to identical enantioselection. Whereas the asymmetric carbolithiation of **39E** gives the (*S*)-alkylated product **46**, the reaction of the **39Z** leads to (*R*)-**51** or (*R*)-**52** (Scheme 20). When the allylic alcohol is unsubstituted a racemic product is formed, as is the case with 2-propen-1-ol, **52**.

It is presumed that the initial step for the intermolecular as well as intramolecular carbolithiation is an energetically favorable coordination of the lithium atom with the π-system, which serves to establish the geometry of the system prior to addition. The chiral benzylic organolithium compound **45**, obtained after the carbolithiation step, reacted diastereoselectively with a number of electrophiles, yielding a formal inversion of the configuration.

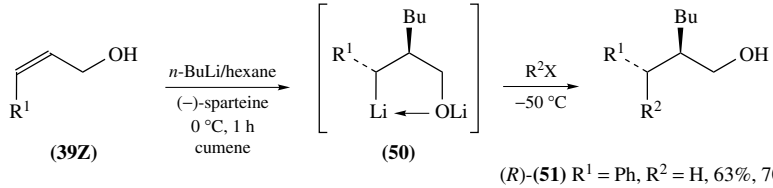
The tandem reactions involving metal enolates constitute important methods for the construction of carbon−carbon bonds[56]. LDA has attained a prominence in organic chemistry



(39E) **(45)**

hexane: (*S*)-**(46)** R = *n*-Bu, R = H, 81%, 78% ee
cumene: (*S*)-**(46)** R = *n*-Bu, R = H, 82%, 80% ee
(47) R = *s*-Bu, R = H, 65%, 72% ee
(48) R = *n*-Bu, R = PhS, 61%, 83% ee
(49) R = *n*-Bu, R = Me, 63%, 82% ee

SCHEME 19



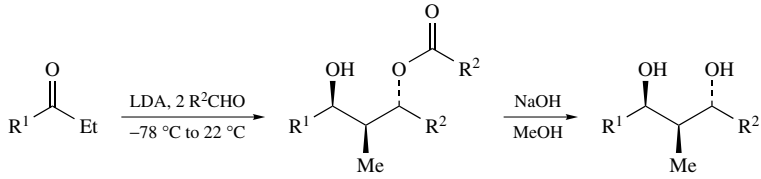
(39Z) **(50)**

(*R*)-**(51)** R^1 = Ph, R^2 = H, 63%, 70% ee
(52) $R^1 = R^2$ = H, 64%, 0% ee
(53) R^1 = Ph, R^2 = PhS, 60%, 40% ee

SCHEME 20

enjoyed by a very few reagents, playing a central role in the generation of enolates and related carbanions[57]; there are several reports that describe stereoselective reactions of lithium ketone enolates[58,59]. Woerpel and coworkers[60] have reported the tandem aldol-Tischenko reaction of lithium enolates, which is a simple method for the synthesis of polyoxygenated organic compounds. Three or five stereocenters were created in a single operation with high stereoselectivity.

When the lithium enolates of ketones **54**, generated with LDA, were treated with 2.2 equivalents of various aldehydes at −78 °C followed by warming to 22 °C, the acetates **55** were obtained; hydrolysis provided the diols **56** with a defined stereochemistry with high diastereomeric excess (de>98%) (Scheme 21). The authors conducted several experiments

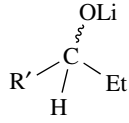


(54) **(55)** **(56)**

(a) R^1 = Ph, R^2 = Me **(d)** R^1 = *i*-Pr, R^2 = Ph
(b) R^1 = Ph, R^2 = Et **(e)** R^1 = *i*-Pr, R^2 = *i*-Pr
(c) R^1 = Ph, R^2 = *i*-Pr

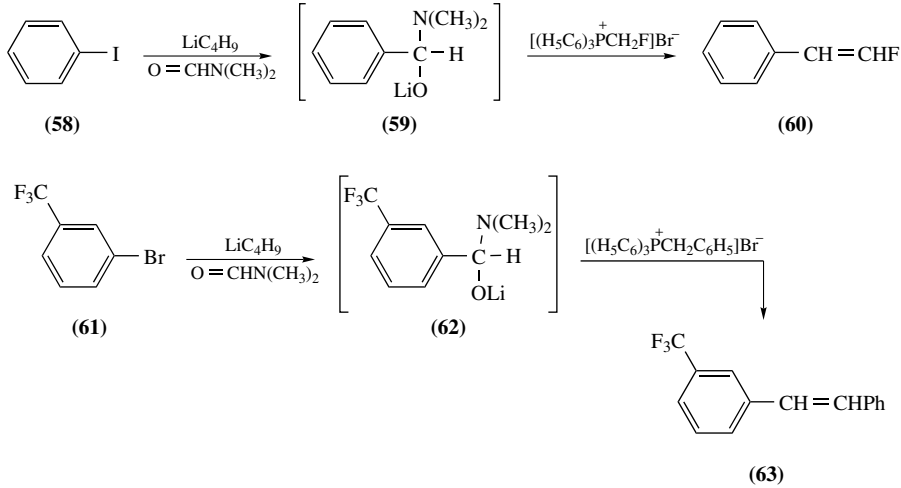
SCHEME 21

to provide insight into the reaction mechanism, and demonstrated that neither the stereochemical relationship of the products nor the nature of the alkyl group is dependent upon the structure of the aldolate, **57**. In addition, the reduction step is slower than aldol addition. The authors concluded that the high stereoselectivity of this reaction can be rationalized by a mechanism involving reversible aldol addition and hemiacetal formation, followed by rate- and stereochemistry-determining hydride transfer from a lithium hemiacetal.



(57)

The nucleophilic addition of an organolithium reagent to a *N*,*N*-disubstituted amide gives an aminoalkoxide intermediate which is generally unstable, giving rise to aldehydes or ketones by decomposition. Schlosser and coworkers[61] used this reaction in a tandem sequence for the synthesis of substituted olefines, by *in situ* addition of phosphorous ylides. The adduct **59** of phenyllithium (from iodobenzene **58** and *n*-BuLi) with *N*,*N*-dimethylformamide afforded *ω*-fluorostyrene **60** (*Z*/*E* 50:50) in excellent yield (87%). The same methodology was applied for the preparation of 3-(trifluoromethyl)stilbene **63** (85%, *Z*/*E* 41:59) starting with 3-bromobenzotrifluoride, **61**, via **62** and benzyltriphenylphosphonium bromide (Scheme 22)[62].



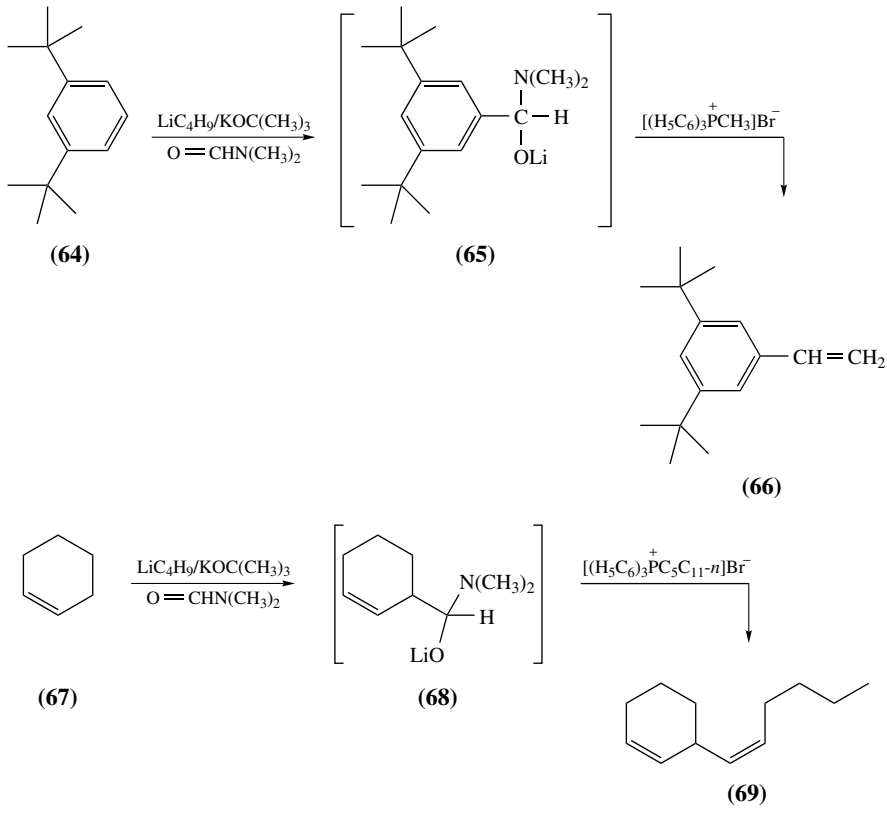
(58) **(59)** **(60)**

(61) **(62)** **(63)**

SCHEME 22

Highly reactive lithium alkoxides are the so-called superbases, SBs. Heavy alkali metal alkoxides undergo a metal interchange with organolithium species, giving rise to heavy alkali metal organic compounds and lithium alkoxides; these types of systems are denominated superbases due to increased reactivity of the organolithium compound[63, 64]. The use of SBs have been demonstrated, e.g. in the metalation[65] of 1,3-di-*tert*-butylbenzene **64** with *n*-BuLi; subsequent addition of *N*,*N*-dimethylformamide to give

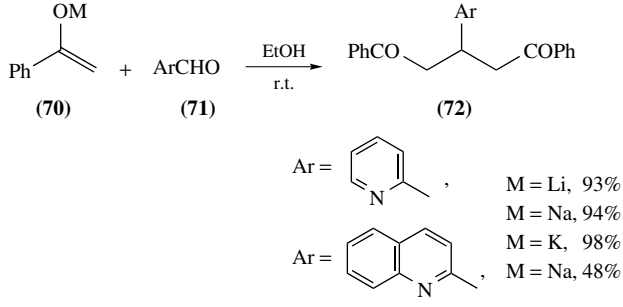
65 and methyltriphenyl-phosphonium bromide gave 3,5-di-*tert*-butylstyrene (**66**) in 85% yield. The (*Z*)-3-(1-hexenyl)cyclohexene (**69**) (51%, *Z*/*E* 97:3) was obtained in a similar reaction sequence employing cyclohexene **67**, via the reaction intermediate **68**, and hexyltriphenylphosphonium bromide as main components (Scheme 23).



SCHEME 23

The Michael reaction involves the addition of a nucleophilic carbon species to an electrophilic multiple bond. The electrophilic partners are typically α,β-unsaturated ketones, esters or nitriles, but other electron-withdrawing substituents can be used to activate the carbon−carbon double bond to nucleophilic attack. A tandem aldol-Michael reaction has been recently described. Wachter-Jurcsak and coworkers[66] reported that the reactions involving 2-pyridinecarboxaldehyde, **71**, and 2-quinolinecarboxaldehyde with the enolates of acetophenone, **70**, afforded the unexpected symmetric 1,5-diphenyl-3-(2-heteroaryl)-1,5-pentanediones (Scheme 24).

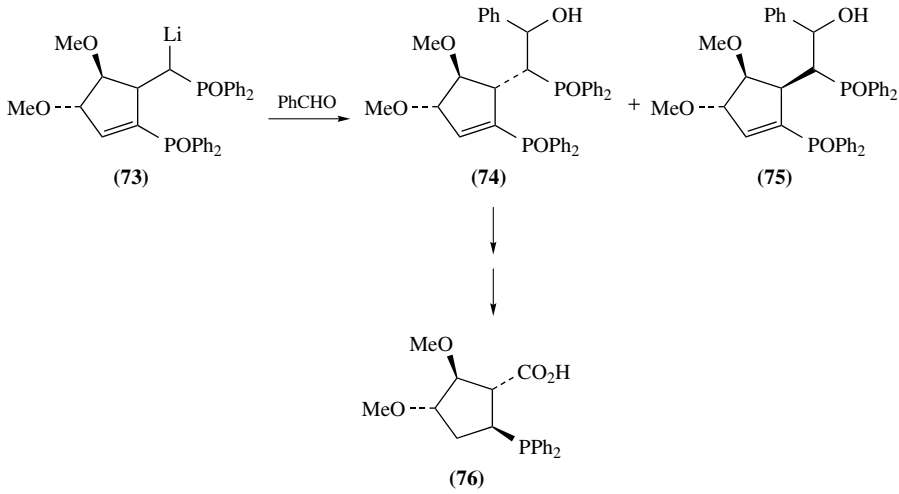
The authors explained these results on the basis of an intramolecular complexation of the metal ion by the enolate, giving a conformation where the pyridinyl ring is *gauche*, rather than *anti*, to the benzoyl group. Thus, β-elimination from the chelated enolate would generate the thermodynamically less stable *cis*-alkene, which rapidly undergoes Michael addition with a second equivalent of the enolate. The addition of pyridine improved the



SCHEME 24

yields of the aldol condensation product since pyridine competes with the aldolate nitrogen for chelation of the metal ion.

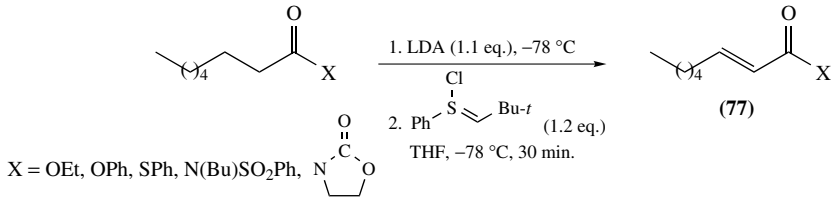
Chiral bisphosphine oxides were stereoselectively reduced to chiral *trans*- and *cis*-bisphosphines that can be useful ligands in catalytic asymmetric hydrogenation[67]. When **73** was treated with benzaldehyde, it gave a cyclized alcohol **74** and its diastereoisomer **75** in 54% and 8% isolated yields, respectively (Scheme 25)[68].



SCHEME 25

Chiral monophosphine bearing an additional functional group, such as a carboxyl, could be a more useful chiral ligand for a metal catalyst. Stereoselective reduction of **74** with superhydride ($LiBEt_3H$) in THF and subsequent Horner–Wadsworth–Emmons olefination with KH gave the corresponding monophosphine oxide. Oxidative conversion of the olefin moiety into a carboxyl group and subsequent esterification, deoxygenation of the oxide and hydrolysis gave the corresponding chiral phosphinocarboxylic acid **76** (Scheme 25). This new monophosphine was successfully applied as a chiral and functionalized monophosphine ligand in a palladium-catalyzed asymmetric allylic alkylation[69,70].

Matsuo and Aizawa[71] have recently reported a new tandem reaction based on the dehydrogenation of ketones to the corresponding α,β-unsaturated ketones, **77**. They employed



SCHEME 26

LDA to generate the corresponding lithium enolate, followed by treatment with *N*-*t*-butylbenzenesulfinimidoyl chloride in THF at −78 °C (Scheme 26).

Matsuo's methodology was applied to several acid derivatives, such as carboxylic esters, thioesters, and amides, with moderate to high yields. Dehydrogenation of carboxylic acid derivatives to the corresponding α,β-unsaturated compounds is an important organic transformation in living organisms as well as in organic synthesis, though direct dehydrogenation of such compounds by noenzymatic (chemical) methods had not been previously achieved[71].

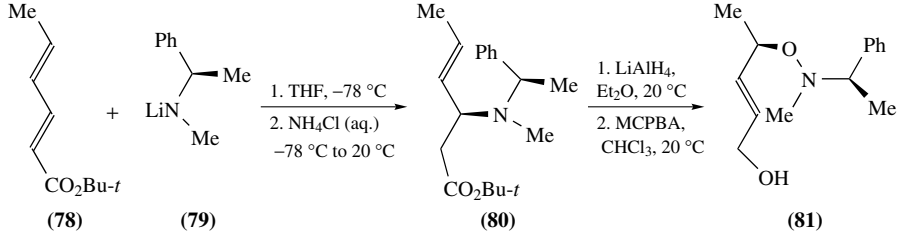
C. Carbon−Heteroatom Bonds

Among organolithium reagents, lithium dialkylamides are frequently used as highly reactive and selective bases for the formation of a wide range of stabilized carbanions, and they have also played a prominent role in the development of carbon−carbon bond-forming reactions. In the search of novel methods to achieve stereoselective C−C bond formation, chiral lithium amides appear as very useful tools. They have been used, e.g. in asymmetric alkylation reactions[72] and in tandem addition−cyclization protocol for asymmetric synthesis[73]. Other lithium amides, such as LDA or LiTMP (lithium 2,2,6,6-tetramethylpiperidide), have been also used to carry out this type of tandem protocol.

The addition−rearrangement constitutes a normal tandem protocol to carry out enantioselective synthesis; organolithium compounds and lithium amides are frequently used in the addition step. Special attention is being paid to the preparation of chiral allylic amines suitable for undergoing a stereospecific Meisenheimer rearrangement. A way to prepare such amines in high enantiomeric purity is to employ the highly diastereoselective conjugate addition to α,β-unsaturated esters of secondary lithium amides derived from α-methylbenzylamine[74]. Thus, the lithium derivative of the *N*-methyl-α-methylbenzylamine **79** was added to the unsaturated ester **78**, which then underwent a Meisenheimer rearrangement. The rearrangement consists of migration of one of the substituents of the tertiary amine *N*-oxide from nitrogen to oxygen, resulting in an *O*-substituted hydroxylamine[75]. If the migration is of an allyl group, the rearrangement is usually a [2,3]-sigmatropic shift[76]. There are not many examples of asymmetric Meisenheimer rearrangements of chiral allylic amine *N*-oxides reported in the literature[77].

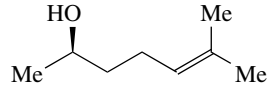
Davies and Smyth[78] have reported a sequence consisting of a highly stereoselective conjugate addition followed by a stereospecific Meisenheimer rearrangement, which affords alcohols in high enantiomeric excess. Accordingly, the conjugate addition of (*R*)-lithium *N*-methyl-(α-methylbenzyl)amine, **79**, to *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate, **78**, gives the ester **80**. Reduction of **80** to the corresponding alcohol afforded a substrate which, upon oxidation, undergoes a stereospecific Meisenheimer rearrangement to give a single diastereomer of the corresponding trialkylhydroxylamine **81** (Scheme 27)[79].

As usual, if the steric bulk of the substituents on nitrogen is reduced, the yield of the sequence increases, although the diastereoselectivity of addition also somewhat



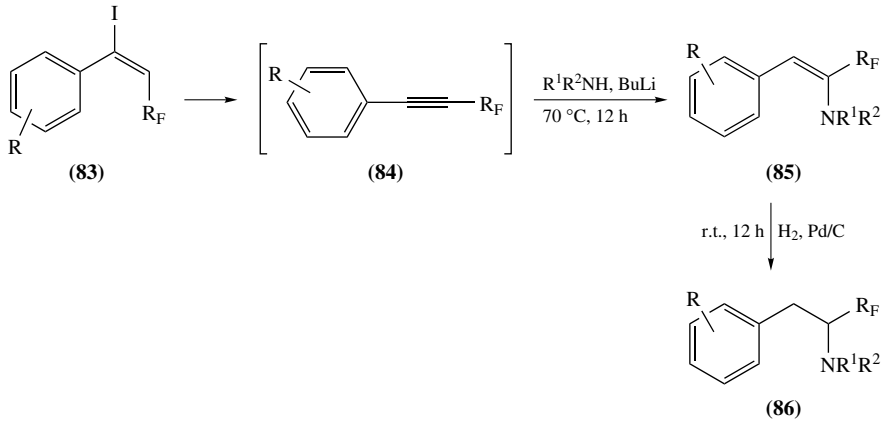
SCHEME 27

decreases. This protocol of a tandem asymmetric conjugate addition reaction and stereoselective Meisenheimer rearrangement has also been applied to the synthesis of the insect pheromone sulcatol **82** [(*R*)-6-methylhept-5-en-2-ol] from *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate[73].



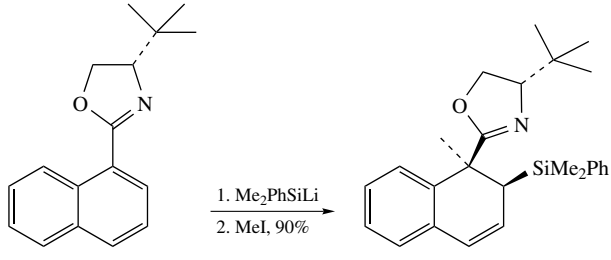
(82)

Despite the importance of amphetamines on the one hand, and fluorinated pharmaceuticals on the other hand, very little work has been done toward the synthesis of fluorinated analogues of amphetamines[80]. A three-step synthesis involving a tandem sequence was employed in the preparation of perfluoroalkylated amphetamines[80]. 1-Aryl-1-iodo-2-(perfluoroalkyl)ethylenes, **83**, were generated by treatment of perfluoroalkyl iodides with several arylalkanes and di-*t*-butyl peroxide. The dehydroiodination of **83**, in the presence of *n*-BuLi, and reaction *in situ* with secondary amines of the formed 1-perfluoroalkyl-2-arylacetylene, **84**, renders 2-aryl-1-perfluoroalkyl enamines, **85**. Subsequent reduction of **85** affords the amphetamine derivative, **86** (Scheme 28). Several 1-aryl-1-iodo-2-(perfluoroalkyl)ethylenes (aryl = phenyl, 3-MeC_6H_4, 4-$F_3CC_6H_4$) and secondary amines were employed in the one-pot sequence, with moderate to good yields (20 to 63%).



SCHEME 28

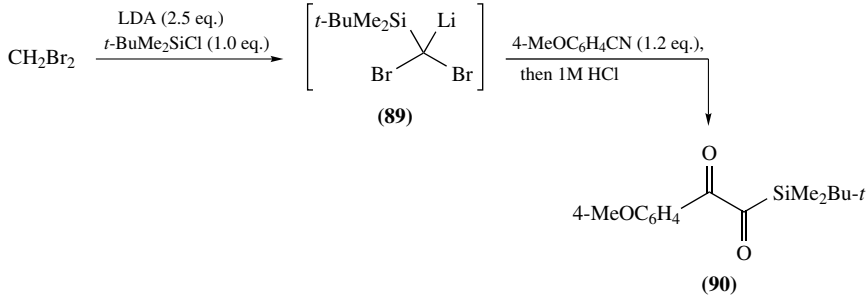
The pharmacological importance of the 2-aminotetralin (2-amino-1,2,3,4-tetrahydronaphthalene) structure has been known for a long time[81]. Meyers and coworkers[82] have recently developed an interesting tandem methodology for the synthesis of 2-aminotetralins, in which the first step is the highly diastereoselective conjugate addition of dimethylphenylsilyllithium to chiral naphthyloxazoline **87**. Electrophilic trapping of the resulting aza-enolate afforded the tandem addition product **88** in high yields as a single diastereomer (Scheme 29). The authors proposed that the silicon served as a surrogate, first for oxygen and later for nitrogen. As oxygen anions are not sufficiently nucleophilic to undergo the tandem addition reaction to naphthyloxazolines, this represents a convenient entry into this important class of compounds[83].



(87) **(88)**

SCHEME 29

Yagi and coworkers[84] reported the preparation of α-keto acylsilanes in a one-pot operation. To a mixture of dibromomethane and *tert*-butyldimethylsilyl chloride in THF, LDA was added at $-78\,^{\circ}C$, forming *tert*-butyldimethylsilyldibromomethyllithium, **89**. To the resulting mixture 4-methoxybenzonitrile was added. Quenching with 1 M HCl afforded α-keto acylsilane, **90**, in 55% yield (Scheme 30).

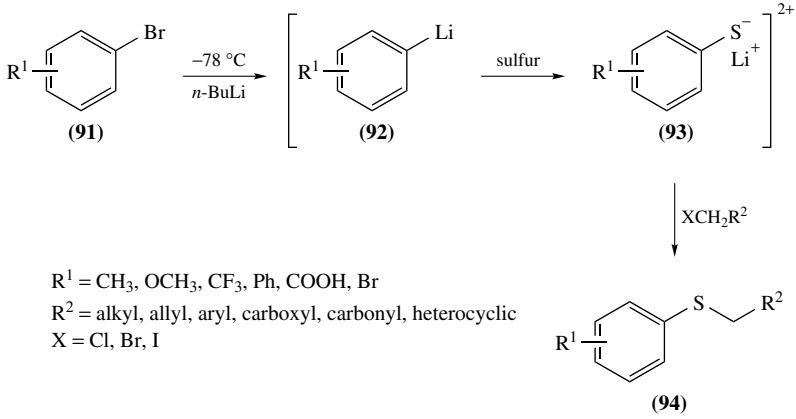


(89) **(90)**

SCHEME 30

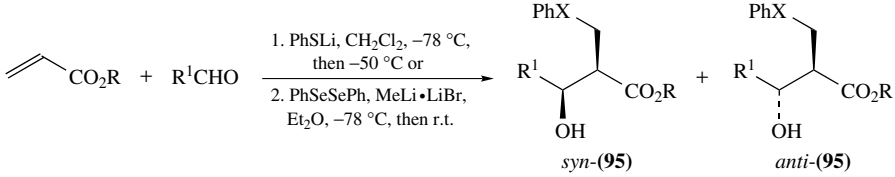
Ham and coworkers[85] have developed a one-pot synthetic method for the formation of aryl-alkyl sulfides, **94**, from various alkyl halides and lithium aryl thiolates **93**, which are prepared *in situ* from **92** formed by lithium–halogen exchange of **91**, employing *n*-butyllithium (Scheme 31). The method avoids the use of unstable arylthiols and a catalyst is not required. Several aryl bromides were successfully employed in the reaction, and the corresponding sulfides were obtained in 71 to 96% yields.

Thiolate anion and its analogues are known as good nucleophiles that quantitatively give Michael adducts. The reaction begins with the nucleophilic attack of thiolate ion



SCHEME 31

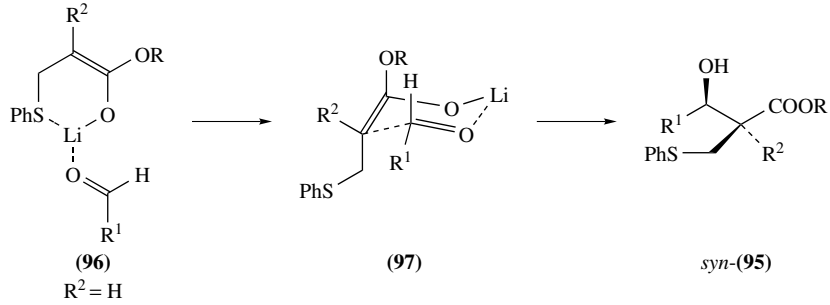
on the β-carbon of a Michael acceptor[86], generating an enolate intermediate. A tandem Michael/aldol process is achieved when the active enolate intermediate is trapped by an aldehyde[87]. The thio functional group serves as a precursor of other functional groups and/or acts as a good activator for a further carbon–carbon bond-forming reaction[88]. A three-component condensation of lithium thiophenolate, an unsaturated ester and an aldehyde afforded Michael/aldol tandem adducts, β-hydroxy-α-(1-phenylthioalkyl) esters, in moderate to good yields with a high *syn*-aldol selectivity (Scheme 32)[89]. The stereoselectivity was significantly improved using *tert*-butyl acrylate, and the tandem adducts *syn*- and *anti*-**95**, starting from other aromatic aldehydes, were prepared in similar yields with high *syn*-selectivity. Analogues of thiolates, such as lithium phenylselenolates, were found to be effective in the reaction[91].



R = Me, R^1 = Ph, X = S, 62%, *syn*:*anti* 71:29
R = *t*-Bu, R^1 = Ph, X = S, 80%, *syn*:*anti* 92:8
R = *t*-Bu, R^1 = 1-naphthyl, X = S, 92%, *syn*:*anti* 88:12
R = *t*-Bu, R^1 = Ph, X = Se, 97%, *syn*:*anti* 87:13

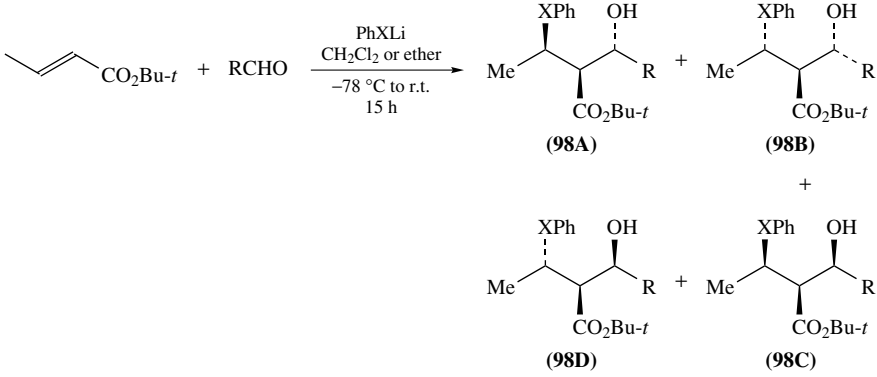
SCHEME 32

The reaction with methacrylate proceeds through a stereochemical course similar to that of the reaction of acrylates[90]. The authors explain the stereochemical course of the reaction as follows. The addition of the acrylate and the aldehyde to the suspension of the lithium thiophenolate in CH_2Cl_2 or ether dissolves the precipitate, giving a homogeneous mixture of *syn*-**95** and *anti*-**95**. The acrylate–thiolate–aldehyde complex **96** undergoes several structural changes to give the complex **97**, which selectively transforms into the aldol adduct *syn*-**95** (X = S, R^2 = H) (Scheme 33)[89].



SCHEME 33

With crotonate esters, it was observed that the presence of the β-methyl group spoiled the electrophilic reactivity: an *anti*-Michael selectivity prevailed over the *syn*-aldol selectivity (Scheme 34). The presence of three contiguous stereogenic centers in adduct **98** affords a mixture of four diastereomers (**98A–98D**), of which **98A** and **98D** were obtained as major isomers[89].



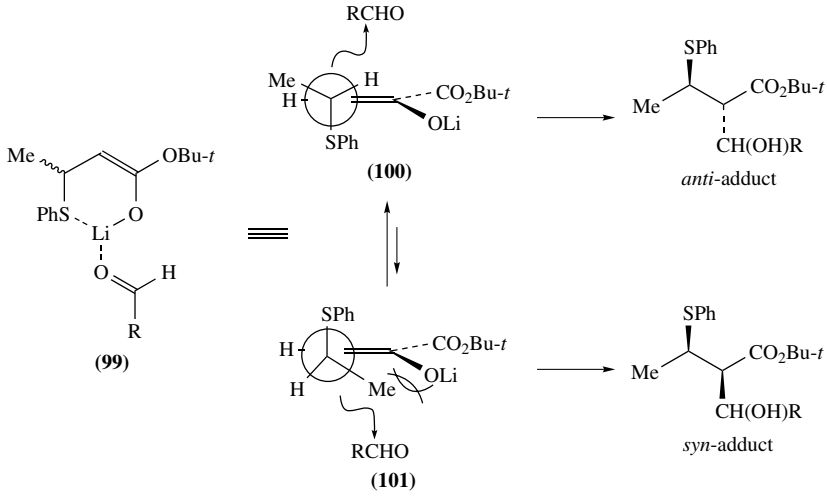
R = Ph, X = S, 55% **98A/98B/98C/98D** 53/1/45/1
R = 1-naphthyl, X = S, 60% **98A/98B/98C/98D** 75/1/15/9
R = Ph, X = Se, 62% **98A/98B/98C/98D** 56/1/42/1

SCHEME 34

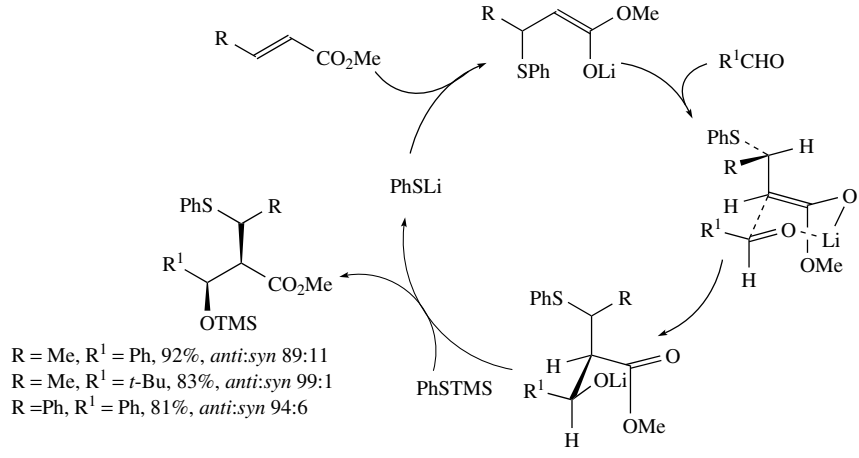
In this case, the stereochemical course of the reaction can be explained by the formation of the three-component complex **99**, which transforms into two isomers through the intermediates **100** and **101** (Scheme 35).

Due to the steric demands of the phenylthio group in conformer **100**, the aldehyde preferentially attacks the top face of the enolate giving an *anti*-Michael adduct, while with conformer **101** the aldehyde comes from the bottom face to give a *syn*-Michael adduct. Conformer **100** should be the more favorable, due to the steric repulsion between the methyl group and the oxygen atom in the enolate unit (Scheme 35).

Recently, a similar Michael-aldol tandem sequence has been reported, using *catalytic* amounts of the organolithium reagent. Reactions of α,β-unsaturated esters with aldehydes were catalyzed by 0.2 equivalents of lithium phenylthiolate in the presence of phenyl



SCHEME 35



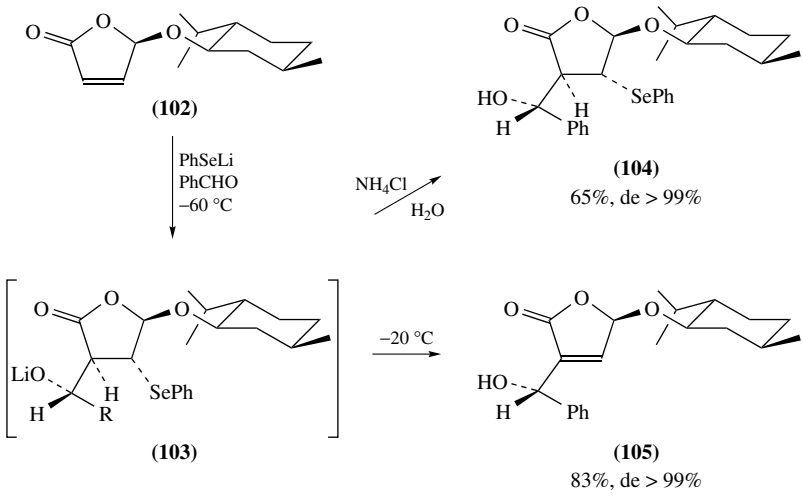
SCHEME 36

trimethylsilyl sulfide to afford *anti*-stereoselectively, and in good to high yields, the conjugate addition-aldol tandem reaction products, after protodesilylation (Scheme 36)[91].

As in the case of crotonate esters, the tandem reaction afforded a mixture of four isomers. The reaction proceeds with *anti* stereoselectivity and high yield: the best results were obtained with *t*-butylcarboxaldehyde, which gave only one isomer. With esters having *E* or *Z* configuration, the addition-aldol tandem product has the same configuration. The stereoselectivity is then the same as that observed by Kamimura and coworkers with crotonate esters, with the advantage of using catalytic amounts of the organolithium reagent[89,90].

Other tandem sequences that have drawn considerable attention over the past few years are the diasteroselective and enantioselective Baylis–Hillman reactions[92]. Chiral activated

olefins, chiral aldehydes, chiral catalysts or chiral solvents had been used, but only with moderate success at atmospheric pressure. A simple protocol for a highly diastereoselective and enantiomeric variant of the Baylis–Hillman reaction was recently reported[93]. The reaction of 4-menthyloxybutenolide, **102**, with benzaldehyde in THF, in the presence of lithium phenylselenide, apparently gave **103** which, after quenching with saturated NH_4Cl solution, gave the Michael-aldol adduct, **104**, in high yield and excellent diastereoselectivity (Scheme 37). On the other hand, simply warming the reaction mixture to −20 °C led to the Baylis–Hillman product **105**, again in excellent yield and diastereoselectivity[93].

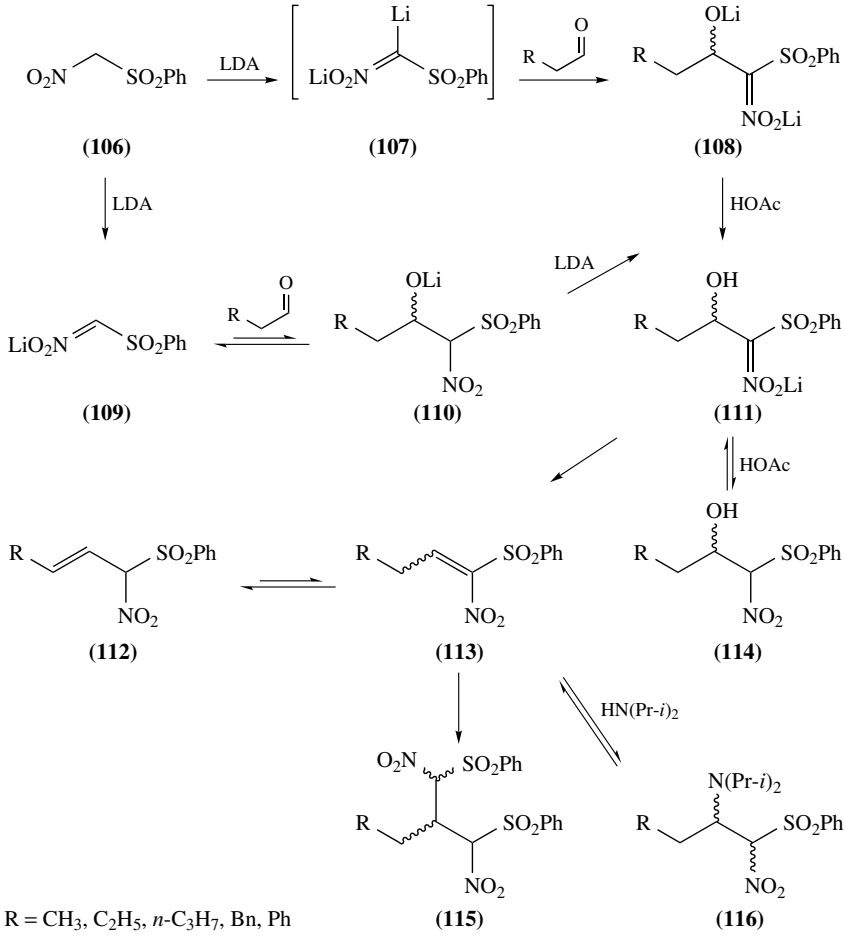


SCHEME 37

An interesting tandem nitroaldol-dehydration sequence was performed employing the dianion of phenylsulfonylnitromethane, **106**[94]. Reaction of **106** with more than 2 molar equivalents of LDA afforded the dilithium salt **107**. Condensation with unbranched aldehydes gives **108**. Another possible mechanism to give **108** is through the lithiated intermediate **109** that adds the aldehydes, giving **110**. Quenching of **108** gives **111** (in equilibrium with **114**) which, by subsequent dehydration, through **113** (in equilibrium with **116**), affords unconjugated β,γ-unsaturated α-nitrosulfones, **112**, in 52–88% yield (Scheme 38). Small amounts of the bis(α-nitrosulfones), **115**, were obtained.

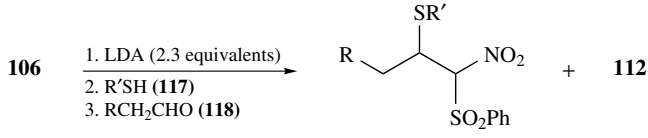
The α,β-unsaturated-α-nitrosulfone intermediate, **113**, in the tandem nitroaldol/dehydration reactions was successfully intercepted with various thiols, **117**, added to the reaction mixture prior to the addition of aldehyde, **118**. In four cases examined, little if any of **112** was formed. The initial products **119–122** were a mixture of diastereomers, although after crystallization, a single diastereomer was obtained in each case with good yields (Scheme 39).

A new synthetic route to tetraaminoethene derivatives developed by Görls and coworkers[95] involves a reduction/substitution sequence: the oxalic amidines, **123**, were reduced with lithium under sonication affording **124**, and the subsequent addition of phenyl isothiocyanate, **125**, afforded the anionic bis(thiocarbamoyl) derivatives **126**. Treatment of **126** with methyl iodide gave, in a nearly quantitative yield, the isothiourea derivative **127** (Scheme 40)[96].



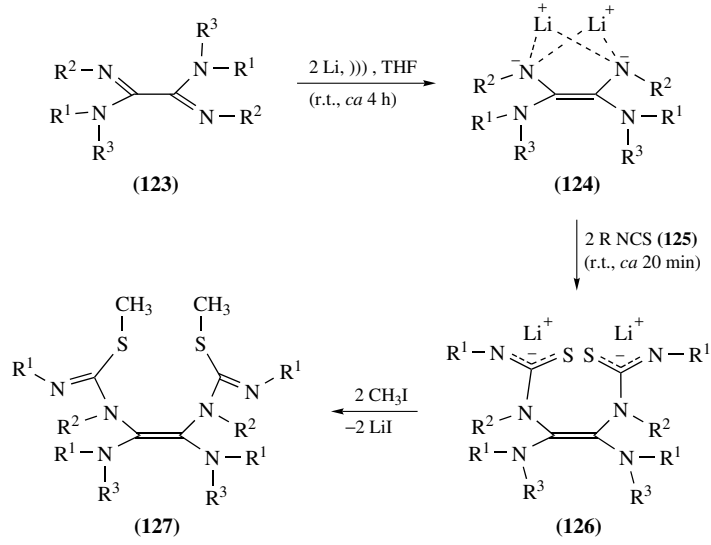
(106) (107) (108) (109) (110) (111) (112) (113) (114) (115) (116)

SCHEME 38



(119) R = CH_3, R′ = Ph
(120) R = CH_3CH_2, R′ = $PhCH_2$
(121) R = $PhCH_2$, R′ = CH_3CH_2
(122) R = R′ = Ph

SCHEME 39



SCHEME 40

It is noteworthy that in this sequence the organolithium reagent is formed *in situ* from lithium metal; there is renewed concern about reactions that occur on metal surfaces[97]. In organic synthesis, special attention is being paid to organometallic reagents that can be obtained from the direct interaction between the metal and the organic substrate[98].

III. CARBOCYCLIC COMPOUNDS

The formation of ring systems by the anionic cyclization of olefinic alkyl, aryl and vinyllithiums is an interesting synthetic transformation that provides a regiospecific and highly stereoselective route to five-membered carbocycles and heterocycles[99]. Most importantly, it is possible to functionalize the initially formed cyclization product by a tandem reaction with electrophiles, a reaction that is not generally possible in the case of radical cyclizations.

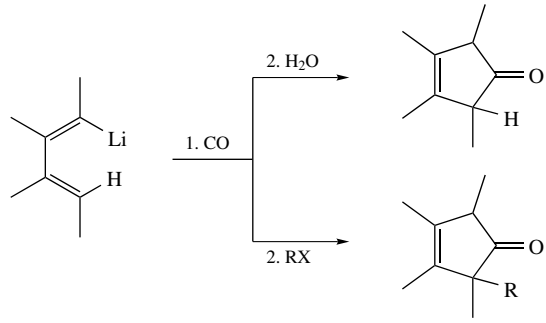
Thus, the intramolecular carbolithiation reaction allows the generation of cyclic systems during the creation of the new carbon–carbon σ-bond, making possible the preparation of functionalized carbocyclic compounds in a direct manner[100]. Among the different methodologies to generate the starting organolithium materials for the intramolecular cyclization are: (a) bromine–or iodine–lithium exchange using an alkyllithium reagent[101]; (b) sulfur–lithium exchange[102] starting from phenyl thioethers using a lithium arene; (c) tin–lithium transmetalation from tri-*n*-butylstannanes and *n*-butyllithium[103]; and (d) cyano–lithium exchange using a lithium arene in special cases[104].

A. Non-aromatic Rings

1. Single rings

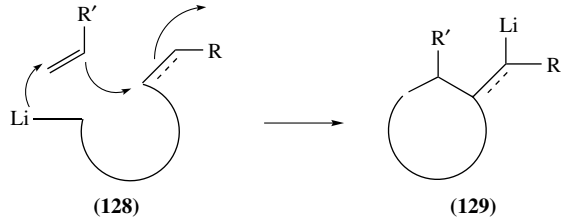
The reaction of 1,4-dilithio-1,3-dienes with CO mentioned in Section II.A constitutes a useful methodology for the tandem synthesis of substituted 3-cyclopenten-1-ones with perfect *trans* selectivity (Scheme 5)[105]. Carbolithiation of unsaturated C–C bonds is a

very important approach for construction of new C−C bonds. Conceptually, acyl-lithiation of unsaturated C−C bonds is more interesting and more useful, since not only new C−C bonds but also carbonyl groups can be introduced into the products. Song and coworkers described the intramolecular acyl-lithiation of C−C double bonds which follows carbonylation of 1-lithio-1,3-dienes with CO to afford 2- or 3-cyclopentenone derivatives in good to excellent yields after hydrolysis. Addition of electrophiles to the carbonylation reaction mixtures affords various multiply-substituted cyclopentenones (Scheme 41).



SCHEME 41

Major advances have been made in the intermolecular carbolithiation of unactivated alkenes (such as **128**) and alkynes in recent years. Wei and Taylor designed a tandem intermolecular–intramolecular carbolithiation sequence, giving rise to cyclic products, **129** (Scheme 42), using organolithium reagents as difunctional reagents[106].



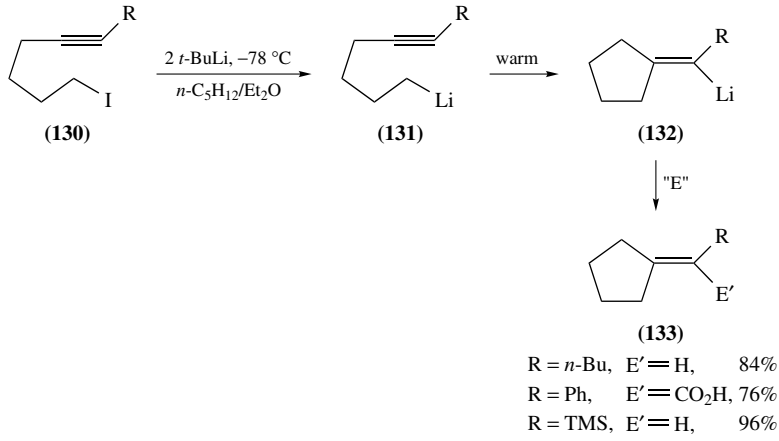
(128) **(129)**

SCHEME 42

The intramolecular addition of an anionic center (alkyl lithium) to an unactivated carbon−carbon triple bond is another example of regiospecific and stereoselective cyclizations. So this methodology constitutes an attractive alternative to other strategies of forming exocyclic alkenes like those based on radical cyclization.

Although the chemistry of anionic cyclizations of organolithium moieties derived from acetylenic systems has been less investigated[38], studies of some acetylenic alkyllithiums, e.g. **131** (formed from **130**), have shown that the ring closure proceeds in a regiospecific and highly stereoselective *syn*-fashion to give exocyclic vinyllithiums **132** (Scheme 43).

The exocyclic vinyllithium (**132**, R = H) produced by cyclization of a 5-hexynyllithium could be trapped by reaction with electrophiles to deliver synthetically useful functionalized derivatives, e.g. **133**, in good to excellent isolated yields (60–90%). The stereochemical requirements for the preferred *5-exo* ring closures of 5-hexynyllithium are in agreement with a chair-like transition state complex.



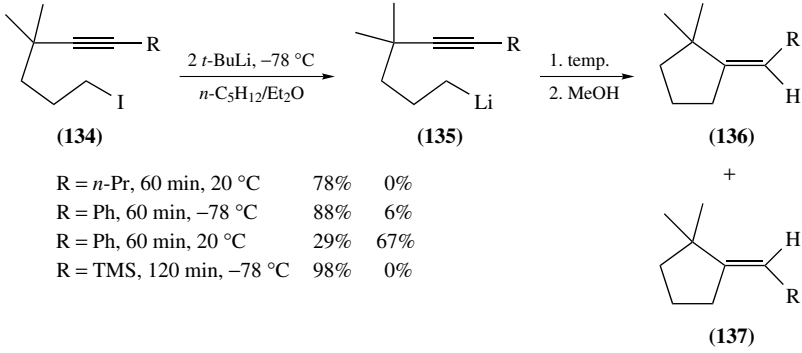
(130) **(131)** **(132)**

(133)

R = *n*-Bu, E′ = H, 84%
R = Ph, E′ = CO_2H, 76%
R = TMS, E′ = H, 96%

SCHEME 43

As is illustrated in Scheme 44, cyclization of a 4-substituted 5-hexynyllithium, **135** (formed from **134**), could yield either the *Z*-isomer **136** or the *E*-isomer **137**, or even their mixture, depending on the nature of R and the cyclization conditions. At low temperatures, the isomerization of the intermediate **132** does not take place, and **136** is obtained as the only or main product.



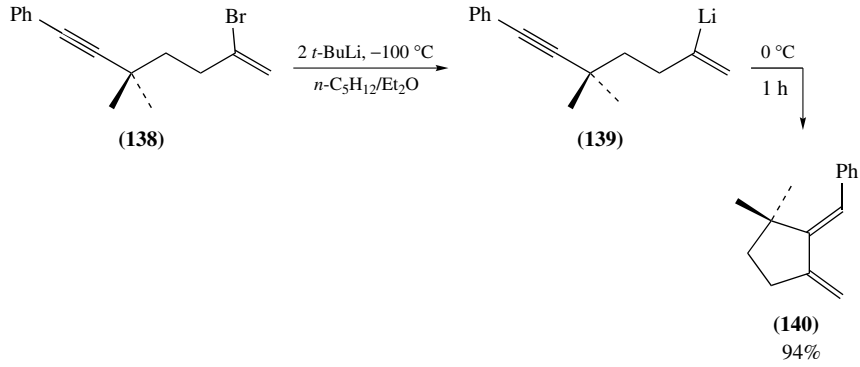
(134) **(135)** **(136)**

R = *n*-Pr, 60 min, 20 °C	78%	0%
R = Ph, 60 min, –78 °C	88%	6%
R = Ph, 60 min, 20 °C	29%	67%
R = TMS, 120 min, –78 °C	98%	0%

(137)

SCHEME 44

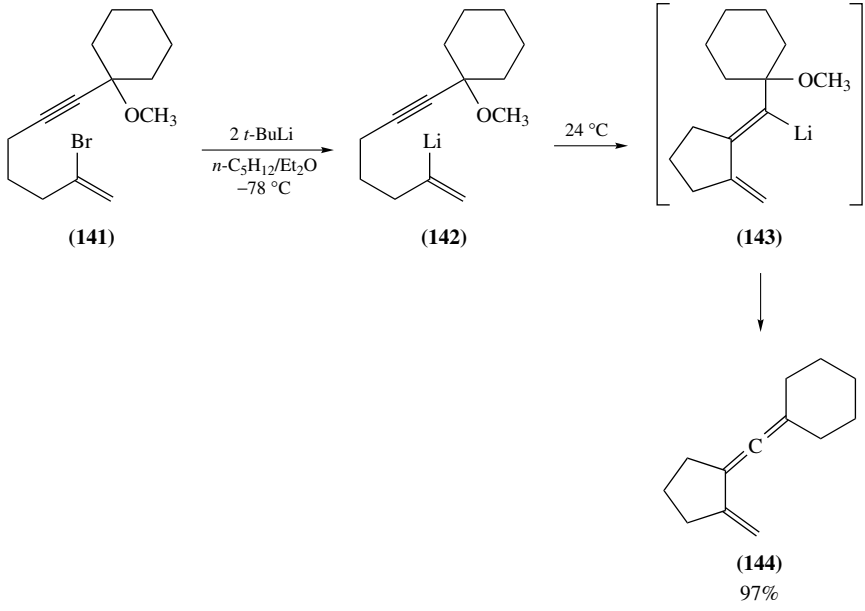
If the molecule contains a vinyl-lithiated functionality and the triple bond, the reaction product is a bis-exocyclic 1,3-diene, which can be used as a precursor of polycyclic compounds through a Diels–Alder reaction, providing a diastereoselective route to polycyclic ring systems[107]. Isomerically pure conjugated bis-exocyclic 1,3-dienes **140** were obtained in good to excellent yield from acetylenic vinyl bromides **138**. The corresponding acetylenic vinyllithiums **139** cyclize on warming to give **140**, following quench with water. Both five-membered and six-membered outer-ring dienes may be prepared. It was found that 5-*exo* closure of an acetylenic vinyllithium tolerates aryl, silyl or alkyl substituents at the distal acetylenic carbon; the corresponding 6-*exo* process is less facile and seems to be confined to substrates bearing an anion-stabilizing substituent such as phenyl or trimethylsilyl at the terminal acetylenic carbon (Scheme 45).



(138) **(139)** **(140)** 94%

SCHEME 45

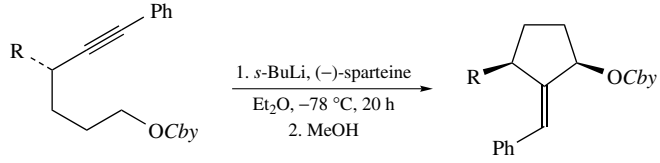
By simple incorporation of a leaving group at the distal propargylic position of the acetylenic vinyllithium, the cyclization methodology described was slightly modified to allow preparation of otherwise relatively inaccessible exocyclic, conjugated allenenes (s-annulated 1,2,4-trienes)[108]. Thus, the vinyllithium **142** generated from bromide **141** cyclizes via **143** to afford the five-membered exocyclic allenene **144** in 97% isolated yield (Scheme 46).



(141) **(142)** **(143)** **(144)** 97%

SCHEME 46

The first stereoselective intramolecular carbolithiation of alkynes was recently achieved by Hoppe and coworkers[109]. Several 4-functionalized 5-hexynyl carbamates, e.g. (*S*-**145**), were efficiently cyclized in the presence of the chiral base (−)sparteine, to **146Z**, providing



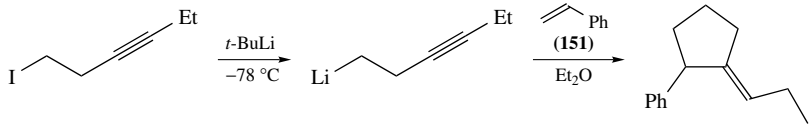
(*S*)-(**145**) (**146Z**)

(**147**) R = Bn_2N, 70%, dr 99:1
(**148**) R = OTBDMS, 82%, dr 95:5

SCHEME 47

enantiopure substituted alkylidenecyclopentanes such as **147** and **148** (Scheme 47). The diastereomeric ratio of the functionalized cyclopentanes directly corresponded to the enantiomeric ratio of each individual cyclic precursor (Scheme 47). The presence of sterically demanding substituent in the propargyl position seems to be the essential feature of the cyclization in order to suppress the abstraction of the remaining propargylic proton. The carbamates undergo the ring closure highly regioselectively (5-*exo* exclusively), diastereoselectively as far as the double bond is concerned (*syn* addition of the lithium–carbanion pair to the triple bond) and diastereoselectively with respect to the newly formed stereocenter (retention of the configuration at the former bearing lithium carbon atom)[52].

On the other hand, the reaction of acetylenic reagent **149** with *t*-BuLi gives **150** which, followed by reaction with **151**, gives substituted cyclopentanes **152** in high yield and stereocontrol[87] (Scheme 48). The preponderance of the *E*-alkene is consistent with the accepted *syn*-carbolithiation mechanism.



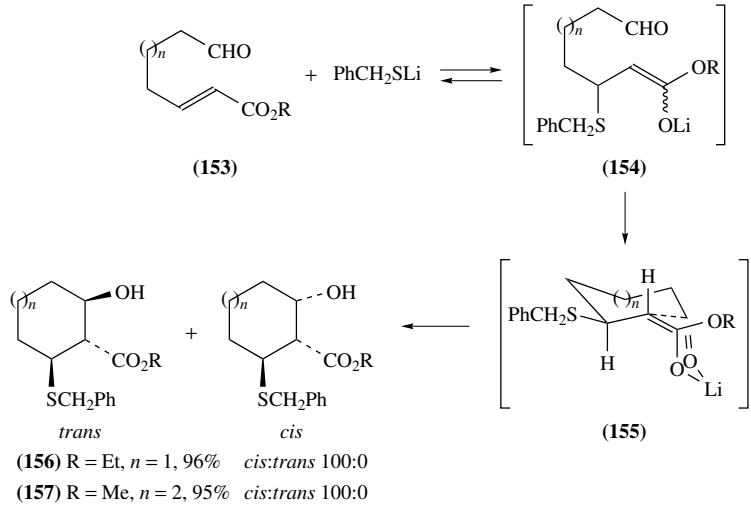
(149) **(150)** **(152)**
61%, *E*:*Z* 97:3

SCHEME 48

An intramolecular tandem Michael aldol reaction was described for esters that have an enolizable aldehyde in the molecule. The lithium ester enolate generated through the Michael reaction undergoes an intramolecular aldol reaction. Thus, the reaction of ω-oxo-α,β-unsaturated esters **153** with lithium benzylthiolate provided the expected cyclization products **156** and **157** via ω-formylenolate **154** in an excellent *cis* stereoselectivity (Scheme 49)[110].

The authors rationalized the formation of *cis*-**156** and *cis*-**157** as major diastereomers through the intermediate **155**. The Michael addition of lithium benzylthiolate with enolate **153** generates the *cis*-enolate **154**; coordination of the lithium by the formyl oxygen gives **155**, where the benzylsulfanyl group is *anti* to the coming formyl group. The more nucleophilic reagent, lithium benzylthiolate, was used, since with benzenethiolate the stereoselectivity was good but poor yields were obtained.

The process was recently extended to the asymmetric cyclization of ω-oxo-α,β-unsaturated esters **158** with the use of a lithium thiolate of 10-mercaptoisoborneol, **159**, as an initiating chiral thiolate, thus providing a new methodology for the asymmetric building of chiral carbocycles (Scheme 50)[111].

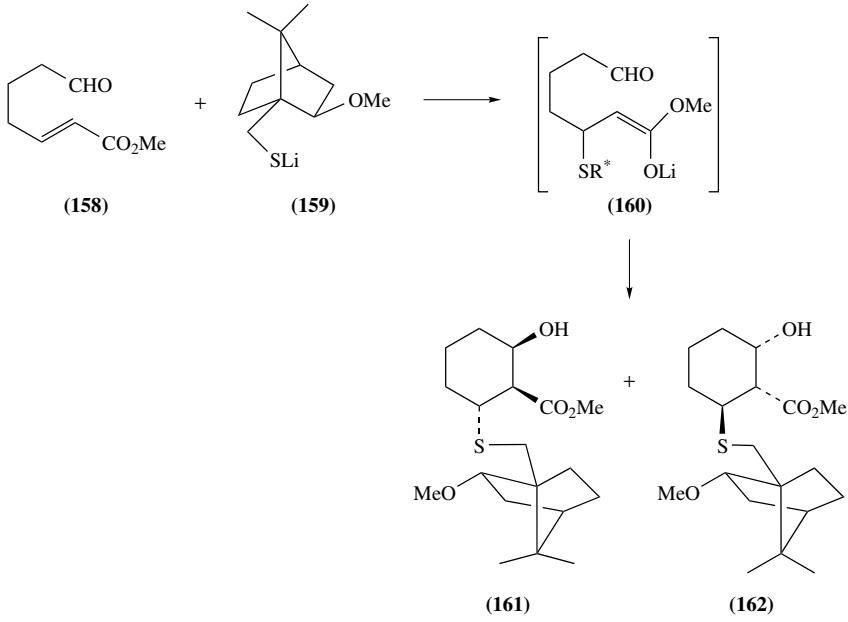


(153) **(154)** **(155)**

(156) R = Et, *n* = 1, 96% *cis*:*trans* 100:0

(157) R = Me, *n* = 2, 95% *cis*:*trans* 100:0

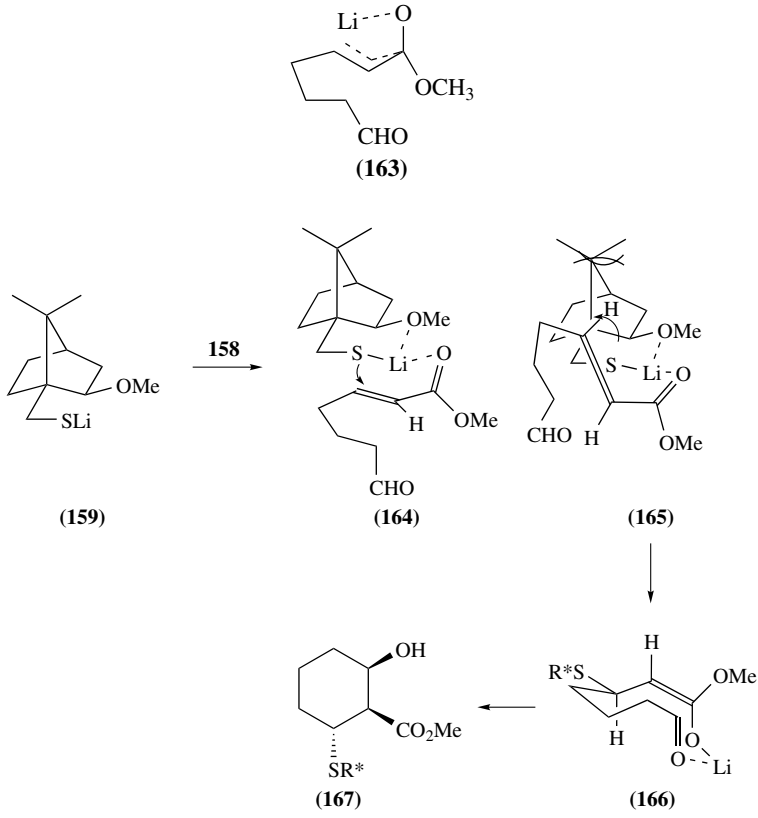
SCHEME 49



(158) **(159)** **(160)** **(161)** **(162)**

SCHEME 50

The cyclization, presumably via **160**, gave the Michael-aldol tandem cyclization products **161** and **162** in a perfect *syn*-aldol stereoselectivity. The stereochemistry of the tandem reaction is rationalized by the model **164**, which is sterically more favorable than **165** (Scheme 51). The oxo-ester **158** reacts in *s-cis* form and generates the *cis*-enolate, **163**,

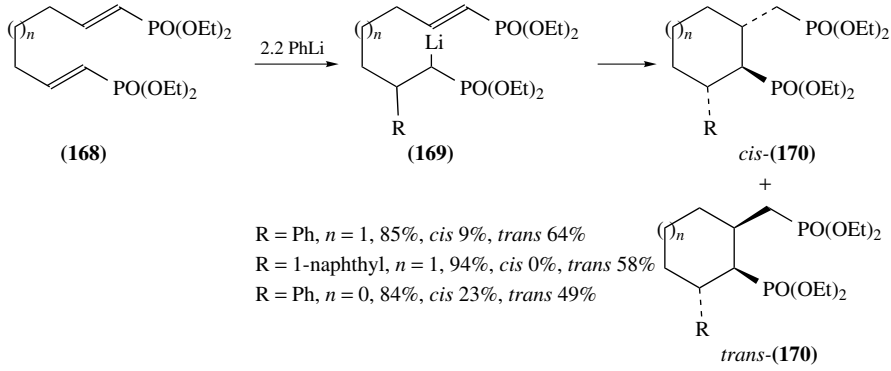


SCHEME 51

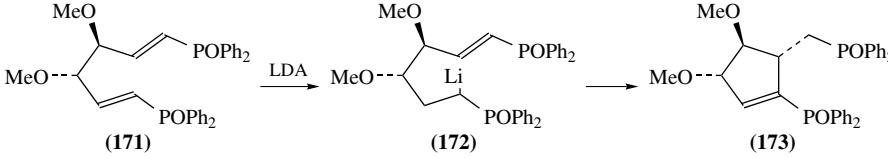
which then reacts intramolecularly with the lithium-coordinated carbonyl group shown in **166** resulting in the observed major *syn*-only aldol product **167**[111].

Another addition–cyclization tandem protocol has been described using alkylphosphonates. They are versatile analogues of natural phosphates, nucleotides, amino acids etc.[112], and are also useful synthetic precursors of olefins as well as chiral phosphine ligands. Efficient synthetic applications of α,β-unsaturated phosphonates were described[113]. Recently, Nagaoka and Tomioka[114] have reported an organolithium-initiated conjugate addition–Michael tandem cyclization of α,β,ψ,ω-unsaturated bisphosphonates, **168**, giving the corresponding carbocycles **170**, bearing two phosphonate moieties (Scheme 52).

The reaction afforded the tandem cyclization product **170** as a mixture of two separable isomers together with an α,β-unsaturated cyclic bisphosphonate, which is formed by a direct deprotonation of the vinylic α-proton of **168** and subsequent intramolecular Michael cyclization. The authors described the formation of **170** by the conjugated addition of **168** to 2.2 equivalents of PhLi and subsequent intramolecular Michael reaction in the intermediate **169**. It is likely that coordination of the lithium atom to the oxygens of the phosphonates favors formation of the *trans*-isomer. As shown in Scheme 52, the reactions with bulky naphthyllithiums gave only the *trans*-**170** isomer. This novel methodology can provide a rapid entry into a variety of cyclic bisphosphonates in good stereoselectivity.



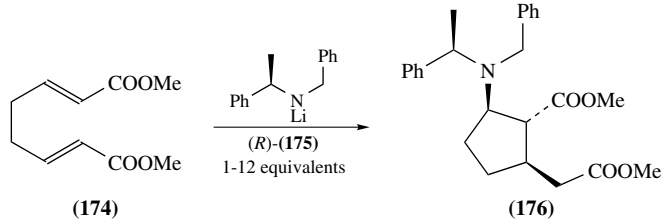
SCHEME 52



SCHEME 53

It was recently reported that, upon treatment with lithium diisopropylamide, achiral and chiral α,β,ψ,ω-unsaturated bisphosphine oxides, **171**, underwent lithiation conjugate addition-tandem-cyclization to **172** to afford the corresponding *endo*-α,β-unsaturated cyclic bisphosphine oxides, **173** (Scheme 53)[115].

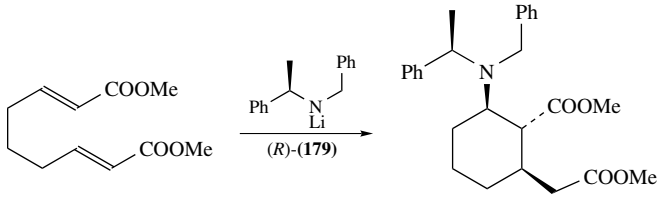
Garrido and coworkers[116] have demonstrated the use of homochiral lithium (α-methylbenzyl)benzylamide **175** to initiate the highly stereoselective conjugate addition–cyclization of dimethyl (*E*,*E*)-octa-2,5-dienoate, **174**, to generate the homochiral cyclopentane derivative (−)-(1R,2R,5R,αR)-**176** with complete control over the configuration of C-1 and C-2 and excellent control over C-5 (Scheme 54).



SCHEME 54

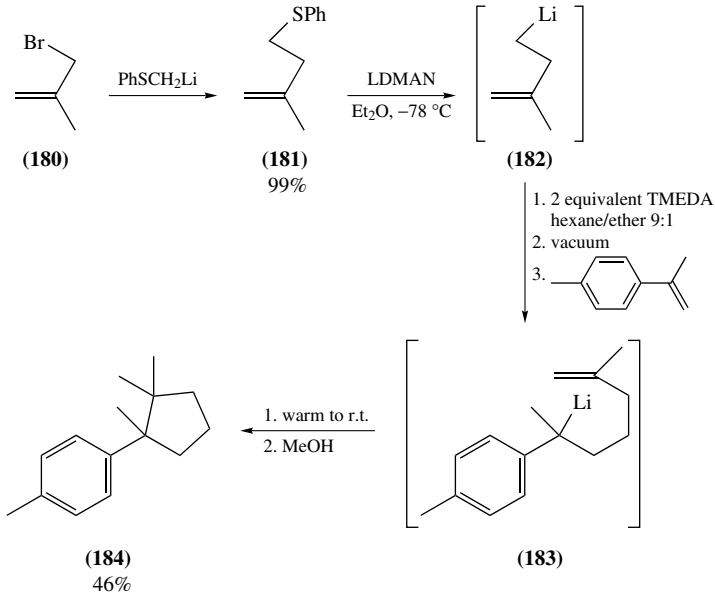
Garrido and coworkers have demonstrated that addition of a slight excess of the lithium amide (*R*)-**175** to dimethyl (*E*,*E*)-nona-2,7-diendioate, **177**, gave stereoselectively (+)-(1*R*, 2*R*, 6*R*, α*R*)-**178** as the unique product in 72% yield (Scheme 55)[117].

A novel radical anion (LDMAN) methodology developed by Cohen and coworkers (see Section III.A.2) was then applied efficiently for the two-pot synthesis of the sesquiterpene (±)-cuparene, **184**, starting from the allyl reagent **180**[118]. The tandem addition/cyclization



SCHEME 55

afforded **184** through the intermediates **181–183**. This methodology renders the synthetic intermediate **184** as the exclusive product in 46% yield, the most efficient procedure reported (Scheme 56)[5].

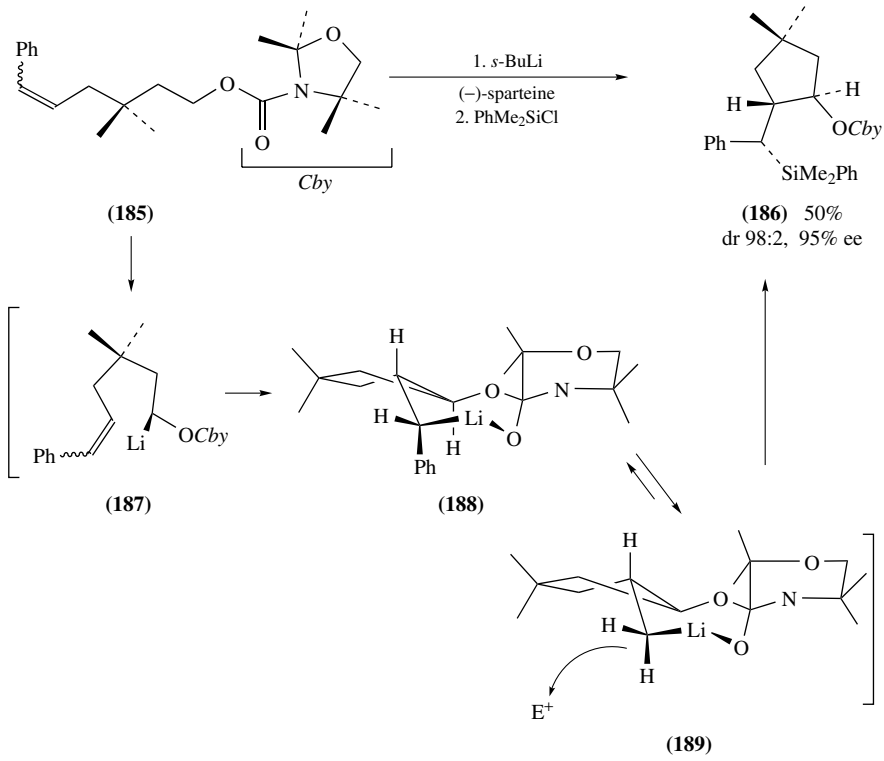


SCHEME 56

A way to confer enantiofacial selectivity in cyclizations of achiral olefinic organolithiums is by the use of chiral ligands. The ability to discriminate between the enantiotopic faces of an inactivated carbon–carbon π-bond tethered to a formally carbanionic center considerably extends the synthetic utility of anionic cyclizations[119].

The enantioselective metalation at the α-position of a carbamate in the presence of (−)-sparteine followed by a diastereoselective intramolecular carbolithiation onto a double[120] or triple bond[121] was recently studied. The precursor **185** was deprotonated with *s*-BuLi/(−)-sparteine in Et_2O at −78 °C, the reaction mixture was stirred for 20 to 30 h at this temperature and the electrophilic reagent was subsequently added (Scheme 57)[60].

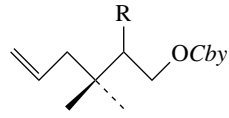
The cyclization showed complete *5-exo* selectivity and led to the *trans*-substituted cyclopentane **186** via a chair-like intermediate **189**. *Syn*-addition to the *cis* double bond



SCHEME 57

formed the intermediate adducts **187** and **188**, which generated the thermodynamically more stable adduct **189** by epimerization. When the *trans* isomer was used, the adduct **189** was formed straightforwardly. The method allowed the stereoselective formation of two C−C bonds and hence the construction of three vicinal stereocenters (Scheme 57).

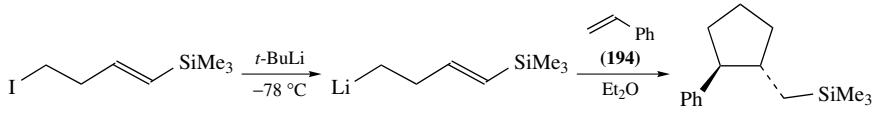
In these cyclizations, the presence of a sterically demanding substituent in the propargylic position seems to be essential to inhibit the abstraction of the remaining propargylic proton. Similarly substituted carbamates, **190**, undergo the ring closure highly regioselectively (*5-exo* exclusively), diastereoselectively as far as the double bond is concerned (*syn* addition of the lithium−carbanion pair to the triple bond), and diastereoselectively with respect to the newly formed stereocenter (retention of the configuration at the former lithium-bearing carbon atom)[52].



(190)

Silylated alkenes, **191**, are useful reagents to be used in tandem reactions of lithiated chain intermediates. Thus, it was reported that the reactions of the lithiated alkene **193**,

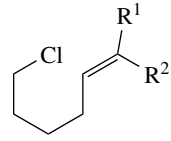
obtained via **192**, with styrene, proceeded in reasonable yield and excellent stereocontrol, yielding the cyclopentane **195** (Scheme 58). It is proposed that the stereoselectivity of the reaction presumably reflects intramolecular coordination of the intermediate vinyllithium to the phenyl group[68]. This considerably expands the variety of products that can be obtained through this methodology.



(192) **(193)** **(195)**
52%, dr 100:0

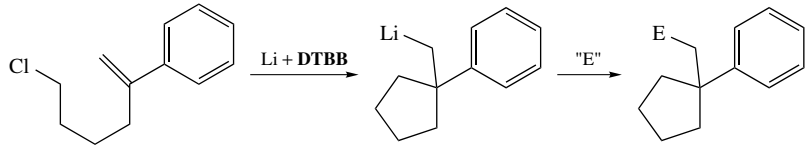
SCHEME 58

Yus and coworkers[40] studied the usefulness of substituted 6-chlorohex-1-ene, **196**, in cyclization reactions of the corresponding lithiated intermediates.



(196)

The carbolithiation reaction followed by additions of various reagents usually renders a mixture of open-chain and cyclic products, as observed in the conventional Barbier reaction[122]. Nevertheless, Yus and coworkers[40] found that when the alkene is substituted by aromatic moieties, only the cyclization reaction takes place (Schemes 59 and 60). They have previously found that the use of an excess of lithium powder and a catalytic amount of an arene (4,4′-di-tert-butylbiphenyl, **DTBB**, is most commonly used) is an adequate procedure to carry out chlorine–lithium exchange under very mild reaction conditions[123].

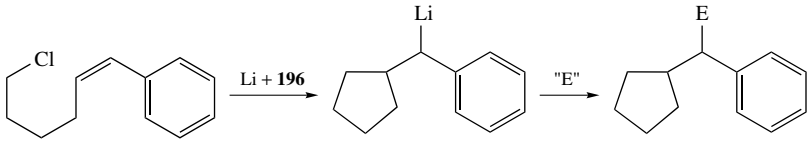


(197) **(198)** **(199)**

E = *t*-BuCHO, PhCHO, Et_2CO, H^+
E′ = *t*-BuCH(OH), PhCH(OH), $Et_2C(OH)$, H

SCHEME 59

For 6-chloro-2-phenylhex-1-ene, **197**, the **DTBB**-catalyzed lithiation, even at −78 °C, gives the cyclic intermediate **198** (probably formed by an intramolecular carbolithiation), which by reaction with some electrophiles afforded, after hydrolysis, the corresponding products **199** (Scheme 59). The conversion is total after about 1 h; the rest of the starting material is transformed into a mixture of compounds, among them the 'reduced' product



(200) **(201)** **(202)**

E = Et_2CO, PhCHO, Me_3SiCl, H_2O
E′ = Et_2COH, PhCHOH, Me_3Si, H

SCHEME 60

(**199**, E = H) resulting from a lithium–hydrogen exchange in intermediate **198**. This hydrogen abstraction from the reaction medium, probably from THF at the α-position, has already been observed in other cases for very reactive organolithium intermediates. The use of Barbier-type reaction conditions did not improve the obtained results[124].

When (*Z*)-6-chloro-1-phenylhex-1-ene **200** was lithiated under **DTBB** catalysis, the cyclized product **202** was always obtained either at −78 or at −30 °C. After the first chlorine–lithium exchange a carbolithiation took place to yield the intermediate **201**, which by reaction with electrophiles, E, and final hydrolysis gave products **202** (Scheme 60). At −78 °C the reaction under Barbier-type conditions did not work. Also in this case, the corresponding 'reduced' product (**202** with E′ = H) was the main by-product detected.

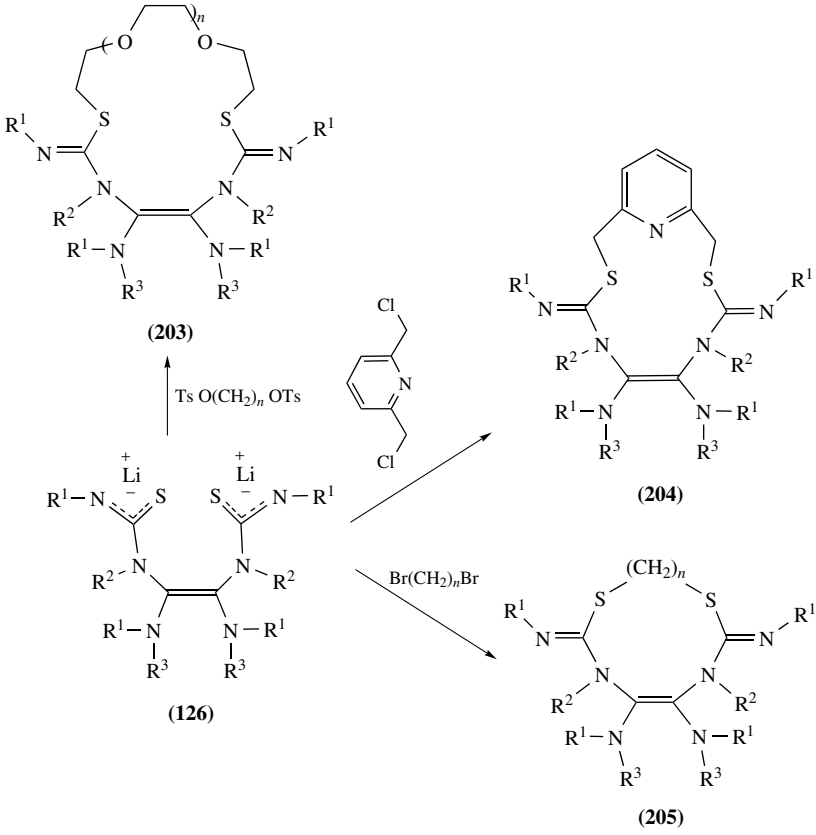
A novel synthetic strategy for the preparation of 3-alkyl-5-hydroxycyclohexen-2-ones was recently reported. The methodology implies an intramolecular cyclization achieved through an aldolic addition/sulfinate elimination tandem reaction[125]. The addition–cyclization protocol is also useful for the one-pot synthesis of new macrocyclic compounds. Hoffmann and coworkers[126] have described a general synthetic method for the incorporation of the lithiomaleonitrile unit into macrocycles containing various donor atoms; the dithiomaleonitrile substructure bears an electron-deficient C=C double bond and therefore reduces the σ-donating ability of the sulfur atoms.

Macrocycles with an electron-rich C=C double bond seem to be of interest owing to their interaction with metal cations and their likely involvement in electron-transfer processes. In this sense, the new synthetic route to tetraaminoethene derivatives developed by Görls and coworkers[95], described in Section II.C, can be used as a strategy for the synthesis of macrocycles. Thus, the open-chain intermediate **126** was used for the synthesis as starting material of several macrocyclic compounds. A ring-closure reaction using a large number of α,ω-dielectrophilic building blocks yielded new macrocyclic compounds, such as **203–205** (Scheme 61)[93]. This approach constitutes a novel general methodology for the synthesis of a wide variety of macrocycles.

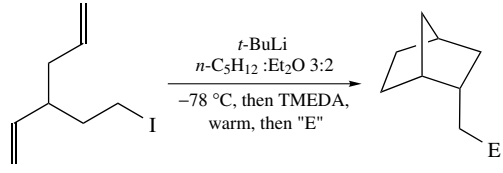
2. Condensed rings

Bailey and coworkers[127] have reported that the tandem cyclization of diolefinic alkyllithiums, formed from acyclic diolefinic alkyl iodides by lithium–iodine exchange at low temperature, proceeds via two highly stereoselective and totally regiospecific 5-*exo-trig*[128] ring closures. Functionalized bicyclic molecules could be obtained in good yield by trapping of the organolithium product, by addition of an electrophile. By this method, *endo*-2-substituted bicyclo[2.2.1]heptanes, **207**, were prepared in isolated yields of 65–80% from the readily available 3-(2-iodoethyl)-1,5-hexadiene, **206** (Scheme 62).

The methodology was useful for the preparation of functionalized benzo-fused carbocycles. Isomerically pure 4-substituted indans, **209**, could be synthesized by cyclization



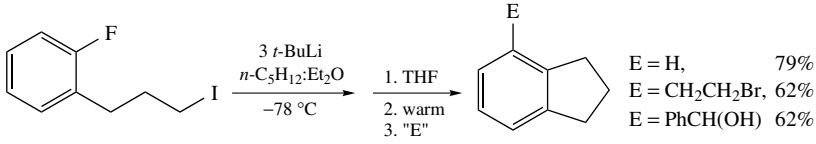
SCHEME 61



(206) **(207)**

E:	H	89%
E:	CO_2H	75%
E:	CHO	72%
E:	$(CH_2)_2Br$	75%
E:	Me_3Si	81%
E:	$(n\text{-}Bu)_3Sn$	71%

SCHEME 62

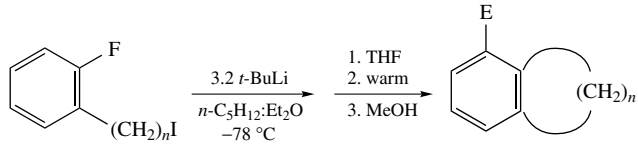


(208) **(209)**

SCHEME 63

of the benzyne-tethered propyllithium generated from 2-fluoro-1-(3-iodopropyl)benzene, **208** (Scheme 63)[127].

Other benzo-fused carbocycles could be prepared in moderate yield by a similar strategy. Isomerically pure 3-substituted benzocyclobutenes or 5-substituted tetralins, **211**, were prepared by a five-step sequence from the appropriate α-(2-fluorophenyl)-ω-iodoalkane, **210** (Scheme 64)[129].



(210) **(211)**

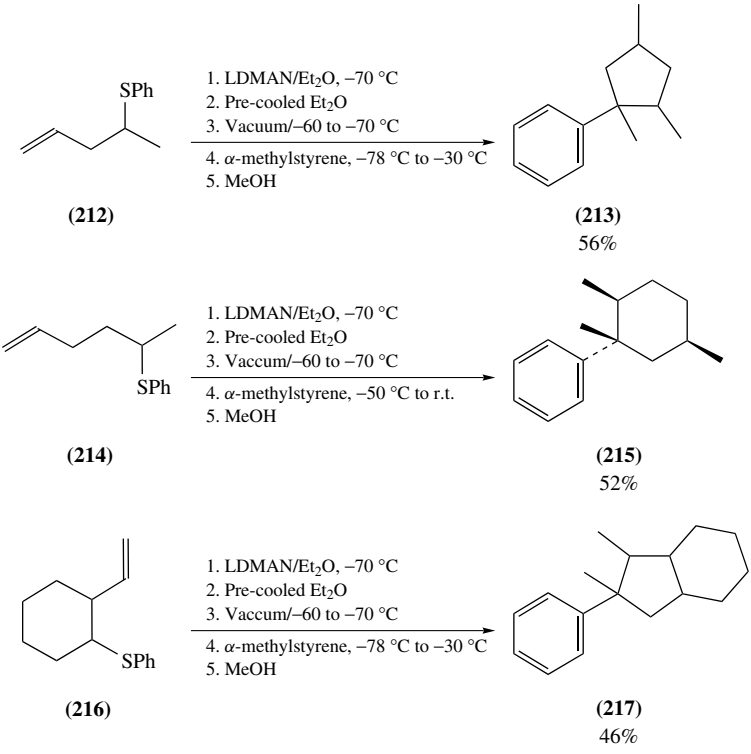
SCHEME 64

We have seen in the preceding sections the versatility of tandem reactions involving organolithium compounds and how, usually, the nature of the reagent and the experimental conditions lead the reactions to occur with high regiochemistry and stereoselectivity[70, 130]. It is then of paramount relevance in the search for new organolithiums or reaction conditions to provide alternative synthetic methodologies. In this sense, the reductive lithiation of phenyl thioethers with aromatic radical-anions is becoming one of the most general methods for organolithium production; its great versatility has been demonstrated repeatedly[130, 131].

Notwithstanding, one disadvantage of this method is the necessity of using THF as the solvent, owing to the ability of organolithiums to remove a proton from the 2-position of THF. As an example, in the tandem addition–cyclization on α-methylstyrene, the yields are compromised by the presence of THF, which promotes an undesired side reaction[102].

When subsequent tandem reactions are desired, *in situ* formation of 2-tetrahydrofuryllithium may be a competitive major problem. To avoid the use of THF, Cohen and coworkers[132] have developed a new radical anion, the lithium 1-(dimethylamino)naphthalenide (LDMAN), in diethyl ether. This finding should considerably enhance the utility of the widely used reductive lithiation for the preparation of organolithium. The strategy developed by Mudryk and Cohen[133] was applied to tandem addition/cyclization of the homoallyl lithium reagents derived from **212**, **214** and **216** to give **213**, **215** and **217**, respectively (Scheme 65).

The addition–cyclization protocol can be also carried out using allylic lithium compounds for the synthesis of cyclopropanes. The allylic substitution of a leaving group by a carbon nucleophile is one of the most important reactions in organic synthesis; in intramolecular variants, the fast formation of five-membered rings is strongly favored[134]. Recently, Cohen and coworkers[135] reported the first synthetic method based on the surprisingly facile lithium-ene cyclization followed by thiophenoxide expulsion to yield



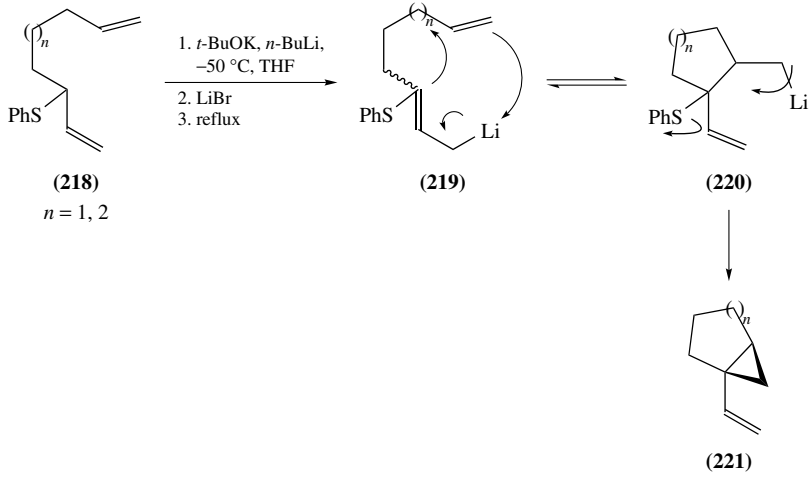
SCHEME 65

vinylcyclopropanes. This is a particularly useful class of compounds that includes the large group of pyrethroid insecticides, as well as other natural products that can be transformed into yet other products.

The protocol for this tandem cyclization involves deprotonation of allylic phenyl thioethers such as **218**[136]. The authors observed that transmetalation with LiBr was required to obtain high yields of the cyclization product. Conversion of the resulting allyllithium **219** to the monocyclic intermediate **220** followed by intramolecular displacement of the thiophenoxide ion efficiently afforded the fused vinylcyclopropane **221** (Scheme 66). Formation of the five-membered ring was quantitative, starting from a substrate in which both alkene functions were monosubstituted[126].

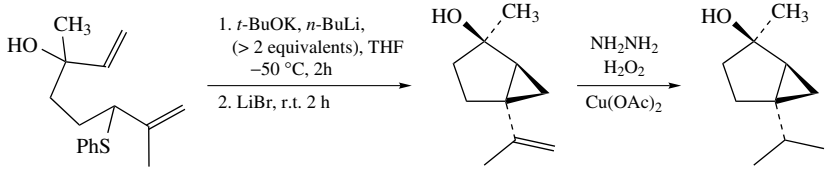
The use of an allylic lithium oxyanionic group is of great significance to enhance reactivity and control stereochemistry in an anionic cyclization. Thus, it was reported that the cyclization of the suitable substrate **222** to **223** occurs at room temperature rather than the reflux temperature required in the absence of allylic hydroxy groups, and proceeds stereoselectively in high yield (Scheme 67). The reduction product **224** was shown to have the hydroxyl *cis* to the cyclopropyl ring. This methodology was applied to achieve the most efficient synthesis of *cis*-sabinene hydrate **224**, a terpene of the thujane class[126].

The intramolecular carbolithiation of carbon−carbon double bonds is an interesting route to functionalized carbocyclic and heterocyclic systems that has been developed in the past years and widely used in organic synthesis. In this context, aryllithiums have been described to carbometalate double bonds allowing the preparation of indanes,



(218) $n = 1, 2$ **(219)** **(220)** **(221)**

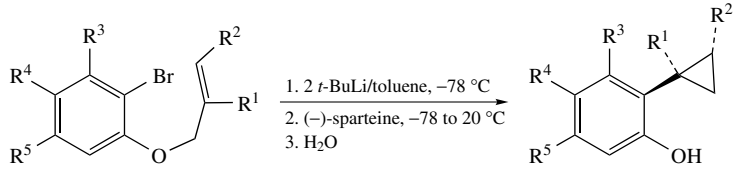
SCHEME 66



(222) **(223)** **(224)**

SCHEME 67

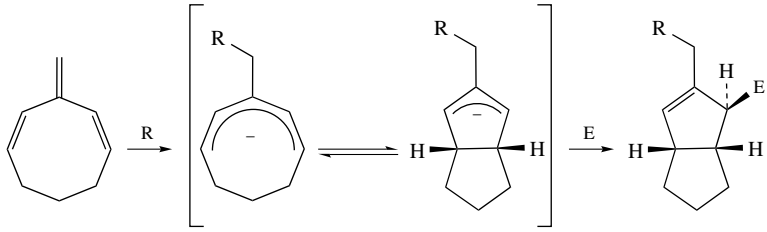
benzofuranes, indolines and isoquinolines. Barluenga and coworkers[137] found that different allyl 2-lithioaryl ethers undergo a tandem carbolithiation/α-elimination in Et_2O/TMEDA affording *o*-cyclopropyl phenol or naphthol derivatives in a diastereoselective manner. The use of (−)-sparteine as a chiral ligand instead of TMEDA allows the synthesis of cyclopropane derivatives **226** from **225** with up to 81% ee (Scheme 68).



(225) **(226)**

SCHEME 68

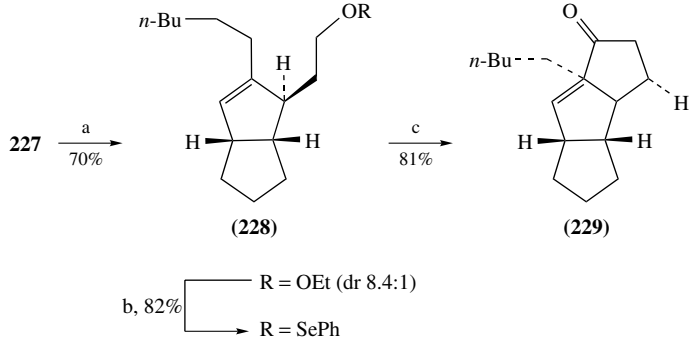
Williams and Reeves[138] developed a powerful cascade reaction process for the construction of functionalized *cis*-bicyclo[3.3.0]octenes. Carbolithiation of 3-methylene-1,4-cyclooctadiene **227** with 1°, 2° or 3° alkyllithium reagents leads to cyclooctadienyl anions,



SCHEME 69

which undergo disrotatory electrocyclization and subsequent trapping with carbon, oxygen, sulfur or silicon electrophiles to provide functionalized *cis*-bicyclo[3.3.0]octenes **228** (Scheme 69).

Transmetalation of the allyllithium intermediates allowed access to the cuprate manifold of reactivity. The rapid construction of a linear triquinane, **229**, using this methodology demonstrates the potential for synthetic application (Scheme 70).

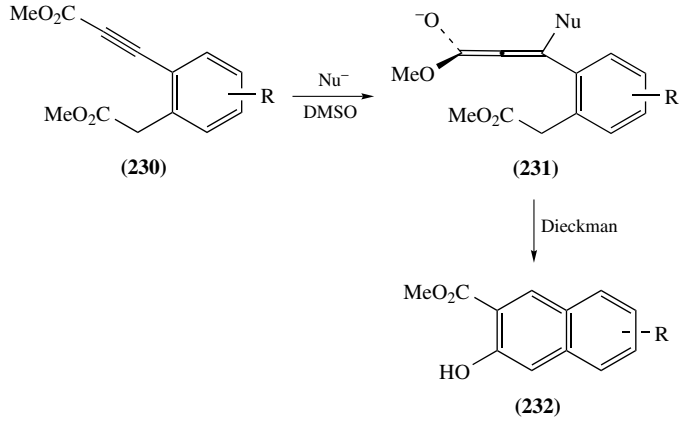


Conditions: (a) *n*-BuLi, (–) sparteine/hexane, −78 °C to r.t., 1 h;
CuCN-2LiCl, THF, −78 °C; ethyl acetate, TMSCl, −78 °C to r.t.
(b) i. LiOH, THF/H_2O; ii. *N*-(phenylseleny)phthalimide, *n*-Bu_3P, THF.
(c) n-Bu_3SnH, AIBN, PhH, reflux

SCHEME 70

B. Aromatic Rings

Martinez and coworkers[139] defined the scope and limitations of the tandem conjugate addition–Dieckmann condensation for the construction of 1,2,3-trisubstituted naphthalenes. Viable nucleophilic partners in this methodology include organocuprates, active methylene compounds and a variety of heteroatom initiators. Numerous accounts have appeared related to the utility of tandem reactions initiated by Michael addition to construct multicyclic arrays with remarkable atom economy[140, 141]. Aside from traditional synthetic sequences to substituted naphthalenes such as the Stobbe condensation/Friedel–Crafts cyclization, a recent method employing an anion accelerated electrocyclization to construct 1-naphthols has been reported[142]. The general approach to substituted naphthalenes, **232**, involves the addition of a nucleophile to an appropriately substituted phenyl alkynyl ester,

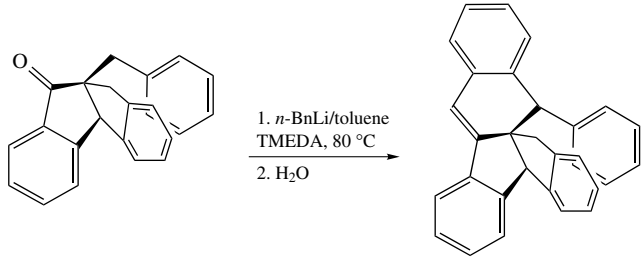


(230) **(231)** **(232)**

SCHEME 71

230, with an *ortho*-disposed methoxycarbonylmethylene group (Scheme 71). Dieckmann condensation and tautomerization affords, via **231**, fully aromatized 3-naphthol products **232**. With the promise of generating unnatural analogues of these polyketide structures, it was deemed necessary to define the scope and limitations of this tandem reaction.

Novel carbon frameworks have been developed from polycyclic hydrocarbons. Thus, Kuck and coworkers[143] have recently reported an unexpected tandem reaction, which formally consists of a condensation/cyclodehydrogenation sequence starting from triptidan-9-one **233** leading to the *trifuso*-tetracyclic propellane **234** (Scheme 72). The reaction of the tribenzo[3.3.3]propellane ketone **233** with benzyllithium/TMEDA afforded an efficient one-pot *peri* annulation of a dihydronaphthalene (Scheme 72). The key step of this unexpected tandem reaction was determined to be a nucleophilic cyclization followed by hydride elimination.



(233) **(234)**
75%

SCHEME 72

IV. HETEROCYCLES

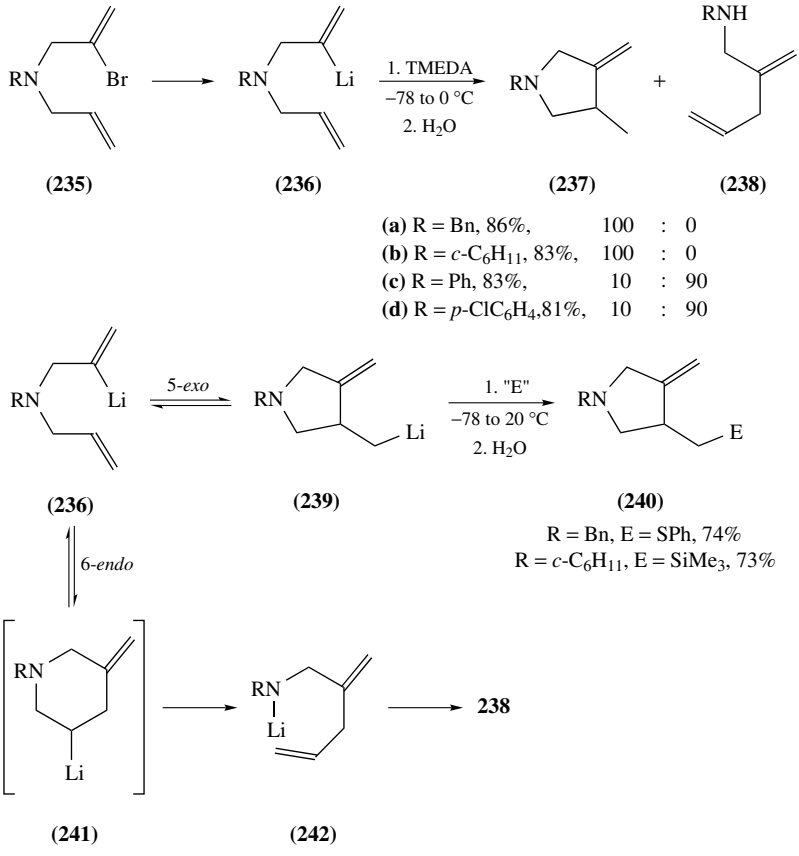
The development of intramolecular anionic cyclization for the preparation of heterocyclic systems provides routes to several oxygen and nitrogen heterocycles. Tetrahydrofurans, pyrrolidines[144], indolines[145] or indoles[146] have been synthesized via intramolecular

carbolithiation reactions. Moreover, the fact that the ring closure of achiral olefinic organolithiums could proceed enantioselectively in the presence of (−)-sparteine dramatically increases the potential use of this kind of process[147, 148].

A. Non-aromatic Heterocycles

1. Single rings

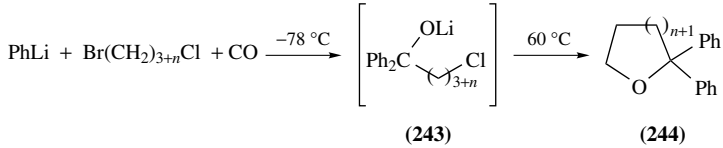
The intramolecular carbolithiation of vinyllithium derivatives of substituted *N*-allyl-*N*-(2-bromoallyl)amine can lead to the formation of 5- or 6-membered cyclic products, through a 5-*exo* or 6-*endo* process depending on the starting amine. There are few precedents for the preparation of six-membered rings by anionic carbocyclization of unactivated double bonds. The first 6-*endo* closure was described by Barluenga and coworkers[149]. Treatment of *N*-allyl-*N*-(2-bromoallyl)amines, **235**, with 2 equivalents of *t*-BuLi at −78 °C gave the vinyllithium derivatives **236**, which undergo intramolecular addition to the double bond in the presence of TMEDA at low temperatures affording **237** (Scheme 73). The ratio of **237** to the open-chain **238** depends on R.



SCHEME 73

The authors explain the mechanism of the reaction through an equilibrium to give **239** (which affords **240**) and **241** which, via the open lithiated intermediate, **242**, renders **238**. The carbolithiation of alkenes and alkynes is a useful transformation for the generation of a new carbon−carbon bond. Similarly to the intramolecular carbolithiation, it is possible to carry out this reaction with high diastereoselectivity.

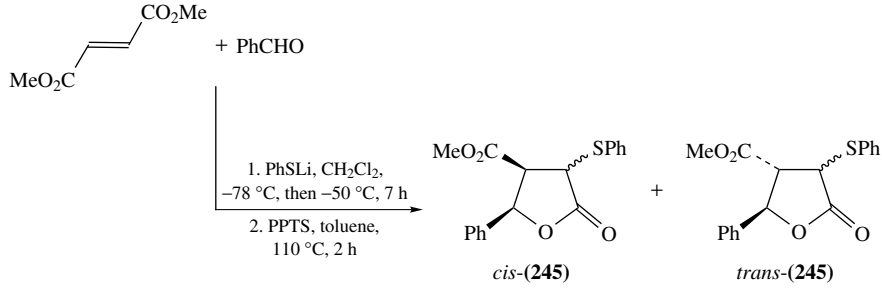
As described in Section II.A, the tandem sequence reaction of organolithium compounds with carbon monoxide followed by reaction with suitable electrophiles provides an useful tool for the preparation of diphenyldialkyl carbinols, and the reaction could be easily extended to produce substituted cyclic ethers in a one-pot synthesis. Thus, by carrying out the carbonylation of phenyllithium in the presence of conveniently substituted chloroalkyl bromides, $Br(CH_2)_{3+n}Cl$, at −78 °C, the oxo-lithiated intermediates **243** are obtained and cyclized to **244** by warming up the reaction mixture (Scheme 74)[21].



(243) **(244)**

SCHEME 74

The Michael-aldol process with methacrylates described in Section II.B can be also applied to the synthesis of substituted tetrahydrofurans, **245**. If the reaction is carried out in THF, the yield and selectivity of the sequence decrease. It was proposed that the lithium coordination with THF molecules hinders the formation of the product **245**. The authors concluded that the Lewis acidity of naked lithium cation is the key driving force for the reaction to proceed successfully. The tandem reaction with lithium thiophenolate, fumarate ester and benzaldehyde constitutes an useful methodology for the preparation of γ-butyrolactone (Scheme 75)[89,90].



cis-**(245)** *trans*-**(245)**

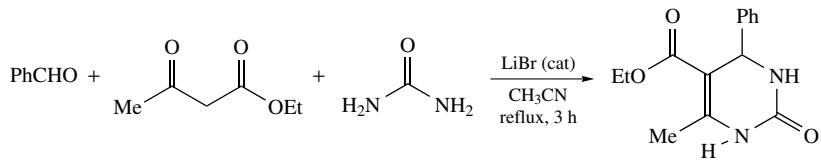
64%, *cis* : *trans* 80:20

SCHEME 75

Very recently, Maiti and coworkers[150] developed a new methodology for the synthesis of dihydropyrimidones, **246**, by a one-pot three-component condensation using a catalytic amount of LiBr, under very mild reaction conditions (Scheme 76).

2. Condensed rings

Carbon−carbon bond formation by an intramolecular carbolithiation (anionic cyclization) reaction to give heterocyclic systems has been gaining increasing use in organic



(246)

SCHEME 76

synthesis[151]. This chemistry has provided a convenient route to diversely substituted cyclopentanes, pyrrolidines[152], tetrahydrofurans, and both fused and bridged bicyclic compounds.

One of the main advantages of the anionic cyclizations is their regioespecificity and stereoselectivity when compared with radical or other types of reactions leading to cyclic systems. This is usually due to the formation of complexes involving the lithiated alkyl, vinyl or aryl substrate and an unsaturated, double or triple, C−C bond. In some cases, a heteroatom is involved in stabilizing the transition state for the reaction. In other cases, the stereoselectivity of the cyclization is determined by the presence of several functional groups in the substrate.

The intramolecular carbolithiation–electrophilic substitution tandem sequence leading to the formation of nitrogen-positional isomers of the azabicyclo[2.2.1]heptane ring system is a very interesting example worthy of examination[154]. These ring systems are present in several natural products and biologically active compounds[153]. The authors generated the organolithium reagent from a tin–lithium exchange from a conveniently substituted pyrrolidine, **247**. The transmetalation occurred with retention of configuration (see below). As shown in Scheme 77, the 7-azabicyclo[2.2.1]heptane ring system **250** can be formed from either diastereomer of a 2,5-disubstituted pyrrolidine, **249**, via **248**, using a chiral organolithium intermediate. Both isomers gave the *exo* product **250**[154].

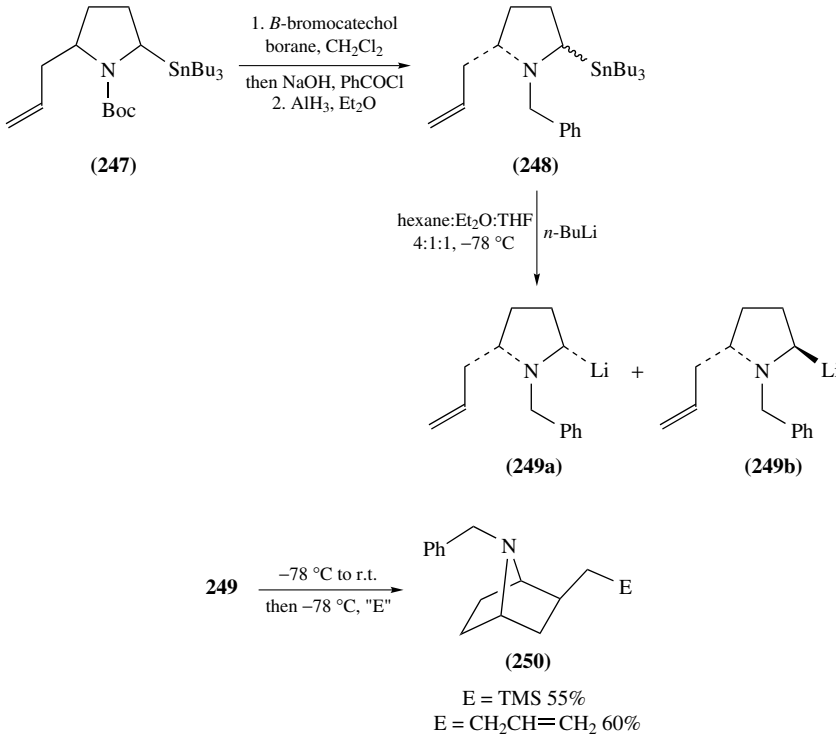
On analyzing the transition states that could lead to this product, it is seen that the *cis*-isomer **249a** would be the more favored since it forms a chair-like transition state where the lithium atom is coordinated to the π-system (see **251** in Scheme 78). Presumably, the *trans* isomer epimerizes to the *cis* isomer to give the product.

A variety of cyclic amine products can be obtained by adding an electrophile to the organolithium intermediate resulting from the anionic cyclization, as is shown in Scheme 79[154]. The authors reported that the yields of the substituted products were modest to good, but the yields could be increased by using a *N*-benzylated 2-tributylstannyl-4-allylpyrrolidine, **252**, which by transmetalation gives **253**.

In this case, the *endo*-**254** product is formed. The authors explain the stereochemistry through a transition state **255** that has a boat conformation. Comparing transition states **251** and **255**, it is clear that, besides allowing complexation of the lithium atom with the π-system, the coordination of the lithium atom with the non-bonded electrons of the *N* is also favored. In both states, the *N* is located on the same side of the π-system. It could be presumed that the isomer which gives the more favorable transition state is mainly determined by the position of the *N* in the bicyclic ring.

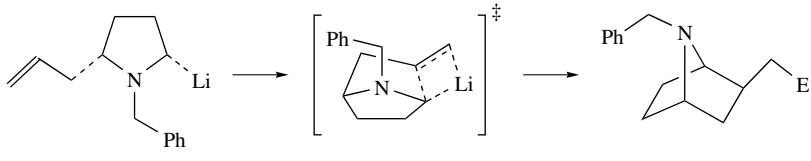
An alternative route to the same bicyclic compound **254** is a sequence of cascade cyclizations starting from the acyclic stannane precursor **256**. The 2-azabicyclo[2.2.1] heptane ring system is formed stereoselectively from **256** in low yield, by a tandem cyclization, together with the product from monocyclization, the pyrrolidine *cis*-**259** (Scheme 80).

The low yields seem to be due to the protonation of the lithiated product of the monocyclization that competes with the second cyclization. The transition state **258** that gives



(247) (248) (249a) (249b) (250)

SCHEME 77

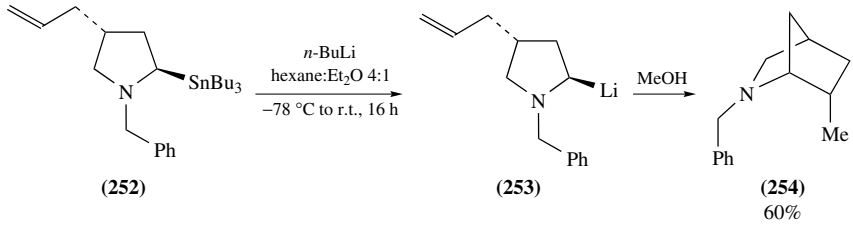


(249a) (251) (250)

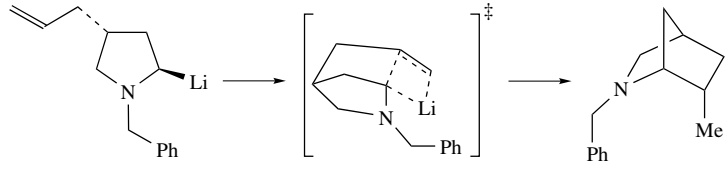
SCHEME 78

the *endo*-product **254** has a chair-like structure but, contrary to **250** and **255**, the *N* is not close to the lithium atom for the coordination to occur. This indicates the influence of the *N* atom on the yields and stereochemistry of the cyclization; the conformations of the transition states **251** (Scheme 78), **255** (Scheme 79) and **258** (Scheme 80) are consistent with the results of semiempirical molecular orbital calculations (MOPAC version 6.0, AM1 Hamiltonian)[154].

The cascade sequence that affords bicyclic systems fails with the lithium derivatives of 2-bromo-*N*,*N*-diallylaniline. The methodology is useful for the synthesis of 3-substituted indolines and indoles, but the substrate undergoes only one anionic cyclization. Alkenyl vinyllithiums and alkenyl aryllithiums have also been employed in the preparation of alkylidenecyclopentanes and indanes. The intramolecular addition of vinyllithium reagents

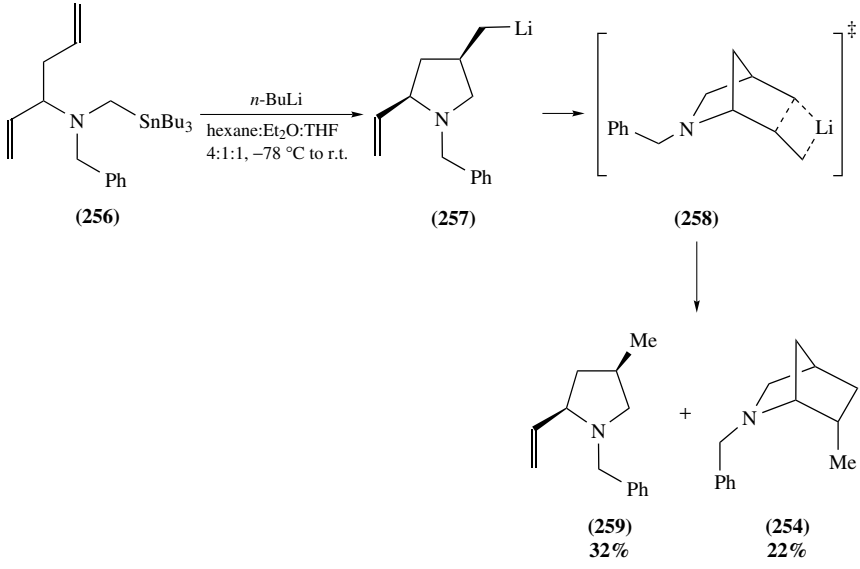


(252) **(253)** **(254)** 60%



(253) **(255)** **(254)**

SCHEME 79

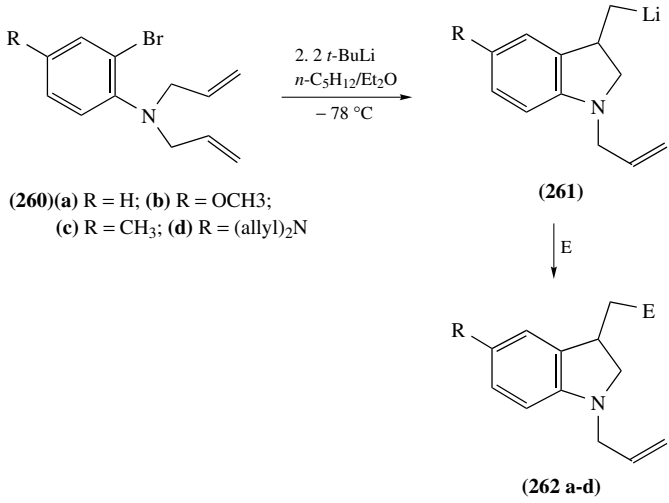


(256) **(257)** **(258)**

(259) **32%** **(254)** **22%**

SCHEME 80

to unactivated alkenes could also incorporate additional functionality (an alkene) into the product. In this context, Bailey and Jiang[155] and Zhang and Liebeskind[156] reported a new procedure that should provide a wide variety of substituted indolines and indoles, rapidly and with minimal effort. *o*-Bromo-*N*,*N*-diallylanilines (**260a–d**) were lithiated at −78 °C, and then the reaction mixtures were allowed to warm to room temperature. The intermediate [(1-allyl-3-indolinyl)methyl]lithium, **261**, was trapped by addition of any of a variety of electrophiles to give 3-substituted indolines (**262a–d**) in good to high yields (61–95%, Scheme 81).

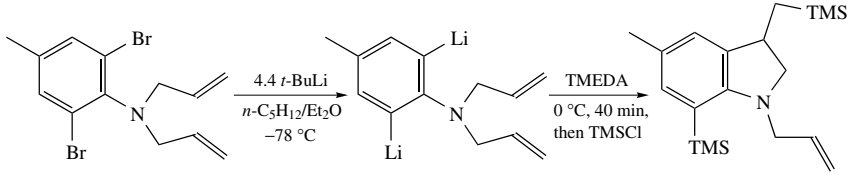


(260)(a) R = H; **(b)** R = OCH3;
(c) R = CH_3; **(d)** R = $(allyl)_2N$

(261)

(262 a-d)

SCHEME 81



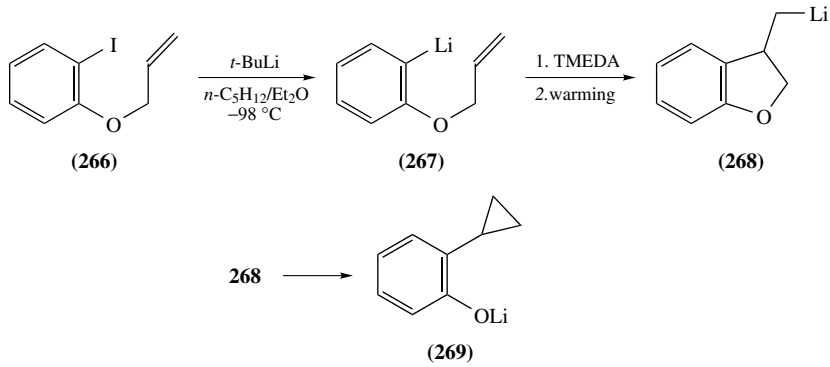
(263) **(264)** **(265)** **64%**

SCHEME 82

Similarly, treatment of the 2,6-dibromo-4-methyl-*N*,*N*-diallylaniline **263** at −78 °C with *t*-BuLi gave **264**, which was used for the synthesis of indolines **265** functionalized in the 3 and 7 positions (Scheme 82)[155].

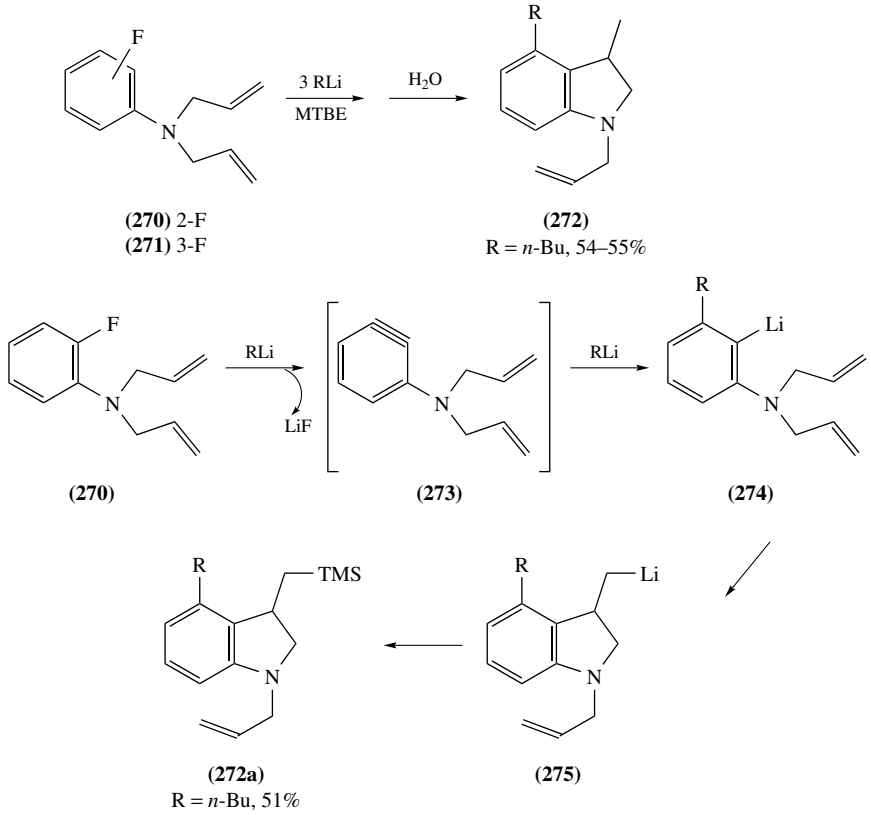
If the same methodology is applied to an analogous oxygen-containing system with the aim of obtaining substituted 2,3-dihydrobenzofurans, the procedure fails since the course of the reaction is different. Bailey and Punzalan[157] studied the possibility of preparing 3-substituted 2,3-dihydrobenzofurans **268** from **266** via cyclization of the 2-(2-propenoxy)phenyllithium **267**. The 5-*exo* cyclization of the aryllithium **267** on warming in the presence of TMEDA gives (2,3-dihydrobenzofuranyl)methyllithium, **268**, which by γ-elimination gives variable amounts of the lithium salt of 2-(cyclopropyl)phenol **269** (Scheme 83).

Another one-pot sequence for the preparation of heterocyclic systems has been recently reported for the regioselective synthesis of 3,4-disubstituted functionalized indoles and other benzo-fused heterocyclic derivatives[158, 159]. The key step in this novel methodology is the generation of a benzyne-tethered organolithium compound, which undergoes an intramolecular anionic cyclization. Further reaction with electrophiles provides functionalization of the cyclized product. The *ortho*-lithiation of either 2-fluoro, **270**, or 3-fluoro *N*,*N*-diallylaniline, **271**, initiates an anionic cascade leading to *N*-allyl-3,4-disustituted indolines **272** (Scheme 84)[160]. The loss of LiF is followed by regioselective intermolecular



(266) **(267)** **(268)** **(269)**

SCHEME 83



(270) 2-F
(271) 3-F

(272)
R = *n*-Bu, 54–55%

(270) **(273)** **(274)**

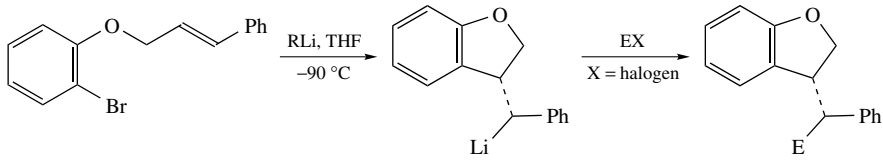
(272a)
R = *n*-Bu, 51%

(275)

SCHEME 84

addition of the organolithium reagent to the benzyne intermediate **273**, and cyclization of the aryllithium **274** giving the 3-lithium substituted indoline derivative, **275**, which could be trapped by electrophiles to give, e.g., **272a** (Scheme 84).

We recently reported a convenient and efficient synthetic route to new 3-substituted 2,3-dihydrobenzo[*b*]furans **278** based on the tandem cyclization–γ-alkylation of 2-bromophenyl (*E*)-3-phenyl-2-propenyl ether **276** whose operational simplicity could find favor in many applications[161]. Previous attempts using 2-bromophenyl (*E*)-2-propenyl ether failed because the cyclic intermediate underwent a γ-elimination. We thought that a likely strategy to overcome the γ-elimination in the cyclic (2,3-dihydrobenzo[*b*]furanyl)methyllithium intermediate could be substitution by a phenyl moiety that could provide increased resonance stabilization to the cyclic lithium intermediate **277** (Scheme 85).



(276) **(277)** **(278)**

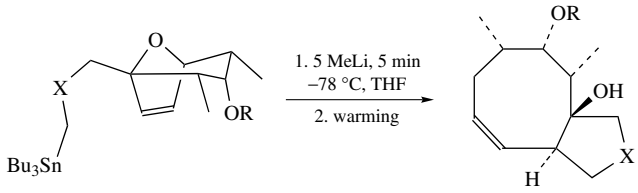
R = *n*-Bu,	E = Et	79%	(dr 79:21)
R = *n*-Bu,	E = *n* -Pr	77%	(dr 99:1)
R = *n*-Bu,	E = *n* -Pr	73%	(dr 97:3)
R = Ph,	E = *n* -Pr	94%	(dr 97:3)
R = Ph,	E = *n* -Pr	100%	(dr 99:1)

SCHEME 85

Indeed, the tandem sequence based on lithiation–cyclization followed by trapping of the lithiated cyclic intermediate **277** by appropriate electrophiles afforded good to excellent yields of alkyl substituted 2,3-dihydrobenzo[*b*]furanes **278** (Scheme 85).

The intramolecular carbolithiation of vinyllithium derivatives of substituted *N*-allyl-*N*-(2-bromoallyl)amine can lead to the formation of 5- or 6-membered cyclic products through a 5-*exo* or 6-*endo* process depending on the precursor amine. There are few precedents for the preparation of six-membered rings by anionic carbocyclization of unactivated double bonds. The first 6-*endo* closure was described by Barluenga and coworkers[149]. An elegant tandem process involving anionic intramolecular cyclization-ring opening of oxabicyclic[3.2.1] systems **279** was reported as a route to polycyclic molecules (Scheme 86)[162]. The anionic intramolecular ring opening of the oxabicyclic compound is efficient for tethers with a variety of substituents in the tether. The bicyclo[5.3.0] systems **280** are generated with complete regio- and stereo-control.

On the other hand, alkenyl aryllithiums can undergo diastereoselective cyclizations in very good yields. Pedrosa and coworkers[163] reported that chiral 2-(*o*-bromophenyl)-substituted perhydro-1,3-benzooxazines **281**, initially transformed to the aryllithium derivative, gave the intramolecular 6-*exo* carbolithiation reaction with unactivated double bonds attached to the nitrogen substituent of the heterocycle (Scheme 87). By adding 2 equivalents of TMEDA to the aryllithium derivative 1,3-benzooxazines **281** prepared at $-90\,^{\circ}C$,



(279) **(280)**

R = H, X = O, 85%
R = Me, X = O, 82%
R = H, X = S, 88%
R = Me, X = S, 80%
R = H, X = NMe, 80%

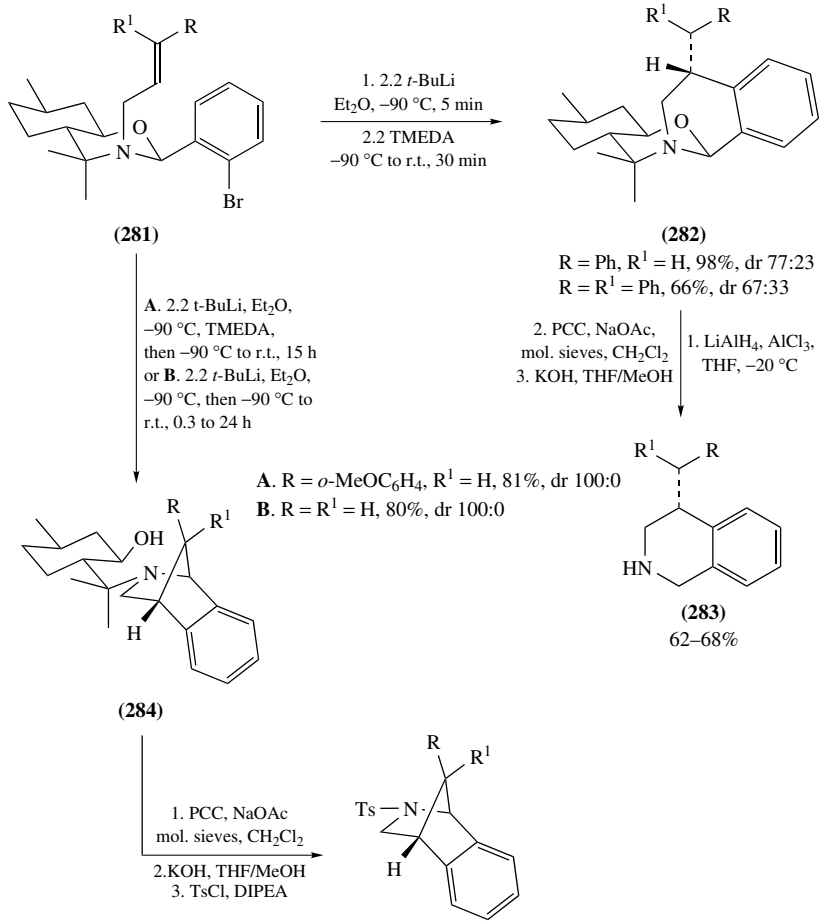
SCHEME 86

and allowing the mixture to reach room temperature slowly over 30 min, the 6-*exo* cyclization products, **282**, were obtained. With longer reaction time or if no TMEDA was used, the cyclized lithium intermediates reacted intramolecularly with the *N*,*O*-acetal system giving 2-azabenzonorbornane derivatives **284**.

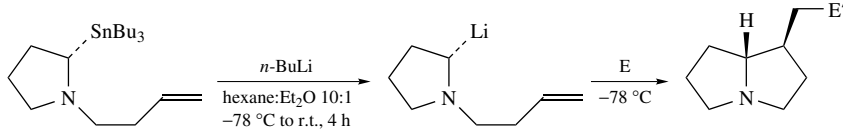
The 6-*exo* cyclization is only faster than the 5-*exo* cyclization if the terminal alkene has a group that stabilizes the lithiated intermediate generated in the cyclization. Cyclization occurs by coordination of the lithium atom with the π-system, followed by a *syn* insertion through a chair-like transition state. In this case, the heteroatom has no influence. In the absence of TMEDA, an intramolecular attack of the alkyllithium on the iminium formed during the opening of the N−O acetal system takes place. The reactions are highly stereoselective and afford a useful methodology for the synthesis of enantiopure 4-substituted tetrahydroisoquinolines **283** or 7-substituted 2-azabenzonorbornanes **285** through an anionic 6-*exo* cyclization of unactivated alkenes.

The usually high configurational stability at the chiral center in enantiomerically enriched organolithium species made them particularly attractive for their use in asymmetric synthesis[164]. A good example of the retention of the stereochemistry at the carbanion center during an anionic cyclization from a chiral α-aminoorganolithium was reported by Coldham and coworkers. Thus, the stannane **286**, on treatment with *n*-BuLi gave the pyrrolizidine **288** with complete diastereoselectivity and enantioespecificity (Scheme 88)[165]. Racemization can usually compete with cyclization, thereby accounting for the loss in enantiopurity. Unusually, the organolithium species **287** is formed at r.t., but no racemization takes place[166]. Trapping of the organolithium resulting from the anionic cyclization with a range of electrophiles constitutes a good synthesis of the derivatives **288**. The stereoselectivity of this anionic cyclization contrasts with the radical cyclizations that lead to racemic products[167].

The Michael adduct can be the precursor of several cyclizations giving rise to new tandem sequences. This has been mainly due to the mechanistic aspects of the process itself and to the synthetic potential of the resultant products. A new stereoselective synthesis of pyrrolo[2,1-*a*]isoindol-5-ones has been described. It consisted of a sequential Michael addition to the *in situ* generated anion of methyl *N*-phthaloylalaninate **289**, onto a series of conjugate acceptors. Cyclization of the resultant anion intermediate by condensation with one of the carbonyl imido groups gave the desired products **291** in good yields as single isomers in only one step (Scheme 89).

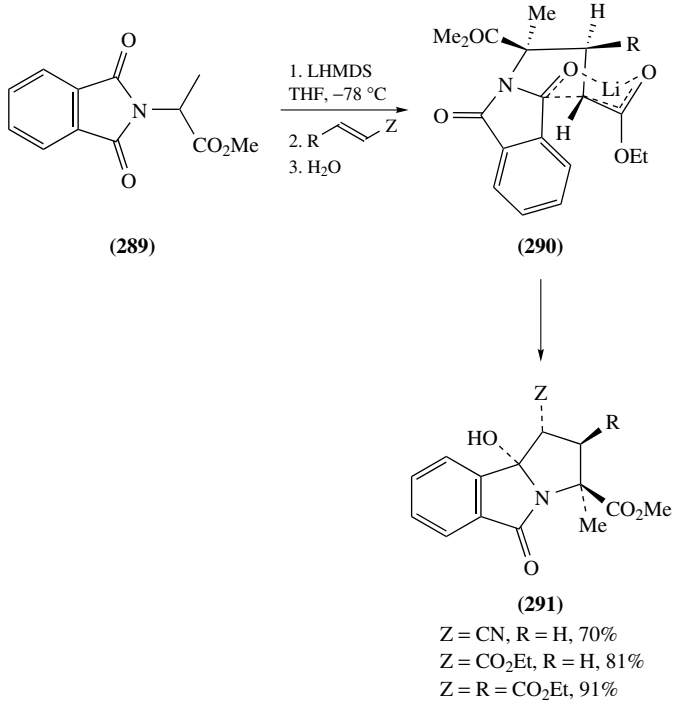


SCHEME 87



E = TMSCl; E′ = TMS, 63%
E = Ph_2CO; E′ = $C(OH)Ph_2$, 62%

SCHEME 88



(289) **(290)**

(291)

Z = CN, R = H, 70%
Z = CO_2Et, R = H, 81%
Z = R = CO_2Et, 91%

SCHEME 89

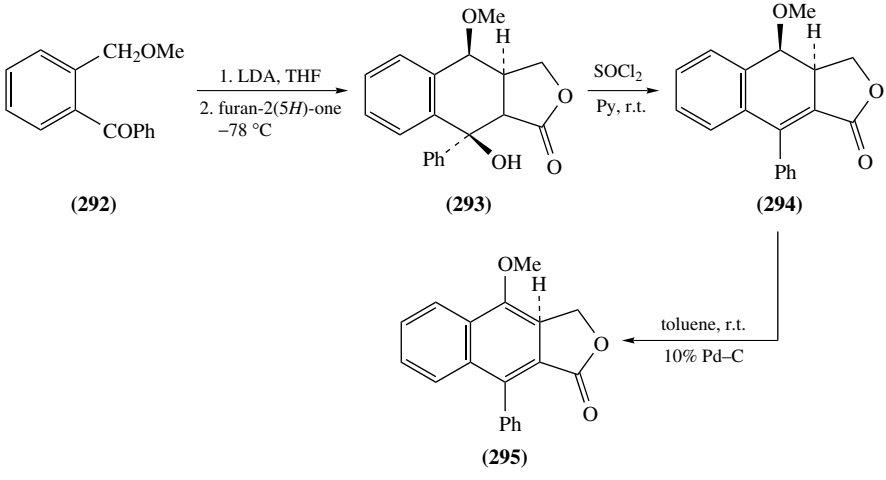
The authors rationalized the high stereoselectivity observed in terms of the six centered chair-like *Z*-enolate transition state (shown as **290** for Z = CO_2Et), which involves the coordination of the two oxygen atoms to the lithium ion.

A tandem Michael addition/cyclization was also the key step in the synthesis of furanone lignan derivatives recently described (Scheme 90).

The tandem sequence occurs between *o*-benzoylbenzyllithiums and furan-2-(5*H*)-one[168]. The *o*-benzoyl-α-methoxybenzyllithium intermediate was generated by deprotonation of 2-methoxymethylphenyl phenyl ketone, **292**, with LDA. Treatment of the α-lithiated product with furan-2-(5*H*)-one afforded the Michael addition/cyclization product, **293**. The 9-aryl-9-hydroxy-3*a*,4,9,9*a*-tetrahydronaphtho[2,3-*c*]furan-1-(3*H*)-one **293** thus obtained was converted into the corresponding 9-aryl-4-methoxy-3*a*,4-dihydronaphtho[2,3-*c*]furan-1-(3*H*)-one **294** in good yield; the subsequent dehydrogenation gave the desired product 4-methoxy-9-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one **295**.

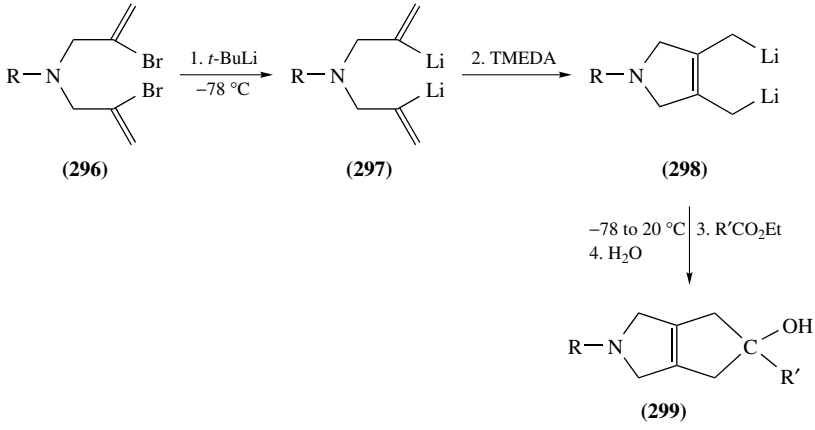
Bis(2-lithioallyl)amines **297**, a class of non-conjugated dilithio reagents which were formed from **296**, were reported by Barluenga and coworkers to react with carboxylic esters affording cyclic alcohols **299** after hydrolysis (Scheme 91)[169]. A dilithiated dihydropyrrol **298** was generated from **297** via intramolecular carbolithiation of a lithiated double bond and served as the key intermediate.

Biehl and coworkers[170] have described a facile one-step preparation of substituted 3-benzyl-1-hydroxynaphthalene-2-carbonitriles **301** and 11-amino-5*H*-anthra[2,3-



(292) **(293)** **(294)** **(295)**

SCHEME 90

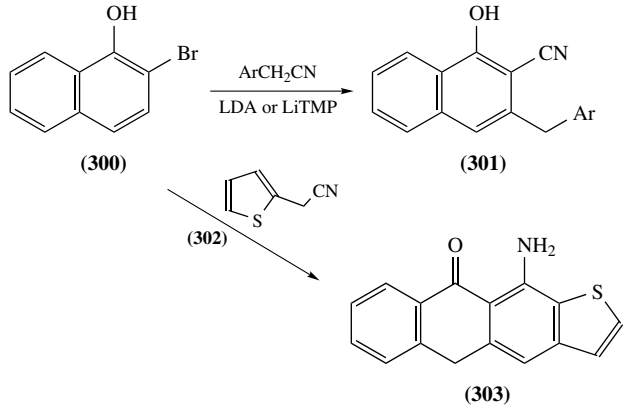


(296) **(297)** **(298)** **(299)**

SCHEME 91

b]thiophen-10-one **303** via 2,3-didehydronaphthalene 1-oxide, starting from 2-bromo-1-naphthol **300** and arylacetonitriles and 3-thienylacetonitrile **302**, respectively, in the presence of LDA or LiTMP (Scheme 92). The reactions proceed via a tandem addition–rearrangement pathway involving a non-synchronous [2 + 2] cycloaddition of *N*-lithiated ketenimine and 2,3-didehydronaphthalene 1-oxide.

The very fast metal–halogen exchange allows intramolecular cyclization reactions, which are known as Parham cyclizations[171]. The potential of Parham cyclizations as a useful stereoselective cyclization procedure has proven to be extremely interesting[172]. Thus, it has been recently demonstrated that iodinated *N*-phenethylimides tolerate iodine–lithium exchange, giving rise to the isoquinoline nucleus **304**, via a Parham-

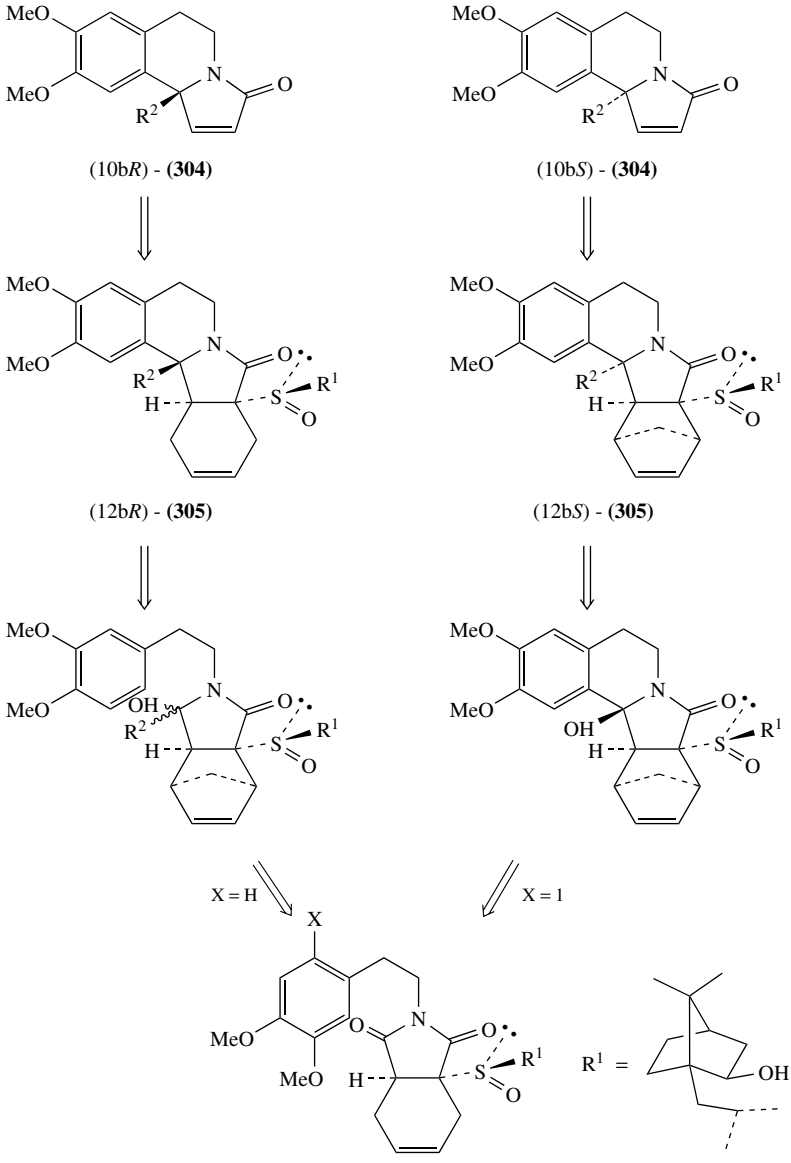


SCHEME 92

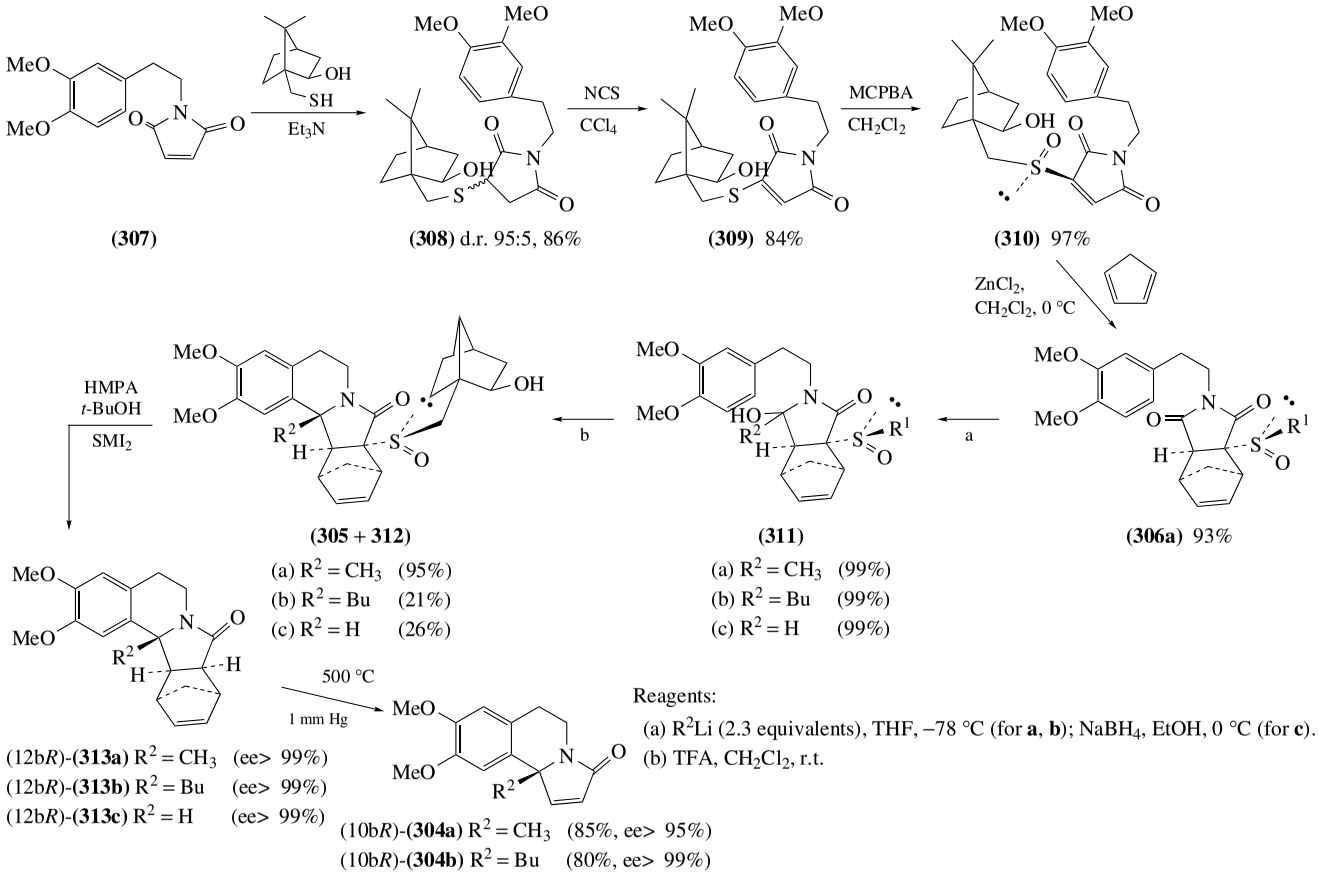
type cyclization[173,174]. The fused isoquinolones **304**, and **305**, obtained from the sulfinylnorbornenedicarboximide **306**, represent immediate precursors of bicyclic *N*-acyliminium ions, which can be transformed into a variety of derivatives via intermolecular α-amidoalkylation with different nucleophiles. This has been illustrated by the synthesis of the isoindolo[1,2-*a*]isoquinoline skeleton of nuevamine-type alkaloids[175,176]; the authors have developed a diastereodivergent synthesis of 1,10*b*-*cis*- and 1,10*b*-*trans*-thiazolo[4,3-*a*]isoquinoline systems based on both types of cyclizations (Scheme 93)[173].

Addition of 10-mercaptoisoborneol to maleimide **307** afforded succinimide **308**. Subsequent treatment with NCS afforded maleimide **309**, which was oxidized with MCPBA to yield sulfinylmaleimide **310** (Scheme 94). The sulfoxide group controls the stereochemistry of an asymmetric Diels–Alder reaction. Thus, reaction of sulfinylmaleimide **310** with cyclopentadiene in the presence of $ZnCl_2$ afforded sulfinylnorbornenedicarboximide **306a**. (Formation of a zinc chelate with sulfinyl and carbonyl oxygen atoms would direct the attack of cyclopentadiene from the less hindered side to afford the *endo* product **306a**.) Addition of MeLi or BuLi (2.3 equivalents) afforded α-hydroxylactams **311a** and **311b**. Reduction of imide **306a** with excess $NaBH_4$ at 0 °C affords hydroxylactam **311c**. Treatment of α-hydroxylactams **311a**, **311b** and **311c** with an excess of TFA at room temperature furnished the expected methaneisoindoloisoquinolines (12b*R*)-**305a**, **305b** and **305c**, together with their derivatives, **312a**, **312b** and **312c**, in which trifluoroacetylation of the hydroxyl group of the auxiliary had occurred. Thus, the intramolecular α-amidoalkylation reaction efficiently afforded the isoquinoline system with complete stereocontrol, as isoindoloisoquinolines **304** and **305** were isolated as single diastereoisomers, (12b*R*)-**305a** and **305b**. The *O*-trifluoroacetyl derivatives **312a** and **312b** were converted separately into the same isoindoloisoquinolines (12b*R*)-**313a** and **313b**. All reactions produced quantitative yields and a single diastereomer.

Parham cyclization of **306b** provided hydroxylactam (12b*S*)-**314** as a single diastereomer, which was submitted to intermolecular α-amidoalkylation with different nucleophiles to afford isoindoloisoquinolines (12b*S*)-**305a**, **305b**, **305c** and **305d** with complete inversion of configuration at C-12b (Scheme 95). Removal of the chiral auxiliary under the previously tested conditions (SmI_2, HMPA, *t*-BuOH) furnished isoindoloisoquinolines (12b*S*)-**315** in good yield and high enantiomeric purity. The use of refluxing *o*-DCB to carry out the retro-Diels–Alder reaction provided enantiomerically pure pyrroloisoquinolines (10b*S*)-**304a** and **304b**.


MeO
MeO
N
O
R2
(10bR) - (304)
(10bS) - (304)
H
S
R1
(12bR) - (305)
(12bS) - (305)
OH
X = H
X = 1
X
(306)
(a) X = H
(b) X = 1
R1 =

SCHEME 93



(307)

(308) d.r. 95:5, 86%

(309) 84%

(310) 97%

(306a) 93%

(311)

(a) $R^2 = CH_3$ (99%)
(b) $R^2 = Bu$ (99%)
(c) $R^2 = H$ (99%)

(305 + 312)

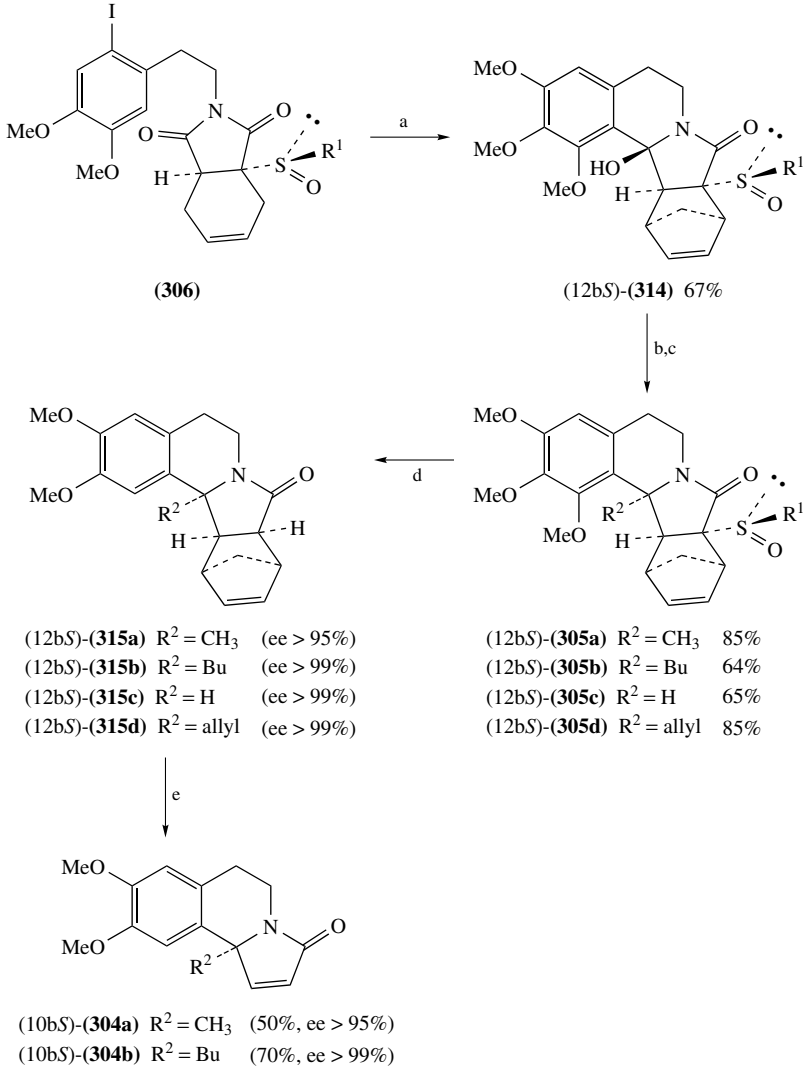
(a) $R^2 = CH_3$ (95%)
(b) $R^2 = Bu$ (21%)
(c) $R^2 = H$ (26%)

(12b*R*)-(**313a**) $R^2 = CH_3$ (ee> 99%)
(12b*R*)-(**313b**) $R^2 = Bu$ (ee> 99%)
(12b*R*)-(**313c**) $R^2 = H$ (ee> 99%)

(10b*R*)-(**304a**) $R^2 = CH_3$ (85%, ee> 95%)
(10b*R*)-(**304b**) $R^2 = Bu$ (80%, ee> 99%)

Reagents:
(a) R^2Li (2.3 equivalents), THF, −78 °C (for **a**, **b**); $NaBH_4$, EtOH, 0 °C (for **c**).
(b) TFA, CH_2Cl_2, r.t.

SCHEME 94



(306)

(12b*S*)-(**314**) 67%

(12b*S*)-(**315a**) $R^2 = CH_3$ (ee > 95%)
(12b*S*)-(**315b**) R^2 = Bu (ee > 99%)
(12b*S*)-(**315c**) R^2 = H (ee > 99%)
(12b*S*)-(**315d**) R^2 = allyl (ee > 99%)

(12b*S*)-(**305a**) $R^2 = CH_3$ 85%
(12b*S*)-(**305b**) R^2 = Bu 64%
(12b*S*)-(**305c**) R^2 = H 65%
(12b*S*)-(**305d**) R^2 = allyl 85%

(10b*S*)-(**304a**) $R^2 = CH_3$ (50%, ee > 95%)
(10b*S*)-(**304b**) R^2 = Bu (70%, ee > 99%)

Reagents: (a) *t*-BuLi, THF, −78 °C. (b) $BF_3{\cdot}Et_2O$.
(c) R_2CuLi or $NaBH_4$/TFA. (d) SmI_2, HMPA, *t*-BuOH. (e) *o*-DCB, reflux.

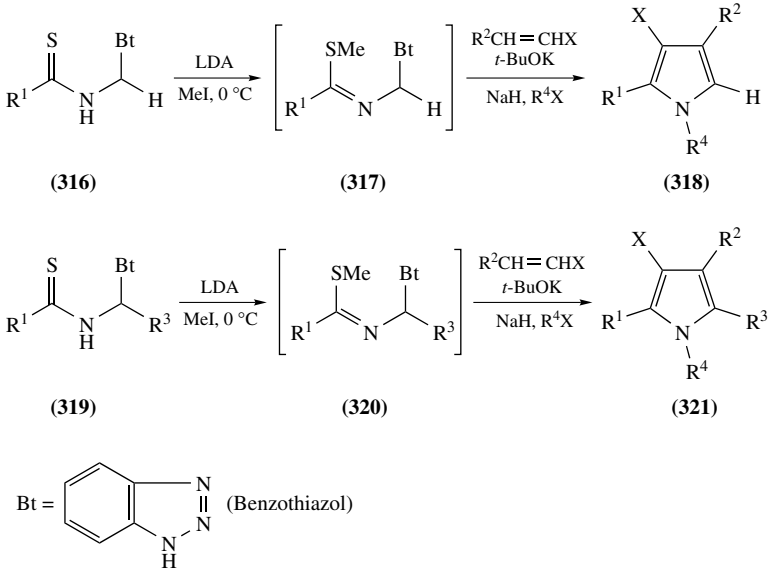
SCHEME 95

B. Aromatic Heterocycles

1. Single rings

LDA has been used to generate enolates in the one-pot synthesis of substituted pyrroles, which are common pharmacophores for numerous natural compounds including antibiotics,

alkaloids and other therapeutic agents with a wide spectrum of biological activity. Katritzky and coworkers[177] have developed an one-pot sequence for the synthesis of polysubstituted pyrroles, starting from thioamides (Scheme 96). By treatment of the thioamides **316** and **319** with LDA at −30 °C (or *t*-BuOK in THF at 0 °C), followed by the addition of MeI, the corresponding *S*-methylthioamidates **317** and **320** were formed. Conversion into the desired pyrroles, **318** and **321**, was achieved by subsequent addition of 3 equivalents of *t*-BuOK and an activated olefin to the reaction mixture at 25 °C. This method allowed the introduction of various substituents.

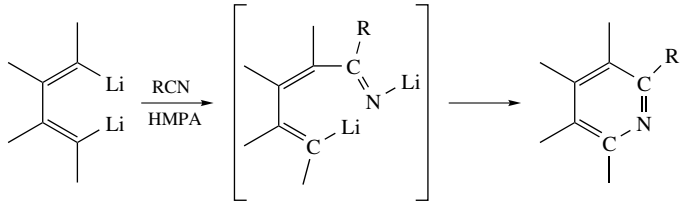


SCHEME 96

The direct cycloaddition reaction of 1,4-dilithio-1,3-dienes with nitriles developed by Xi and coworkers[178] affords *N*-containing heterocycles such as pyridine derivatives. *N*-lithioketimines, the addition reaction intermediates of organolithium diene compounds to nitriles, may be intramolecularly trapped to afford cyclic *N*-containing compounds such as pyridines derivatives. Thus, subsequent intramolecular nucleophilic substitution of organohalides has been used for the synthesis of *N*-containing heterocycles, as demonstrated by Kristensen, Begtrup and coworkers[179].

Surprisingly, the 1,4-dianion **6** of the 1,4-dilithio-1,3-dienes reacted with nitriles in the presence of HMPA at room temperature for 1 h to give, via **322**, the substituted pyridines, **323**, as well as the 2, 2′-bipyrimidines and tetrahydroisoquinolines in high yields (Scheme 97)[180]. No dihydropyridines or related intermediate products were observed in the reaction mixtures before work-up, as determined by NMR spectroscopy.

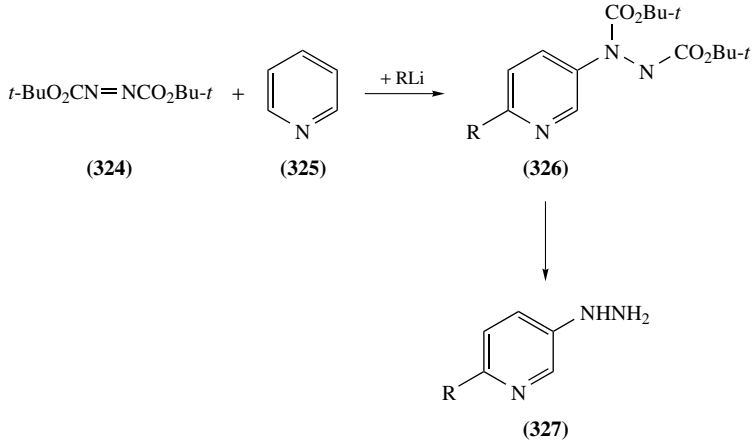
The alkyllithium reagents to be used in tandem reactions can be prepared by direct alkylation or by an aldol reaction involving nucleophilic addition of the alkyllithium as the first step. Several complex heteroaromatic compounds, which can serve as pivotal intermediates in synthetic strategy of biologically active species, could be synthesized by this procedure. The preparation of polysubstituted pyridines has been an active research area for many years[181]. The synthesis of 2-alkyl- or 2-aryl-5-hydrazinopyridines **327** has never been performed directly from pyridine. The reported methods involve several steps



(6) **(322)** **(323)**

SCHEME 97

and expensive intermediates[182]. Zhang and Tan[183] described a new one-pot method for the synthesis of 2-alkyl- and 2-phenyl-5-hydrazinopyridine using C−Li compounds. The complex alkyl-substituted pyridines **326** were generated from pyridine **325** by reaction with an organolithium compound followed by reaction with di-*t*-butyl azodicarboxylate (DBAD, **324**). The novel feature of this synthesis is to carry out three chemical reactions, i.e. double nucleophilic addition and aromatization in one pot (Scheme 98).



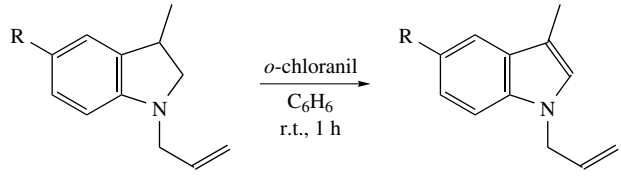
(324) **(325)** **(326)** **(327)**

SCHEME 98

The first nucleophilic addition of the organolithium compound to pyridine **325** occurred between −10 °C and 20 °C; the second nucleophilic addition, of dihydropyridines to DBAD, was carried out initially at −70 °C followed by warming to room temperature. Finally, stirring of the 2,5-disubstituted dihydropyridines at room temperature in air afforded the aromatic products **326**, which after removing the *t*-Boc moiety produced **327** (Scheme 98).

2. Condensed rings

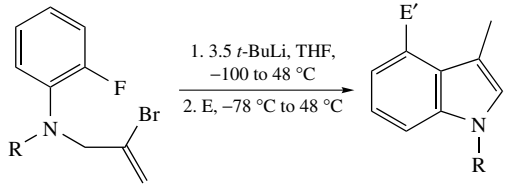
The indolines **328** were oxidized to their respective indoles, **329**, by employing several oxidants. Two representative examples are presented in Scheme 99 by using 1 molar equivalent of *o*-chloranil at room temperature. A variety of protocols are available for *N*-deallylation of the resulting *N*-allylindoles[184].



(328) **(329)**
R = H 82%
R = CH_3 80%

SCHEME 99

The reaction of *N*-(2-bromoallyl)-*N*-2-fluoroaniline alkyl **330** with 3.5 equivalents of *t*-BuLi in THF at −110 to −40 °C for 3 h, followed by treatment with different electrophiles at −78 to 20 °C, produces 1,3-dialkyl-4-functionalized indoles **331** in moderate to good yields (Scheme 100)[158].



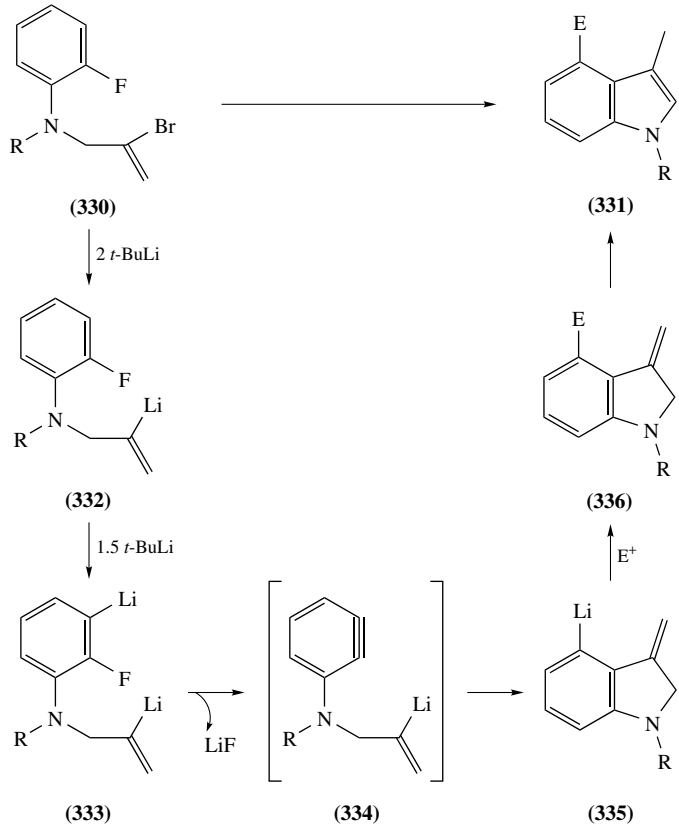
(330) **(331)**

(a) R = Me	E = MeBr;	E′ = H	75%
(b) R = Me	E = Me_2CO;	E′ = Me_2COBr	73%
(c) R = $CH_2CH{=}CHCH_3$	E = H_2O;	E′ = H	72%

SCHEME 100

It was shown that the amine **330** (R = CH_3) reacted with *t*-BuLi to give *N*-(2-lithioallyl)amines **332** through halogen–metal exchange, and by the additional equivalents of *t*-BuLi it probably undergoes proton abstraction *ortho* to the fluorine atom giving the intermediate **333**. The subsequent elimination of LiF produces the benzyne intermediate **334**, which was efficiently trapped by the 2-lithioallyl unit, affording a C-4-lithiated 3-methyleneindoline derivative **335**. Treatment of **335** with electrophiles (e.g. Bu_3SnCl, PhCHO, $(CH_3)_2CO$, $ClCO_2Et$, ClC_6H_4CN, Ph–CH=NH–Ph) allowed the functionalization through **336** to the corresponding indole derivatives **331** (E = Bu_3Sn, PhCHOH, $(CH_3)_2C(OH)$, CO_2Et, C_6H_4CN, Ph–C(H)NH–Ph) (Scheme 101). The authors examined the use of the 2-fluorophenyl ether and thioether as potential substrates that could afford oxygen and sulfur heterocycles by the same methodology, but in those cases the cyclization did not take place because the intermediate underwent β-elimination.

The carbolithiation of unactivated alkenes has also proven very successful for the synthesis of complex polycyclic systems. This has typically been achieved by reaction sequences utilizing an intramolecular carbolithiation process to generate a variety of carbocycles[185] and heterocycles[186]. To achieve the intermolecular carbolithiation reaction required to initiate a controlled cascade reaction sequence for the generation of indole ring scaffold, Kessler and coworkers[44] have expanded the synthetic utility of the styrene



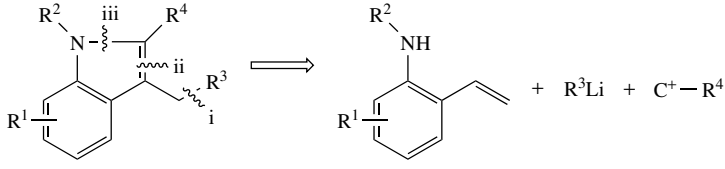
SCHEME 101

carbolithiation reaction for the specific case of *ortho*-substituted aminostyrenes **337**. Upon generation of the intermediate anion via organolithium addition, followed by a subsequent reaction with specific electrophiles, a cascade reaction process could be set up between the reacted electrophile and the amine components, facilitating an *in situ* ring closing and dehydration to generate indole ring systems, **338**.

The formation of the bonds (ii) and (iii) is not unusual for an indole synthesis; what is unique is that the process is initiated by the formation of the exocyclic carbon–carbon bond in (i), which in the process introduces a further diversity point into the products (Scheme 102).

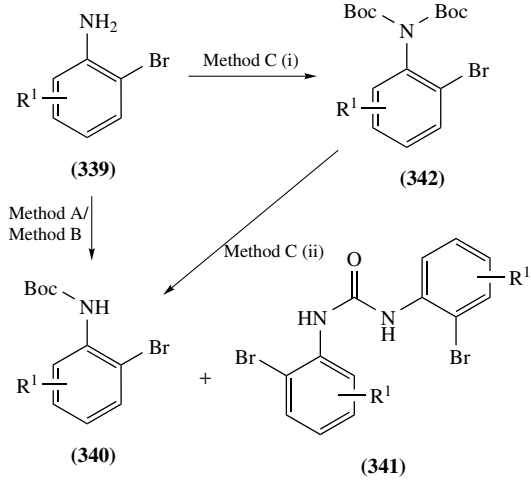
N-Boc protection of the commercially available 2-bromoanilines **339** was carried out by using a 2.5-fold excess of Boc_2O in the presence of a catalytic amount of DMAP (Scheme 103, method C)[187]. This resulted in the formation of the di-Boc-protected substrates **342**, from which the selective removal of one Boc group using trifluoroacetic acid in CH_2Cl_2 could be readily achieved giving the desired products **340** and **341** (Scheme 103).

Suzuki–Miyaura cross-coupling of **343** with 2,4,6-trivinylcyclotriboroxane–pyridine complex proved to be a very efficient method for the generation of the styrenes **337**, R^2 = Boc in high yields (Scheme 104)[188]. The procedure was tolerant to all the aryl substituents attempted and to the three different nitrogen substituents.



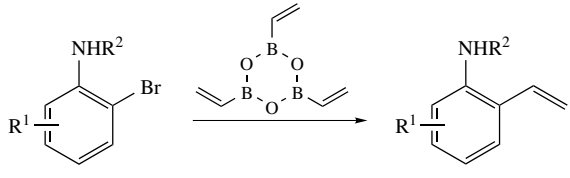
(338) **(337)**

SCHEME 102



Method A: 1 equivalent Boc, 0.1 equivalents DMAP, THF, reflux 24 h.
Method B: 2.5 equivalents Boc_2O in THF, reflux 24 h.
Method C: i) 2.5 equivalents Boc, 0.1 equivalents DMAP, THF, reflux 24 h.
ii) CF_3COOH, CH_2Cl_2, to r.t., 16 h

SCHEME 103



Conditions: $Pd(PPh_3)_4$ 5%, K_2CO_3, DME/H_2O, reflux, 20 h.

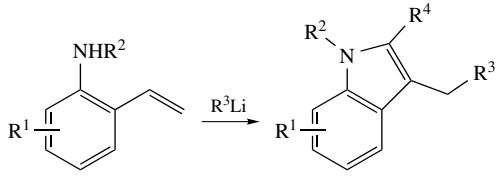
SCHEME 104

Kessler and coworkers[44] investigated the indole synthesis using DMF as the electrophile, which in the reaction sequence provides the unsubstituted C2 carbon of the indole ring. In a typical procedure, the organolithium reagent was added dropwise over 30 min to a solution of styrene in dry diethyl ether at $-78\,^{\circ}C$ under an inert nitrogen

atmosphere. The reaction mixture was then stirred for 1 h at −78 °C. In the case of less reactive primary alkyllithiums, the additive TMEDA was included and the reaction temperature allowed to rise to −25 °C and maintained for 2 h at this temperature. The electrophile, DMF, was then added at −78 °C, and after 10 min the reaction mixture was acidified with 2 M HCl.

The reaction sequence was shown to be successful in generating the indole ring with a wide distribution of substituents in the 1, 3, 4, 5 and 7 positions. The reaction sequence was tolerant of varying substituents (Me, OMe, F) in the *meta* position to the vinyl group of the aminostyrenes **339** with the isolated yields varying from moderate to excellent.

The mild acidification conditions chosen allowed the retention of the Boc group on the indole nitrogen, which could be advantageous for further synthetic transformation of these products. The *N*-ethyl- or N-benzyl-substituted substrates **337** also yielded their corresponding nitrogen-substituted indoles, demonstrating an alternative direct route to *N*-alkyl- or N-benzylindoles. The reaction was tolerant for the tested series of *tert*-, *sec*- or *n*-butyl with each of the alkyllithiums, resulting in good yields with few exceptions. The deprotection of *N*-Boc-substituted indoles was readily accomplished by stirring at room temperature with 12 M HCl in ethyl acetate, generating **338** in excellent yields (Scheme 105).

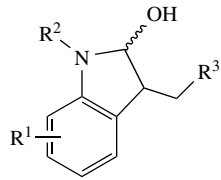


(337) **(338)**

Conditions: i) R^3Li, −78 °C, 1.5 h, or −25 °C with TMEDA, 2.5 h, Et_2O;
ii) DMF, −78 °C, 10 min; iii) 2M HCl, THF, 5 h.

SCHEME 105

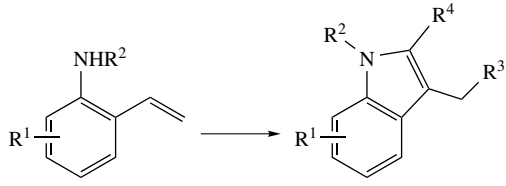
The authors proposed the following reaction sequence for the indole formation: the aniline nitrogen is deprotonated upon the addition of the first equivalent of organolithium, and a second equivalent carbolithiates the vinyl double bond leading to a new benzylic lithiated species. This reacts with the electrophile DMF to give an aldehyde precursor, which after acidification undergoes a ring closure to a substituted 2-hydroxy-2,3-dihydroindole **344**, which dehydrates to generate the final indole products. Using milder acidification conditions, one derivative of **344** ($R^1 = H$, $R^2 =$ Boc, $R^3 = t$-Bu) was isolated and characterized.



(344)

The use of DMF as an electrophile precludes the direct introduction of a substituent at the C2 of the indole ring. The inclusion of functionality at this position was achieved by a

change of the electrophile to a substituted nitrile. The reaction of nitriles is slower than that of DMF, and an efficient reaction was achieved by stirring at −25 °C for 2 h. Subsequent treatment of the reaction mixture with 12 M HCl in ethyl acetate was successful for the direct generation of the *N*-unsubstituted 2,3,5-substituted indoles **338** in acceptable yields (Scheme 106). This methodology was capable of introducing a range of C2 substituents, including phenyl, thienyl and sterically bulky *tert*-butyl groups.



(337) **(338)**

Conditions: i) R^3Li, −78 °C or −25 °C with TMEDA, 1.5 h, Et_2O;
ii) R^4CN, −25 °C, 2 h; iii) 12 M HCl, EtOAc, 16 h.

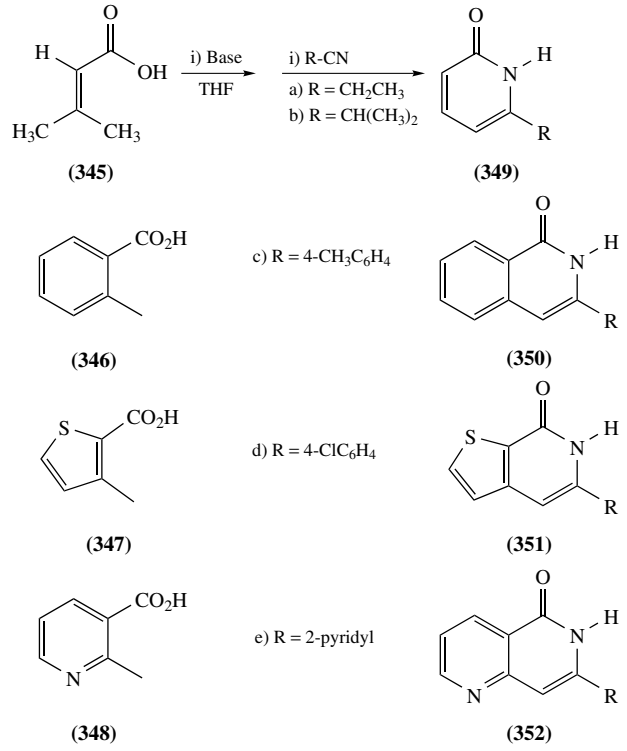
SCHEME 106

The generation of a very reactive organometallic intermediate via metalation or halogen−metal exchange followed by an intramolecular ring-closure reaction is a powerful way of constructing complex polycyclic molecules[189]. Development of new approaches to the 2-pyridone ring constitutes a very important area of interest due to the high number of biologically active molecules containing this moiety[190] and to the facile conversion of pyridones to the corresponding pyridines[191]. Tautomerism between 2-pyridones and 2-hydroxypyridines receives constant attention, because these compounds may act as simple models for investigating the mechanisms of some enzymatic reactions or for discerning the behavior of nucleic acids bases in connection with mutations due to base mispairing[192].

The usefulness of 2-pyridones as intermolecular connectors between building blocks in material science has been demonstrated[193]. Thus, despite the large number of methods known for their synthesis, new procedures are continuously being developed[194]. Brun and coworkers[195] reported the synthesis of substituted 2-pyridones, **349**, from accessible carboxylic acids and nitriles based on the reactivity of dienediolates from unsaturated carboxylic acids[196]. The same authors[197] studied an extension to the synthesis of condensed heteroaromatic systems by introduction of heterocyclic nitriles using 3-methyl-2-butenoic **345**, *o*-toluic **346**, 3-methyl-2-thiophenecarboxylic **347** and 2-methylnicotinic **348** acids which, after double deprotonation, afford the corresponding lithium dianions (Scheme 107) that give rise to trisubstituted-2-pyridones, **350–352**, respectively.

The nature and amount of the amine used for acid deprotonation determines the reaction yield. In most cases, dienediolates of unsaturated carboxylic acids can be generated, without Barbier's reduction or Michael adduct formation, by deprotonation of the corresponding acid with butyllithium in the presence of a catalytic amount of amine[198]. This renders dienediolates compatible with a large number of functional groups, as happens with nitriles where self-condensation is minimized under these conditions. Unfortunately, this cannot be considered a general rule and it is convenient to optimize the amine and its amount for each acid and nitrile.

2-Pyridinecarbonitrile is specially prone to give self-condensation under the basic conditions used, leading to complicated reaction mixtures until the right conditions, usually a catalytic amount of amine, were found. In some cases only the pure trimerization product,



(345) **(349)**

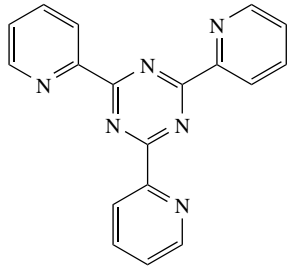
(346) **(350)**

(347) **(351)**

(348) **(352)**

i) THF (2 mL), Base (dialkylamine) (1 equivalent); R-CO_2H, (2.25 mmol), −78 °C, then 60 min at 0 °C. Nitrile, (2.25 mmol) in 2 mL THF; 24 h at r.t.

SCHEME 107

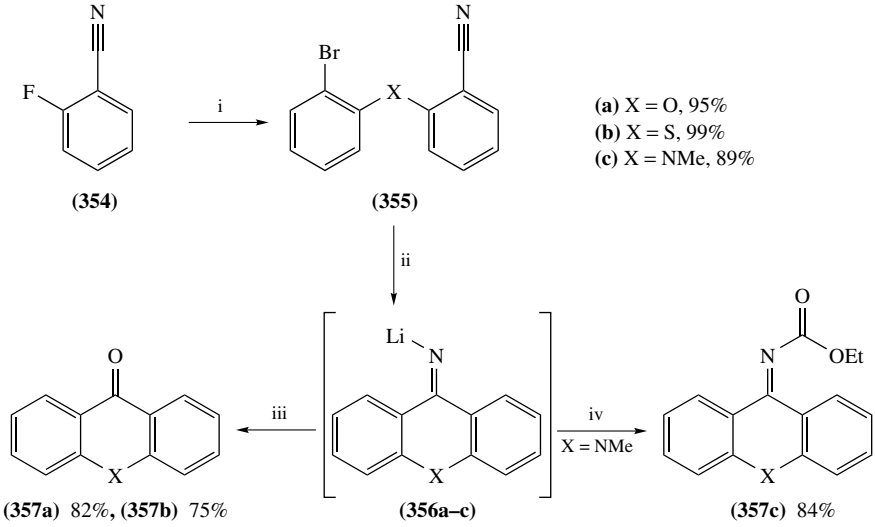


(353)

2,4,6-tris(2-pyridyl)-1,3,5-triazine **353**, is formed. Both amidic and phenolic tautomeric forms of compound **352** precipitate from water in a 2:1 ratio.

Kristensen and coworkers[179a] reported the design and execution of new anionic cascade reactions based on the cyano group functioning as an electrophile giving access to condensed aromatic heterocycles. They reported the intramolecular trapping of metalated

pyrazole derivatives[199]. Scheme 108 outlines the generalization of this approach to the synthesis of xanthone derivatives **357**. Substrates **355a–c** were prepared in one step via nucleophilic aromatic substitution of the fluorine in 2-fluorobenzonitrile, **354**, in very good to near quantitative yields.



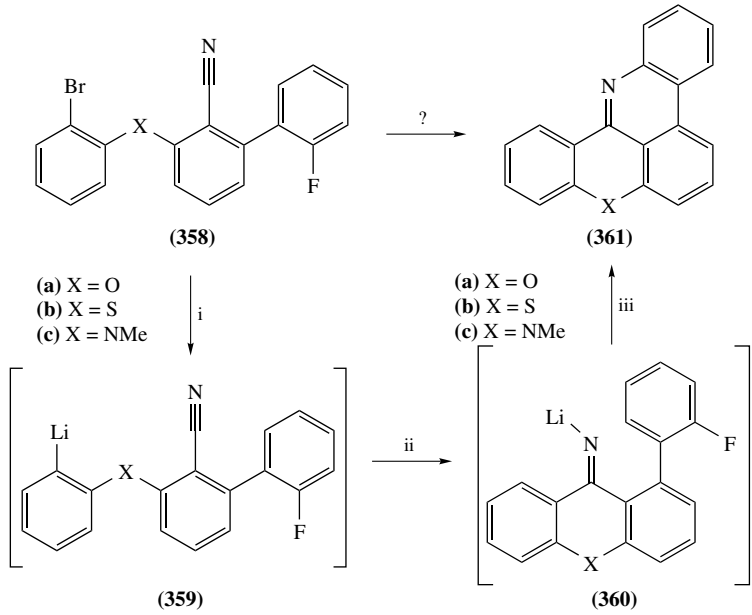
i) **(355a)** 2-bromophenol, K_2CO_3, DMF, 100 °C, 48 h
(355b) 2-bromothiophenol, K_2CO_3, DMF, 100 °C, 24 h
(355c) 1) 2-bromoaniline, *t*-BuOK, DMSO, r.t., 2) MeI
ii) 1) *t*-BuLi, THF, −78 °C to r.t.; 2) MeI
iii) 4 N HCl, 70 °C, 12 h
iv) EtOCOCl

SCHEME 108

The reaction of imine **356c** with ethyl chloroformate gives **357c** in 84% yield. This demonstrates that the intermediate lithioimines could be trapped with electrophiles.

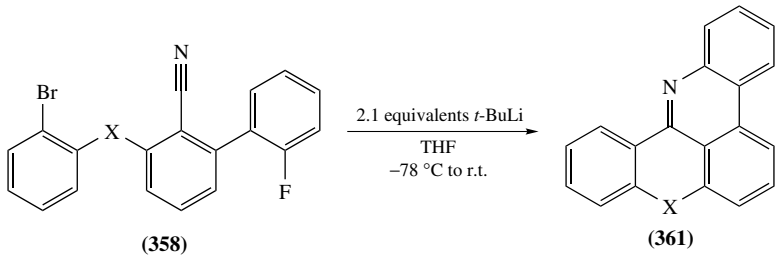
The same authors reported the synthesis of 6-substituted phenanthridines **360** via *intra*-molecular trapping of imine anions **359**[179b]. They speculated that these two observations could lead to the pentacyclic systems **361a–c** from **358a–c** via the cascade process indicated in Scheme 109. They also reported that compounds **358** could be converted into pentacyclic 13-azadibenzo[α, *de*]anthracenes **361** (Schemes 109 and 110).

The required substrates **358a–c** were prepared in two steps: Suzuki–Miyaura coupling[200] of commercially available 2-chloro-6-fluorobenzonitrile, **354**, with 2-fluoroarylboronic ester[201] gave a biaryl in 78% yield. Subsequent regioselective nucleophilic aromatic substitution of the fluorine *ortho* to the activating cyano group, using the conditions described in Scheme 109, gave **361a–c** in 78–92% yield. Addition of **358a–c** to 2.1 equivalents of *tert*-butyllithium in THF at −78 °C followed by warming to room temperature gave the pentacyclic 13-azadibenzo[*a,de*] anthracenes **361a–c** in 74–91% yield. This class of compounds has been reported as potent telomerase inhibitors with potential applications for anti-cancer therapy[202].



Proposed cascade process.
i) Br-Li exchange
ii) intramolecular addition to CN
iii) intramolecular S_NAr

SCHEME 109



(a) X = O (89%)
(b) X = S (91%)
(c) X = NMe (74%)

SCHEME 110

V. CONCLUSIONS

The use of organolithium intermediates in tandem synthetic sequences combines the versatility of the very well known organolithium reagents and their highly stereoselective chemistry, with the economic and environmentally friendly advantages of the 'one-pot' and/or 'cascade' strategy, when compared with the conventional stepwise synthetic pathways.

The present chapter is organized from the synthetic chemist's point of view, describing methodologies for the build-up of C−C or C−heteroatom bonds that give rise to several types of functionalized chains, as well as single and condensed carbocycles and heterocycles, of aromatic or non-aromatic nature. Tandem addition−carbolithiation−substitution sequences allows one to modify both the backbone and the functionality in one tandem operation; furthermore, if the reaction is carried out in the presence of chiral ligands that promote stereoselectivity in pro-chiral compounds, the reaction usually proceeds with high stereochemical control. The use of organolithium reagents followed by stereoselective rearrangements or translocation such as Meisenheimer or Wittig rearrangements produces new, otherwise difficult to obtain, organolithium compounds, able to undergo *in situ* tandem sequences. Several diastereo- or enantioselective tandem Michael-aldol, aldol-Tischenko, aldol-Michael, Michael-aldol-Baylis-Hillman protocols are also discussed. Although the purpose of this chapter is not to show the synthesis of special targets but to provide synthetic routes to carry out specific transformations, some prototype protocols for the synthesis of various molecules used as pharmaceuticals, feromones, alkaloids, pyrethroids etc. are shown as examples. The high reactivity of the anionic intermediates combined with the high stereochemical control allows the triggering of a reaction sequence producing complex molecules in a very efficient mode and minimizing the waste. Since the amounts of solvents, reagents, adsorbents and energy are dramatically decreased, an ever-increasing development of tandem synthetic strategies for the economic and environmentally friendly production of complex molecules is expected.

VI. ACKNOWLEDGMENTS

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CHAPTER 3

The chemistry of acyllithium derivatives

CARMEN NAJERA and MIGUEL YUS

Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, E-03080 Alicante, Spain
Fax: +34 96 590 3549; e-mails: cnajera@ua.es and yus@ua.es

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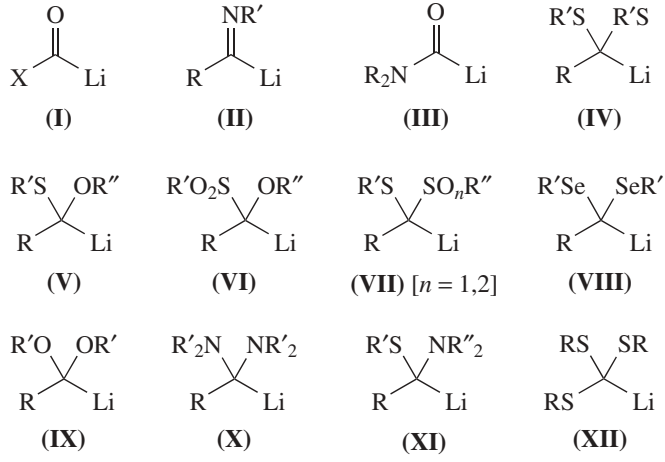
I. INTRODUCTION

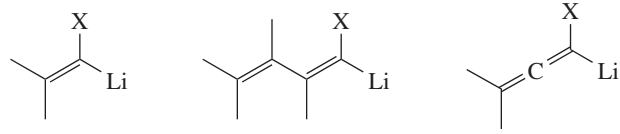
The acylation reaction of electrophilic substrates with acyllithium derivatives is a fundamental process in synthetic organic chemistry. The reversal polarity of the carbonyl group leads to acyl (**I**), imidoyl (**II**) and carbamoyl (**III**) acyllithium derivatives[1–5]. Due to the high reactivity of these reagents, many masked organolithium derivatives and synthetic equivalents have been developed[6–13]. In this chapter, the preparation and synthetic applications of three types of acyllithiums will be considered: (a) Unprotected acyllithium derivatives such as species **I–III**. (b) Different protected acyllithiums in which the carbonyl group has been transformed into thioacetals **IV**, thioethers **V**, α-sulfonyl ethers **VI**, thiosulfoxides and thiosulfones **VII**, selenoacetals **VIII**, acyclic and cyclic acetals **IX**, aminals **X**, aminothioacetals **XI** and orthothioesters **XII**. (c) The last part will concern other acyllithium equivalents, such as α-substituted sp^2-hybridized organolithium compounds **XIII–XV**. These types of organolithium compounds, which have mainly been used as formyl, acyl and carboxylic anions in synthetic organic chemistry, are considered umpoled d^1-reagents according the Seebach's terminology[14]. Stability, structural features and mechanistic aspects will also be considered.



(I) **(II)** **(III)** **(IV)**

(V) **(VI)** **(VII)** [n = 1,2] **(VIII)**

(IX) **(X)** **(XI)** **(XII)**



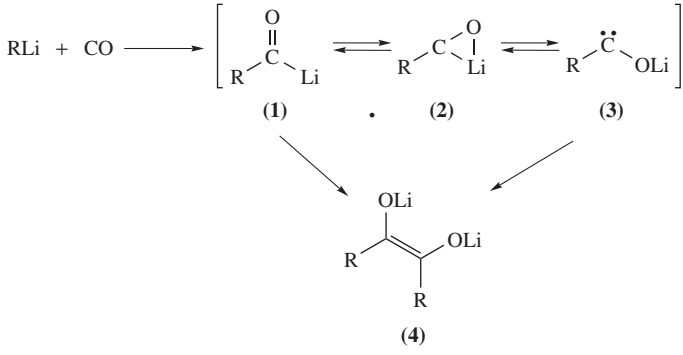
(XIII) **(XIV)** **(XV)**

II. UNPROTECTED ACYLLITHIUM DERIVATIVES

In this section intermediates **I–III** will be considered[1–5]. They present low stability and have to be prepared at very low temperatures and in some cases the electrophile has to be present in the reaction medium.

A. Acyllithiums

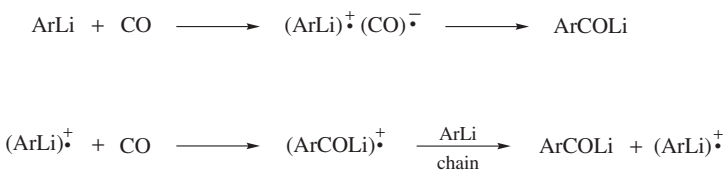
For the preparation of acyllithiums, aryl[15] and alkyllithium[16] reagents are treated at very low temperatures with carbon monoxide. Only one example has been described in the literature[16], in which deprotonation of non-enolizable aldehydes (2-cyclohexyl-2,2-dimethylacetaldehyde or trimethylacetaldehyde) was carried out with lithium tetramethylpiperidide[17]. The carbonylation step takes place at very low temperatures and the generated acyllithium suffers dimerization even at −120 °C giving the dimeric species **4** (Scheme 1). This behavior suggests that the intermediate structure can be either the metal-bridged **2** or the carbene **3**, instead of the species **1**. Theoretical studies performed on LiCHO showed that a lithium atom bridges the C−O as in the structure **2** and that the compound has a strong carbene character[18]. The carbonylation process has been proposed to proceed by an electron transfer mechanism, proving the existence of radical anions by ^{13}C NMR and ESR spectroscopic studies[19–22].



(1) **(2)** **(3)** **(4)**

SCHEME 1. Dimerization mechanism for acyllithiums

The radical anion–radical cation pair can suffer evolution to the corresponding acyllithium[18, 23, 24] in equilibrium with structures **2** and **3** (Scheme 1). The carbonylation reaction can be inhibited by some radical inhibitors. On the other hand, a chain mechanism in which radical cationic species are involved as chain carrying intermediates has also been proposed (Scheme 2)[21].



SCHEME 2. Radical mechanism for the carbonylation of aryllithiums

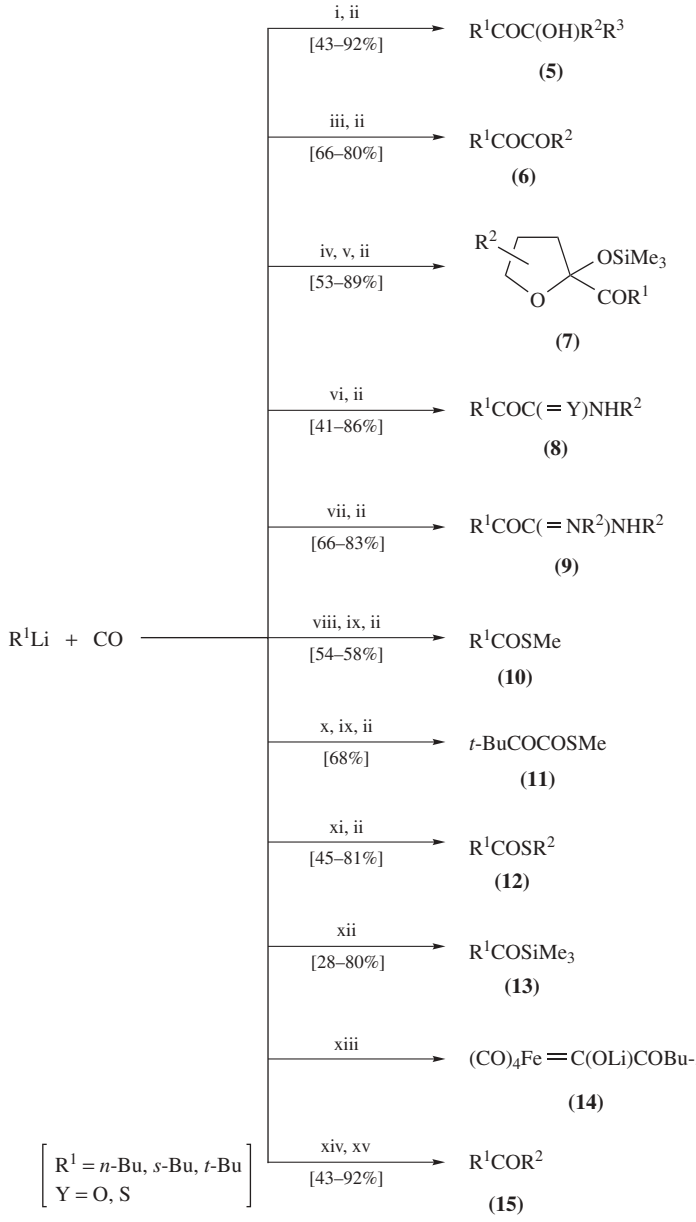
Solutions of acyllithiums generated by reaction of alkyl and aryllithium compounds with CO in liquid xenon at low temperature have been studied by IR spectroscopy[25]. In the case of *n*-butyllithium, the carbonyl adduct was detected at 2047 cm^{-1} at $-100\,^{\circ}C$, which after warming up to $-30\,^{\circ}C$ gave a new absorption at 1635 cm^{-1}. These experimental results are in good agreement with intermediates **2** and **3**. Calculations performed as second-order perturbation theory with the Moller–Plesset partitioning of the Hamiltonian MP2/6-31+G* of MeCOLi indicate two minima on the potential energy surface corresponding to structures **2** and **3** (Scheme 1), the former being the most stable one[26].

The synthetic applications of acyllithiums, generated by reaction of organolithium compounds with carbon monoxide, by treatment with electrophiles started when Nudelman and coworkers found that phenyllithium reacted with carbon monoxide in the presence of alkyl bromides to yield diphenylalkylcarbinols[24,27]. α-Hydroxy-α-phenylacetophenone was also obtained resulting from the dimerization of the carbene intermediate of type **3**. In the absence of electrophiles α,α-diphenylacetophenone was obtained in 94% yield, attributed to the dimerization of the corresponding aroyl anion radical[28].

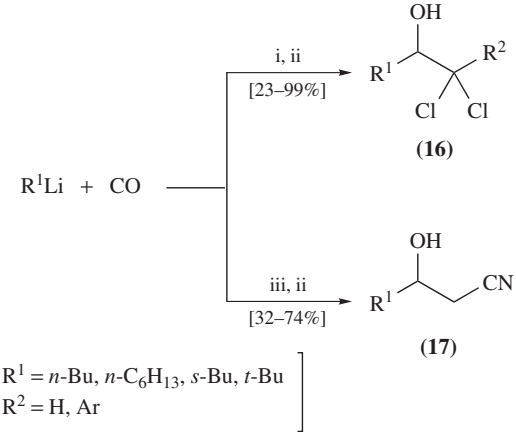
Seyferth and coworkers reported that alkyllithiums and carbon monoxide gave, in the presence of electrophiles, the corresponding acylated products[29–41]. The use of aldehydes and ketones[29–31], esters[32,33], lactones[34], isocyanates and isothiocyanates[35], carbodiimides[36], carbonyl sulfide and carbon disulfide[37], organic disulfides[38], chlorosilanes[16,39], pentacarbonyliron[40] and trialkylboranes[41] gave the corresponding products **5–15** (Scheme 3).

The treatment of the above-mentioned acyllithiums with compounds having acidic protons, such as dichloromethane[42,43], aryldichloromethane[42,43] or acetonitrile[44], produced α,α-dichloroalcohols (**16**) or β-hydroxynitriles (**17**), respectively (Scheme 4). These processes occurred by protonation of the acyllithium by proton abstraction from the dichloro reagent or acetonitrile to give the corresponding aldehyde and the stabilized carbanion. Final reaction between both reagents gave the corresponding addition products.

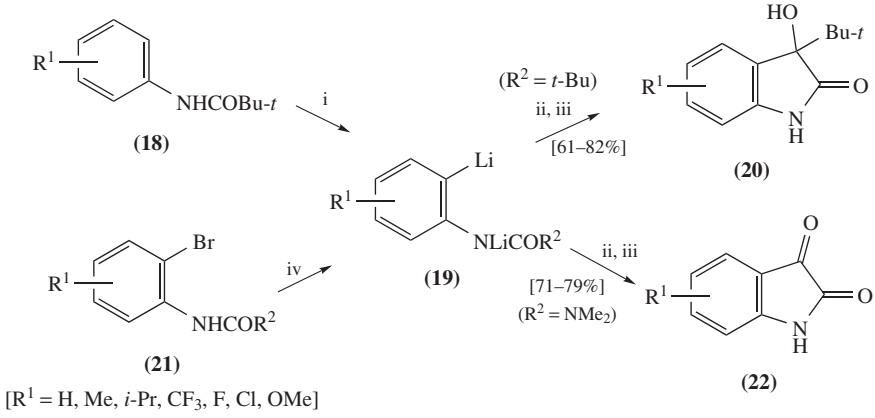
The studies carried out with aryllithium/CO systems showed that they dimerized in the absence of electrophilic substrates to give 1,2-diketones ArCOCOAr[45]. Only in the case of hindered aryllithiums was it possible to trap the corresponding intermediates with carbonyl compounds and esters[46,47]. The slower reaction of aryllithiums with CO compared to the same process with alkyllithiums, probably by a SET mechanism[19], makes difficult the applicability of these intermediates in intermolecular reactions with electrophiles. However, aromatic acyllithiums suffer intramolecular trapping when an amide group is at the *ortho*-position[48–51]. Double lithiation of *N*-pivaloylanilines (**18**) followed by reaction with CO at $0\,^{\circ}C$ gave the corresponding 3-*tert*-butyldioxindoles (**20**) (Scheme 5)[48,49]. When *N′*-(2-bromoaryl)-*N*,*N*-dimethylureas (**21**) were lithiated to the corresponding aryllithium (**19**, $R^2 = NMe_2$) and then allowed to react with CO at $0\,^{\circ}C$, isatins **22** were obtained (Scheme 5)[50,51].



SCHEME 3. Reagents: (i) R^2R^3CO, −110 °C; (ii) NH_4Cl, rt; (iii) $R^2CO_2R^3$, −110 °C; (iv) substituted γ-lactone, −110 °C; (v) Me_3SiCl; (vi) $R^2N{=}C{=}Y$ (Y = O, S); (vii) $R^2N{=}C{=}NR^2$; (viii) CS_2, −110 °C; (ix) MeI; (x) COS, −110 °C; (xi) $(R^2S)_2$, −110 °C; (xii) Me_3SiCl, −110 °C; (xiii) $Fe(CO)_5$, −110 °C; (xiv) $R^2{}_3B$; (xv) H_2O_2, NaOH



SCHEME 4. Reagents: (i) CH_2Cl_2 or $ArCHCl_2$, −100 °C; (ii) NH_4Cl, 0 °C; (iii) CH_3CN, −110 or −78 °C

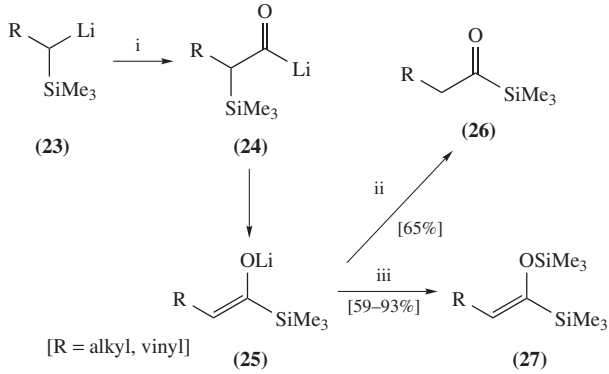


SCHEME 5. Reagents: (i) *n*-BuLi, 0 °C; (ii) CO, 0 °C; (iii) NH_4Cl; (iv) MeLi, 0 °C

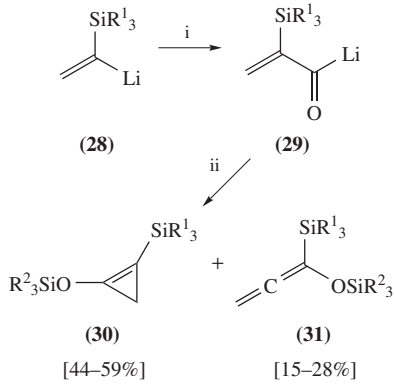
(Trimethylsilyl)alkyl-[52] and allyllithiums[53] **23** reacted with carbon monoxide at 15 °C to give the corresponding acyllithiums **24**, which underwent 1,2-silicon shift (Brook rearrangement) to give the corresponding lithium enolates and dienolates derived from acylsilanes **25** in a stereoselective manner (Scheme 6). The quenching was performed either with water or with Me_3SiCl affording acylsilanes **26** or silyl enol ethers **27**, respectively.

When (trimethylsilyl)vinyllithiums **28** reacted with CO at 15–25 °C it gave intermediate **29**, which after quenching with a chlorosilane afforded mixtures of 1-silyloxycyclopropenes **30** and silylated allenolates **31** (Scheme 7)[54].

Intramolecular reactions have been observed when a phenyl ring is at the β-position in the vinyllithium reagent. Thus, intermediate **32** reacted with CO at 15 °C and yielded,



SCHEME 6. Reagents: (i) CO, 15 °C; (ii) H_2O; (iii) Me_3SiCl



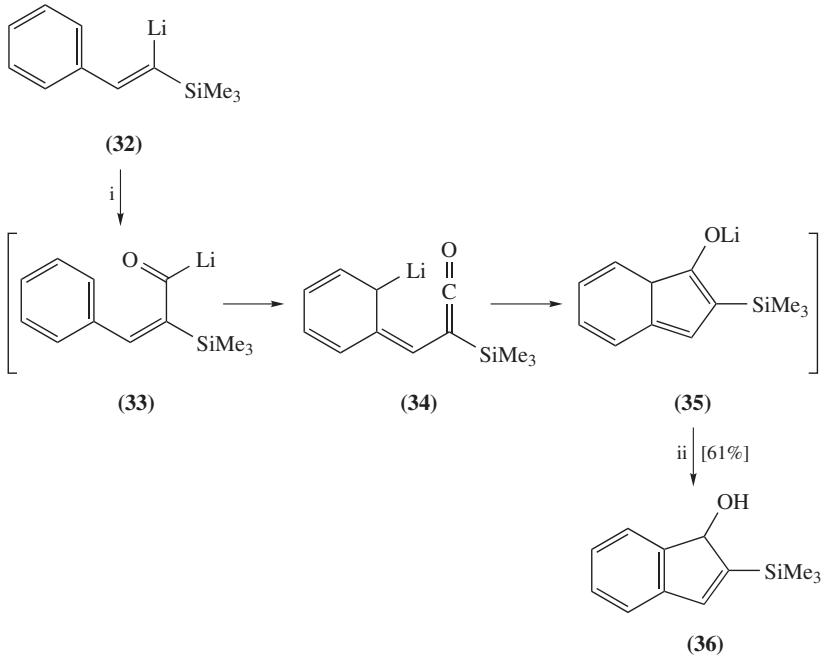
SCHEME 7. Reagents: (i) CO, 15–25 °C; (ii) $R^2{}_3SiCl$, −78 °C

after hydrolysis, the indenol **36** (Scheme 8)[54]. A plausible mechanism could involve the formation of the ketene carbanion **34** from the acyllithium **33**, followed by intramolecular nucleophilic attack to give the intermediate **35**.

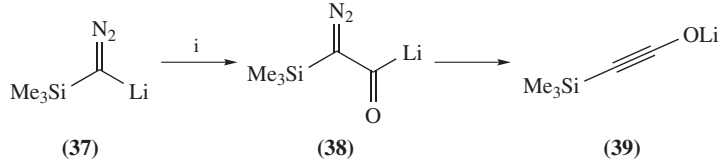
The deprotonation of (trimethylsilyl)diazomethane with *n*-butyllithium afforded the lithium silyldiazomethane **37**, which reacts with CO at −78 °C to give an acyllithium **38**[55, 56]. This intermediate underwent nitrogen extrusion generating the silylynolate **39** used as ketenylating reagent (Scheme 9).

In the case of the α-stannylmethyllithium **41**, generated from tri-*n*-butylstannylmethyl iodide (**40**), it reacted with CO at −78 °C to give the acyllithium **42**. This intermediate underwent 1,2-migration at very low temperature (much faster than for the silyl group) to give the enolate **43**, derived from the corresponding acyltin compound (Scheme 10)[57].

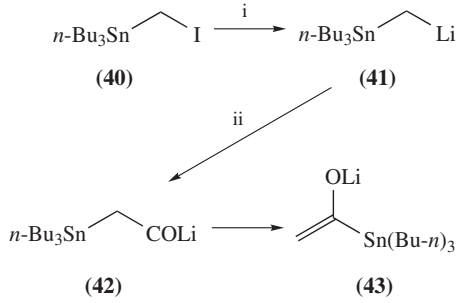
Another access to alkyl and aryl acyllithiums is based on a tellurium–lithium exchange[58]. Thus, telluroesters **44** reacted with *n*-BuLi at −105 or −78 °C in the presence of pinacolone or chlorotrimethylsilane to afford products **45** or **46**, respectively (Scheme 11). However, selenoesters and acylstannanes did not give the corresponding adducts under similar reaction conditions.



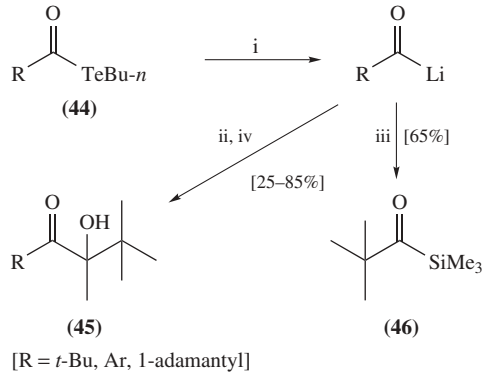
SCHEME 8. Reagents: (i) CO, 15 °C; (ii) H_2O



SCHEME 9. Reagents: (i) CO, −78 °C



SCHEME 10. Reagents: (i) *t*-BuLi, −50 °C; (ii) CO, −78 °C



SCHEME 11. Reagents: (i) *n*-BuLi, −105 or −78 °C; (ii) *t*-BuCOMe; (iii) Me_3SiCl (for R = *t*-Bu); (iv) H_2O

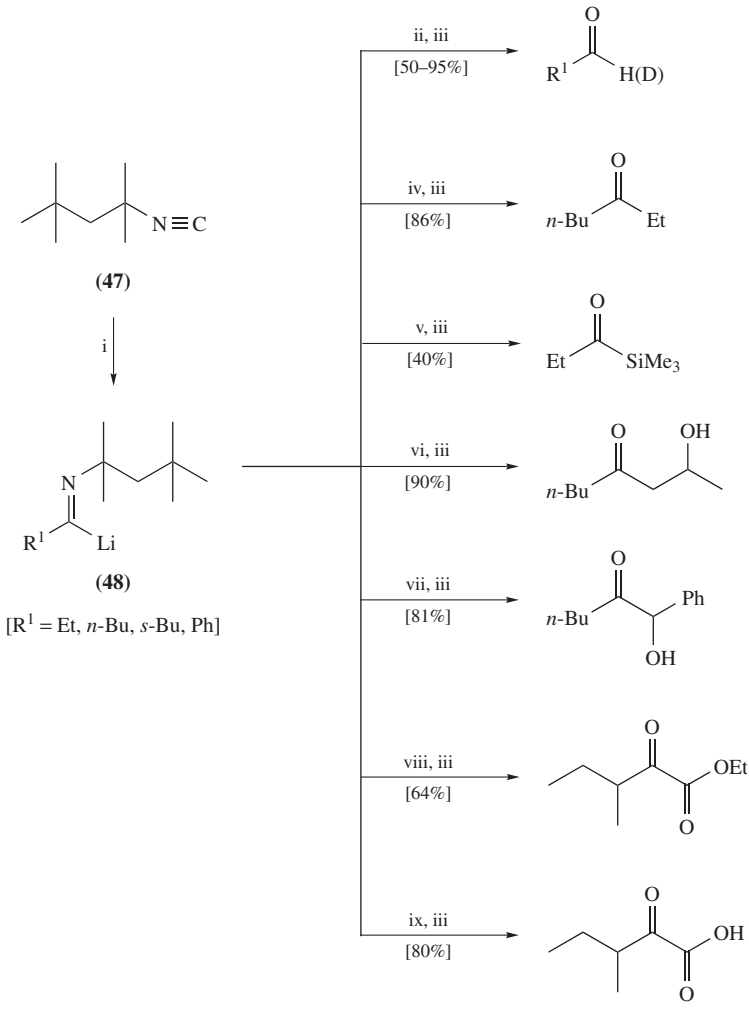
B. Imidoyllithiums

Imidoyllithium intermediates (**II**; see Introduction), also referred to as lithium aldimines, act as masked acyl anions by reaction with electrophiles, generating after hydrolysis the corresponding carbonyl compounds. They have been described as an equilibrium between the imidoyl anion and the amino-carbene structures[59]. They are generated by addition of organolithiums to isocyanides[60,61], tin–lithium exchange[62], iodine-or chlorine–lithium exchange[63,64] and by an arene-catalyzed lithiation of imidoyl chlorides[65].

Isocyanides are electronically very similar to carbon monoxide and undergo nucleophilic addition of lithium reagents to give the corresponding imidoyllithiums. Only aryl or *tert*-alkyl isocyanides, without containing α-hydrogens, provide imidoyllithium intermediates by using this methodology[61,66]. Primary, secondary and tertiary aliphatic lithium reagents, as well as phenyllithium, react with 1,1,3,3-tetramethylbutylisocyanide (**47**) to produce aldehydes, after hydrolysis. The obtained lithium aldimines **48** undergo reactions with other electrophiles such as deuterium oxide, alkyl halides, trimethylsilyl chloride, epoxides, aldehydes, ethyl chloroformate and carbon dioxide to afford the expected products (Scheme 12)[66,67]. Carboxylation or carboethoxylation of lithium aldimines derived from chiral amines followed by hydroboration and further debenzylation allowed the asymmetric synthesis of amino acids[68]. Other electrophiles, such as dialkylchloroboranes[69,70] and aminohaloboranes[71], gave ketones or trialkylcarbinols and carbiminoboranes, respectively.

The coupling with sp^2- or sp-hybridized halides seems to proceed through a halogen–metal exchange (to give compounds **49**) followed by nucleophilic addition of the newly generated organolithium compound to give, after hydrolysis of the imines **50**, the expected ketones (Scheme 13)[72]. The imidoyllithium can be transmetallated to the corresponding acylcopper(I) derivative, the conjugate addition to α,β-unsaturated carbonyl compounds taking place in the presence of $BF_3{\bullet}OEt_2$ in a regioselective manner to provide either 1,4-diketones or iminoketones, depending on the hydrolysis conditions[73].

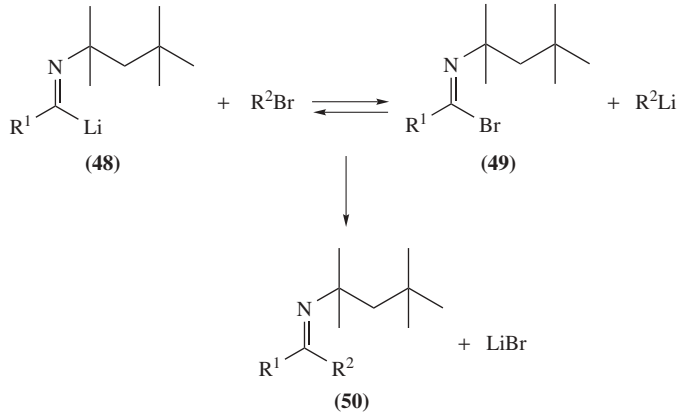
Some imidoyllithiums **52** derived from triphenylmethyl isocyanide (**51**) dissociate to produce nitriles, which react with an organolithium reagent to give the corresponding imines and, after their hydrolysis, ketones. The intermediate nitrile can be isolated working at −78 °C, whereas for the isolation of imines or ketones, after addition of the organolithium, the reaction was allowed to warm to room temperature (Scheme 14)[74]. The structure of the imidoyllithium intermediate has been assigned by IR spectroscopy



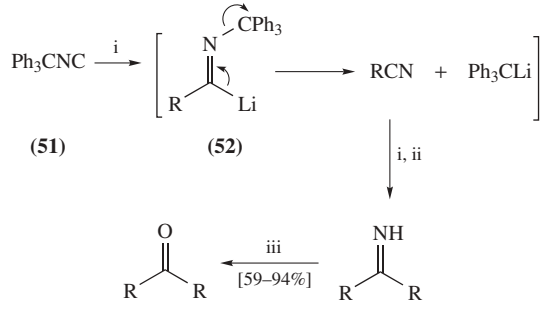
SCHEME 12. Reagents: (i) R^1Li, $-5\,^\circ C$; (ii) H_2O or D_2O; (iii) $(CO_2H)_2$; (iv) EtBr (for $R^1 = n$-Bu); (v) Me_3SiCl (for $R^1 = Et$); (vi) $MeCH(O)CH_2$ (for $R^1 = n$-Bu); (vii) PhCHO (for $R^1 = n$-Bu); (viii) $ClCO_2Et$ (for $R^1 = s$-Bu); (ix) CO_2 (for $R^1 = s$-Bu)

in the reaction of *tert*-butyl isocyanide with *t*-BuLi in liquid xenon at $-20\,^\circ C$ ($\nu_{C=N}$: 1510 cm^{-1})[25].

In the case of phenyl isocyanide, both the addition of *t*-BuLi and an *ortho* lithiation took place in the presence of TMEDA to provide the intermediate **53** and finally compounds **54** and **55** (Scheme 15)[75]. The corresponding 3-metalloindolines (metal = S, P, Si, Ge, Sn) were obtained by reaction of the dilithium intermediate **53** with metal dihalides. The obtained benzazaphospholes and benzazarsoles **54** (M = *t*-BuP, MeAs) can be converted into the aromatic 1*H*-1,3-benzazaphospholes and benzazarsoles **55** by flash vacuum pyrolysis[76].

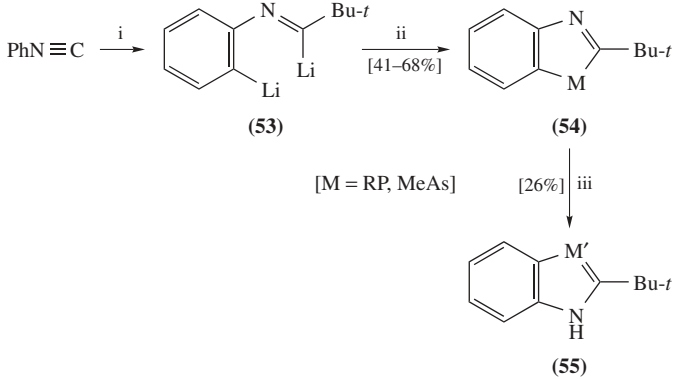


SCHEME 13. Mechanism for the cross-coupling of imidoyllithiums with sp^2- or sp-hybridized halides



[R = *n*-Bu, *s*-Bu, *t*-Bu, Ph]

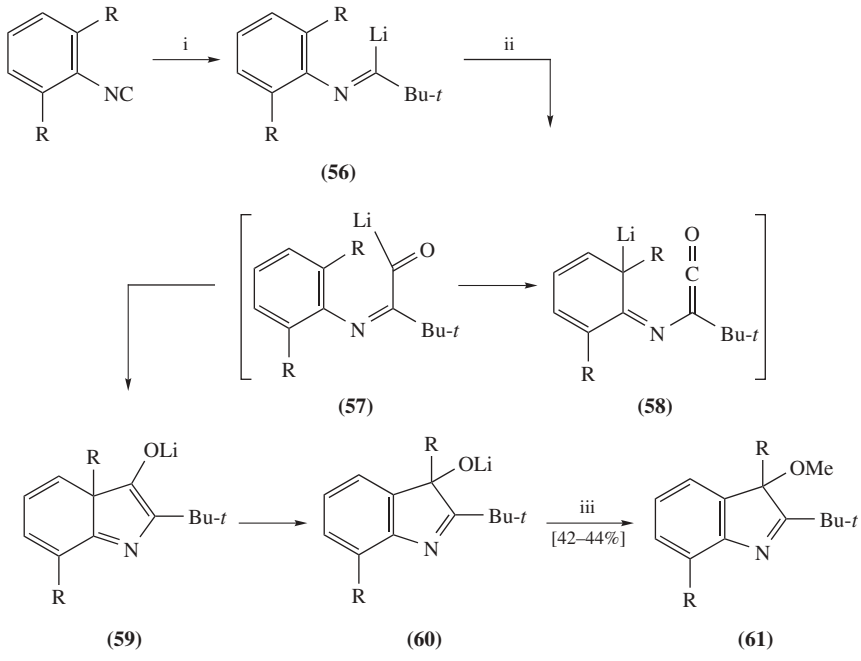
SCHEME 14. Reagents: (i) RLi, −78 °C to rt; (ii) H_2O; (iii) HCl−H_2O



[M = S, RP, MeAs, Ph_2Si, Me_2Si, Me_2Ge, Me_2Sn; M′ = P, As]

SCHEME 15. Reagents: (i) 2 *t*-BuLi, −78 °C to rt; (ii) MCl_2; (iii) flash vacuum pyrolysis

The reaction of aromatic *ortho*-substituted imidoyllithiums **56** with carbon monoxide and methyl iodide afforded 1*H*-isoindole derivatives **61** in moderate yields (Scheme 16)[77]. In this process the formation of an acyllithium **57** was proposed to occur which, after formation of intermediate **58**, cyclized to give the compound **59**. The rearrangement of the alkyl group giving the aromatic product **60**, followed by quenching with methyl iodide at −78 °C, gave indolines **61**.

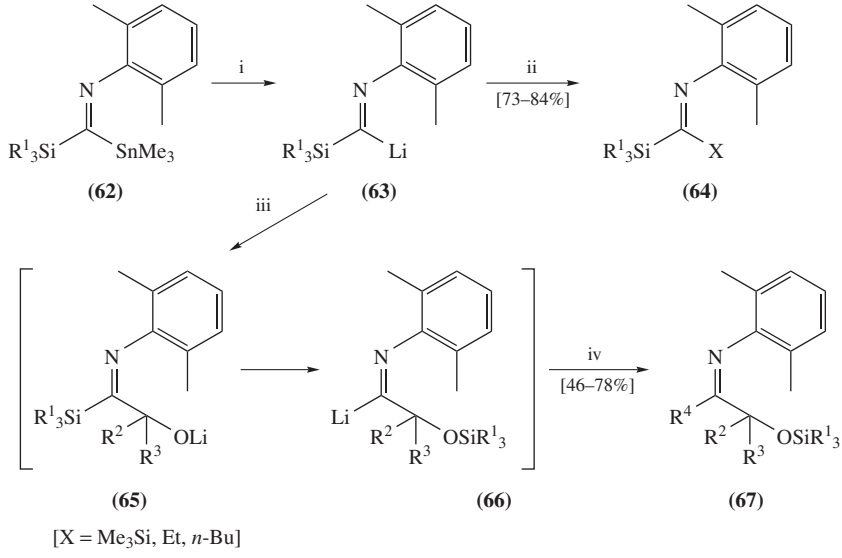


[R = Me, Et, *i*-Pr]

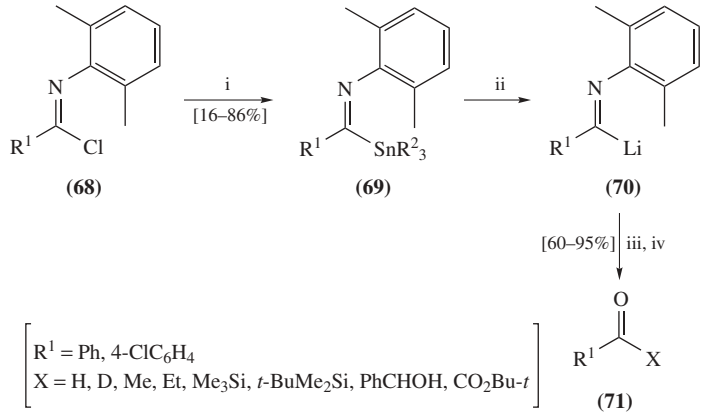
SCHEME 16. Reagents: (i) *t*-BuLi, −78 °C to rt; (ii) CO; (iii) MeI, −78 °C to rt

The palladium-catalyzed bis-metallation of isocyanides with silylstannanes gave adducts **62**. These compounds can be selectively transmetallated with *n*-BuLi at −78 °C to give imidoyllithiums **63**, which reacted with a variety of electrophiles to give products **64** (Scheme 17)[62, 78], the corresponding alkylated compounds being easily hydrolyzed to acylsilanes. When carbonyl compounds are used as electrophiles, a Brook-type migration of the organosilyl group from the iminyl carbon to the alkoxy oxygen occurred in intermediates **65** to give new imidoyllithiums **66**. Final reaction of these intermediates with alkyl halides provided compounds **67**, which can be hydrolyzed to the corresponding α-hydroxy ketones. It is noteworthy that with only one equivalent of *n*-BuLi two electrophiles are introduced, acting compounds **62** as formyl dianion equivalents. Imidoyllithiums of type **63** can give conjugate addition to α,β-unsaturated carbonyl compounds through the corresponding organocopper reagents[79].

Imidoylstannanes **69** can be prepared by reaction of imidoyl chlorides **68** with triorganostannyllithiums at −78 °C. The transmetallation with methyllithium gave the corresponding imidoyllithiums **70**. The reaction of these intermediates with different electrophiles gave, after hydrolysis, the corresponding imines or ketones **71** (Scheme 18)[80].



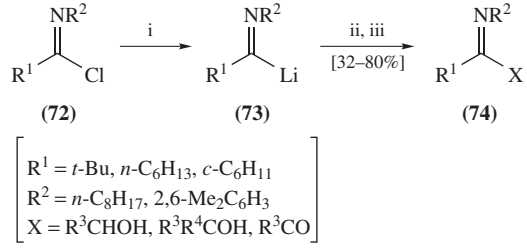
SCHEME 17. Reagents: (i) *n*-BuLi, −78 °C; (ii) EX = Me_3SiCl, EtBr, *n*-BuBr; (iii) R^2COR^3; (iv) R^4Hal



SCHEME 18. Reagents: (i) $R^2{}_3SnLi$, −78 °C; (ii) MeLi, −78 °C; (iii) EX = H_2O, D_2O, MeI, EtBr, Me_3SiCl, *t*-$BuMe_2SiCl$, PhCHO, $ClCO_2Bu$-*t*; (iv) HCl-H_2O

A more direct access to imidoyllithiums was to perform the lithiation of imidoyl chlorides **72** with lithium and substoichiometric amounts of naphthalene at low temperatures so that intermediates **73** were generated (Scheme 19)[65,81]. Aldehydes, ketones and acyl chlorides have been used as electrophilic reagents to afford imines **74** or the corresponding ketones, depending on the hydrolysis conditions.

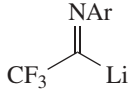
Trifluoroacetimidoyllithiums **75** have been prepared from imidoyl iodides by reaction with *n*-BuLi at −78 °C and have been trapped with aldehydes, ketones, epoxides,



(72) **(73)** **(74)**

$R^1 = t\text{-Bu}, n\text{-}C_6H_{13}, c\text{-}C_6H_{11}$
$R^2 = n\text{-}C_8H_{17}, 2,6\text{-}Me_2C_6H_3$
$X = R^3CHOH, R^3R^4COH, R^3CO$

SCHEME 19. Reagents: (i) Li, $C_{10}H_8$ (4 mol%), $-78\,^{\circ}C$; (ii) $EX = R^3CHO, R^3R^4CO, R^3COCl$; (iii) H_2O

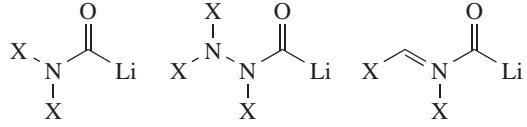


(75)

Me_3SiCl, $n\text{-}Bu_3SnCl$, $ClCO_2Et$ and DMF to give, after hydrolysis, the corresponding trifluoromethylated imines **74** ($R^1 = CF_3$) in 20–84% yield[63,64].

C. Carbamoyllithiums

Dialkylaminocarbonyllithiums **IIIa** are the most useful and best studied carbamoyllithiums[4,5]. Other related intermediates, such as carbazoyllithiums **IIIb**[82] and iminic derivatives **IIIc**[77], have also been described.

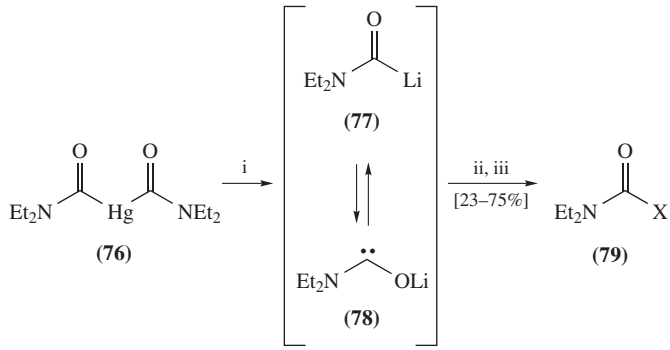


(IIIa) **(IIIb)** **(IIIc)**

In the initial studies about the reaction of *N*,*N*-disubstituted formamides with alkaline metals to give glyoxylic amides, the participation of carbamoyl metal derivatives as intermediates was postulated[83]. The first preparation of the carbamoyllithium **77** was described two years later by a mercury–lithium transmetallation from compound **76** at $-75\,^{\circ}C$ (Scheme 20)[84]. The authors proposed also an aminocarbene structure **78** and studied its reactivity with methanol, methyl iodide, carbonyl compounds, esters, acyl chlorides, mercury(II) chloride and tri-*n*-butyltin chloride providing compounds **79**.

Carbamoyllithiums can be prepared by four general methods: (a) Lithium amides carbonylation; (b) deprotonation of formamides with alkyllithiums; (c) tellurium–lithium or chlorine–lithium exchange; and (d) tin–lithium transmetallation.

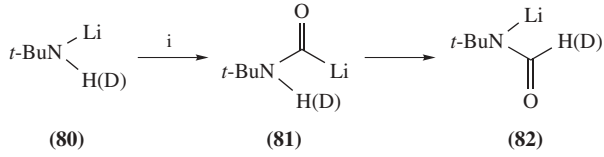
The carbonylation of alkali metal amides was described in 1967[85]; the reaction of lithium *tert*-butylamide (**80**) with CO at $50\,^{\circ}C$ was reported in 1971 to give apparently an orange solution of *tert*-butylcarbamoyllithium (**81**), which was trapped with trimethylelement chlorides derived from silicon, germanium and tin[86]. When this reaction was performed at $-75\,^{\circ}C$ it was found that carbamoyllithium equilibrated to the



[X = H, D, Me, PhCHOH, PhC(OH)Me, Ph_2COH, PhCO, HgCl, n-Bu_3Sn]

SCHEME 20. Reagents: (i) t-BuLi, $-75\,^{\circ}C$; (ii) EX = MeOH, MeOD, MeI, PhCHO, PhCOMe, Ph_2CO, PhCOCl, $PhCO_2Et$, $HgCl_2$, n-Bu_3SnCl; (iii) H_2O

corresponding N-lithioformamide (**82**), according to the experiments carried out also with the deuteriated starting material (Scheme 21)[87].



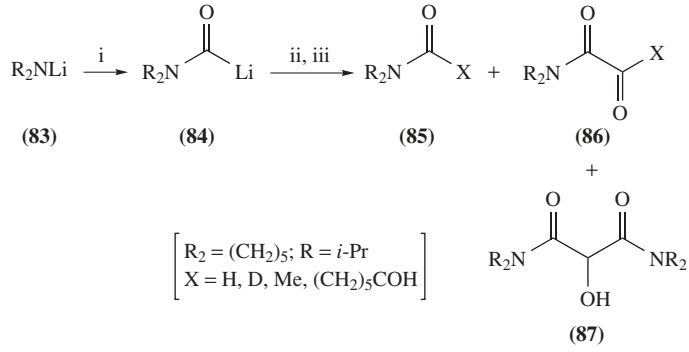
(80) **(81)** **(82)**

SCHEME 21. Reagents: (i) CO, $-75\,^{\circ}C$

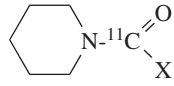
The same authors found that secondary lithium amides **83**, such as lithium piperidide and diisopropylamide, reacted with CO at $-75\,^{\circ}C$ to give the corresponding carbamoyllithiums **84**[88]. These intermediates reacted with water, deuterium oxide, methyl iodide and cyclohexanone to yield glyoxylic derivatives **86**, resulting from a second insertion of CO, and products **87**, derived from the reaction of the initially formed carbamoyllithium with the initially generated adduct between compound **84** and CO. The ratio and yield of the obtained products depend on the time of CO bubbling through the reaction medium. These side reactions can be avoided by keeping a very low concentration of CO, so it was possible to synthesize carbon-11 labelled carboxamides **88** by carbonylation of lithium piperidide with ^{11}CO and quenching with water or alkyl iodides[89]. Nudelman and coworkers have studied the reaction conditions to obtain chemoselectively different types of these compounds[90–93]: whereas by complexation with LiBr formamides **85** (X = H) can be obtained, using THF:HMPA as solvents a 1:1 mixture of compounds **85** and **86** was isolated. In addition, in the presence of free amine, hydroxytartronamides **87** are almost exclusively formed (Scheme 22).

It has been demonstrated that intermediates **89** reacted with their lithium amide precursors to give the new intermediates **90**, which are the real precursors of the resulting formamides **91** (Scheme 23)[94].

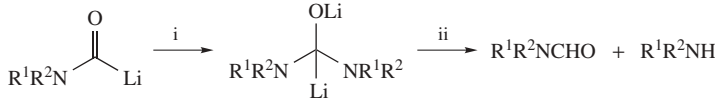
Saturated heterocyclic amines do not suffer double insertion of CO due to the formation of aggregates between the carbamoyllithium and the free amine, which transfer intramolecularly the proton to give exclusively formamides[22,95–97].



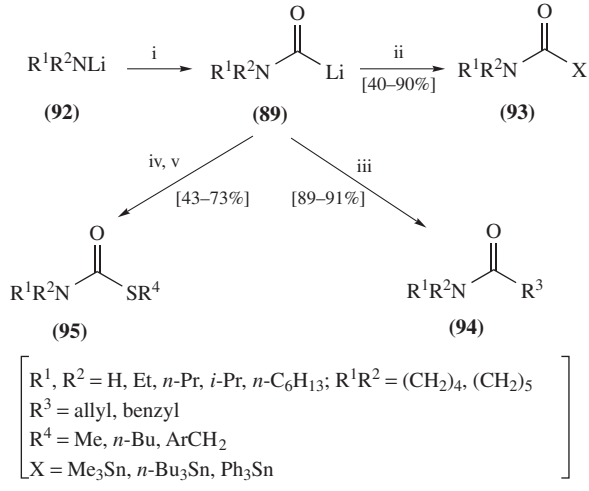
SCHEME 22. Reagents: (i) CO, −75 °C; (ii) EX = H_2O, D_2O, MeI, $(CH_2)_5CO$; (iii) H_2O



(88) X = H, R



SCHEME 23. Reagents: (i) R^1R^2NLi; (ii) H_2O



SCHEME 24. Reagents: (i) CO, −78 °C; (ii) EX = R_3SnCl; (iii) R^3Hal; (iv) S_8, −78 to 0 °C; (v) R^4Hal

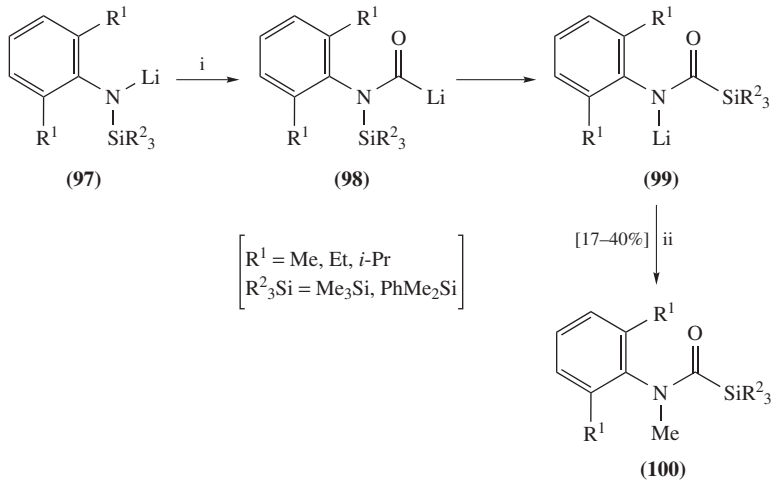
The lithium salts of acyclic secondary amines **92** can be conveniently transformed into the corresponding carbamoyllithiums **89** at −78 °C. Under these reaction conditions they react with trialkyltin chlorides to give carbamoyl stannanes **93** (Scheme 24)[98]. In the case of benzyl and allyl halides, an alkylation can occur affording products **94**. However, when trialkylsilyl chlorides were used as electrophiles no carbamoyl silanes could be detected. *S*-Alkyl thiocarbamates **95** can be prepared by reaction of the same intermediates **89** with sulfur followed by *S*-alkylation at 0 °C (Scheme 24)[99].

The same alkyl thiocarbamates **95** can be prepared in 35–72% yield by reaction with disulfides and with carbon disulfide followed by alkylation with alkyl halides[100]. When carbonyl sulfide was used as electrophile, lithium *N*,*N*-dialkyldioxamates were formed, which after reaction with benzyl bromide gave thiooxamates **96** in 37–56% yield[100].

$R_2NCOCOSCH_2Ph$

(96)

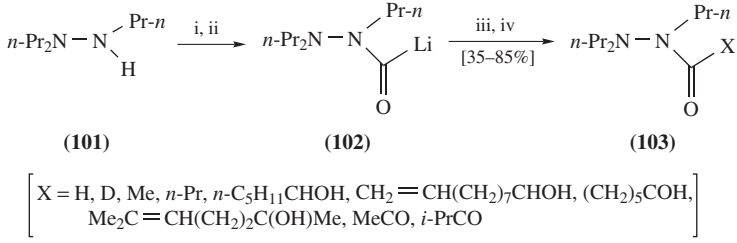
Carbamoyl silanes **100** could be prepared by reaction of lithium silylamides **97** with CO at room temperature and under pressure (30 atm) followed by reaction with methyl iodide (Scheme 25)[101]. The intermediate carbamoyllithium **98** suffers a rearrangement of the silyl group to afford a new lithium (silylcarbonyl)amide **99**, which is finally methylated.



SCHEME 25. Reagents: (i) CO (30 atm); (ii) MeI

Tri-*n*-propylcarbazoyllithium **102** is another type of carbamoyl intermediate (of type **IIIb**), which is prepared at −78 °C by reaction of the corresponding hydrazine **101** with *n*-BuLi and CO (Scheme 26)[82]. This intermediate has been trapped with different electrophiles to provide the corresponding products **103**.

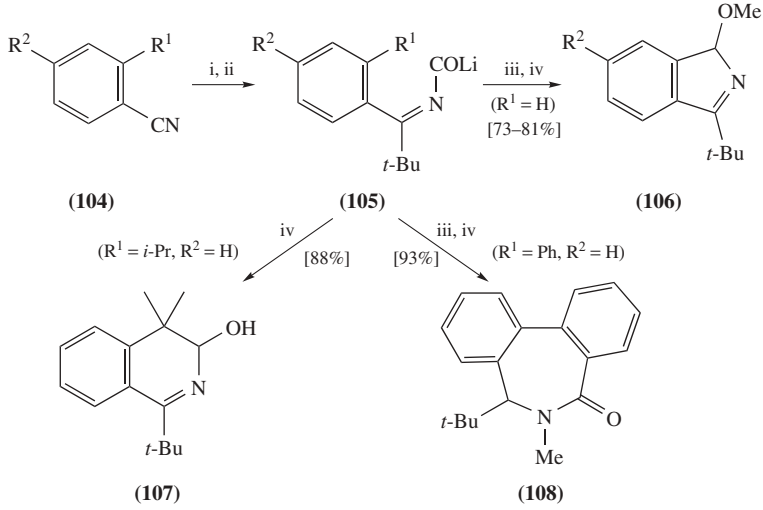
The other type of carbamoyllithiums **IIIc** can also be prepared by reaction of CO with *N*-lithioketimines, resulting from the addition of *tert*-butyllithium to aryl cyanides **104**[77, 102]. These intermediates **105** underwent selective cyclization to give 1*H*-isoindole derivatives **106**[77] and six- (**107**)[102] or seven-membered (**108**)[102] cyclic products (Scheme 27). Compounds **107** result either by insertion of the carbene structure into the benzylic carbon–hydrogen bond, as in the case of carbamoyllithiums[96], or by intramolecular protonation.



(101) **(102)** **(103)**

[X = H, D, Me, *n*-Pr, *n*-C_5H_{11}CHOH, CH_2=CH$(CH_2)_7$CHOH, $(CH_2)_5$COH, Me_2C=CH$(CH_2)_2$C(OH)Me, MeCO, *i*-PrCO]

SCHEME 26. Reagents: (i) *n*-BuLi, −75 °C; (ii) CO; (iii) EX = H_2O, D_2O, MeI, *n*-PrI, RCHO, R^1R^2CO, RCO_2Et; (iv) H_2O

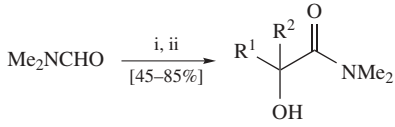


SCHEME 27. Reagents: (i) *t*-BuLi, −78 °C to rt; (ii) CO (1 atm), rt; (iii) MeI, −78 °C to rt; (iv) NH_4Cl

As mentioned before, the direct deprotonation of formamides is the second general method for the preparation of carbamoyllithiums **IIIa**. The deprotonation of DMF (**109**) was carried out with LDA at −78 °C in the presence of aldehydes and ketones to yield the corresponding α-hydroxy amides **110** (Scheme 28)[103]. Related formamides **111** bearing a methoxymethyl group at the nitrogen atom gave the corresponding α-hydroxy amides under the same reaction conditions[104].

Dimethyl thiocarbamoyllithium (**113**) was generated at −100 °C in the absence of the electrophile by deprotonation of *N*,*N*-dimethylthioformamide (**112**) (Scheme 29)[105]. This intermediate was trapped with D_2O, methyl iodide, carbonyl compounds and esters to provide the expected products **114**.

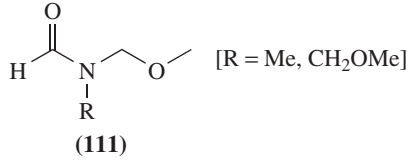
When the deprotonation of formamides is carried out using an alkyllithium instead of LDA[104, 106], the corresponding equilibrium is shifted to the total formation of the expected carbamoyllithium[107, 108]. Thus, the reaction of the amide **115** was performed at −95 °C in a Trapp's mixture of solvents (THF/Et_2O/pentane: 4/4/1) with *tert*-butyllithium to give the intermediate **84**, which reacted with D_2O, benzyl bromide, carbonyl compounds and ethyl benzoate to give the expected products **85** in good yields (Scheme 30).



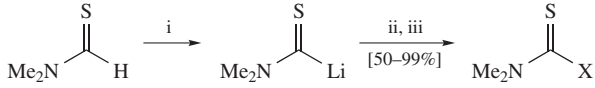
(109) **(110)**

[R^1R^2CO = PhCHO, PhCH=CHCHO, *t*-BuCHO, Ph_2CO, *c*-$(CH_2)_5CO$]

SCHEME 28. Reagents: (i) LDA, R^1R^2CO, −78 °C; (ii) NH_4Cl



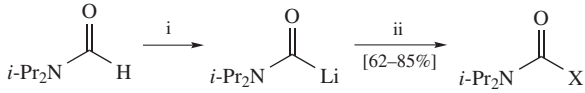
(111)



(112) **(113)** **(114)**

[X = D, Me, EtCHOH, Ph_2COH, PhC(OH)Me, Me_2COH, *c*-$(CH_2)_5COH$, PhCO]

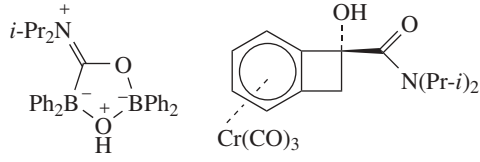
SCHEME 29. Reagents: (i) LDA, −100 °C; (ii) EX = D_2O, MeI, RCHO, R^1R^2CO, $PhCO_2Et$; (iii) AcOH



(115) **(84**; R = *i*-Pr**)** **(85)**

[X = D, $PhCH_2$, EtCHOH, PhCHOH, Me_2COH, *c*-$(CH_2)_5COH$, PhCH=CHCHOH, Ph_2COH, PhCO]

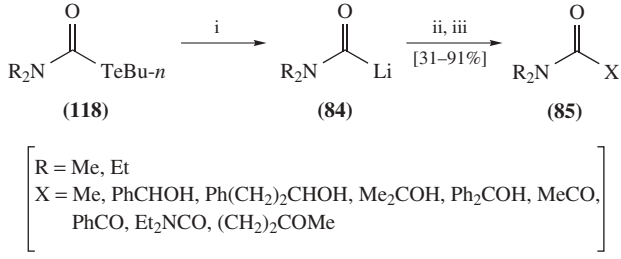
SCHEME 30. Reagents: (i) *t*-BuLi, −95 °C; (ii) EX = D_2O, $PhCH_2Br$, RCHO, R^1R^2CO, $PhCO_2Et$



(116) **(117)**

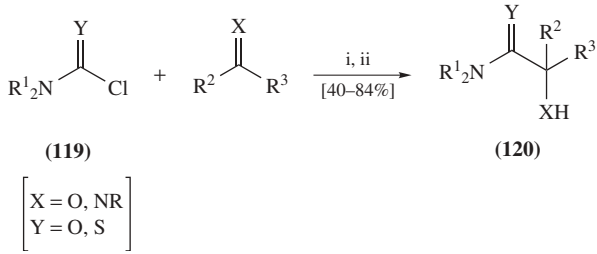
When diphenylbromoborane was used as electrophile, an acylborane **116** was obtained in 80% yield[109]. In the case of using (benzocyclobutenone)tricarbonylchromium(0) as electrophile, a diastereoselective addition of compound **84** took place yielding the product **117** in 72% yield[110].

The tellurium–lithium exchange used in the case of acyllithiums[58] was also assayed for carbamoyllithiums **118**, prepared by reaction of dialkylcarbamoyl chlorides with lithium *n*-butyltellurate[111,112]. The corresponding dialkylcarbamoyllithiums were prepared with *n*-butyllithium at −78 °C and trapped with different electrophiles including acyl chlorides and methyl vinyl ketone, which suffered conjugate addition (Scheme 31).



SCHEME 31. Reagents: (i) *n*-BuLi, −105 or −78 °C; (ii) EX = MeI, RCHO, R^1R^2CO, RCOCl, CH_2=CHCOMe; (iii) NH_4Cl

A more direct way for the preparation of carbamoyl and thiocarbamoyllithiums started from carbamoyl and thiocarbamoyl chlorides **119** and used lithium powder and a catalytic amount of naphthalene (3 mol%)[113,114]. The lithiation was performed at −78 °C in the presence of carbonyl compounds and imines as electrophiles to yield products **120** (Scheme 32). Phenyl isocyanate and DMF afforded oxamides in modest yields (21 and 42%, respectively).

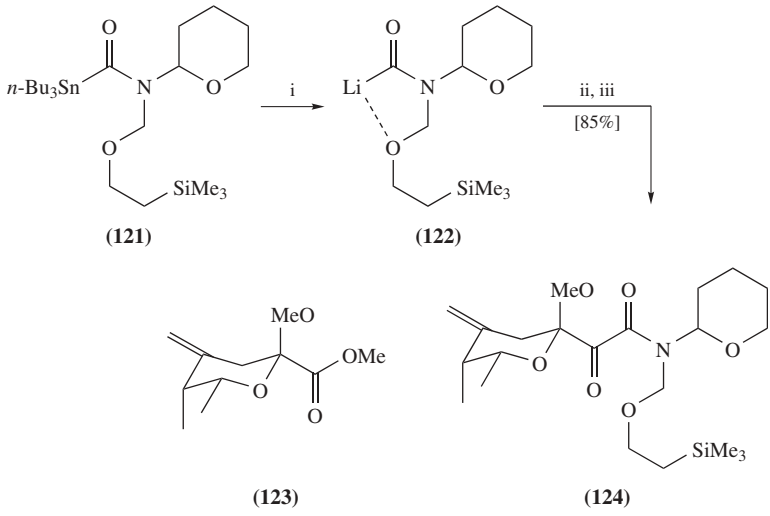


SCHEME 32. Reagents: (i) Li, $C_{10}H_8$ (3 mol%), −78 °C to rt; (ii) H_2O

Finally, the carbamoyllithium **122** was prepared by tin–lithium transmetallation at −105 °C from the corresponding carbamoylstannane **121**. This tin compound was prepared by addition of tri-*n*-butyltin lithium to an isocyanate followed by quenching with SEMCl [2-(trimethylsilyl)ethoxymethyl chloride]. The functionalized intermediate **122** was acylated with the ester **123** to give the product **124** in a model study towards the synthesis of mycalamides (Scheme 33)[115].

III. PROTECTED ACYLLITHIUM EQUIVALENTS

The protection of formaldehyde or other aldehydes as acyclic dithioacetals, sulfanylethers, sulfonylethers, thiosulfoxides, diselenoacetals, aminothioacetals and aminals, as well as cyclic dithioacetals, dioxolanes, oxazolidines and imidazolidines, allows the preparation of different type of protected acyllithium derivatives **IV–XI** by deprotonation (see



SCHEME 33. Reagents: (i) *n*-BuLi, −105 °C; (ii) **123**; (iii) $NaHCO_3$, NH_4Cl-H_2O

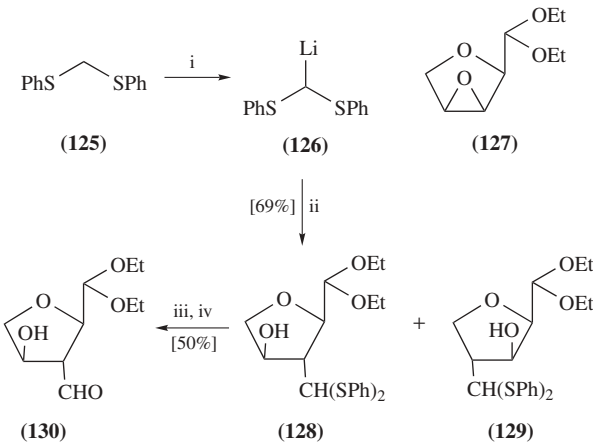
Section I)[13]. In the case of the carboxylic anion, the lithiation of acyclic and cyclic orthothioesters allows the preparation of intermediates **XII**[12]. All these stabilized organolithium reagents have been widely used in organic synthesis and in this section their application as acylating agents by this defensive strategy will be mainly considered.

A. Acyclic α-Lithiothioacetals

For the preparation of acyclic thioacetals, the aldehyde is protected with the corresponding thiol and in the case of the methylenic derivatives, dihaloalkanes or dimethoxymethane are allowed to react with thiolates or with thiols under acidic conditions. The lithiation of these dithioacetals usually is performed with alkyllithiums in THF at low temperatures, the resulting α-lithiothioacetals being good acylating agents. Thioacetal hydrolysis or deprotection methods regenerate the carbonyl group whereas desulfanylation affords the methylene group.

Bis(ethylsulfanyl)methane was initially deprotonated by lithium amide in liquid ammonia[116], but the related bis(phenylsulfanyl)methane as well as 1,3-dithiane were the first dithioacetals lithiated with *n*-butyllithium[117]. Bis(phenylsulfanyl)methane **125**[118] is more acidic than 1,3-dithiane[119] and can be lithiated in THF at 0 °C, the corresponding bis(phenylsulfanyl)methyllithium **126** being stable at least for 12 hours at this temperature[117]. The monoalkylation process can be performed with primary and secondary alkyl halides and the use of TMEDA or HMPA as additives increases the yields[117,118,120–128]. Separated ion pairs are completed in the presence of 3 equivalents of HMPA, the reaction rate being increased with alkyl halides[128]. α-Substituted thioacetals are alkylated with primary alkyl halides using *n*-BuLi-TMEDA in hexane at 0 °C[122]. Intramolecular alkylation to give cyclopropanedithioacetals takes place when a phenylsulfanyl group is at the γ-position[129]. Bis(phenylsulfanyl)methyllithium **126** has been silylated with 1,2-dichloro-1,1,2,2-tetramethyldisilane[130,131]. The thioacetal derived from acetaldehyde has been lithiated with *n*-BuLi-TMEDA and silylated with chlorotrimethylsilane[132,133]. Epoxide opening by bis(phenylsulfanyl)methyllithium takes

place regio- and stereoselectively[134–137] and has been used in the synthesis of 3′-*C*-substituted nucleosides[137,138]. Thus, when the epoxide **127** was opened with the anion **126** (prepared by deprotonation of compound **125**) a 6:4 mixture of regioisomers **128** and **129** was obtained, the former being transformed into the corresponding aldehyde **130** after deprotection with mercury(II) oxide and $BF_3{\bullet}OEt_2$ (Scheme 34)[138].



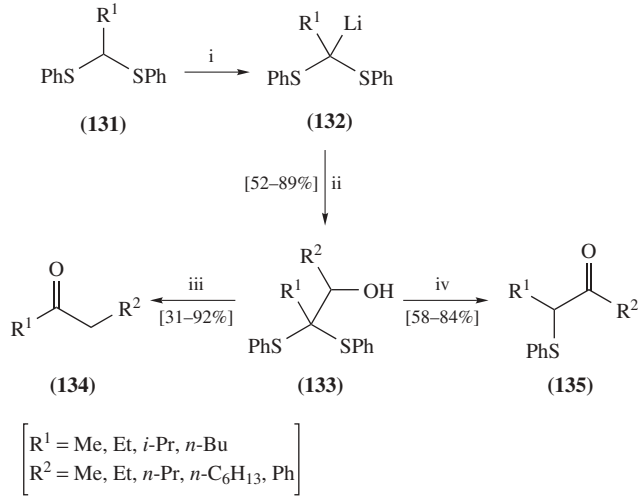
SCHEME 34. Reagents: (i) *n*-BuLi, HMPA, 0 °C; (ii) **127**, 0 °C; (iii) Ac_2O, Py; (iv) HgO, $BF_3{\bullet}OEt_2$

The nucleophilic addition of compound **126** to carbonyl compounds takes place at 0 °C to give the corresponding α-hydroxydithioacetals in good yields[117,120,121,123]. In the case of aldehyde-derived dithioacetals, the deprotonation has to be carried out in the presence of TMEDA[120]. The regioselective deprotection of adducts **133** (prepared from dithioacetals **131** through intermediates **132**) with trifluoroacetic acid gave ketones **134** and with *p*-toluenesulfonic acid, α-phenylsulfanyl ketones **135** (Scheme 35)[120].

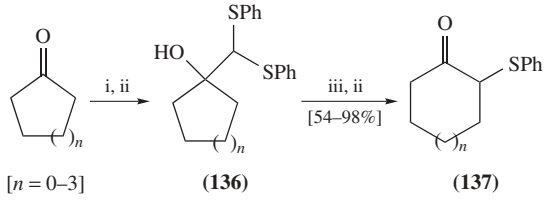
In the case of the lithiated benzaldehyde dithioacetal, it did not react with carbonyl compounds but can be acylated with benzoyl chloride and, after reduction with zinc borohydride, afforded compounds of type **133** ($R^1 = R^2 = Ph$). Ketone adducts are transformed into α-(phenylsulfanyl)ketones after treatment with TFA[120] or with copper(I) triflate in refluxing benzene and in the presence of ethyldiisopropylamine[139]. In the case of cyclic ketones, either the treatment with TsOH[120] or with CuOTf[139] produces ring expansion to afford the corresponding cyclic α-(phenylsulfanyl)cycloalkanones **137**. The same rearrangement takes place when the cycloalkanone adducts **136** are treated with two equivalents of methyllithium or *sec*-butyllithium (Scheme 36)[140].

Carbonyl compound adducts have also been lithiated with lithium in the presence of a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) at −78 °C to provide, after reaction with carbonyl compounds, the corresponding 1,3-diols **138** (Scheme 37)[141,142].

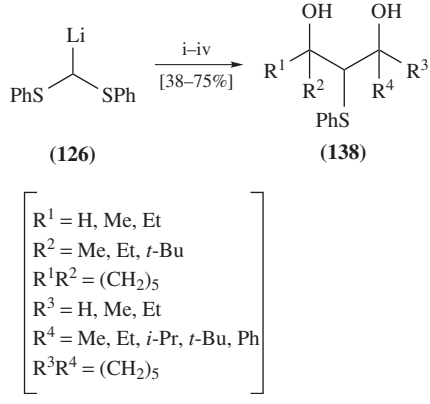
When α,β-unsaturated carbonyl compounds were used as electrophiles, aldehydes gave 1,2-addition products[139,143–145], whereas ketones underwent 1,4-addition[146] as in the case of 2-lithio-1,3-dithiane (see next Section III.B). However, chalcone gave the 1,2-addition product, even in the presence of HMPA[147]. Conjugate addition was mainly observed when copper(I) iodide was added so, after deprotection of the resulting thioacetal unit, 1,4-diketones were obtained[148,149]. This strategy has been applied to the synthesis of



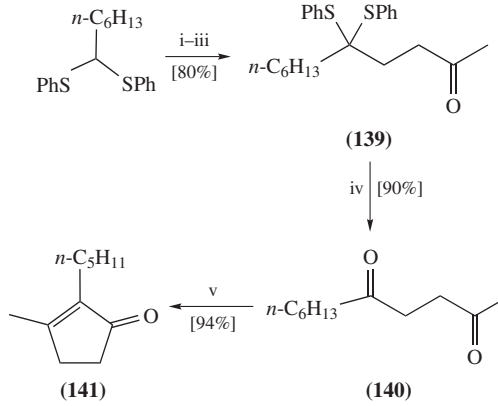
SCHEME 35. Reagents: (i) *n*-BuLi, TMEDA, THF, 0 °C; (ii) R^2CHO; (iii) TFA; (iv) TsOH



SCHEME 36. Reagents: (i) **126**, −78 °C; (ii) H_2O; (iii) 2 MeLi or *s*-BuLi, −78 to 0 °C



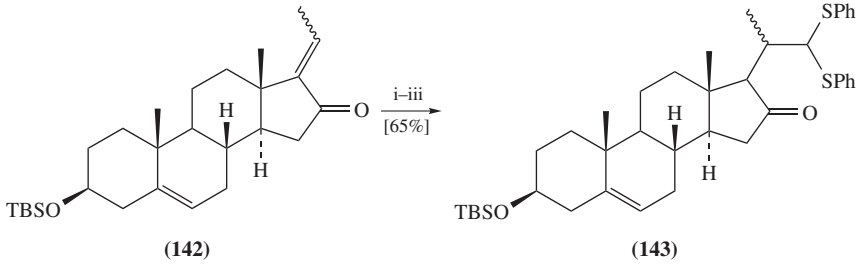
SCHEME 37. Reagents: (i) R^1R^2CO, −40 °C; (ii) Li, DTBB (5 mol%), −78 °C; (iii) R^3R^4CO, −78 °C; (iv) H_2O, −78 °C to rt



SCHEME 38. Reagents: (i) *n*-BuLi, −40 to −30 °C; (ii) CuI (0.5 eq), −78 °C; (iii) CH_2=CHCOMe; (iv) $CuCl_2$, CuO, Me_2CO, H_2O; (v) NaOH, EtOH, reflux

the diketone **140** (from the dithioacetal **139**), a direct precursor of dihydrojasmone **141** (Scheme 38)[148].

In the case of the enone **142**, an intermediate in the synthesis of the anticancer natural product OSW-1, the Michael addition of bis(phenylsulfanyl)methyllithium **126** took place in the presence of HMPA, whereas 2-lithio-1,3-dithiane gave the 1,2-addition product (Scheme 39)[150]. Unfortunately, this strategy was abandoned because compound **143** could not be further alkylated.

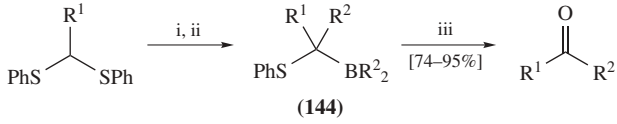


SCHEME 39. Reagents: (i) **126**, −78 °C; (ii) HMPA, rt; (iii) NH_4Cl

The reaction of bis(phenylsulfanyl)alkyllithiums with trialkylboranes provides the adduct **144**, after elimination of phenylsulfanyllithium. Final oxidation with hydrogen peroxide–dioxane in aqueous sodium acetate afforded aldehydes or ketones in good yields (Scheme 40)[151, 152]. However, this process cannot be carried out with 2-lithio-1,3-dithiane because the initially formed borate did not undergo the spontaneous alkyl migration reaction[152].

The acylation of the organolithium **126** has been studied with the lactone **145** affording stereoselectively the β-lactol **146** (Scheme 41). The *C*-disaccharide **149** has been prepared by reaction of compound **148** (prepared from the same starting material **126** and the triflate **147**), with **145** followed by reduction and final dehydroxylation[153].

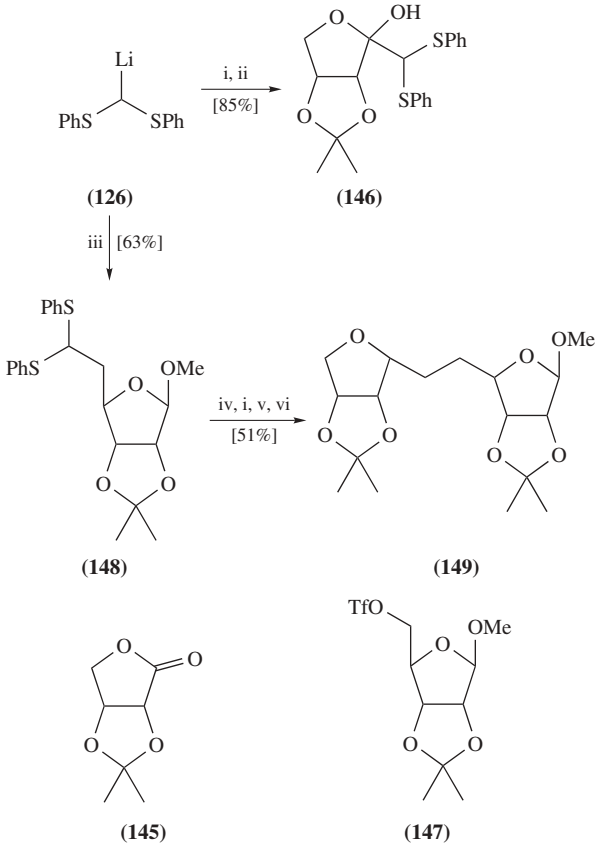
Bis(methylsulfanyl)methyllithium **151** is an analogous acyclic 2-lithiodithioacetal of compound **126**, which can be prepared by deprotonation of bis(methylsulfanyl)methane



(**144**)

R^1 = H, *n*-Bu
R^2 = *n*-Bu, *n*-C_6H_{13}, Bn, $PhCHMeCH_2$, *c*-C_5H_9, *c*-C_6H_{11}

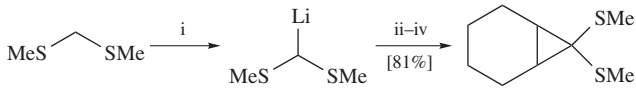
SCHEME 40. Reagents: (i) *n*-BuLi, −30 °C; (ii) $R^2{}_3B$; (iii) 30% H_2O_2, NaOAc, 15 °C



SCHEME 41. Reagents: (i) **145**, −78 °C; (ii) NH_4Cl; (iii) **147**, −78 °C; (iv) *n*-BuLi, −78 °C; (v) Ra–Ni; (vi) Et_3SiH, $BF_3{\bullet}OEt_2$

150 with *n*-BuLi at temperatures ranging between −78 and 0 °C in THF. The reactivity of this reagent was first studied with epoxides for the preparation of cyclopropane thioacetals[154, 155]. By a one-pot procedure, after the epoxide opening, the corresponding alcoholate was tosylated and final deprotonation afforded an intramolecular tosylate displacement giving, in the case of cyclohexene oxide, the

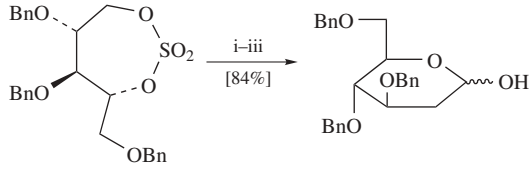
expected product **152** (Scheme 42). The silylation[156, 157] and stannylation[158] of compound **151** provided α-silylated or stannylated derivatives, which have been used in Peterson olefination reactions.



(150) **(151)** **(152)**

SCHEME 42. Reagents: (i) *n*-BuLi, −78 to −25 °C; (ii) cyclohexene oxide, −78 to 0 °C; (iii) TsCl, −78 to 0 °C; (iv) *n*-BuLi, −78 to 0 °C

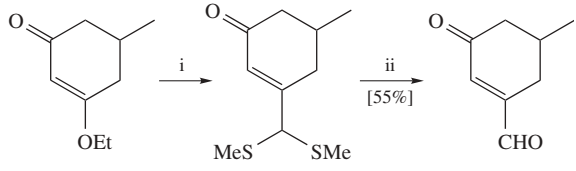
Successive double deprotonation–alkylation of the dithioacetal **150** has also been performed in a one-pot procedure[159–161] and used in cyclization processes for the preparation of indoles[160] and the phenanthrene nucleus[161]. The dialkylation has been performed with primary alkyl iodides and bromides without additives. The cyclic sulfate **153** has been acylated by means of compound **151** and, after further deprotection of the thioacetal moiety, transformed into the corresponding 2-deoxy-D-arabinohexopyranose **154** (Scheme 43)[162].



(153) **(154)**

SCHEME 43. Reagents: (i) **151**, −40 °C; (ii) H_2SO_4; (iii) NBS, 0 °C

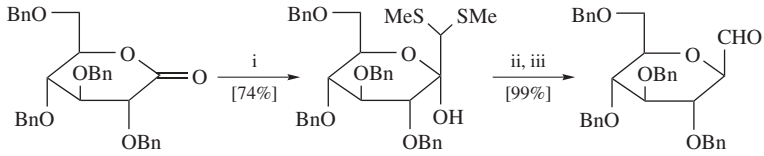
β-Hydroxy thioacetals were obtained by addition of bis(methylsulfanyl)alkyllithiums to carbonyl compounds[163, 164]. In the case of cyclohex-2-enone only 1,2-addition was observed, whereas α-silylated bis(methylsulfanyl)methyllithium gave 1,4-addition products, which were deprotected to provide 1,4-diketones[163]. Regioselective vinylic substitution was observed in the case of 3-alkoxycyclohex-2-enones[165–167] to give, after deprotection, the expected aldehydes as is illustrated by the transformation of compound **155** to the corresponding products **156** and **157** (Scheme 44)[167].



(155) **(156)** **(157)**

SCHEME 44. Reagents: (i) **151**, 0 to 20 °C; (ii) HgO, $BF_3 \bullet OEt_2$

Acylation of bis(methylsulfanyl)methyllithium **151** has been performed with α,α-diethoxypropanenitrile[168] as well as with lactones[169–171]. Tetrabenzyl-D-glucono-1,5-lactone suffered β-addition to the carbonyl group and the resulting product has been



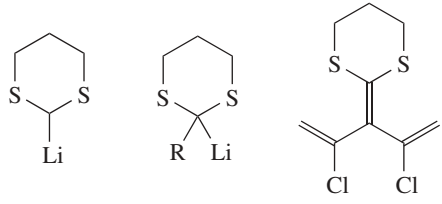
(158) **(159)** **(160)**

SCHEME 45. Reagents: (i) **151**, −60 °C; (ii) BF_3•OEt_2, Et_3SiH, −78 °C to rt; (iii) MeI, $CaCO_3$

applied to the synthesis of valiolamine and related compounds[169, 170]. β-1-Formyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside **160** has been prepared by addition of 4 equivalents of compound **151** to the lactone **158** at −60 °C, followed by reduction of the anomeric hydroxyl group and deprotection of the thioacetal moiety in compound **159** (Scheme 45)[171].

B. 2-Lithio-1,3-dithianes

Since 1965, in which Corey and Seebach[117, 172–174] reported the preparation of 2-lithio-1,3-dithiane **161**, the number of applications of 2-lithio-1,3-dithiane derivatives **162** in synthetic organic chemistry[2, 6–9, 13, 175–181] have been increased over the years and have become a general and classical strategy for the preparation of complex aldehydes and ketones in numerous total syntheses of natural products[182]. 2-Lithio-1,3-dithiane is used as masked formyl anion and as the corresponding dianion when, after the introduction of the first electrophile, it is again deprotonated and allowed to react with a second electrophile. α-Alkylated 1,3-dithianes can also be prepared by thioacetalization of the corresponding aldehyde with 1,3-propanedithiol under Lewis or Brönsted acid catalysis[6]. Recently, 2-[2-chloro-1-(1-chlorovinyl)allylidene]-1,3-dithiane (**163**) has been used as a non-thiolic odorless 1,3-propanethiol equivalent for the preparation of 1,3-dithianes under methanol reflux[183]. The second lithiation requires in most cases the use of *tert*-butyllithium, better than *n*-butyllithium, and the addition of TMEDA or HMPA.



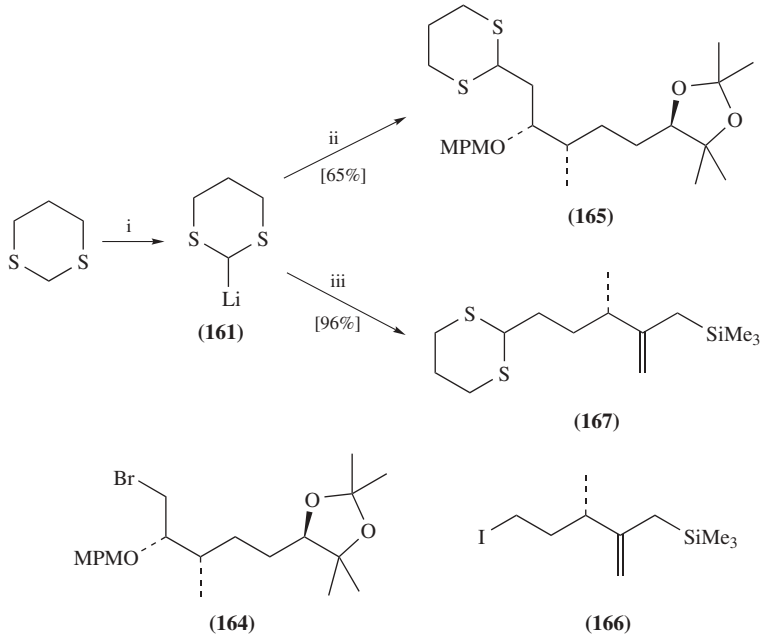
(161) **(162)** **(163)**

The mentioned stabilized cyclic anions are quite stable species, the lithium atom occupying an equatorial position with respect to the dithiane ring[9].

All types of electrophiles have been used with 2-lithio-1,3-dithiane derivatives, including alkyl halides, sulfonates, sulfates, allylic alcohols, arene–metal complexes, epoxides, aziridines, carbonyl compounds, imines, Michael-acceptors, carbon dioxide, acyl chlorides, esters and lactones, amides, nitriles, isocyanates, disulfides and chlorotrialkylsilanes or stannanes. The final deprotection of the dithioacetal moiety can be carried out by means of different types of reagents in order to regenerate the carbonyl group by heavy metal coordination, alkylation and oxidation[184] or it can be reduced to a methylene group with Raney-nickel, sodium or $LiAlH_4$.

1. Alkylation of 2-lithio-1,3-dithianes

The alkylation of intermediates **161** or **162** can be performed with allylic, propargylic and benzylic chlorides, as well as primary alkyl bromides and iodides. Some recent selected examples of monoalkylation of compound **161**[174] with the bromide **164** and the iodide **166** afforded products **165** and **167**, respectively, which are intermediates in the synthesis of the marine natural products, octalactin A[185] and leucascandrolide A[186], respectively (Scheme 46).

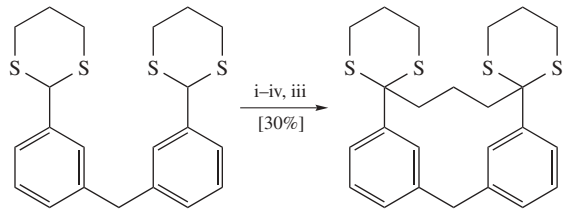


SCHEME 46. Reagents: (i) *n*-BuLi, THF, −30 °C; (ii) **164**, −30 °C; (iii) **166**, −78 to 0 °C

Different 2-substituted intermediates of type **162** have been alkylated with primary iodides and used in the synthesis of naturally occurring compounds[182], such as the sex pheromone of cigarette beetle serricornin[187], the immunomodulators (−)-rapamycin[188–190] and (−)-27-demethoxyrapamycin[190,191], (−)-FK506[190,192] and (−)-mycestericin E[193], the macrolide antibiotic bafilomycin A_1[194–196], the C10–C26 portion of the marine derivative polyether macrocycle pinnatoxin A[197,198], the oral adjuvant for nasal influenza vaccine pinellic acid[199], the macrocyclic core of the marine macrolide leucascandrolide A[200] and the 18-membered (+)-13-deoxytedanolide[201] of marine origin with promising all-killing activity. Other applications involving alkyl bromides and 2-substituted 2-lithio-1,3-dithianes **162** are the synthesis of the key biochemical intermediate 10,11-dihydro-12-oxo-LTB_4[202], *gem*-dideuteriated tetradecanoic acids for enzymatic studies[203], homoterpenoids emitted from elm leaves after elicitation by beetle eggs[204] and bicyclic acetals dioxaspiro[5.5]undecanes[205]. Some examples used allylic chlorides, such as in the synthesis of a juvenile hormone mimic (±)-echinolone[206] and the *Stemona* alkaloid (−)-stenine[207]. Benzylic chlorides worked as good electrophiles in the asymmetric synthesis of resorcylic macrolides radicol and monocillin I[208] and cycloproparadicicol[209],

which exhibit antifungal, antibiotic and anticancer properties, as well as β-naphthol derivatives[210]. Several aminoalkynyldithianes with calcium channel antagonist activity have been prepared by alkylation, for instance, of 2-lithio-2-phenyl-1,3-dithiane with 3-(trimethylsilyl)propargyl chloride and other propargyl bromides[211].

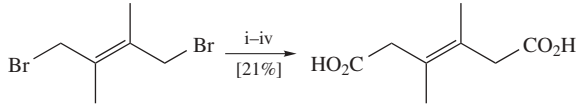
When 1-bromo-3-chloropropane is used as dielectrophile, the bis(dithiane) **168** can be dialkylated stepwise providing the bridged dithiane **169** in an intramolecular process, which was desulfurated by Raney-nickel reduction to give the corresponding [5.1]metacyclophane (Scheme 47)[212]. 1,3-Dibromopropane was used as linchpin for tetrahydropyranylated 2-(4-hydroxybutyl)-1,3-dithiane anion (generated with *t*-BuLi at −78 °C in the presence of HMPA) giving the corresponding adduct in 89% yield[213].



(168) **(169)**

SCHEME 47. Reagents: (i) *n*-BuLi, −60 °C; (ii) $Cl(CH_2)_3Br$, −60 °C to rt; (iii) HCl; (iv) LDA, −60 °C to rt

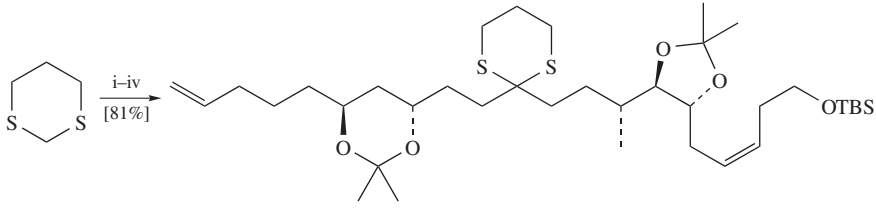
(*E*)-3,4-Dimethyl-3-hexenedioic acid (**171**) was also prepared by an intermolecular diacylation of the dibromide **170** with 2-lithio-1,3-dithiane (**161**), followed by deprotection and final oxidation (Scheme 48)[214].



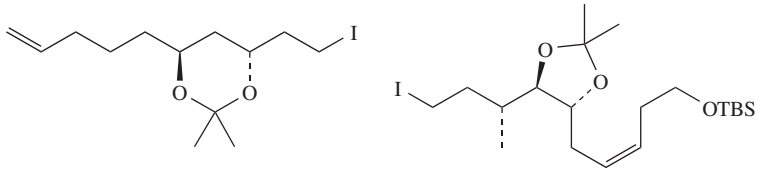
(170) **(171)**

SCHEME 48. Reagents: (i) **161**; (ii) $PhI(O_2CCF_3)_2$; (iii) TsOH; (iv) Jones oxidation

Intermolecular dialkylations of 1,3-dithiane have been carried out by stepwise lithiation–alkylation for the preparation of unsymmetrical ketones in natural product synthesis[182]. Thus, the fungal germination self-inhibitor (−)-gloeosporone and an analogue were prepared using twice (*S*)-2-(bromoethyl)oxirane as electrophile[215,216]. 3-Bromopropanol protected as tetrahydropyranyl derivative and (2*E*,4*E*)-1-bromo-2,4-hexadiene have been used for the dialkylation of 1,3-dithiane in the synthesis of the hydronaphthalene moieties of mevinic acids[217]. ω,ω'-Dialkenyl ketones were prepared by successive dialkylation of dithiane using alkenyl bromides in order to prepare spiro compounds by intramolecular 1,3-dipolar cycloadditions[218]. In the first total synthesis of pinnatoxin A by Kishi and coworkers, dithiane was used as linchpin for the assembly of two fragments as alkyl iodides[219]. The female pheromone components of the spring hemlock and the pitch pine loopers have been prepared by successive *gem*-dialkylation of dithiane with (*S*)-2-methyloctyl iodide followed by Raney-nickel hydrogenation[220]. Attenols A and B, which exhibit cytotoxicity against P388 cells, have been prepared using the precursor dithiane **174**, which was obtained by stepwise dialkylation of 1,3-dithiane



(174)



(172) **(173)**

SCHEME 49. Reagents: (i) *t*-BuLi, DMPU, −78 °C; (ii) **172**; (iii) *t*-BuLi, HMPA, −78 °C; (iv) **173**, −78 °C to rt

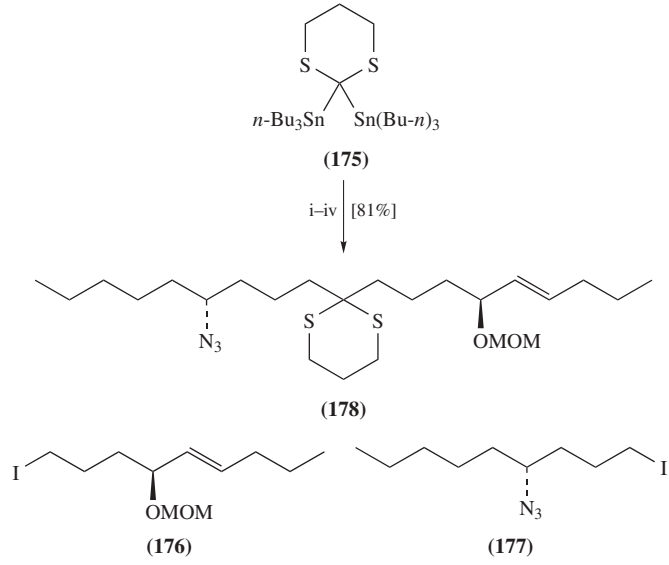
with iodides **172** and **173** (Scheme 49)[221]. The synthesis of (±)-perhydrohistrionicotoxin, a spirocyclic alkaloid isolated from the Columbian 'poison arrow' frogs, is based on the in situ successive dialkylation of 1,3-dithiane with 2-(3-chloropropyl)dioxolane[222].

For the fast *gem*-dialkylation of 1,3-dithiane dianion, tin–lithium transmetallation at the 2-position of dithiane is a much faster process than the corresponding deprotonation. 2,2-Bis[tri(*n*-butyl)stannyl]dithiane (**175**)[223] can be alkylated sequentially: it was transmetallated with *n*-BuLi at −78 °C, after 5 minutes treated with the first alkyl halide and after 10 more minutes the process was repeated providing dialkylated products[224]. This strategy has been used in the total synthesis of (−)-perhydrohistrionicotoxin, namely preparing the key compound **178** employing successively iodides **176** and **177** as electrophiles (Scheme 50)[224].

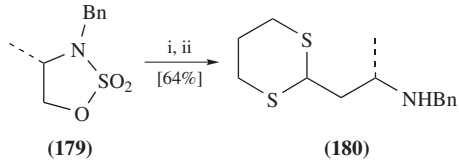
Triflates have also been employed as alkylating agents in the synthesis of natural products[182], such as macrocyclic lactam-lactones with antibiotic activity myxovirescins M_2[225], A_1 and A_2[226–228], the C- and D-ring systems of the polycyclic ether hemibrevetoxin-B[229] and the northern half C1–C16 of bryostatins[230]. A cyclic sulfate has been used as electrophile for the construction of a key intermediate in the total synthesis of swinholide A[231]. The cyclic sulfamidate **179** reacted with the intermediate **161** with displacement of sulfate to give the amine **180** (Scheme 51)[232].

Intramolecular alkylations of appropriate 2-substituted 1,3-dithiane anions allow the synthesis of cyclic ketones. This strategy was performed in the synthesis of six-membered ring analogues of 6α-carba-PGI_2. The treatment of bromide **181** with LDA gave the spiro thioacetal **182** in almost quantitative yield, whereas the use of the corresponding benzenesulfonate (as the leaving group) afforded the same reaction product but with lower yield (Scheme 52)[233].

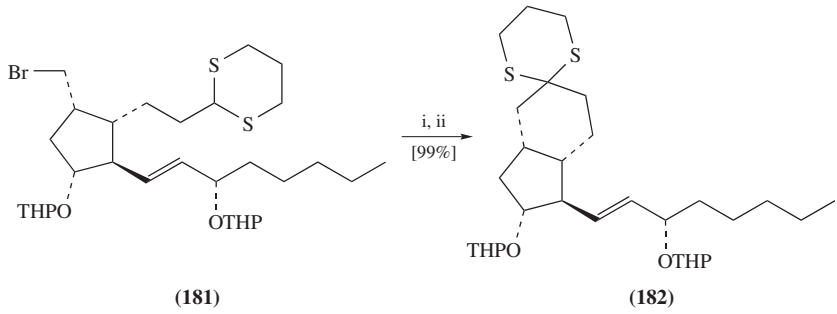
1,3-Dithianes derived from 2-deoxy-D-ribose bearing tosylates as leaving groups at the adequate position underwent intramolecular displacement reactions to form three-, four- and five-membered carbocyclic rings[234]. Similar studies have been carried out with mannose and glucose dithiane derivatives bearing a tosyl or an epoxide in the open chain to give cyclopropane, cyclobutane, cyclohexane and cycloheptane derivatives[235]. This strategy has been applied to the synthesis of validatol and 4-*epi*-validatol[236].



SCHEME 50. Reagents: (i) *n*-BuLi, −78 °C; (ii) **176**; (iii) *n*-BuLi, −78 °C; (iv) **177**, −78 °C to rt

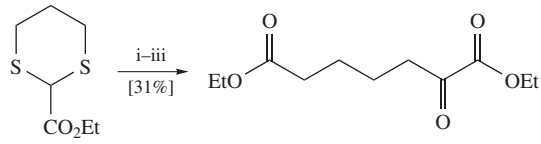


SCHEME 51. Reagents: (i) **161**, −25 °C to rt; (ii) H_2SO_4



SCHEME 52. Reagents: (i) LDA, −78 to 20 °C; (ii) H_2O

2-Ethoxycarbonyl-1,3-dithiane (**183**), easily accessible from ethyl glyoxylate diethyl acetal, can be lithiated-alkylated to afford, after deprotection, α-ketoesters as exemplifies the product **184** (Scheme 53)[237]. This methodology has been used in the preparation of 3-deoxy-D-manno-2-octulosonic acid (KDO) derivatives[238] and of the ABC ring system of manzamine A[239].



(183) **(184)**

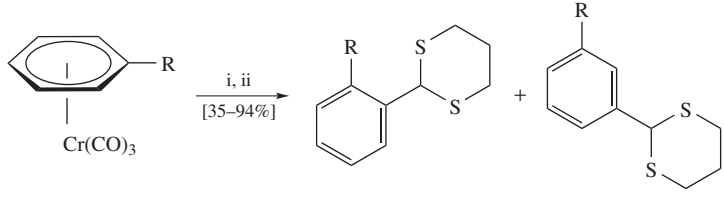
SCHEME 53. Reagents: (i) *n*-BuLi, −78 °C; (ii) Ethyl 5-bromovalerate, −78 °C to rt; (iii) NBS, $AgNO_3$, 2,6-lutidine

Allylic alcohols can be used as alkylating agents of organolithium compounds, such as intermediate **161**. By mixing a lithium alkoxyallylcuprate and *n*-butyllithium, to give a mixed cuprate, followed by addition of *N*,*N*-methylphenylaminotriphenylphosphonium iodide, an amino cuprate complex is formed. Final addition of compound **161** gave the corresponding 2-allylated 1,3-dithiane[240, 241].

2. Arylation of 2-lithio-1,3-dithianes

Reactions of 2-lithio-1,3-dithiane (**161**) with nitroarenes gave 1,4- and 1,6-addition products whereas 2-methyl and 2-phenyl-1,3-dithiane derivatives provide only 1,6-addition products. These conjugate-addition products are transformed into the respective nitroaromatic compounds by in situ oxidation with oxygen or DDQ. In the case of 4-chloronitrobenzene, the 1,4-addition product with respect to the nitro group was mainly obtained[242]. A SET mechanism was proposed[242], as in the case of alkyl iodides[243].

Activation of aromatic compounds by transition-metal complexes was initially studied with $Cr(CO)_3$ complexes. Nucleophilic addition of 2-lithio-1,3-dithianes to arene-chromium(0) complexes **185** followed usually by iodine-promoted decomplexation affords the corresponding 2-arylated 1,3-dithianes **186**. The reaction of η^6-(toluene)- and (anisole)tricarbonylchromium (**185**) with compound **161** gave mixtures (52:46 and 10:90, respectively) of *ortho* and *meta* substituted derivatives (**186**) (Scheme 54)[244]. The *meta* directing effect was also observed (mainly better than 95%) with amino and fluoro substituted complexes[245].



(185) **(186)**

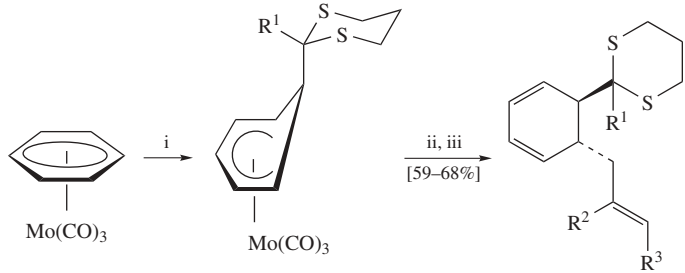
[R = Me, MeO]

SCHEME 54. Reagents: (i) **161**, −78 to 0 °C; (ii) I_2

In the case of *N*-methylindoletricarbonylchromium(0), the addition of compound **161** took place at the 7-position giving directly, after quenching with NH_4Cl, the corresponding aromatic derivative in 41% yield[246]. 2-Lithio-2-methyl-1,3-dithiane gave mainly nucleophilic substitution at the C13 in the methyl podocarpa-8,11,13-trien-19-oate tricarbonylchromium complex, after treatment with iodine[247]. The anionic addition products

using benzene-$Cr(CO)_3$ and 1-methoxynaphthalene-$Cr(CO)_3$ can be trapped by methyl iodide, and after Ph_3P-induced carbonylation the cyclohexadiene and dihydronaphthalene derivatives were obtained[248]. This methodology has been applied to the synthesis of akavinone, the aglycone of the antibiotic anthracyclinone aclacynomycine[249]. The marine natural product (+)-ptilocaulin has been synthesized by addition of compound **161** to the 1-crotyl-2-methoxy-3-(trimethylsilyl)benzenetricarbonylchromium complex as the key step[250–252].

The η^6-benzenemolybdenumtricarbonyl complex **187** also suffered nucleophilic addition of 2-lithio-1,3-dithiane or its 2-methyl derivative at −78 °C to give the η^3-cyclohexadienyl anionic complexes **188**, which were trapped with allylic bromides to yield, after CO insertion under CO pressure, *trans*-5,6-disubstituted 1,3-cyclohexadiene derivatives **189** (Scheme 55)[253]. Analogous reactions with [(η^6-benzene)$Cr(CO)_3$] give directly the corresponding cyclohexadiene in which the CO has been inserted in the allyl group.



(187) **(188)** **(189)**

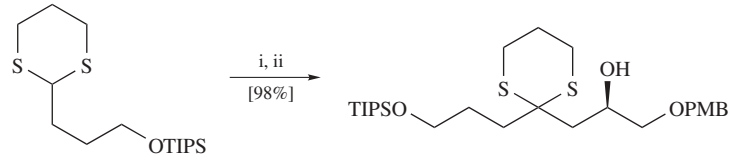
[R^1, R^2, R^3 = H, Me]

SCHEME 55. Reagents: (i) $(\overline{CH_2)_3SCHR^1S}$, *n*-BuLi; (ii) $R^3CH{=}CR^2CH_2Br$, −78 °C to rt; (iii) CO, 4 atm

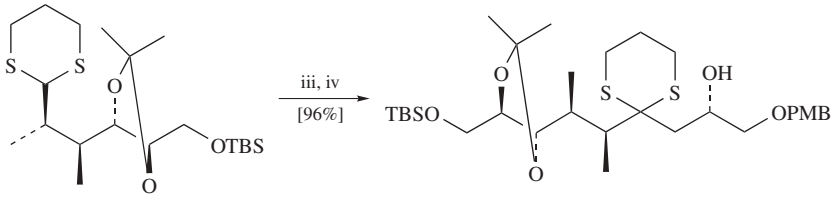
3. Reactions with epoxides and aziridines

Epoxide ring opening by 2-lithio-1,3-dithiane derivatives[175–181] is an attractive strategy specially for the synthesis of chiral aldols and has been applied widely to the total synthesis of many natural products[182]. This reaction proceeds via a S_N2 mechanism with high regioselectivity at the less substituted side of the epoxide. In several examples glycidol derivatives are used as electrophiles, such as in the synthesis of the C1–C12 unit of amphotericin B[254], the marine lipid diol (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol[255], the C1–C11 fragment of tedanolide and 13-deoxytedanolide[256], the antiviral marine natural product (−)-hennoxazole A[257, 258], the antimitotic (+)-discodermolide[259] and some building blocks of the selective apoptosis induced natural product apoptolidin[260]. Recent examples on the reaction of glycidyl 4-methoxybenzyl ether **192** with dithianes **190** and **191** have been used in the synthesis of the C16–C28 spiroketal fragment of spongistatins (**193**)[261] and the JKLM-ring fragment of ciguatoxin (**194**)[262], respectively (Scheme 56).

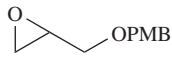
In connection with carbohydrates, (1*S*,3*S*,5*R*)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane has been prepared from dithiane and D-glucose[263]. An epoxide derived from D-xylose **195** has been opened regioselectively by means of compound **161** at the 4-position in 90% yield[264]. In the case of the methyl 2,3-anhydro-α-D-lyxofuranoside **196** the ring



(190) **(193)**

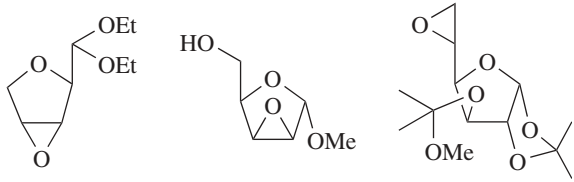


(191) **(194)**



(192)

SCHEME 56. Reagents: (i) *n*-BuLi, rt; (ii) (*R*)-**192**, −20 to 0 °C; (iii) *t*-BuLi, −78 °C; (iv) (*S*)-**192**, HMPA, −78 to −45 °C

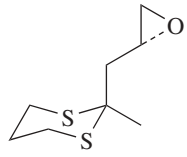


(195) **(196)** **(197)**

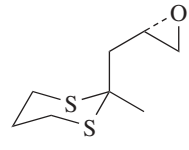
opening with intermediate **161** occurred at the 3-position[265]. The D-glucose derived epoxide **197** has also been opened with the same reagent in the presence of HMPA in 93% yield[266].

Several applications of the opening of epoxides with lithiated dithianes in natural product synthesis[182] are debromoaplysiatoxin[267] and aplysiatoxin[267–269], a segment of roflamycoin[270], the C1–C9 intermediate towards maytansine[271], (+)-tautomycin[272, 273], an antibiotic with strong antifungal activity against *Sclerotonia sclerotiorum,* (−)-PA-48153C (pironetin) from L-quebrachitol[274] and from (1*S*,5*S*,6*R*)-5-hydroxybicyclo[4.1.0]heptan-2-one[275], the marine metabolite (+)-calyculin A and (−)-calyculin B[276], kurzilactone[277], the antitumor agent fostriecin (CI-920)[278], the tetrahydropyranyl and spiroacetal moieties of bistramide A[279], the core structure of apicularen A[280], both enantiomers of flavanone and 2-methylchromanone[281], strictifolione[282], the FGHI ring domain of azaspiracids[283], altohyrtin C (spongistatin 2)[284, 285], the 1,4-polyketide amphidinoketide I[286], the C8–C19 region of the cytotoxic macrolide peloruside A[287] and the boron-containing ion carrier antibiotic macrodiolide tartrolon B[288].

When enantiomerically enriched epichlorohydrins are used as electrophiles, inversion of the configuration was observed[153]. Dithianes **198** and **199**, prepared from (*R*)- and



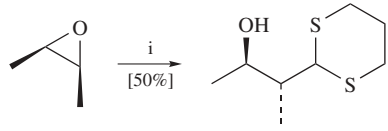
(198)



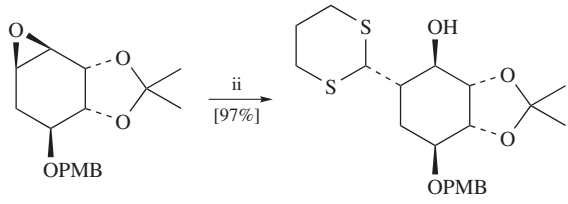
(199)

(*S*)-epichlorohydrin, have been used in the synthesis of leucascandrolide A[289] and (−)-hennoxazole A[290], respectively.

In the case of 1,2-disubstituted epoxides, such as compounds **200** and **201**, the reaction with 2-lithio-1,3-dithiane **161** takes place diastereoselectively to afford products **202**[291] and **203**[292], respectively (Scheme 57).



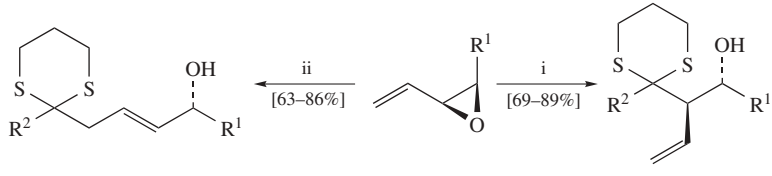
(200) **(202)**



(201) **(203)**

SCHEME 57. Reagents: (i) **161**, −20 to 0 °C; (ii) **161**, HMPA, −20 °C

Vinyl epoxides can be regioselectively opened depending on the substitution at the 2-position of the 2-lithio-1,3-dithiane. Thus, the S_N2 adducts *anti*-**204** were obtained with unencumbered dithiane anions, whereas S_N2' adducts **205** were produced with sterically encumbered ones (Scheme 58)[293].

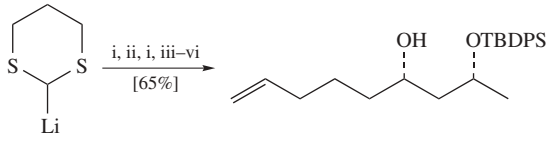


(205) **(204)**

[R^1 = *n*-C_8H_{17}, *c*-C_6H_{11}, $CH_2OTBDPS$, CH_2CH_2OBn]

SCHEME 58. Reagents: (i) **161** or **162** (R^2 = Ph, Me_3Si), −78 °C to rt; (ii) **162** (R^2 = Et, *i*-Pr, *i*-Pr_3Si), −78 °C to rt

In some total syntheses of natural products[182] two different electrophiles have been successively introduced at the 2-position of the 1,3-dithiane ring. Thus, for the synthesis of 11-oxo-13-tetradecanolide, propylene oxide and 1-tetrahydropyranyloxy-10-bromodecane were successively employed[294]. In the synthesis of the macrocyclic lactone lasiodiplodin[295] and attenols A and B[296] an alkyl halide and then an epoxide have been used as electrophiles. Dialkylation of 1,3-dithiane with (*S*)-*O*-benzylglycidol gave a symmetrical ketone[297]. In the asymmetric synthesis of the C1–C9 fragment of bryostatins, 1,3-dithiane was dialkylated with two different chiral epoxides[298], as well as in the case of altohyrtin A (spongistatin 1)[299]. Compound **206** has been prepared by in situ successive metallation–alkylation of 1,3-dithiane with propylene oxide and 5-iodo-1-pentene (Scheme 59). This resulting protected diol **206** is an intermediate in the synthesis of (−)-pinidinol[300].



(161) **(206)**

SCHEME 59. Reagents: (i) *n*-BuLi, −40 °C; (ii) propylene oxide, −40 to 0 °C; (iii) 5-iodopent-1-ene, −40 to 0 °C; (iv) TBDPSCl, imidazole, DMAP; (v) $HgCl_2$; (vi) $NaBH_4$

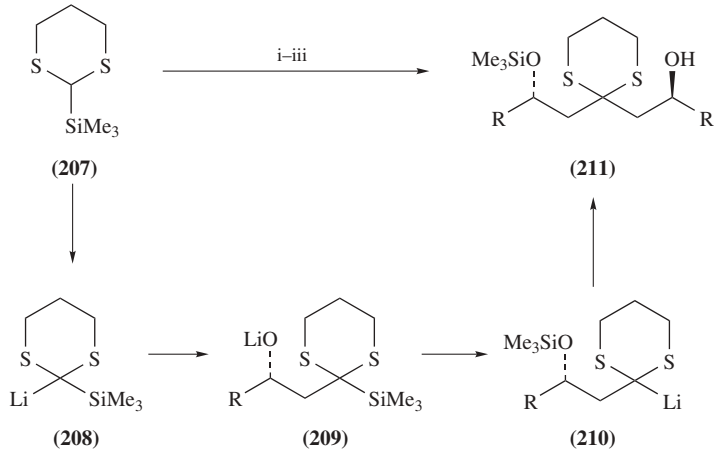
As mentioned before (Section III.B.1), 2,2-bis(tri-*n*-butylstannyl)-1,3-dithiane (**175**) can be used as formyl dianion precursor. In two syntheses of roflamycoin, a subsequent double alkylation of compound **175**, either with an alkyl iodide and an epoxide[301] or with an epoxide first and then with an alkyl bromide[302], has been performed.

Multicomponent linchpin couplings can be carried out with 2-trialkylsilyl substituted 1,3-dithianes **207** and epoxides and was successfully used in the synthesis of natural products[182]. Tietze and coworkers[303] found out that 2-lithio-2-trimethylsilyl-1,3-dithiane **208** reacted with two equivalents of a chiral epoxides in the presence of a crown ether to give first the monoadduct **209**, which suffered 1,4-Brook rearrangement[304] generating a new dithiane anion **210**. Final reaction with an epoxide afforded products **211**, which are equivalents of acetone aldol products (Scheme 60).

Working with only one equivalent of *n*-BuLi, a double alkylation of 2-(trialkylsilyl)-1,3-dithiane is also possible. Smith and coworkers improved two aspects of this transformation by reducing the reaction times and by the use of two different epoxides[305]. Thus, using 2-(*tert*-butyldimethylsilyl)-1,3-dithiane (**212**) and Williams and coworkers' lithiation conditions [*t*-BuLi, −78 °C, THF/HMPA (10%), 5 min][306], the dialkylation with the same epoxide took place in 30 minutes. When using two different epoxides, control of the Brook rearrangement was achieved by using appropriate solvents[307,308]. The deprotonation has to be carried out in ether in order to avoid the rearrangement and, after reaction with the first epoxide, HMPA or DMPU should be added before the reaction with the second epoxide, so compounds **213** were obtained (Scheme 61)[305]. This methodology has been studied with terminal epoxides, epichlorohydrin and vinyl epoxides[309].

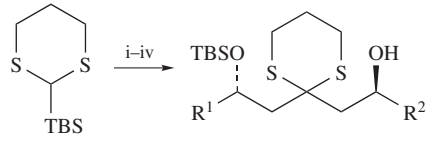
The former one-pot multicomponent linchpin coupling protocol has been applied as the key step in numerous syntheses of complex molecules[182]. Some significant examples are the C16–C18 fragment of the macrolide antibiotics mycoticins A and B[310], the spiroketal segments of spongistatins[311–315] and the C1–C18 polyol fragment of mycosamine glycosylated polyene macrolide, (+)-rimocidin[316].

The already called Smith–Tietze coupling reaction has been used in the synthesis of the bryostatin B ring by using glycidol **192** as the only electrophile[317]. When C_2-symmetric



(207) **(208)** **(209)** **(210)** **(211)**

SCHEME 60. Reagents: (i) *n*-BuLi, −30 to 0 °C; (ii) (*R*)-RCH(O)CH_2 (2 eq), 12-crown-4, −20 °C; (iii) H_2O

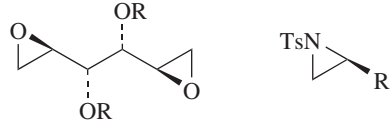


(212) **(213)**

SCHEME 61. Reagents: (i) *t*-BuLi, ether, −78 to 45 °C; (ii) (*R*)-$R^1CH(O)CH_2$, −78 °C to rt; (iii) HMPA; (iv) (*R*)-$R^2CH(O)CH_2$, −78 °C to rt

bis epoxides **214**, derived from D-mannitol, were used as electrophiles, a tandem alkylation–cyclization took place with lithiated **212** to give mixtures of 6- and 7-membered cyclitols and aminocyclitols[318–320].

The ring opening of enantiopure *N*-tosyl aziridines **215** with 2-substituted 2-lithio-1,3-dithianes takes place at the less substituted carbon atom in good yields (59–92%)[321]. The corresponding adducts gave β-tosylamino carbonyl compounds after reaction with methyl iodide under acetone reflux.

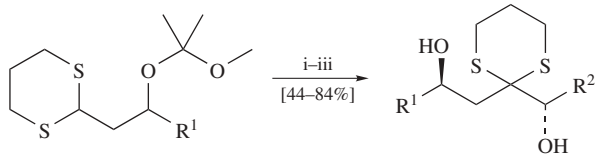


(214) **(215)**

4. Reactions with carbonyl compounds and imines

Aldehydes react very fast with 2-lithio-1,3-dithiane (**161**) even at very low temperatures, whereas ketones need higher temperatures[175–181]. Stereochemical control of the new stereocenter can be achieved with α-substituted aldehydes or conveniently with 2-substituted

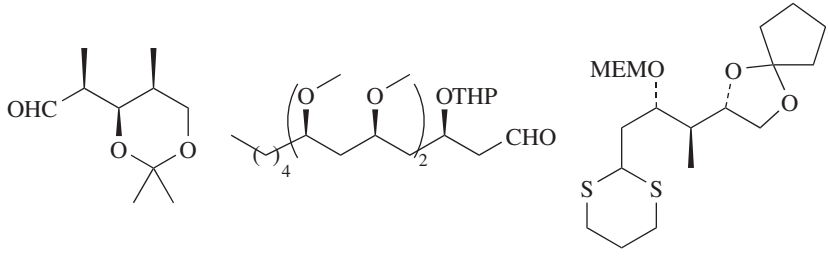
2-lithio-1,3-dithianes. In the case of protected α-hydroxy aldehydes derived from carbohydrates, the corresponding Cram chelation control *syn*-products are mainly obtained[322–324]. The Garner aldehyde gave, after reaction with compound **161**, the expected *anti*-products in the presence of $BF_3{\bullet}OEt_2$ and CuI[325]. 1,4-Asymmetric induction has been observed when the 1,3-dithiane has a 2-hydroxyalkyl group at the 2-position, giving mainly *anti*-products **217**, which have been cyclized to give the corresponding *trans*-2,5-disubstituted tetrahydrofurans (Scheme 62)[326,327]. However, very low 1,5-asymmetric induction has been obtained in the case of the dithianes homologous of compound **216**[328].



(216) **(217)**

SCHEME 62. Reagents: (i) *n*-BuLi; (ii) R^2CHO, $-78\,^{\circ}C$; (iii) $HCl-H_2O$

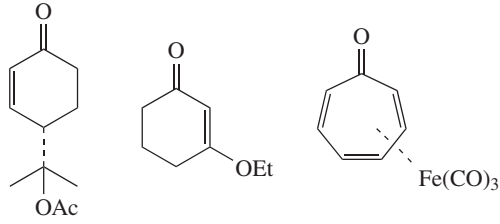
Asymmetric 1,2- to 1,4-inductions have been applied to the synthesis of several natural products[182]. 9-Dehydrocrytronolide was prepared using the aldehyde **218**, which suffered addition of compound **161** giving the corresponding *syn*-product[329]. The β-alkoxy aldehyde **219** reacted with the intermediate **161** to afford a 1,3-*syn*-polyol derivative[330]. The lithiated dithiane **220** gave in the reaction with a dienal a 1:1 mixture of diastereomers, used in the synthesis of (−)-*N*-methylmaysenine[331] and maytansine[332].



(218) **(219)** **(220)**

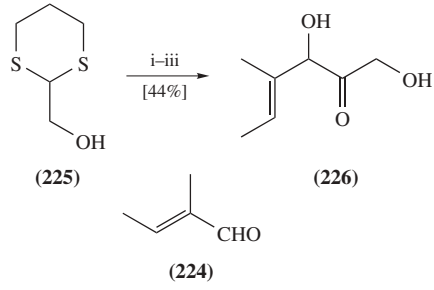
Other examples gave also, in general, mixtures of diastereomers, such as in the total synthesis of (+)-phyllanthocin[306], the aglycon of the antileukemic (+)-phyllanthoside, the C10–C19 fragment of FK506[333,334], in the total synthesis of zaragozic acid A by Nicolaou and coworkers[335,336] and in the mentioned synthesis of spongistatins by Smith and coworkers[313,314,337]. Recently, the addition of cerium(III) and zinc(II) chlorides allowed a better diastereoselectivity (>20:1) in the last coupling to this subunit of spongistatins[338]. In both syntheses of CP-263,114 and CP-225,917 by Danishefsky's[339] and Nicolaou's[340–344] groups, mixtures of diastereomers were obtained as well as in the synthesis of zaragozic acid D[345,346], in the case of the BC-ring segment of ciguatoxin 1B[347], and in the synthesis of the ABCD ring system of azaspiracid[348] and apoptolidin[349,350]. Alkylation of 1,3-dithiane by an epoxide followed by addition to a carbonyl compound in an intramolecular manner has been performed in the synthesis of the rocaglamide skeleton[351].

α,β-Unsaturated aldehydes and ketones gave the corresponding 1,2-addition products in the reaction with dithiane anions and without additives (for 1,4-addition reactions, see Section III.B.5). Some examples are enones **221**[352] and **222**[353], which have been used in the synthesis of a cannabinoid terpene synthon[352] and the bicyclo[7.3.1]tridecenediyne system of the antitumor antibiotic dynemycin-A[353], respectively. Tricarbonyl(tropone)iron **223** suffered also 1,2-addition of 2-lithio-1,3-dithiane (**161**) at the opposite side to the $Fe(CO)_3$ group[354].



(221) **(222)** **(223)**

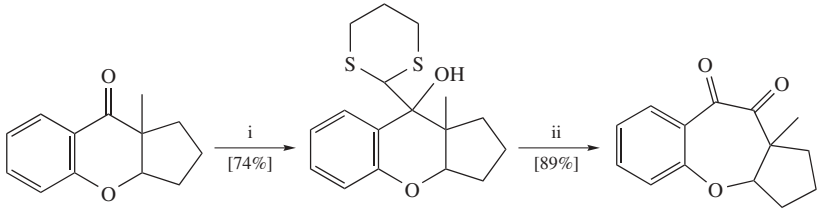
In the case of tiglic aldehyde (**224**), dithiane **225** was used, and the resulting 1,3-dihydroxyketone **226** was employed in the preparation of the furopyridine antibiotic 2-*epi*-CJ-16,170 (Scheme 63)[355].



(225) **(226)** **(224)**

SCHEME 63. Reagents: (i) *n*-BuLi, −78 °C; (ii) **224**, −78 °C; (iii) $PhI(OCOCF_3)_2$

Dithiane anions and cyclic ketone adducts suffer rearrangement on treatment either with mercury chloride and fluoroboric acid[356] or with *N*-chlorosuccinimide[357] to give the corresponding one-carbon ring expanded 1,2-diketones. A selected example is the case of the ketone **227**, which was transformed into the adduct **228** and, after treatment with NCS, into the diketone **229** (Scheme 64)[357].



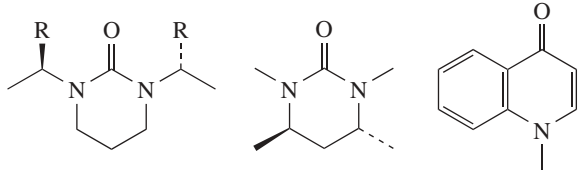
(227) **(228)** **(229)**

SCHEME 64. Reagents: (i) **161**, −25 °C; (ii) NCS, CH_2Cl_2, H_2O

Recently, it was described that the addition of the 5,5-bis(hydroxymethyl)-1,3-dithiane to an in situ generated *N*-silylated imine provided the corresponding amine, used for the preparation of photolabile phospholipids[358].

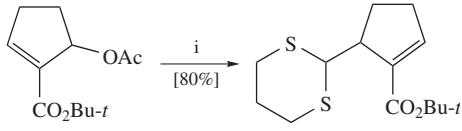
5. Michael-type reactions

2-Lithio-1,3-dithiane (**161**) shows a lower preference than bis(phenylsulfanyl)methyllithium (**126**) to give conjugate addition with α,β-unsaturated carbonyl compounds (see Section III.A). 1,4-Addition of 2-lithio-1,3-dithiane derivatives to unsaturated carbonyl compounds is a direct strategy for the preparation of 1,4-dicarbonyl systems. α,β-Unsaturated aldehydes gave mainly 1,2-addition products. However, enones suffer conjugate addition in THF at higher temperatures and for longer reaction times[359]. The presence of HMPA[147,360–362] as additive favored the formation of solvent-separated ion pairs and 1,4-addition products are mainly or exclusively obtained[363,364]. Alternatively, DMPU can be used instead of HMPA but with lower regioselectivity[365,366]. Recently, enantiopure DMPU derivatives **230** and **231** have been used as chiral Lewis bases as promoters in the regio- but not enantioselective addition of 2-lithio-1,3-dithiane (**161**) to cyclohex-2-en-1-one, but only compound **231** gave mainly conjugate addition[366]. Steric hindrance in the substrate or nucleophile also favors 1,4-addition products[9]. In the reaction of 2-lithio-1,3-dithianes with 1-methyl-4-quinoline **232**, conjugate addition was obtained and the resulting enolates have been trapped with electrophiles[367].



(230) **(231)** **(232)**

α,β-Unsaturated carboxylic acid derivatives, such as esters, amides and nitriles, suffer 1,4-addition of 2-lithio-1,3-dithiane derivatives. The addition to ethyl crotonate takes place cleanly[368] and the ester **233** gave in the presence of copper(I) iodide, after addition–elimination, the corresponding product **234** (Scheme 65), which has been used for the synthesis of the matrix metalloproteinase inhibitors 5-substituted 2-(biarylsulfanyl) cyclopentanecarboxylic acids[369].

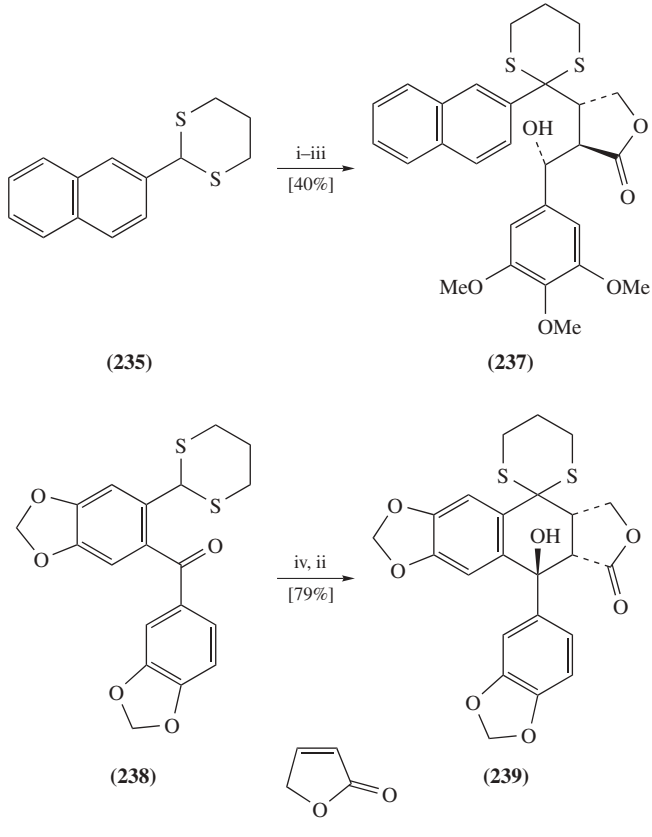


(233) **(234)**

SCHEME 65. Reagents: (i) **161**, CuI, −78 °C

α,β-Unsaturated lactones have been used as Michael acceptors of 2-aryl substituted 1,3-dithiane anions. The addition to but-2-enolides[370–377] has been applied to the total synthesis of stegane lignanes, which show significant antitumor activity. The synthetic strategy involves the conjugate addition to the α,β-butenolide **236** followed by reaction

of the resulting enolate with an aromatic aldehyde. For example, the synthesis of the naphthalene analogue **237** of lignanes was performed from the dithiane **235**, the butenolide **236** and an aldehyde (Scheme 66)[377]. A rapid entry towards the podophyllum lignans, such as taiwanin E and chinensinaphthol, involves a Michael ring closure reaction between the dithianes **238** and 5*H*-furan-2-one **236** to give the final product **239** (Scheme 66)[378, 379].



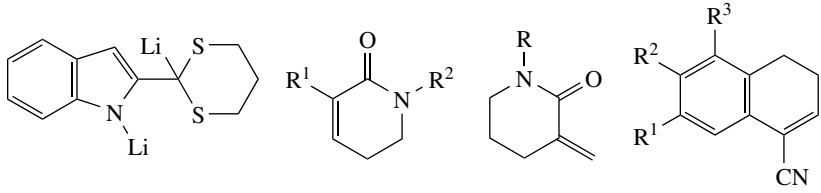
(235) **(237)**

(238) **(239)**

(236)

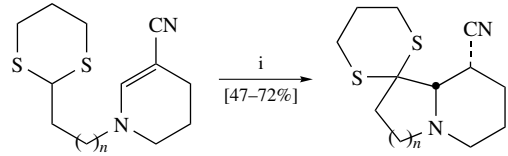
SCHEME 66. Reagents: (i) *n*-BuLi, −78 °C; (ii) **236**; (iii) 3,4,5-$(MeO)_3C_6H_2CHO$, TMEDA, −50 °C; (iv) LDA, −78 °C

For the addition to α,β-unsaturated carboxylic acids, two equivalents of 2-lithio-1,3-dithiane have to be used[380]. Alternatively, and in order to avoid polymerization, α-silylated α,β-unsaturated carboxylic acid salts are better Michael acceptors[381]. α,β-Unsaturated amides[382, 383] and thioamides[384] are also good substrates for tandem conjugate addition-α-alkylation after quenching with alkyl halides and other electrophiles. 2-Indolyl-1,3-dithiane dianion **240** has been used as nucleophile for the conjugate addition to cyclic α,β-unsaturated lactams **241** and **242** followed by ring closure for the synthesis of different *Strychnos* alkaloids[385–393], such as 20-epidasycarpidone[392], 20-epiuleine[392] and aspidospermidine[393]. α,β-Unsaturated nitriles such as compounds **243** are excellent Michael acceptors for compound **161** to give mainly the corresponding *cis*-adducts[394].



(240) **(241)** **(242)** **(243)**

Intramolecular conjugate additions with nitriles **244** have been performed by deprotonation with *n*-BuLi in the presence of 12-crown-4 at room temperature, giving mainly indolizidine and quinolizidine derivatives **245** with the cyano group in an axial orientation (Scheme 67)[395]. The deprotection of the final dithioacetal has been achieved with bis(trifluoroacetoxy)iodobenzene[396].

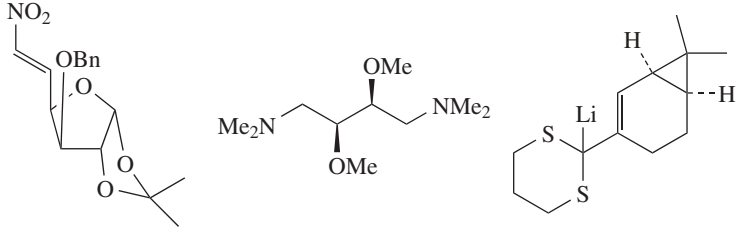


(244) **(245)**

[*n* = 1, 2]

SCHEME 67. Reagents: (i) *n*-BuLi, 12-crown-4, rt

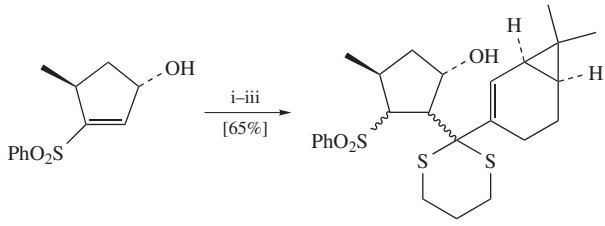
Nitroalkenes, vinyl sulfones and vinylphosphonium salts have been shown as good Michael acceptors for 2-lithio-1,3-dithiane derivatives. Nitroalkene sugar derivative **246** has been used as electrophile for the synthesis of branched-chain cyclitols[397–399]. Seebach and Langer studied the addition to simple nitroalkenes using the chiral solvent (*S*,*S*)-DDB (**247**) with some degree of diastereoselectivity[400, 401].



(246) **(247)** **(248)**

The addition of the anion **248** derived from the corresponding dithiane to the vinyl sulfone **249**, to afford the corresponding product **250**, has been applied to the synthesis of jolkinol C (Scheme 68)[402].

The addition of the intermediate **161** to cycloalkenylphosphonium salts has been used for the preparation of chiral ligands for the palladium-catalyzed asymmetric allylic alkylation[403, 404].

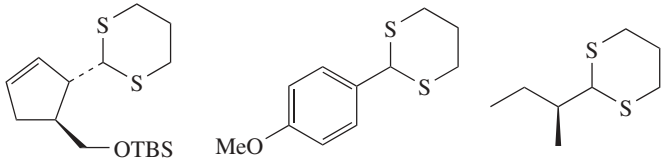


(249) **(250)**

SCHEME 68. Reagents: (i) MeLi, −78 °C; (ii) **248**; (iii) NH_4Cl

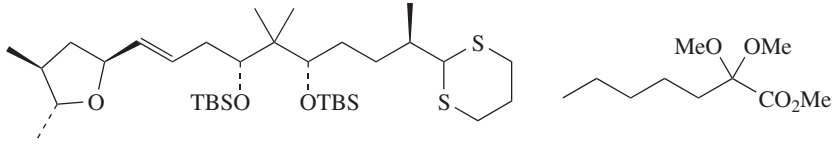
6. Acylation of 2-lithio-1,3-dithianes

The most common acylating reagents for organolithium compounds, such as carbon dioxide and alkyl chloroformates, have been used only in few cases with lithiated 1,3-dithianes. The synthesis of α-ketoacids by reaction of lithiated dithianes **251**[405] and **252**[406] with carbon dioxide has been used for the preparation of a precursor of prostaglandin A_2[405] and of pulvinic acid pigments[406]. Methyl chloroformate was recently used as electrophile with chiral dithianes, such as compound **253**, to give the corresponding ketoester in 54% yield[407] and for the preparation of α,α'-difluoroesters by reaction of different 2-alkyl substituted dithiane anions with ethyl chloroformate[408].

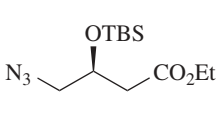


(251) **(252)** **(253)**

Less common acylation reagents of organolithium compounds are esters or lactones due to overaddition reactions. However, in the case of 2-lithio-1,3-dithiane derivatives the nucleophilic substitution takes place cleanly to afford the corresponding α-ketodithianes. In the total synthesis of the boron-containing antibiotic aplasmomycin, the dithiane **254** was deprotonated with *n*-BuLi and TMEDA at −30 °C and allowed to react with dimethyl oxalate in the presence of HMPA in 96% yield[409]. Acylation of 2-lithio-1,3-dithiane (**161**) with the ester **255** gave the corresponding α-ketodithiane in 85% yield, which was used in the synthesis of dihydrojasmone, dihydrojasmolone and precursors of methylenomycins A and B[410]. Lower yield (44%) was obtained in the case of the ester **256** but it could not be used in the synthesis of slagenins, because the corresponding deprotection of the thioacetal moiety failed[411]. In the case of the acylation of dithiane **257** with the ester **258**, the resulting α-ketodithiane was reduced with Raney-nickel to give, after deprotection, difluorinated [6]-gingerol[412].



(254) **(255)**



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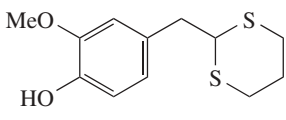
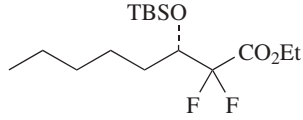


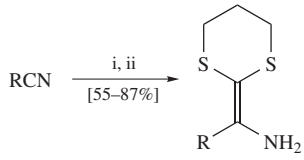
(257)



(258)

Lactones derived from protected D-glucose[413] and D-erythrose **145**[153] suffer stereoselective attack by compound **161** at the β- and α-face, respectively, to give the corresponding lactols.

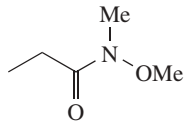
Nitriles can be used as acylating agents to afford the corresponding ketones after acidic work-up[166]. However, the addition of the intermediate **161** to a solution of the corresponding nitrile yielded, after quenching with aqueous NH_4Cl, ketene thioacetals **259** (Scheme 69), which reacted with α,β-unsaturated ketones giving δ-diketones[414–418].



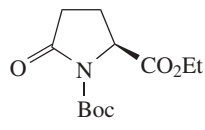
(259)

SCHEME 69. Reagents: (i) **161**, −78 °C to rt; (ii) NH_4Cl

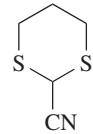
Carboxamides, especially DMF, have been widely used as acylating agents. Formylation of different 2-substituted 2-lithio-1,3-dithianes was employed in the preparation of (−)-pestalotin[419], of an approach to the alkaloid oycorenine[420], octahydroindoles[421], (−)-pyrenophorin[422,423] and norpyrenophorin[422], (+)-pyrenophorin and hexafluoropyrenophorin[424], (−)-maytansinol[425] and the biochemical intermediate 12-oxo-LTB_4[426]. The Weinreb amide **260**[427] and the pyroglutamate **261**[428] have also been used as electrophiles with the intermediate **161**. Triphenylmethyl isocyanate reacts with compound **161** to give 2-cyano-1,3-dithiane **262** in 83% yield, which has been lithiated and alkylated with excellent yields[429].



(260)



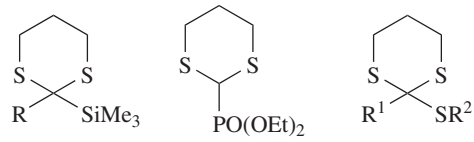
(261)



(262)

7. Reactions with other electrophiles

2-Lithio-1,3-dithiane (**161**) reacted with silyl[430–432], germyl[431] and stannyl[223,431] chlorides to give the corresponding 2-substituted 1,3-dithianes. The application of 2-trialkylsilyl derivatives **207** and **212** as linchpins for molecular construction by the Smith–Tietze procedure[190] was described in Section III.B.3. 2,2-Bis[tri(*n*-butyl)stannyl]-1,3-dithiane **175**[223] has also been used as linchpin acting as a formyl dianion precursor (see Sections III.B.1 and III.B.3). Substituted trimethylsilyl derivatives **263** have recently been used for the synthesis of aliphatic acylsilanes (**13**) by deprotection with MeI and



(263) **(264)** **(265)**

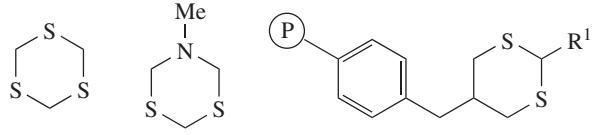
$CaCO_3$[433]. Silyl fluorides can also act as electrophiles for the silylation of intermediate **161**[434].

The use of diethyl chlorophosphate[435] as electrophile in the reaction with compound **161** gives the phosphate **264**, which after metallation can be condensed with carbonyl compounds providing ketene dithioacetals[436,437]. This strategy has been employed for the preparation of the C1–C9 fragment of the coccidioastat salinomycin[436]. Ketene dithioacetals can also be prepared from 2-lithio-2-trimethylsilyl-1,3-dithiane derivatives[154,438,439].

Disulfides are good electrophiles for the introduction of an alkyl or arylsulfanyl group at the 2-position of 2-lithio-1,3-dithianes[141,151,440]. By treatment of the resulting orthothioesters **265** with Lewis acids[441], 1,3-dithian-2-yl carbenium ions can be generated, as in the case of ketene dithioacetals with Brönsted acids[439].

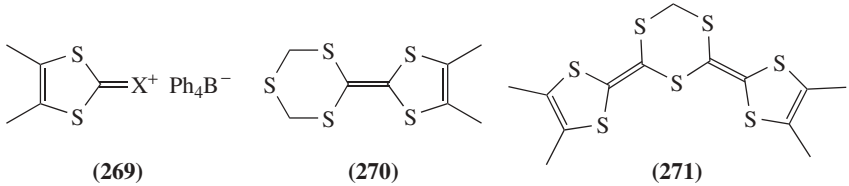
C. Other Cyclic 2-Lithiodithioacetals

Several cyclic thioacetals **266–268**, closely related to 1,3-dithiane, have been described as formyl anion equivalents. 1,3,5-Trithiane (**266**)[442,443], as well as 4,5-dihydro-5-methyl-1,3,5-dithiazine (**267**)[444–446], can be deprotonated with *n*-butyllithium at −78 °C to give the corresponding protected formyllithium derivatives, as in the case of 1,3-dithiane, which react with alkyl halides and carbonyl compounds for intermediate **267**. However, the deprotonation of the corresponding 2-alkyl derivatives could not be performed and for alkylated trithianes the second lithiation occurred at an unsubstituted carbon atom. For the deprotection step mercury(II) chloride can also be used, and in the case of 1,3,5-trithiane derivatives, iodine in DMSO[447] gave good yields of the corresponding carbonyl compounds.



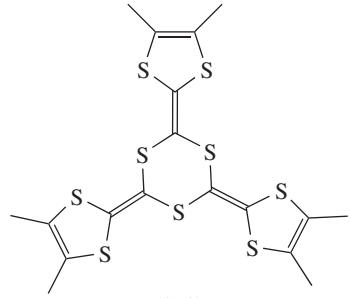
(266) **(267)** **(268)**

Trithiane **266** has been successively lithiated and allowed to react with compounds **269** to give permethylated mono-, di- and tri-fulvathianes **270–272**[448].



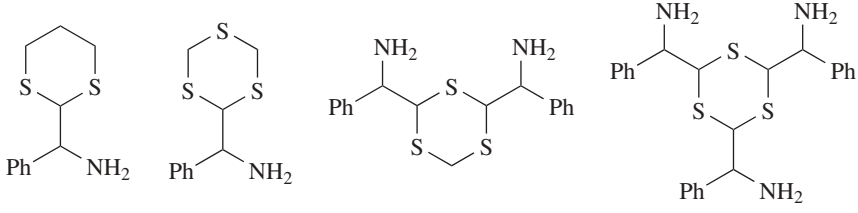
(269) **(270)** **(271)**

[X = SMe, $N(CH_2)_4$-*c*]



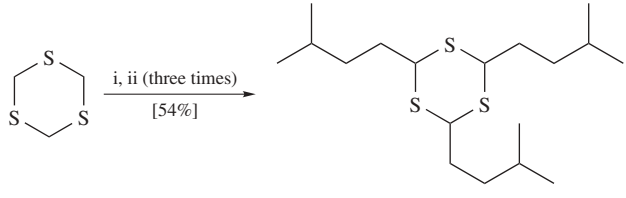
(272)

2-Lithio-1,3-dithiane and 2-lithio-1,3,5-trithiane have been transformed into 2-substituted benzylamines **273** and **274**, respectively, by reaction with a mixture of benzaldehyde and lithium hexamethyl disilazide[449]. In the case of compound **266**, the corresponding derivatives **275** and **276** have also been prepared. Related compounds were used for the preparation of photolabile molecular hosts.



(273) **(274)** **(275)** **(276)**

Trialkylated 1,3,5-trithiane **277** has been evaluated as low inhibitor of strogen receptor α-coactivator binding (Scheme 70)[450].

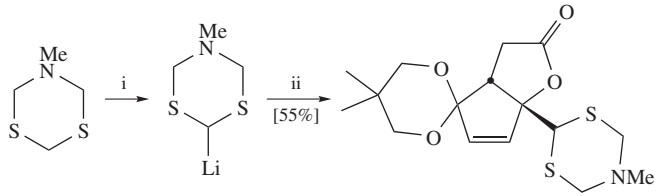


(266) **(277)**

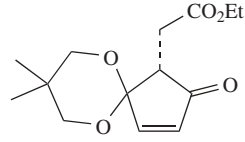
SCHEME 70. Reagents: (i) *n*-BuLi, −35 °C to rt; (ii) 3-methylbutyl bromide, −20 °C to rt

2-Lithiodithiazine **278** gave regio- and stereoselectively 1,2-addition to the α,β-unsaturated ketone **279** followed by lactonization, to give compound **280**, a precursor of didemnenones (Scheme 71)[445].

Amino acid-based dithiazines **281** were lithiated and allowed to react with benzaldehyde, giving products **282** in good yields but with low diastereoselectivity (Scheme 72)[451]. These adducts underwent externally sensitizer photofragmentation with quantum efficiency comparable to the parent dithiane and trithiane adducts.

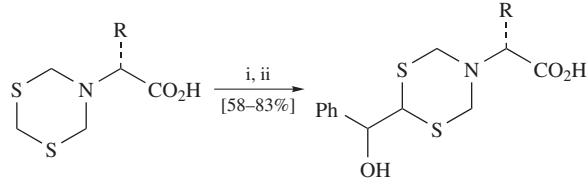


(266) **(278)** **(280)**



(279)

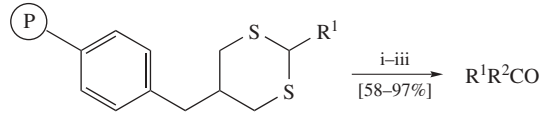
SCHEME 71. Reagents: (i) *n*-BuLi, −78 °C; (ii) **279**



(281) **(282)**

[R = H, *i*-Pr, *i*-Bu, Bn]

SCHEME 72. Reagents: (i) *n*-BuLi, −78 °C; (ii) PhCHO, −78 °C



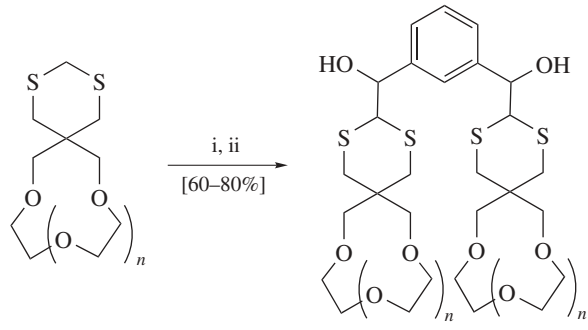
(268)

R^1 = Ph, 2-thienyl, Bn
R^2 = Me, Et, *n*-Bu, *n*-C_6H_{13}

SCHEME 73. Reagents: (i) *n*-BuLi, −40 °C to rt; (ii) R^2Hal, −25 to −10 °C; (iii) H_5IO_6 or $Hg(ClO_4)_2$

The alkylation of different polymeric reagents **268** (prepared from the corresponding odorless 1,3-dithiols and aldehydes) has been performed by successive deprotonation with *n*-BuLi and reaction with alkyl bromides and iodides. Final oxidation with periodic acid or with mercury(II) perchlorate gave the corresponding ketones (Scheme 73)[452].

Novel dithiane-spiro-crown ethers **283** have been prepared from 5,5-di(hydroxymethyl)-1,3-dithiane. These compounds **283** were lithiated and, after reaction with isophthalic aldehyde, furnished products **284**, which are capable of efficient liquid membrane transport of methyl viologen (Scheme 74)[453].

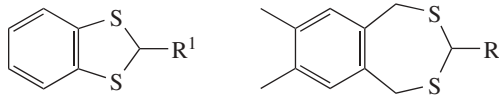


(283) **(284)**

[$n = 2$–4]

SCHEME 74. Reagents: (i) *n*-BuLi, −20 °C; (ii) isophthalic aldehyde, −78 °C to rt

1,3-Benzodithioles **285** (R^1 = H) and 7,8-dimethyl-1,5-dihydro-2,4-benzodithiepins **286** (R = H) have been used as precursors of formyl and acyl anion derivatives. The lithiation of compounds **285** takes place at −30 °C with *n*-BuLi and these anions are stable for long periods of time at this temperature[454]. They react with alkyl iodides, carbonyl compounds and epoxides, the addition to cyclohex-2-enone taking place at the carbonyl group. The deprotection has also been carried out with mercury(II) oxide and BF_3•OEt_2.

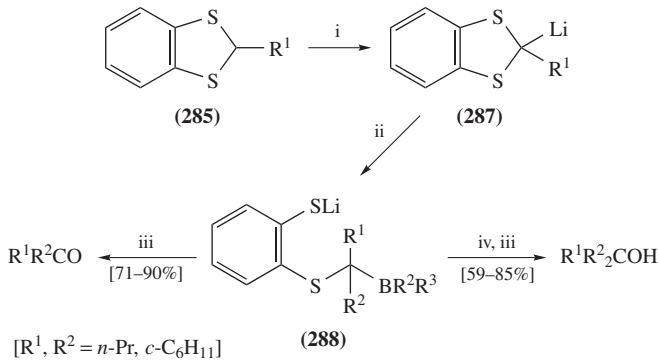


(285) **(286)**

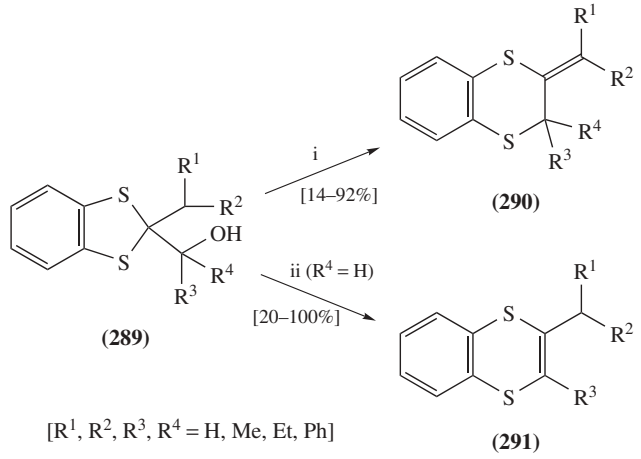
When the anions **287** derived from compounds **285** were allowed to react with trialkylboranes, followed by oxidation, the expected ketones were obtained[455]. A similar process is described in Scheme 40 for bis(phenylsulfanyl)alkyllithiums[151, 152]. Successive treatment of the obtained trialkylborane adducts **288** with mercury(II) chloride and hydrogen peroxide yielded tertiary alcohols (Scheme 75)[456]. The last reactions failed with bis(phenylsulfanyl)alkyllithiums.

Adducts **289** derived from carbonyl compounds and anions **287** behave similarly to bis(phenylsulfanyl)alkyllithium adducts **133** (Scheme 35) when they are treated with thionyl chloride in triethylamine, so 2-alkylidene-1,4-benzodithianes **290** were obtained. However, the treatment with *p*-toluenesulfonic acid or trifluoroacetic acid afforded products **291** (Scheme 76)[457].

In an analogous manner, benzodithiepins **286** can be lithiated with *n*-BuLi at −40 to −20 °C and reacted with alkyl bromides[458] and with epifluorohydrin[459]. The enantiomers of 1,7-dioxaspiro[5.5]undecane and 4-hydroxy-1,7-dioxaspiro[5.5]undecane, components



SCHEME 75. Reagents: (i) *n*-BuLi, −30 °C; (ii) $R^2{}_2R^3B$, −30 °C to rt; (iii) H_2O_2, NaOH; (iv) $HgCl_2$, −78 to 0 °C

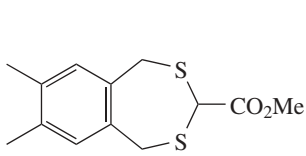


SCHEME 76. Reagents: (i) $SOCl_2$, Et_3N, 0 °C; (ii) TsOH or TFA

of the olive fly pheromone, have been prepared by alkylation of the lithiated intermediate **287** ($R^1 = H$)[460]. This reagent has some advantages compared with 2-lithio-1,3-dithiane, so neither the starting dithiol nor the benzodithiepins have unpleasant odors and, moreover, are crystalline compounds. Other applications are the preparation of a sex pheromone of the male greater waxmoth *Galleri amellonella L.*[458] and the pheromone of the western corn rootworm[461].

Methyl glyoxylate dithioacetal **292**, after lithiation, reacted with a protected D-mannitol triflate in the presence of HMPA. This methodology has been applied to the synthesis of 3-deoxy-D-manno-2-octulosonic acid (KDO)[462]. A related ethyl glyoxylate dithioacetal **293** gave conjugate addition to different Michael acceptors, such as α,β-unsaturated esters, lactones and lactams[463,464].

The chiral binaphthyl-derived dithiepin **294** has been lithiated and allowed to react with aldehydes for the synthesis of enantiomerically enriched α-hydroxy ketones (up to 80% ee), after deprotection with mercury(II) perchlorate[465].



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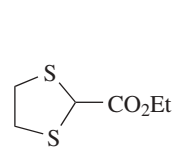

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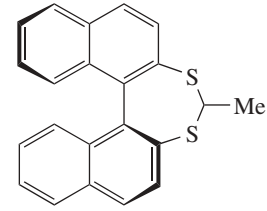
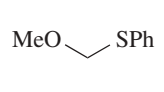


(294)

D. α-Lithio-α-thioethers

Acyclic **295** and cyclic **296** hemithioacetals have been shown as precursors of formyllithium intermediates[13]. For the preparation of the starting methoxy(phenylsulfanyl) methane **295**[466] two main procedures can be used: (a) nucleophilic substitution of chloromethyl methyl ether with thiophenol under basic conditions[467,468] and (b) boron trifluoride etherate-catalyzed condensation of thiophenol and dimethoxymethane[166]. 1,3-Oxathiane and its derivatives can be prepared by acetalization of the corresponding carbonyl compound with 3-mercaptopropanol.



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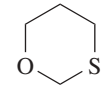


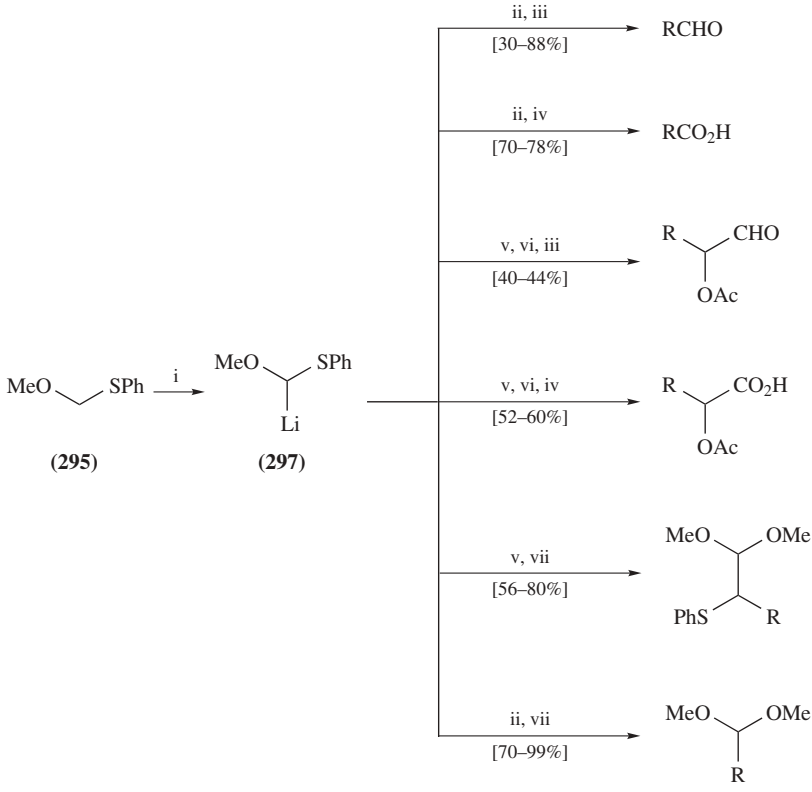
(296)

Methoxy(phenylsulfanyl)methane **295** can be deprotonated with LDA at −78 °C[469], *n*-BuLi at −30 °C[469] or *s*-BuLi in the presence of TMEDA at −78 °C[166]. Methoxy(phenylsulfanyl)methyllithium **297** can be monoalkylated with alkyl halides[468,469] and phenylated with iodobenzene by addition of 0.5 equivalent of copper(I) iodide[470]. β-Hydroxy derivatives are obtained by reaction with carbonyl compounds[468,469,471,472]. Deprotection of alkylated and *O*-acylated aldol products to give the corresponding aldehydes or carboxylic acids can be done by reaction with MCPBA or by Jones oxidation, respectively (Scheme 77)[469,473]. When the oxidation with MCPBA was followed by heating in situ at 120 °C, the intermediate sulfoxides provided enol ethers. Alkylated products derived from the anion **297** can also be transformed into acetals by treatment with *p*-toluenesulfonic acid in refluxing methanol, whereas β-hydroxy derivatives gave α-(phenylsulfanyl)acetals (Scheme 77)[469,473]. Phenylsulfanyl migration occurred by treatment of β-hydroxy derivatives with thionyl chloride in pyridine[472] or with methanesulfonyl chloride and triethylamine[474], or by tosylation[475] to provide the corresponding α-phenylsulfanyl aldehydes.

Different cyclohexanones **298** reacted with **297** to give adducts **299** and, after treatment with mercury(II) chloride, cycloheptenones **300**, resulting from a ring enlargement reaction (Scheme 78)[476,477].

Acylated or mesylated aldehyde adducts **301** react with enol silyl ethers **302** to provide products **303**, after a phenylsulfanyl migration reaction. Oxidation of compounds **303** with MCPBA followed by heating under mesitylene reflux and acidic hydrolysis afforded 1,3-diketones **304**, whereas treatment with potassium *tert*-butoxide followed by acidic hydrolysis provided 1,4-diketones **305** (Scheme 79)[478].

Aldol-type products **301** with X = H have been transformed into xanthates (by reaction with CS_2 and methyl iodide), which suffer radical reductive elimination by treatment with

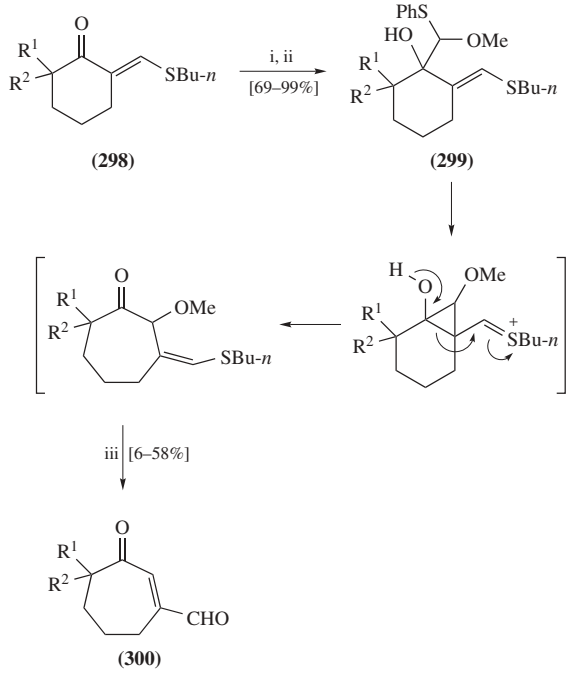


SCHEME 77. Reagents: (i) *n*-BuLi, −78 °C; (ii) RI; (iii) MCPBA, 0 to 40 °C; (iv) CrO_3, H_2SO_4, 0 °C; (v) RCHO; (vi) AcCl; (vii) TsOH, MeOH reflux

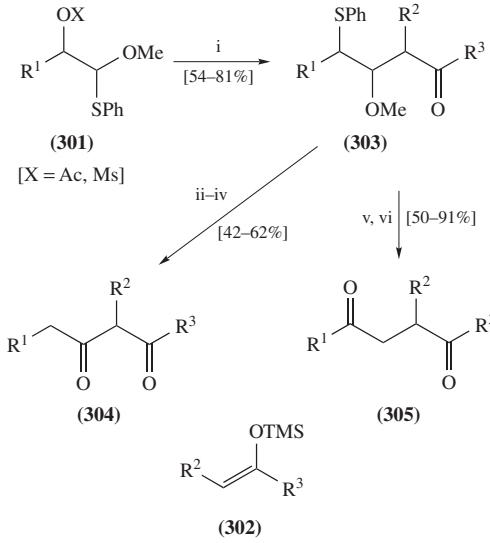
tri-*n*-butylstannane to provide vinyl ethers in good yields[479]. Compounds **306** are good precursors of tetrahydrofurans **307** by regioselective ionization and cyclization promoted by dimethyl(methylsulfanyl)sulfonium tetrafluoroborate (DMTSF) (Scheme 80)[480].

The acylation of intermediate **297** can be carried out with *N*,*N*-dimethylalkanamides in good yields[481]. The resulting ketones **308** have been transformed into furans[481] and methyl α-(phenylsulfanyl)allyl ethers **309**[482,483]. These compounds **308** can be lithiated and alkylated at the α-position giving, after acid-catalyzed thiallyl rearrangement, products **310**. The second deprotonation–alkylation gave compound **311** which, after oxidation, provided α,β-unsaturated carbonyl compounds **312** (Scheme 81). According to these transformations, compounds **309** have been considered as homoenolate and acyl dianion equivalents.

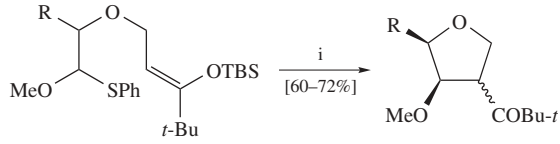
β-Alkoxyenones **313** reacted with compound **297** via a 1,2-addition to afford unsaturated 1,4-dicarbonyl compounds **314** after acidic hydrolysis (Scheme 82)[166]. However, when the same process was performed with bis(methylsulfanyl)methyllithium, the mercury(II) chloride deprotection failed. Conjugate addition of compound **297** to (3*E*)-2-(phenylsulfonyl)-1,3-pentadiene, followed by Jones oxidation and potassium *tert*-butoxide-promoted dehydrosulfonylation, provides ascorbic acid[484]. Alkylboronic esters $R^1B(OR^2)_2$ can be alkylated with intermediate **297** to afford, after deprotection with $HgCl_2$ and final oxidation with hydrogen peroxide, homologated aldehydes[485,486].



SCHEME 78. Reagents: (i) **297**, −78 °C; (ii) NH_4Cl; (iii) $HgCl_2$, HCl, 80–90 °C

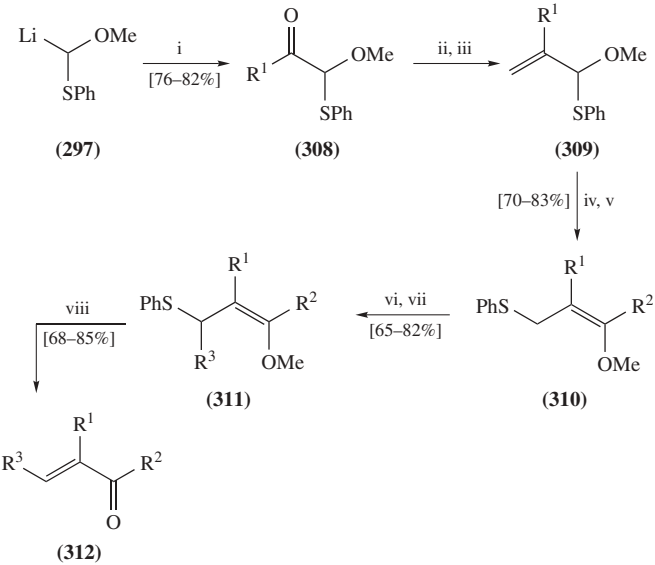


SCHEME 79. Reagents: (i) **302**, $SnCl_4$, −78 °C; (ii) MCPBA; (iii) $NaHCO_3$, mesitylene reflux; (iv) $ZnCl_2$, TFA; (v) *t*-BuOK; (vi) TFA



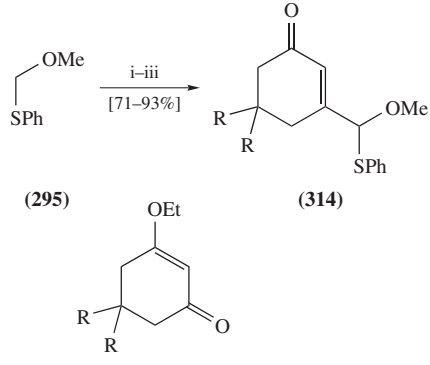
(306) **(307)**

SCHEME 80. Reagents: (i) DMTSF, DBU, −40 °C



(297) **(308)** **(309)** **(310)** **(311)** **(312)**

SCHEME 81. Reagents: (i) R^1CONMe_2; (ii) Me_3SiCH_2MgCl; (iii) NaH; (iv) LDA, R^2Hal, −78 °C; (v) SiO_2; (vi) *n*-BuLi, TMEDA, 0 °C; (vii) R^3Hal; (viii) $NaIO_4$

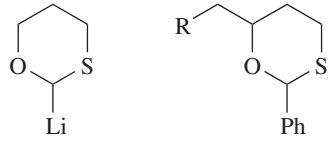


(295) **(314)** **(313)**

[R = H, Me]

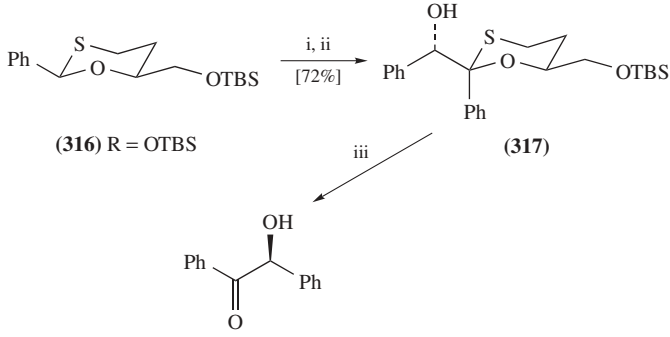
SCHEME 82. Reagents: (i) *s*-BuLi, TMEDA, −78 °C; (ii) **313**; (iii) H_2SO_4

The lithiation of 1,3-oxathiane (**296**) takes place with *s*-BuLi at −78 °C to give 2-lithio-1,3-oxathiane (**315**), an analogue of 2-lithio-1,3-dithiane (**161**), but with lower stability[487]. This intermediate reacts with different electrophiles, such as alkyl halides, carbonyl compounds, benzonitrile, dimethyl disulfide, dimethyl diselenide, trimethylplumbyl acetate and trimethylsilyl, germyl and stannyl chlorides[488,489]. However, further deprotection of 2-substituted 1,3-oxathianes has not been reported yet.



(315) **(316)**

2,4-Disubstituted 1,3-oxathianes **316**, prepared from benzaldehyde and the corresponding 3-mercaptoalkanol, have been stereoselectively deprotonated at the equatorial position to yield, after reaction with electrophiles, 2,2-disubstituted products. (*S*)-Benzoin was obtained in 75% ee in the case of using compound **316** (R = OTBS), after reaction with benzaldehyde and final deprotection of the major product **317** with NCS and silver nitrate (Scheme 83)[490].



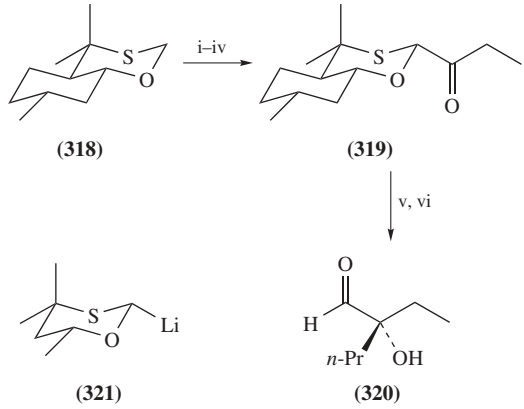
(316) R = OTBS **(317)**

SCHEME 83. Reagents: (i) *s*-BuLi, −78 °C; (ii) PhCHO; (iii) NCS, $AgNO_3$

1,3-Oxathiane **318** derived from (+)-pulegone was deprotonated at the equatorial position with *n*-BuLi at −78 °C. The reaction of the corresponding intermediate with propanal, followed by oxidation to the corresponding ketone **319**, allowed the diastereoselective addition of a Grignard reagent, so the final deprotection with NCS and $AgNO_3$ led to the α-hydroxyaldehyde **320** in up to 90% ee (Scheme 84)[491,492]. This methodology has been used for the synthesis of (−)-mevalolactone[492]. A similar asymmetric synthesis has been studied with 4,4,6-trimethyl-1,3-oxathiane derived organolithium compound **321**[493].

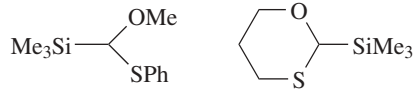
Silylated derivatives **322**[494] and **323** derived from hemithioacetals **295** and **296**, respectively, can also be deprotonated with *n*-BuLi or *s*-BuLi.

Methoxy(phenylsulfanyl)(trimethylsilyl)methyllithium **324** has been used as acyllithium and, depending on the electrophile and the deprotection conditions, it can transfer the acyltrimethylsilyl, the methoxycarbonyl or the (phenylsulfanyl)carbonyl group. By alkylation of intermediate **324** with primary alkyl iodides, bromides and chlorides in the presence of HMPA, followed by oxidation of compound **325** with $NaIO_4$, acylsilanes



(318) **(319)** **(321)** **(320)**

SCHEME 84. Reagents: (i) *n*-BuLi, −78 °C; (ii) EtCHO; (iii) NH_4Cl; (iv) DMSO, TFAA, Et_3N; (v) *n*-PrMgBr; (vi) NCS, $AgNO_3$

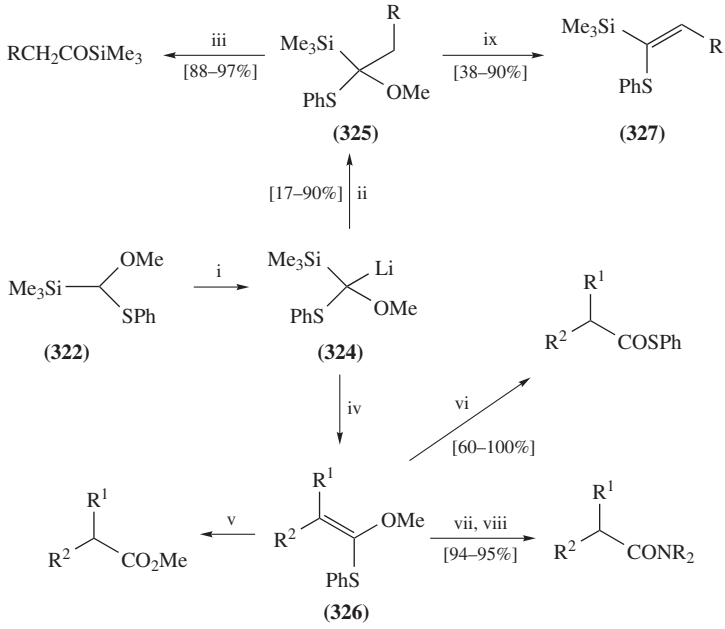


(322) **(323)**

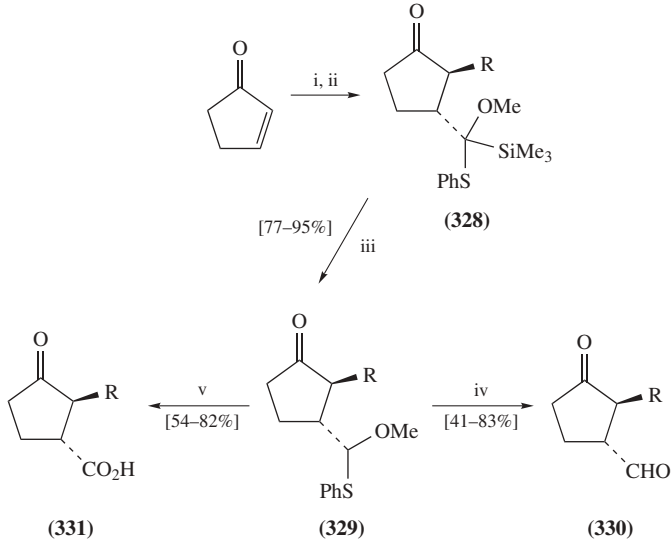
were obtained (Scheme 85)[495]. Peterson olefination gave ketene *O*,*S*-acetals **326** which, after deprotection with mercury(II) chloride, gave methyl esters[496]. This procedure was applied to the synthesis of (±)-β-eudesmol[496]. Related lithiated α-methoxythioanisole has been alkylated with alkyl halides or trimethylsilyl chloride to afford the corresponding alkylated products in 76–99% yields[497]. Cleavage of ketene *O*,*S*-acetals **326** with in situ generated iodotrimethylsilane or with methylsulfanyllithium gave phenyl thioesters[498]. The nucleophilic demethylation of these ketene *O*,*S*-acetals **326** with methylsulfanyllithium followed by addition of an appropriate amine provided the corresponding carboxamides[498]. Alkylated products **325** can eliminate methanol in a stereoselective manner using oxygen and triethylborane, through a radical pathway, to give the expected ketene *S*,*Si*-acetals **327**[499].

Michael addition of anion **324** to cyclic enones took place in the presence of HMPA[500, 501]. In the case of cyclopentenone, the resulting enolate can be trapped with alkyl halides to give stereoselectively the corresponding *trans*-2,3-disubstituted cycloalkanones **328**. This acyllithium equivalent **324** gave better regioselectivity than intermediate **297**, which afforded a 6:4 mixture of 1,2- and 1,4-addition products. The trimethylsilyl group in compounds **328** was removed with TBAF and the resulting monothioacetals **329** were transformed into aldehydes **330** by the DABCO•2Br_2 adduct or to carboxylic acids **331** by Jones oxidation (Scheme 86)[501]. The mentioned methodology was applied to the synthesis of sarkomycin[501] and of an intermediate in the synthesis of prostaglandins[502].

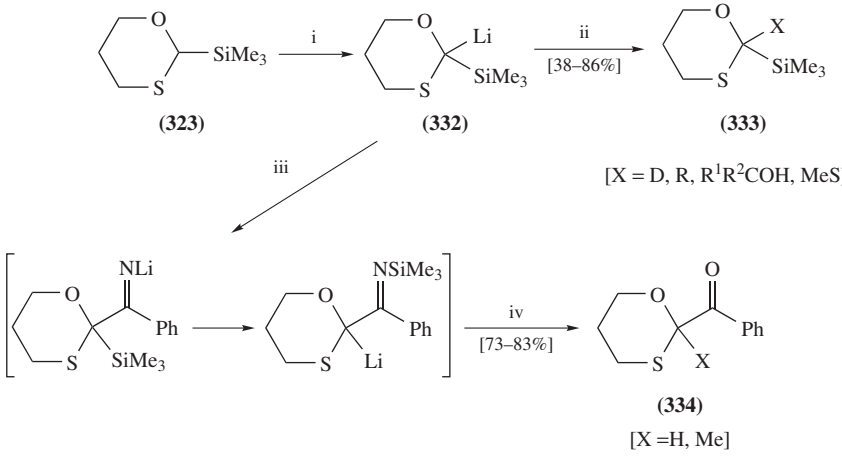
2-(Trimethylsilyl)-1,3-oxathianyllithium **332** was obtained by deprotonation of compound **323** with *s*-BuLi at −78 °C and reacted with different electrophiles such as deuterium oxide, alkyl iodides, dimethyl disulfide and carbonyl compounds, providing the corresponding products **333** in moderate to good yields. However, the reaction with benzonitrile, followed by acid hydrolysis, gave 2-benzoyl-1,3-oxathiane **334** (X = H) (Scheme 87)[503, 504]. When the last reaction was quenched with methyl iodide before



SCHEME 85. Reagents: (i) *n*-BuLi or *s*-BuLi, TMEDA, −78 °C; (ii) RCH_2Hal, HMPA; (iii) $NaIO_4$, H_2O; (iv) R^1R^2CO; (v) $HgCl_2$; (vi) TMSCl, NaI; (vii) MeSLi; (viii) R_2NH; (ix) O_2, Et_3B



SCHEME 86. Reagents: (i) **324**, HMPA, −78 °C; (ii) RHal, −40 °C; (iii) TBAF; (iv) DABCO•$2Br_2$; (v) CrO_3, H_2SO_4

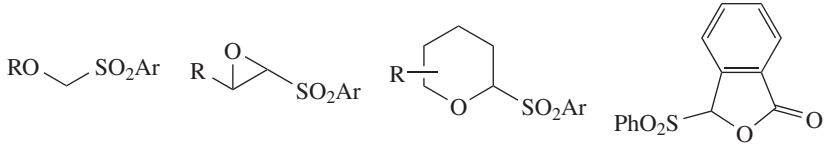


SCHEME 87. Reagents: (i) *s*-BuLi, −78 °C; (ii) EX = D_2O, RI, R^1R^2CO, Me_2S_2; (iii) PhCN; (iv) EX = H_2O, MeI

hydrolysis, compound **334** with X = Me was obtained in 45% yield, acting intermediate **332** as an acyl dianion equivalent. This process involves a C−N migration of the TMS group, after reaction of compound **332** with benzonitrile to give a 2-lithio derivative, which can be alkylated with methyl iodide. The final product, 2-benzoyl-2-methyl-1,3-oxathiane (**334**, X = Me), could be deprotected with nitryl oxide to give 1-phenylpropane-1,2-dione in 83% yield.

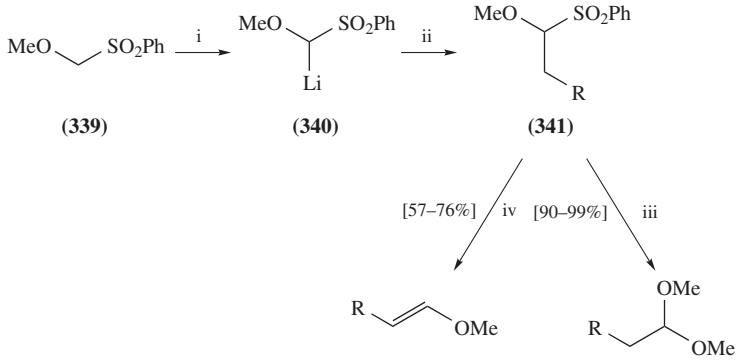
E. α-Lithio-α-(arylsulfonyl) Ethers

Sulfones[505–513] bearing an alkoxy or acyloxy functionality at the α-position **335–338**[514] can be considered as masked acetals because they have a high tendency to suffer α-elimination of the arylsulfonyl group[515] regenerating the carbonyl group. Alternatively, base-promoted β-elimination of arylsulfinic acid gave rise to enol ethers. Due to the ability of the arylsulfonyl group to stabilize carbanions, α-lithio-α-(arylsulfonyl) ethers can be considered as protected acyllithium derivatives[6, 8, 13, 177, 178, 473].



(335) **(336)** **(337)** **(338)**

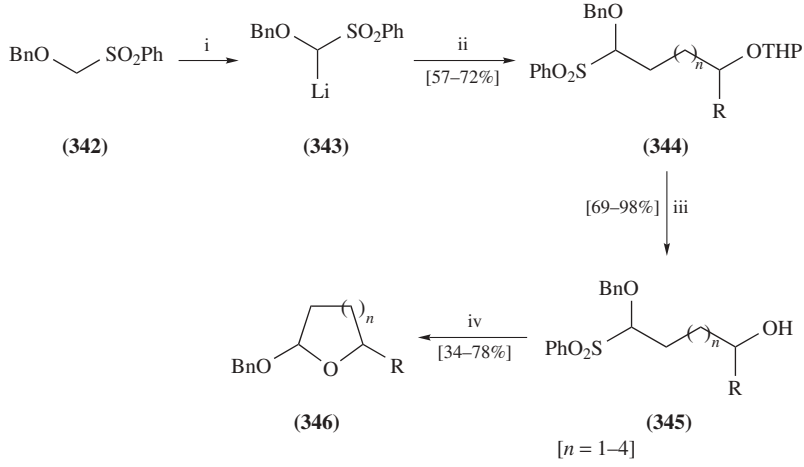
(α-Alkoxy)methyl aryl sulfones **335**[514] can be deprotonated with *n*-BuLi or LDA at low temperature. Methoxy(phenylsulfanyl)methyllithium **340** was prepared from compound **339** with LDA[516] and its reactivity studied at the same time as its phenylsulfanyl analogue **297**[469]. By contrast, the alkylated products **341** (derived from intermediate **340**) did not suffer rearrangement after treatment with *p*-toluenesulfonic acid in refluxing methanol (Scheme 88)[469]. Desulfonylation occurred easily by treatment of compounds



SCHEME 88. Reagents: (i) LDA, THF, −78 °C; (ii) RCH_2Hal; (iii) TsOH, MeOH reflux; (iv) *t*-BuOK

341 with potassium *tert*-butoxide in THF providing stereoselectively (*E*)-enol ethers. Methoxymethyl phenyl sulfone **339** has been metallated with *t*-BuLi in DME at −78 °C and alkylated with a primary alkyl iodide in 83% yield[517].

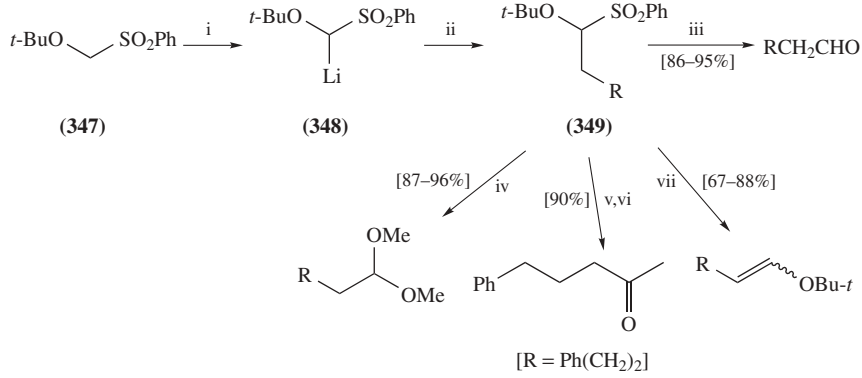
The homologous benzyl derivative **342** has been lithiated under the last reaction conditions and alkylated with *O*-tetrahydropyranyl protected bromoalcohols to afford products **344** and **345**, precursors of cyclic lactol ethers **346** (Scheme 89)[518]. Alkylation of the intermediate **343** with epoxides has been performed in the presence of $BF_3{\bullet}OEt_2$ for the synthesis of tetrahydropyrans[480].



SCHEME 89. Reagents: (i) *t*-BuLi, DME, −78 °C; (ii) $THPOCHR(CH_2)_nCH_2Br$; (iii) TsOH; (iv) $MgBr_2{\bullet}OEt_2$, $NaHCO_3$

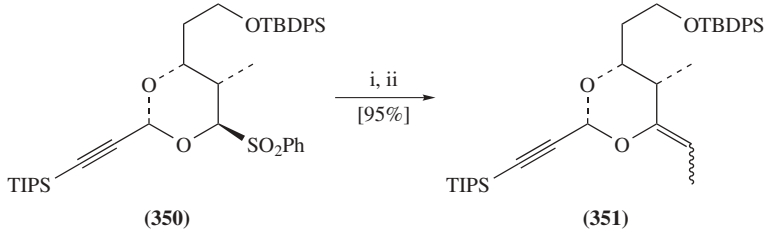
The related *t*-butyl derivative **347** was metallated with *n*-BuLi and the resulting organolithium compound **348** was alkylated with alkyl and allyl iodides, bromides and chlorides in the presence of HMPA[519]. From **349**, several different types of deprotection reactions were possible. Direct hydrolysis to the corresponding aldehydes has been performed under

mild reaction conditions, such as montmorillonite K10, TFA, silica and aqueous ether. The corresponding dimethyl acetals were prepared by reaction with Amberlyst-15 in MeOH at room temperature. Alkylated products **349** [R = $Ph(CH_2)_2$] can be lithiated and methylated to give 5-phenyl-2-pentanone after aqueous work-up (Scheme 90)[519]. Treatment of compounds **349** with *t*-BuOK under THF reflux gave vinyl ethers[520].



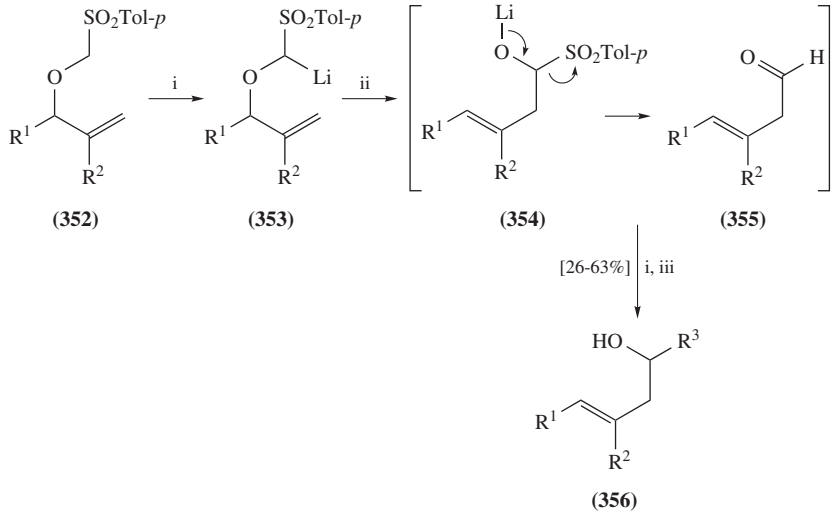
SCHEME 90. Reagents: (i) *n*-BuLi, −78 °C; (ii) RCH_2Hal, HMPA; (iii) LiBr, K_2CO_3, Et_2O, H_2O reflux; (iv) Amberlyst-15, MeOH; (v) MeLi, −100 °C; (vi) MeI, HMPA, −78 °C; (vii) *t*-BuOK, THF reflux

The Julia protocol for the olefination reaction consisting in the treatment of α-sulfonyl organolithium compounds with the intermediate **348** gave vinyl ethers[520]. Similar olefination took place by reaction of the anion derived from the alkoxymethyl sulfone **350** with α-chloroethylmagnesium chloride to afford the corresponding product **351**, as a 1:1 mixture of *Z*/*E*-diastereomers, which is an intermediate in the synthesis of the C20–C28 subtarget of phorborazole (Scheme 91)[521].



SCHEME 91. Reagents: (i) *n*-BuLi; (ii) MeCH(Cl)MgCl

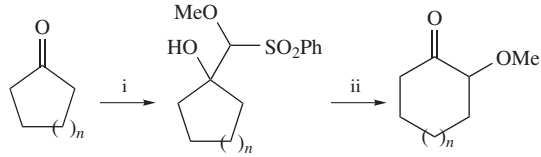
Allyloxymethyl tolyl sulfones **352**, prepared from allyl alcohols and tosyldiazomethane, have been lithiated with *n*-BuLi to give intermediates **353** and alkylated in the presence of HMPA, as described above for compounds **339, 342** and **347**. Anions **353** derived from sulfonyl ethers **352** underwent [2,3]-Wittig rearrangement to give alkoxides **354** which, after α-elimination, gave intermediate aldehydes **355**. Final addition of a second equivalent of the alkyllithium reagent and hydrolysis led to the formation of unsaturated alcohols **356** (Scheme 92)[522]. This methodology has been applied to the stereocontrolled synthesis of a C14–C20 building block for the macrolide antibiotic amphotericin B[523].



(352) (353) (354) (355) (356)

SCHEME 92. Reagents: (i) R^3Li, ether, $-78\,^{\circ}C$; (ii) HMPA, -78 to $-40\,^{\circ}C$; (iii) NH_4Cl

The reaction of α-oxy sulfonyl organolithium compounds derived from sulfones **335** with aldehydes gave the corresponding adducts[517,519,524], which in the case of **347** derivatives have been hydrolyzed to the corresponding α-hydroxy aldehydes[519]. Ketone adducts **357** have been used for ring expansion reactions, also called Trost–Mikhail ketone homologation[525]. The reaction of compound **340** with acyclic and cyclic ketones followed by treatment with a Lewis acid gave α-methoxy ketones (Scheme 93). As Lewis acid, diisobutylaluminium chloride can be used at $-78\,^{\circ}C$, this strategy being applied to prostaglandin synthesis[526,527]. Zirconium tetrachloride[528,529] allowed to perform the mentioned rearrangement at room temperature in high yields and was applied to conduritols synthesis[529].



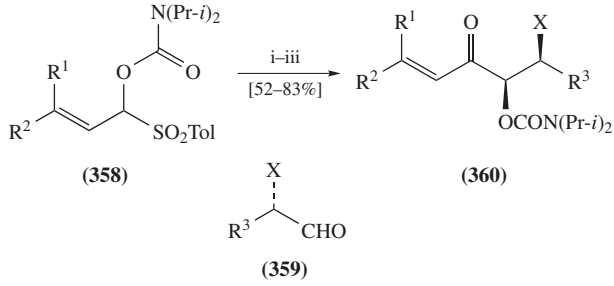
[n = 1, 2] (357)

SCHEME 93. Reagents: (i) **340**, $-78\,^{\circ}C$; (ii) Lewis acid

Allylic α-carbamoyloxy sulfones **358** have been lithiated with n-BuLi and reacted with chiral α-oxy and α-amino aldehydes **359** in the presence of titanium tetraisopropoxide to provide enones **360** with high diastereoselectivity, according to the Felkin–Anh model, after α-elimination of lithium p-tolylsulfinate (Scheme 94)[530–532].

The acylation of methoxy(phenylsulfonyl)methyllithium **340** has only been performed with an ester to provide in 86% yield the corresponding β-keto sulfone used for the synthesis of rapamacin[517].

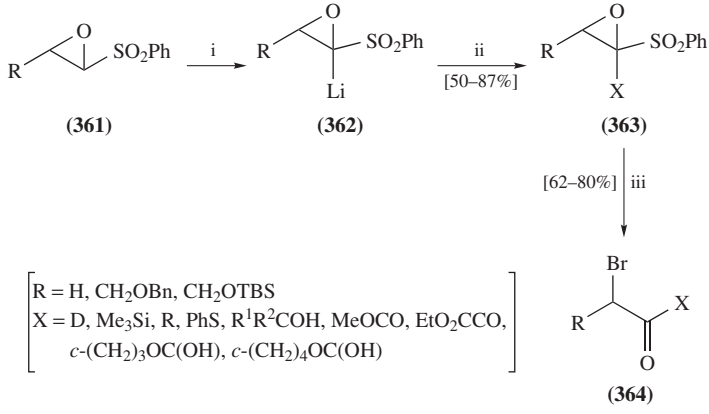
Epoxidation of vinyl sulfones is the most common procedure for the preparation of α,β-epoxy sulfones[514]. Organolithium compounds derived from α,β-epoxy sulfones **336**



SCHEME 94. Reagents: (i) *n*-BuLi, −78 °C; (ii) **359**, Ti(OPr-*i*)$_4$, −78 °C; (iii) 2 M HCl

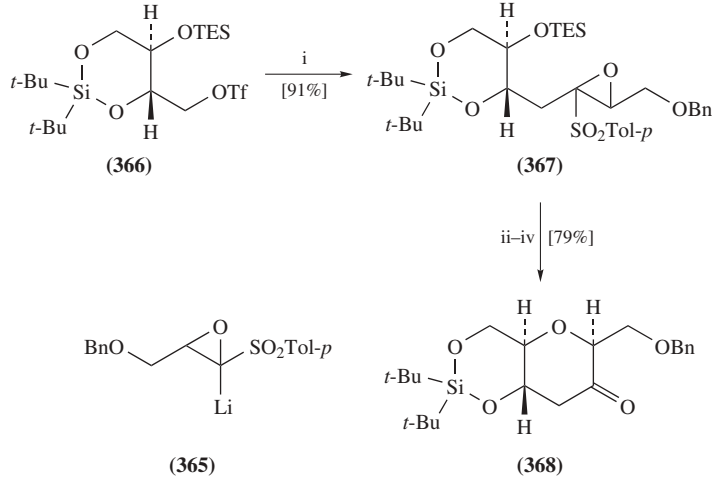
have been shown to be very unstable and decomposed above −100 °C[533–537]. They are configurationally stable and the deprotection takes place with retention of the configuration. α-Lithiated epoxy sulfones derived from (*E*)-epoxy sulfones are stable at −95 °C. By contrast, intermediates derived from (*Z*)-epoxy sulfones isomerize within 3 minutes at −100 °C to give the more stable (*E*)-isomers[536]. This isomerization can be avoided working under Barbier conditions[536].

2-Lithio-2-(phenylsulfonyl)oxiranes **362** (prepared by deprotonation of compounds **361**) reacted with different electrophiles to give the expected products **363** which, by treatment with $MgBr_2$•OEt_2, afforded α-bromo carbonyl compounds **364** (Scheme 95)[534–537].



SCHEME 95. Reagents: (i) *n*-BuLi, −105 °C; (ii) EX = D_2O, Me_3SiCl, RI, $(PhS)_2$, R^1R^2CO, MeOCOCl, EtO_2CCOCl, γ-butyrolactone, δ-valerolactone; (iii) $MgBr_2$•OEt_2, rt

Very fast alkylation of lithiated epoxy sulfone **362** with (*Z*)-configuration (R = CH_2OTBS) took place by using triflates as electrophiles[538]. This methodology has been used for the iterative preparation of *trans*-fused tetrahydropyrans and polycyclic ethers[539–543] focused on the synthesis of hemibrevetoxin B[544,545]. Protected erythritols **367** have been prepared by alkylation of intermediate **365** with the triflate **366**, followed by deprotection and treatment with $MgBr_2$•OEt_2 to give a bromo ketone, which was finally cyclized with DBU, affording the product **368** (Scheme 96)[546].



SCHEME 96. Reagents: (i) **365**, −100 °C; (ii) TsOH; (iii) $MgBr_2 \bullet OEt_2$; (iv) DBU

Lactols and their acetals can be transformed easily into their 2-arylsulfonyl derivatives **337** by reaction with a sulfinic acid under Lewis acid activation. The corresponding organolithiums are prepared by deprotonation with *n*-BuLi or LDA and, after reaction with electrophiles, a β-elimination of sulfinic acid afforded a cyclic α-substituted enol ether[514,547,548]. 2-Lithio-2-(arylsulfonyl)tetrahydropyrans equilibrated to give mainly the anomer with the lithium atom at the equatorial position[549].

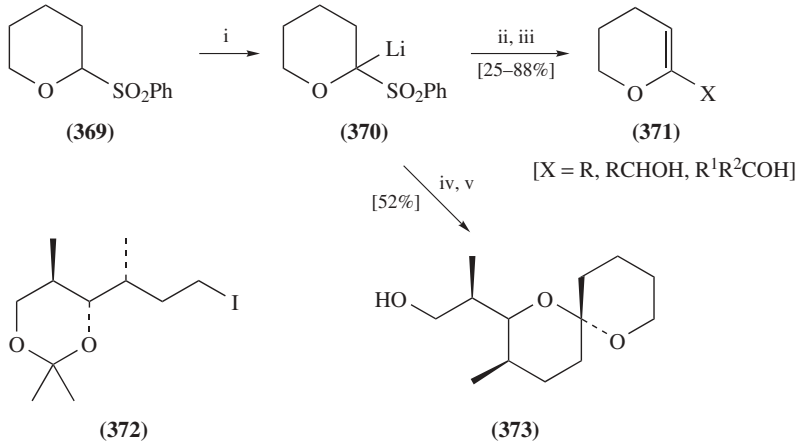
2-(Phenylsulfonyl)tetrahydropyran **369** has been lithiated with *n*-BuLi at −78 °C to give the anion **370**, which has been allowed to react with alkyl halides and carbonyl compounds (Scheme 97)[548]. The corresponding 2-substituted derivatives suffered after aqueous work-up spontaneous β-elimination of benzenesulfinic acid to give products **371**. When the alkyl halide has an additional protected hydroxy group at the γ- or δ-position (such as in compound **372**), spiroketals (e.g. compound **373**, Scheme 97) were obtained, this methodology having been applied to the synthesis of ionophore antibiotic CP 61,405 (routiennocin)[550].

The alkylation of substituted 2-(phenylsulfonyl)tetrahydropyran anions, such as compound **375** (prepared from the starting material **374**), with the iodide **376** bearing an allylsilane moiety, led to the formation of spirocyclic ethers **377** (Scheme 98)[551].

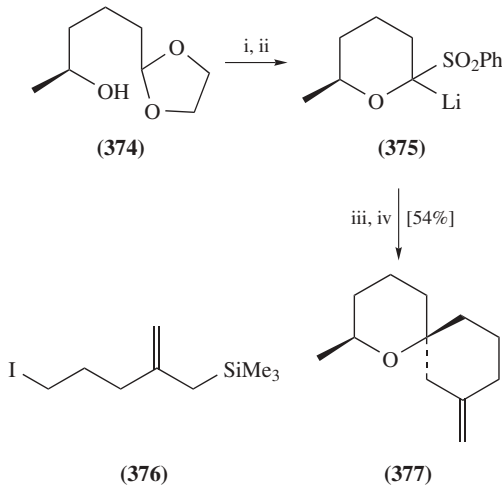
Epoxides, bearing a 2-hydroxyethyl substituent, such as compound **379**, were used as electrophiles, allowing the preparation of spiroketals (e.g. **380** from the starting material **378**), such as the C11−C25 fragment of (+)-milbemycin β_1 (Scheme 99)[552,553].

Ley and coworkers have found that dispiroketals[383], such as 1,8,13,16-tetrahydrooxadispiro[5.0.5.4] hexadecanes, show a wide range of synthetic applications[554]. For the preparation of these compounds, 2-(tri-*n*-butylstannyl)dihydropyrans can be used[554–556]. The reaction of 2-lithio-6-methyl-2-(phenylsulfanyl)tetrahydropyran (**375**) with tri-*n*-butylstannyl chloride gave compound **381**, which has further been transformed into the dispiroketal **382** (Scheme 100)[555].

The acylation of the 2-(phenylsulfanyl)tetrahydropyran **383** derived anion has been performed with an acyl benzotriazol **384** because the acyl chloride or activated esters gave problems. The resulting sulfone was transformed into the methylated acetal **385**



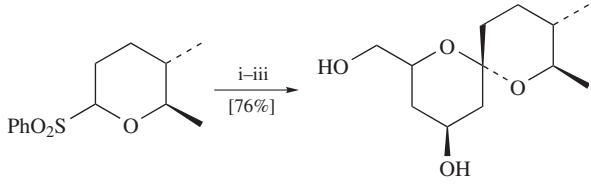
SCHEME 97. Reagents: (i) *n*-BuLi, −78 °C; (ii) EX = RHal, RCHO, R^1R^2CO; (iii) H_2O; (iv) **372**, DMPU; (v) 10-camphorsulfonic acid



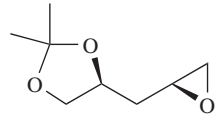
SCHEME 98. Reagents: (i) $PhSO_2H$, $CaCl_2$; (ii) *t*-BuLi, −78 °C; (iii) **376**, −78 °C to rt; (iv) Dowex-50

used for the synthesis of the bispyran subunit of altohyrtin C (Scheme 101)[557,558]. In the total synthesis of bryostatin 2, a triflate was used as alkylating agent of another high functionalized 2-lithio-2-(phenylsulfonyl)tetrahydropyran[559,560].

3-(Phenylsulfonyl)phthalide **338** was deprotonated with LDA or with *t*-BuOLi at −78 °C to give the stabilized phthalide anion **386**, which has been used in Michael additions for the synthesis of anthra- and naphthaquinones[514,561–585]. The process developed by Hauser and Prasanna[562] has been summarized in Scheme 102,

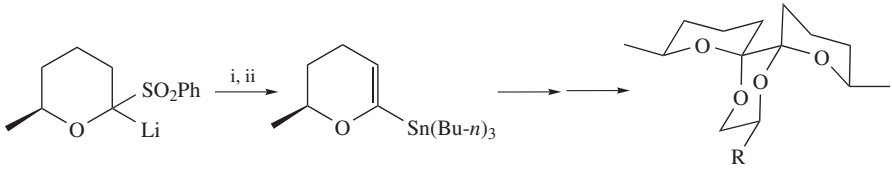


(378) **(380)**



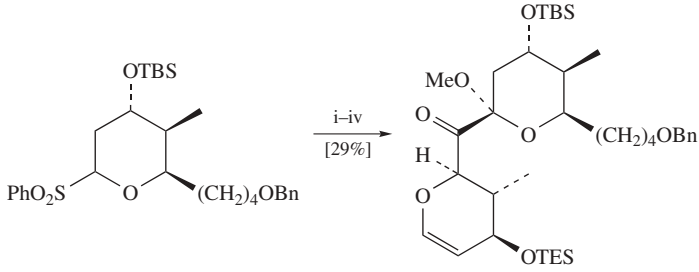
(379)

SCHEME 99. Reagents: (i) *n*-BuLi, −78 °C; (ii) **379**, −78 °C; (iii) 10-camphorsulfonic acid

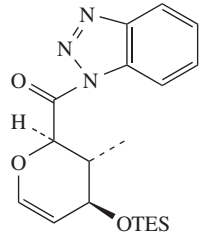


(375) **(381)** **(382)**

SCHEME 100. Reagents: (i) *n*-Bu_3SnCl, −20 °C; (ii) *i*-Pr_2NEt

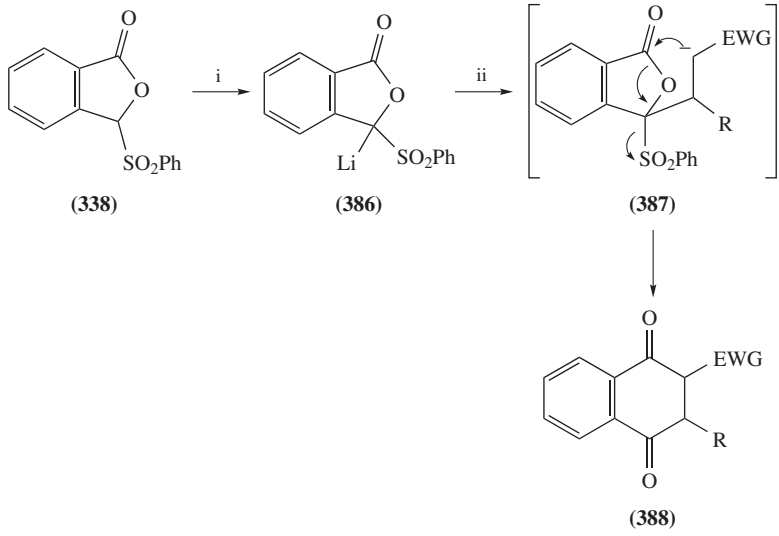


(383) **(385)**



(384)

SCHEME 101. Reagents: (i) LDA, −78 °C; (ii) **384**; (iii) ZnI_2, MeOH; (iv) $MgBr_2 \bullet OEt_2$, MeOH



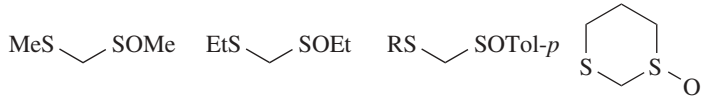
(338) **(386)** **(387)** **(388)**

SCHEME 102. Reagents: (i) LDA, −78 °C; (ii) RCH=CHEWG

where products **388** were prepared through intermediates **387**. As Michael acceptors acyclic enones, α,β-unsaturated esters and lactones, and nitroolefins have been employed. Several natural products have been prepared following this methodology, including kidamycinone[563], aklavinones[564, 565], daunomycinones[566–569], nanaomycin and kalafungin[570], isokalafugin[571], adriamycinones[572], citromycinone[573], the pigment G2N[574], shinkonin and alkannin[575], methyl rishiliride B[576], biphyscion[577], radermachol[578], aquayamycin[579] and vitamins K[580]. Other examples of the Hauser strategy are the synthesis of models for fredericamycin[581], anthracyclines[582–584] and benzo[*a*]anthraquinones[585].

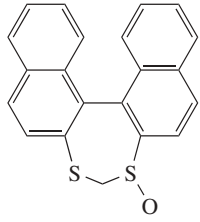
F. α-Lithio-α-thiosulfoxides and Bis(sulfoxides)

Monooxidized thioacetals with acyclic **389–391** and cyclic structures **392** and **393**, as well as bis(sulfoxides) **394** and **395**, present higher activity than the corresponding thioacetal precursors and can be used as acyllithium reagents[6, 8, 13]. α-Lithiothiosulfoxides can be used as formyl and acyllithiums whereas bis(sulfoxides) gave, after deprotection, thioesters. An additional hit of the use of sulfoxides is the possibility of using also enantiomerically enriched reagents for asymmetric synthesis[586]. In many cases, sodium anions have been shown more reactive than the corresponding lithium anions.

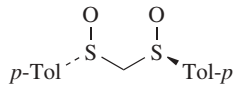


(389) **(390)** **(391)** **(392)**

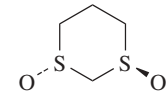
Methyl (methylsulfanyl)methyl sulfoxide **389** was initially deprotonated–alkylated with sodium hydride and hydrolyzed with a catalytic amount of sulfuric acid to afford aldehydes and dimethyl disulfide[587]. Dialkylation and hydrolysis to the corresponding ketones



(393)



(394)



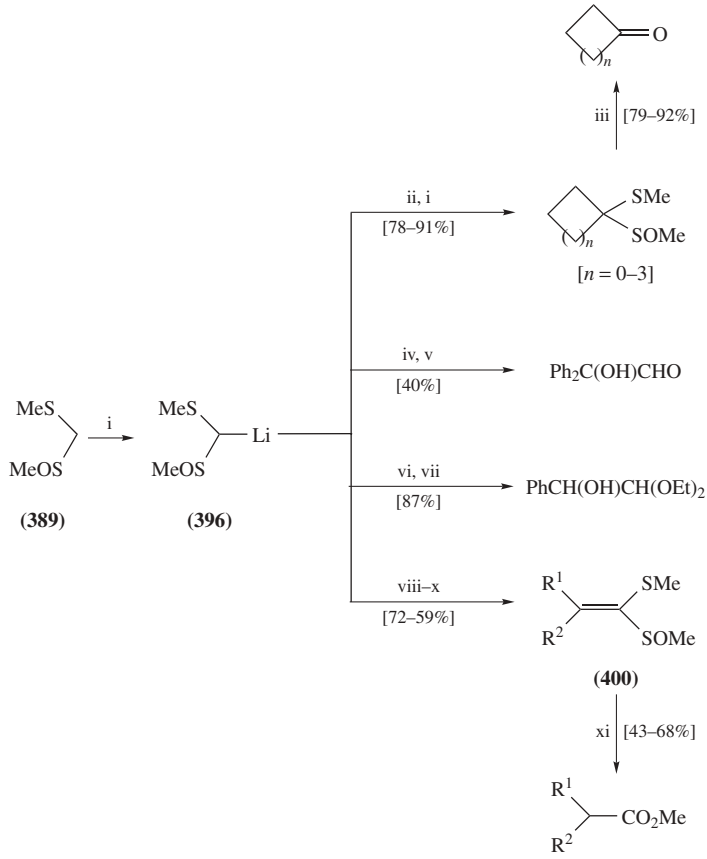
(395)

have also been performed by using an excess of sodium[588] or potassium hydride[589]. Alternatively, *n*-BuLi can be used at $-10\,^{\circ}C$ for the deprotonation of compound **389**, the subsequent dialkylation taking place either with 1,ω-dibromo or bis(tosyloxy) alkanes to give, after hydrolysis, cyclic ketones in good yields (Scheme 103)[590]. This process has been applied to the preparation of (*S*)-4-hydroxycyclopent-2-enone, an important starting material for the synthesis of many natural products[591]. α-Lithio-α-thiosulfoxide **396** was alkylated with the diiodide **397** and deprotected to the corresponding cyclopentenone with Amberlyst 15. In the synthesis of (+)-isocarbacyclin, compound **396** was dialkylated with the bis(mesylate) **398**[592], and for the preparation of [4.4.2]propellatetraenes the bis(tosylate) **399**[593] was employed as electrophile.

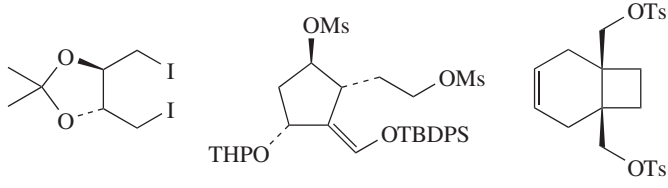
The reaction of α-lithio-α-thiosulfoxide **396** with ketones followed by treatment with concentrated hydrochloric acid in THF at room temperature gave α-hydroxy aldehydes[594]. The alkylation of the hydroxy group for the benzaldehyde adduct, followed by deprotection with copper(II) chloride, provided α-alkoxy aldehydes[594]. If the benzaldehyde adduct was treated with concentrated sulfuric acid in the presence of ethyl orthoformate, phenylglycelic aldehyde diethylacetal was obtained (Scheme 103)[594]. Ketone adducts can be transformed into ketene thiosulfoxides **400** by acylation–elimination reactions and hydrolyzed to give the corresponding esters (Scheme 103)[595]. Addition of the anion **396** or its α-methyl derivative to cyclic enones afforded mixtures of 1,4- and 1,2-adducts[596].

Analogous ethyl (ethylsulfanyl)methyl sulfoxide **390** has been deprotonated with *n*-BuLi or LDA at $2\,^{\circ}C$ to give the organolithium **401**, which presents a good stability even at elevated temperatures[597]. This reagent seems to give much better yields (>95%) than compound **396** in alkylation reactions with alkyl iodides and bromides. The second deprotonation–alkylation gave dialkylated products in higher than 90% yield. The treatment of alkylated products with 9 N hydrochloric acid and mercury(II) chloride gave rise to the corresponding aldehyde or ketone (80–95% yield) uncontaminated with the diethyl disulfide (Scheme 104)[597]. α-Alkylated α-lithio-α-thiosulfoxides **402** ($R^1 = Et$) gave clean 1,4-additions to α,β-unsaturated esters, lactones and enones without additives (Scheme 104)[598]. This methodology has been used in the synthesis of *cis*-jasmone[599]. The anion **401** also reacts with aldehydes, ketones, esters and acyl chlorides, the corresponding adducts having been transformed into dimethyl acetals by treatment with methyl orthoformate, and finally into α-hydroxy- or α-oxoaldehydes (Scheme 104)[600].

Enantiomeric enriched α-thiosulfoxides **391** can be prepared by addition of α-thiomethyllithiums to *p*-tolyl sulfinate[601]. The deprotonation of *p*-tolyl (*p*-tolylsulfanyl)methyl sulfoxide (**403**) took place with *n*-BuLi at $-78\,^{\circ}C$ to afford the enantioenriched lithium derivative **404**[602]. The addition to benzaldehyde followed by methylation of the hydroxy group and deprotection gave α-methoxyphenylacetaldehyde with 70% ee. This chiral formyl anion gave diastereoselectively Michael addition to α-substituted cyclopentenones[603]. The acylation of compound **404** followed by LAH reduction allowed the diastereoselective preparation of compounds **405** up to 99% de (Scheme 105)[604].

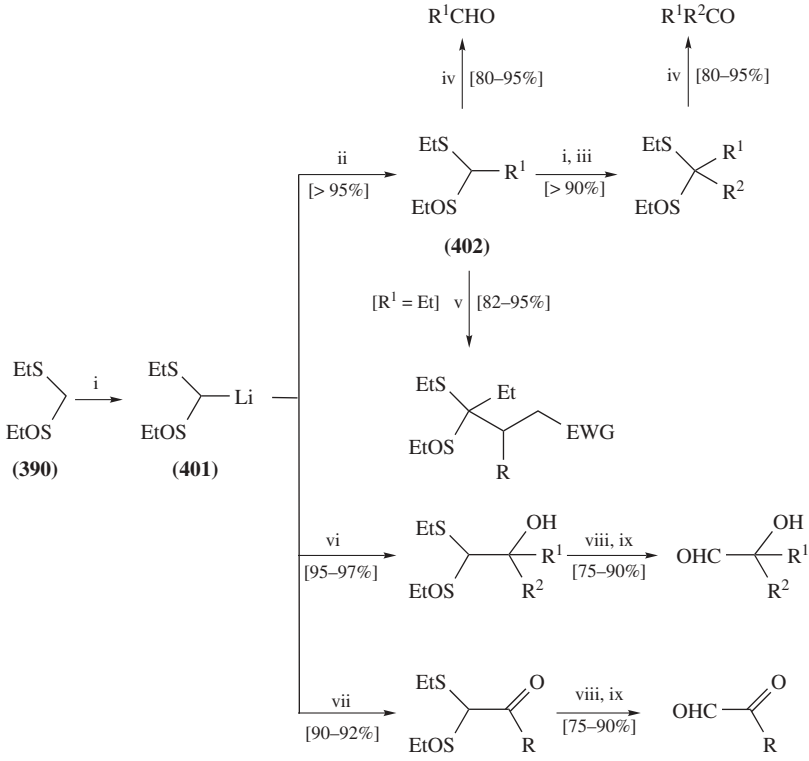


SCHEME 103. Reagents: (i) *n*-BuLi, −10 °C; (ii) $TsOCH_2CH_2(CH_2)_nOTs$; (iii) 9 N H_2SO_4, Et_2O; (iv) Ph_2CO; (v) conc. HCl, THF, rt; (vi) PhCHO; (vii) conc. H_2SO_4, $HC(OEt)_3$; (viii) R^1R^2CO; (ix) Ac_2O; (x) *t*-BuOK; (xi) HCl_g, MeOH

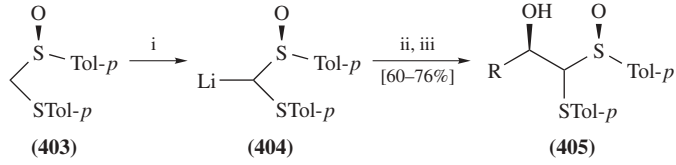


(397) **(398)** **(399)**

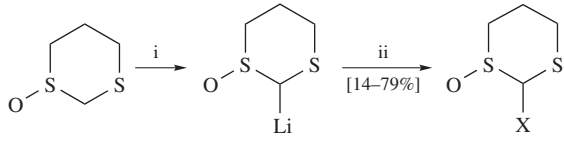
The cyclic α-lithio-1,3-dithiane *S*-oxide **406** was generated from compound **392** with *n*-BuLi at −10 °C and reacted with deuterium oxide, alkyl halides, carbonyl compounds and esters to afford the corresponding products **407** as mixture of diastereomers (Scheme 106)[605–607]. *N*-Acyl imidazoles were better acylating agents than esters[608]. However, compound **406** has not been employed properly as acyl anion. Intermediate



SCHEME 104. Reagents: (i) *n*-BuLi, 2 °C; (ii) R^1Hal; (iii) R^2Hal; (iv) 9 N HCl, $HgCl_2$; (v) RCH=CHEWG; (vi) R^1R^2CO; (vii) RCO_2Et or ROCl; (viii) $HC(OMe)_3$, H_2SO_4; (ix) $HCl-H_2O$



SCHEME 105. Reagents: (i) *n*-BuLi, −78 °C; (ii) RCOX; (iii) $LiAlH_4$

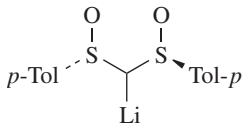


[X = D, R, R^1R^2COH, RCO]

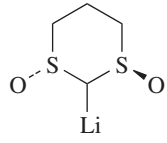
SCHEME 106. Reagents: (i) *n*-BuLi, −10 °C; (ii) EX = D_2O, RHal, R^1R^2CO, RCO_2Et

406 or related 2-substituted organolithium compounds have been used when 1,3-dithianes cannot be deprotonated or gave poor results in the reaction with electrophiles. After oxidation of the 2-substituted dithiane with MCPBA, lithiation with MeLi or *n*-BuLi and reaction with electrophiles, the final deoxygenation with P_2I_4 regenerated the dithiane before deprotection[609]. This strategy has been used for the synthesis of a fragment of the antibiotic boromycin[609] and in the total synthesis of (+)-zaragozic acid C[610]. Chiral sulfoxide **393**, derived from dithiepine, has been lithiated with *n*-BuLi at −78 °C and reacted diastereoselectively with methyl iodide, benzaldehyde or acetophenone[611,612]. Similarly, deprotection methods to complete its use as acyl anion have not been described.

Racemic and enantiopure 1,1-bis(*p*-tolylsulfinyl)methane **394** and the *trans*-1,3-dithiane *S*,*S*-dioxide **395** are C_2-symmetric bis(sulfoxides), which have been employed in organic chemistry[613]. Lithiated derivatives of these bis(sulfoxides) **408**[614] and **409**[615–618] can be prepared with LDA, LiHMDS or *n*-BuLi and gave diastereoselectively addition to carbonyl compounds. However, only compound **409** has been used as chiral acyllithium for the synthesis of α-hydroxy acid derivatives[617,618]. (*R*,*R*)-1,3-Dithiane *S*,*S*-dioxide **395** derived anion **409** afforded lower diastereoselectivity in the addition to aldehydes than the corresponding sodium derivative. The adducts can be transformed, after protection of the hydroxy group and reaction with ethylsulfanyllithium, into *O*-tetrahydropyranyl-*S*-ethyl α-hydroxy thioesters.



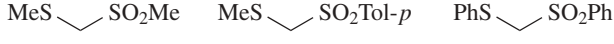
(408)



(409)

G. α-Lithio-α-thiosulfones

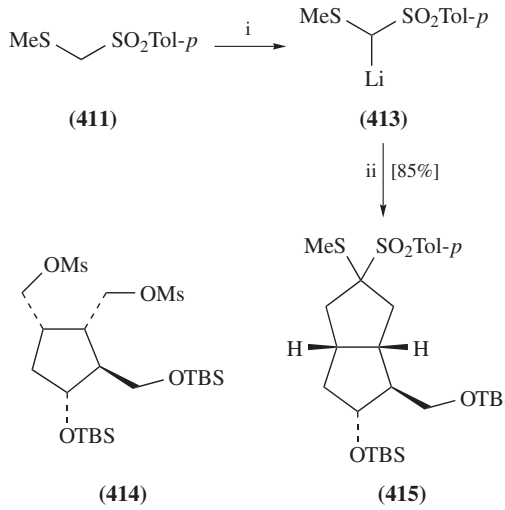
The sulfone moiety is a good acidifying group, so (methylsulfanyl)methyl sulfones **410** and **411** can be deprotonated and mono- or dialkylated with sodium hydroxide under PTC conditions or with sodium hydride[619–622]. The alkylated products can be easily hydrolyzed with hydrochloric acid in refluxing methanol, having been applied to the synthesis of acyclic and cyclic ketones. The acylation of compound **410** derived sodium anion has been performed with esters[620]. For the lithiation of α-thiosulfones **411**[622] and **412**, *n*-BuLi, *t*-BuLi or LDA at −78 °C can be used.



(410) **(411)** **(412)**

The lithiated sulfone **413** has been alkylated with alkyl bromides[623] in the presence of HMPA and with 1,4-dihaloalkanes[623,624], acting as an acyl dianion. For instance, treatment of intermediate **413** with the dimesylate **414**[625] has been applied to the synthesis of the cyclopentane derivative **415**, a precursor in the synthesis of 3-oxocarbacyclins (Scheme 107)[625]. Compound **415** was hydrolyzed to the corresponding cyclopentenone with 50% sulfuric acid in ethanol.

The alkylation of the α-lithio-α-(methylsulfanyl) phenyl sulfone derived from compound **411** with a chiral epoxide has been used for the synthesis of 2-deoxynucleosides[626]. In the case of the starting material **416**, the epoxide **417** was employed as electrophile in



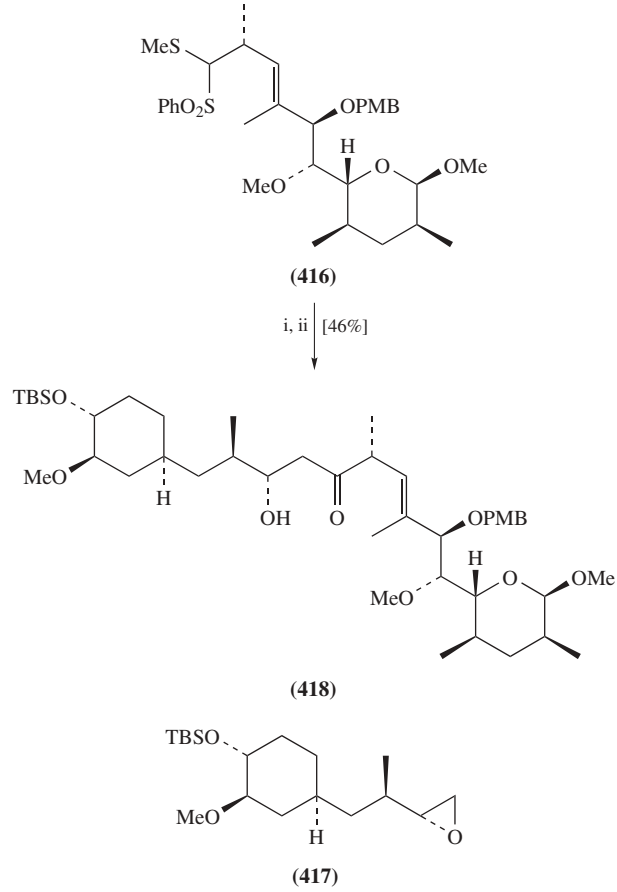
SCHEME 107. Reagents: (i) *n*-BuLi, −78 °C; (ii) **414**, HMPA, −78 to 10 °C

the synthesis of rapamycin[627]. The corresponding deprotonation had to be carried out with *t*-BuLi and the alkylation step needed the activation of the epoxide with BF_3 for the ring opening to take place, so after final deprotection the corresponding ketone **418** was isolated (Scheme 108)[627]. The anion **413** has also been alkylated with chiral *N*-tosylaziridines, this reaction being used for the asymmetric synthesis of piperidines[199].

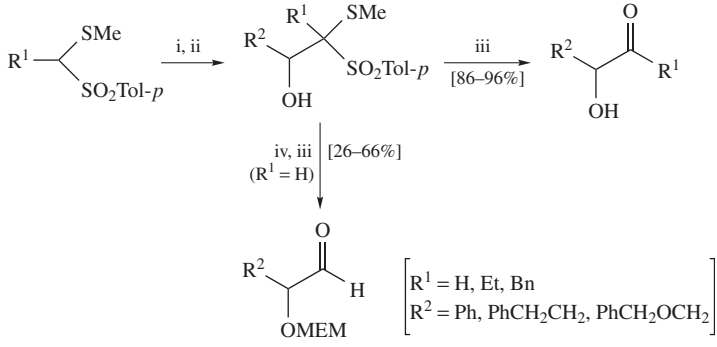
α-Hydroxy aldehydes and ketones can be prepared by using intermediate **413** and its α-substituted derivatives as acyllithiums in the reaction with aldehydes as electrophiles (Scheme 109)[628]. The deprotection of the masked carbonyl group works under very smooth and simple reaction conditions, but the hydroxy functionality of α-hydroxy aldehydes must be previously protected as acetyl, methoxymethyl or THP derivatives. This method seems to be superior to other protected acyllithium reagents.

The Trost–Mikhail ketones ring expansion procedure described before (see Section III.E) for the addition of α-lithio-α-methoxy sulfone **340** to cyclic ketones to give α-methoxycycloalkanones (Scheme 93) can be carried out with compound **419** to yield α-(phenylsulfanyl)cycloalkanones[525]. Smooth addition of intermediate **419** to ketones took place in the presence of diethylaluminium chloride and subsequent warm-up afforded the corresponding α-phenylsulfanyl ketones **420** (Scheme 110)[525].

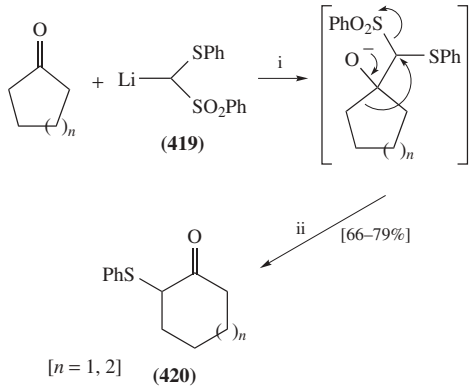
Aldehyde adducts of anions **413** have been silylated in situ to give the corresponding alkylidene derivatives[629]. A similar reaction has been carried out with intermediate **419** followed by acylation of the alkoxy group with Ac_2O[630]. These alkylidene derivatives have been used as intermediates for the diastereoselective synthesis of *syn*-β-hydroxy-α-amino acids[631]. As a typical example, D-threonine has been prepared from *O*-silylated lactaldehyde by condensation with compound **413** followed by mesylation. After acid hydrolysis of compound **421**, conversion into the corresponding trichloroacetylcarbamate and final treatment with potassium carbonate, oxazolidinone **422** was obtained. Oxidation of compound **422** to the corresponding sulfoxide followed by deprotection and final hydrolysis gave the expected amino acid (Scheme 111)[631].



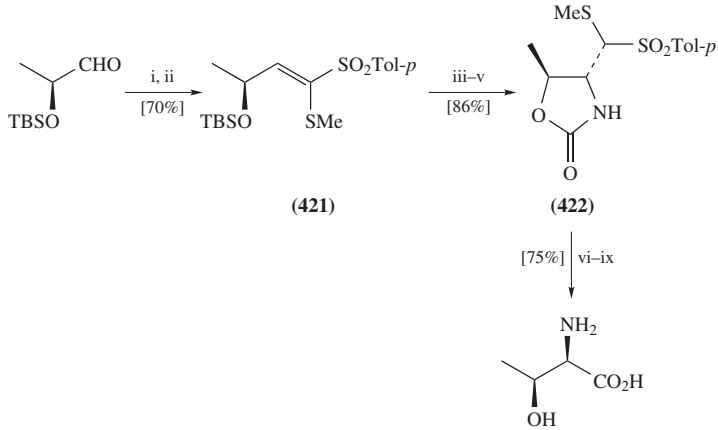
SCHEME 108. Reagents: (i) *t*-BuLi; (ii) **417**, $BF_3{\bullet}OEt_2$, −78 to 0 °C



SCHEME 109. Reagents: (i) *n*-BuLi, −78 °C; (ii) R^2CHO, −78 °C to rt; (iii) SiO_2; (iv) $CH_2(OMe)_2$, P_2O_5



SCHEME 110. Reagents: (i) Et_2AlCl, -78 to $0\,^{\circ}C$; (ii) $NaHCO_3$

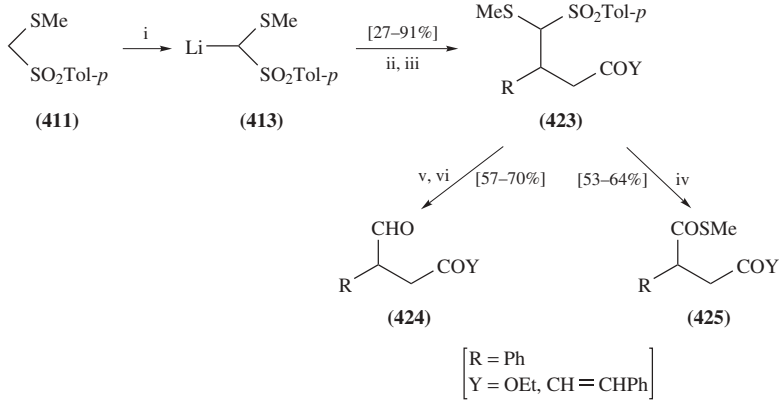


SCHEME 111. Reagents: (i) **413**, $-78\,^{\circ}C$; (ii) MsCl, Py; (iii) 1 N HCl; (iv) CCl_3CONCO; (v) K_2CO_3, MeOH; (vi) MCPBA; (vii) $(CF_3CO)_2O$, Py; (viii) K_2CO_3, H_2O; (ix) 6 N HCl

Michael-type reactions have been performed with the anion **413** and α,β-unsaturated ketones and esters to afford products **423** (Scheme 112)[632]. The resulting adducts have been transformed into deprotected aldehydes **424** by photolysis in aqueous dioxane[633]. Alternative hydrolysis to thioesters **425** can be carried out by oxidation to the corresponding sulfoxides and final acid hydrolysis. In the case of α,β-unsaturated aldehydes, 1,2-addition was exclusively observed[629,632]. The anion **419** gave conjugate addition to a cyclic enone, this reaction being applied to the synthesis of the alkaloid lepadin B[634].

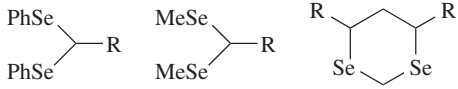
H. 2-Lithioselenoacetals

Acyclic bis(seleno)acetals **426** (R = H) must be deprotonated with LDA at $-78\,^{\circ}C$, because *n*-BuLi produces lithium–selenium exchange[8,13,635–639]. α-Lithioselenoacetals can also be prepared by this transmetallation from selenoorthoesters **427** (R = SeMe) with *n*-BuLi[638,639]. α-Alkyl substituted selenoacetals **426** (R = alkyl) can be deprotonated with LDA or lithium tetramethylpiperidide in the presence of HMPA at $-30\,^{\circ}C$[640].



SCHEME 112. Reagents: (i) *n*-BuLi, −78 °C; (ii) RCH=CHCOY, −25 °C; (iii) NH_4Cl; (iv) *hν*, 254 nm, dioxane, H_2O; (v) MCPBA; (vi) conc. HCl, reflux

Cyclic selenoacetals **428** (R = H)[641,642] can be lithiated with LDA and 4,6-dimethyl-1,3-diselenane **428** (R = Me)[643] with *n*-BuLi at −78 °C at the equatorial position. Axial functionalization has been achieved through a Se/Li exchange upon reacting 4,6-dimethyl-2-methylselanyl-1,3-diselenane with *n*-BuLi[643]. However, these 2-lithio-1,3-diselenanes have not been used as acyllithium reagents.



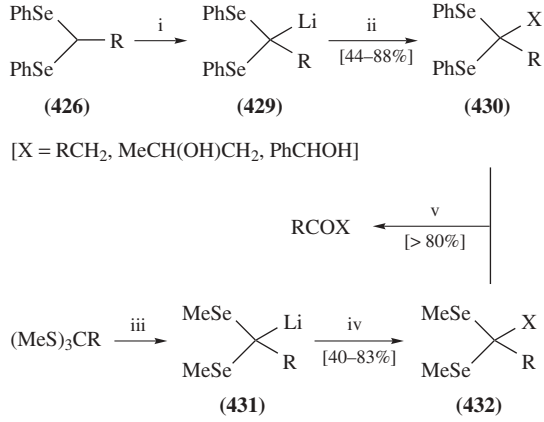
(426) **(427)** **(428)**

Bis(phenylselanyl)methyllithiums **429** (R = H) are stable till 0 °C and were initially trapped with deuterium oxide, methyl iodide and benzophenone[639]. α-Substituted organolithium intermediate **429** (R = Me, n-C_6H_{13}), prepared with LiTMP in THF/HMPA at −20 °C, reacted with alkyl bromides, ethylene oxide and benzaldehyde to give products **430** in good yields (Scheme 113)[640]. Bis(methylselanyl)methyllithiums **431** have been allowed to react with different electrophiles to afford products **432** (Scheme 113)[640]. Alkylated products have been deprotected with mercury(II) chloride or copper(II) chloride/copper(II) oxide, and by oxidation with hydrogen peroxide or benzeneseleninic anhydride[644]. Deprotection of selenoacetals to ketones can also be performed with sulfuric acid[645].

Intramolecular alkylation can be performed with 3-chloro-1,1-bis(phenylselanyl) propanes to provide cyclopropanone diselenoacetals[646]. Conjugate addition has been observed mainly when HMPA[361,647] or DME[647] were present in the reaction medium prior to the addition to enones[361]. However, in the case of chalcone, opposite regiochemistry was observed, 1,2-addition being almost exclusively observed even in the presence of HMPA[147]. For α,β-unsaturated aldehydes and esters, the presence of HMPA also increases the 1,4-/1,2-addition ratio[648].

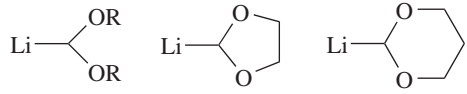
I. 2-Lithioacetals

Although acetal-derived anions are more unstable than the corresponding thioacetals, the final hydrolysis of the protecting moiety can be performed under milder conditions.



SCHEME 113. Reagents: (i) LiTMP, HMPA, −30 °C; (ii) EX = RCH_2Br, $RCH(O)CH_2$, PhCHO; (iii) *n*-BuLi, −78 °C; (iv) EX = RCH_2Br, Me_3SiCl, $MeCH(O)CH_2$, R^1R^2CO; (v) $CuCl_2/CuO$

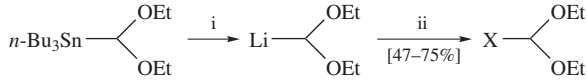
Dialkoxymethyllithiums **433**[649] and **434**[649–651], 2-lithio-1,3-dioxolane **435**[649] and 2-lithio-1,3-dioxane **436**[649] are formyl anion equivalents, which have been prepared either by reductive lithiation of 2-(phenylsulfanyl) substituted precursors at −95 °C[649] or by transmetallation of 2-(tri-*n*-butylstannyl) substituted compounds at −110[649] or −78 °C[651]. The starting acyclic phenylsulfanyl precursors can be prepared from the corresponding orthoformates by reaction with (phenylsulfanyl)trimethylsilane and trimethylsilyl triflate as catalyst (for compounds **433** and **434**). The cyclic derivatives (**435, 436**) were prepared from 1,2-bis(1,3-dioxolan-2-yloxy)ethane and propane, in the same way[649].



(433) R = Me
(434) R = Et
(435) **(436)**

(Diethoxymethyl)tri-*n*-butylstannane **437** was prepared by reaction of ethyl orthoformate with tri-*n*-butylstannylmagnesium chloride in the presence of galvinoxyl in 60% yield[649]. (Dimethoxymethyl)tri-*n*-butylstannane was prepared in similar yield by addition of tri-*n*-butylstannylmagnesium chloride to a mixture of methyl orthoformate and boron trifluoride etherate[649]. For acyclic acetals the transmetallation with *n*-BuLi was performed at −110 °C, whereas for the corresponding cyclic reagents the reaction was carried out at −78 °C. The lithiation of acyclic 2-phenylsulfanyl acetals has been performed with lithium 4,4-di-*tert*-butylbiphenylide for 1 min at −95 °C and in the case of cyclic acetals with lithium naphthalenide at −78 °C for 20 min[649]. The acyclic stannanes can also be prepared by reaction of dialkoxymethyl acetates with tri-*n*-butylstannylmagnesium chloride and cyclic stannanes by transmetallation of the acyclic (dialkoxymethyl)tri-*n*-butylstannane with diols in the presence of *p*-toluenesulfonic acid[649,651]. The reagent **434** was generated using this methodology by transmetallation with *n*-BuLi during 2 min and trapped with different electrophiles during 1 min. The reactivity of diethoxymethyllithium **434**

has been studied by Quintard and coworkers with benzyl bromide, chlorosilanes and germanes, carbonyl compounds and methyl benzoate (Scheme 114)[651]. Michael addition to cyclopent-2-enone has to be performed with the corresponding cyanocuprates and, in the reaction with benzoyl chloride, diaddition to the corresponding alcohol was observed. The deprotection of acetals **438** to unstable formyl silanes[651] and germanes was performed in an aqueous solution of hydrochloric acid in acetone. Formylsilanes have also been prepared from 2-lithio-1,3-dioxolane (**435**), generated from the corresponding stannane precursor. The deprotection has been performed with monoamine oxidase to afford the corresponding aldehyde hydrates, which have been transformed into their 2,4-dinitrophenylhydrazones[652].

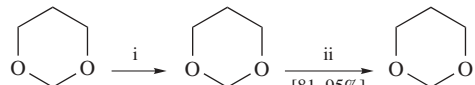


(437) **(434)** **(438)**

[X = $PhCH_2$, Me_3Si, $PhMe_2Si$, Et_3Ge, RCHOH, R^1R^2COH, PhCO]

SCHEME 114. Reagents: (i) *n*-BuLi, −78 °C, 2 min; (ii) EX = $PhCH_2Br$, Me_3SiCl, $PhMe_2SiCl$, Et_3GeCl, RCHO, R^1R^2CO, $PhCO_2Me$, 1 min

The reactivity of anions **433–436** with electrophiles has been studied by Shiner and coworkers. The cyclic derivatives **435** and **436** are relatively stable at −78 and −45 °C, respectively, the transformation of 2-lithio-1,3-dioxane **436** (generated from the corresponding precursor **439**) into derivatives **440** occurring in high yields (Scheme 115)[649]. Michael addition to cyclohex-2-enone took place in the presence of CuI•P(Bu-*n*)$_3$ and BF_3•OEt_2.



(439) **(436)** **(440)**

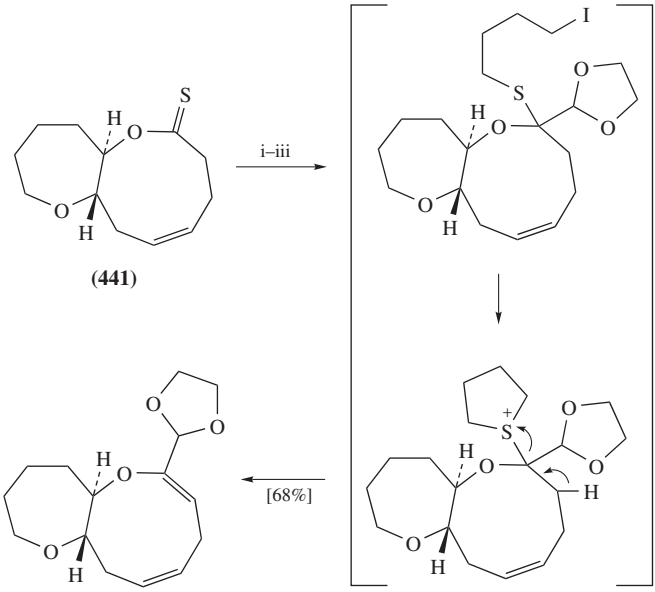
[X = RCHOH, R^1R^2COH, Me, $Ph(CH_2)_3$]

SCHEME 115. Reagents: (i) $LiC_{10}H_8$, THF, −78 °C, 20 min; (ii) EX = RCHO, R^1R^2CO, Me_2SO_4, $Ph(CH_2)_3Br$, −78 to −40 °C

The addition of 2-lithio-1,3-dioxolane (**435**) to the thionolactone **441**, followed by quenching with 1,4-diiodobutane, afforded the diene **442** in 68% yield, the postulated mechanism being shown in Scheme 116[653]. The oxanonacene prepared is a unit of brevetoxine A.

Enantiopure 2-stannyl-1,3-dioxolanes derived from chiral diols have been transmetallated to give chiral 2-lithio-1,3-dioxolanes **443** and **444** but, after addition to aldehydes, very low diastereomeric ratios were obtained[654].

Acyclic and cyclic ketals derived from aromatic aldehydes have been deprotonated with *n*-BuLi (4 h) at −45 °C or LDA (24 h) at −45 °C to room temperature, and the corresponding organolithiums **445** and **446** deuteriated with MeOD[655,656]. 2-Aryl acetal anions show a great tendency to rearrange and/or fragment[657] when they bear the electron-withdrawing oxazoline moiety at the *para*-position.

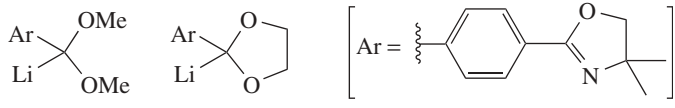


(441) **(442)**

SCHEME 116. Reagents: (i) **435**, THF; (ii) $I(CH_2)_4I$; (iii) 1,2,2,6,6-pentamethylpiperidine

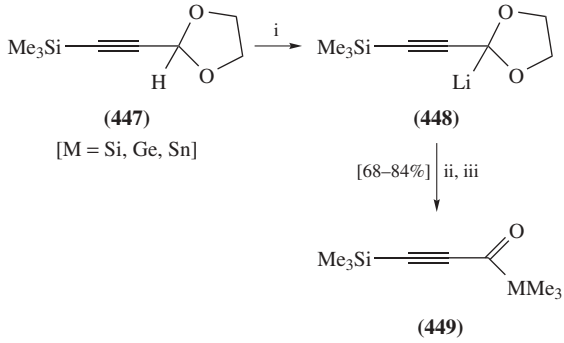
(443) **(444)**

[R = Me, Cy, Ph, CMe_2OMe, CMe_2OBn]



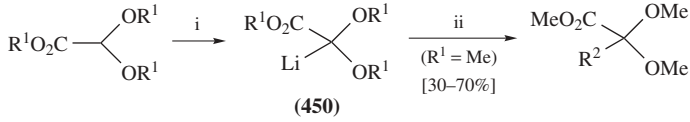
(445) **(446)**

Silyl, germanyl and stannyl alk-1-ynyl ketones have been prepared from 2-lithio-2-(trimethylsilylethynyl)-1,3-dioxolane **448**. The deprotonation of the dioxane **447** with *n*-BuLi at $-65\,^{\circ}C$ afforded the acyl anion **448** which, after reaction with trimethylsilyl, trimethylgermanyl and trimethylstannyl chloride, gave the expected derivatives (Scheme 117)[658]. Hydrolysis of these products with 0.01 M sulfuric acid at room temperature in aqueous acetone gave the corresponding acyl derivatives **449**. On the other hand, the reaction of the intermediate **448** with alkyl halides allows the synthesis of acetylenic ketones[659].



SCHEME 117. Reagents: (i) *n*-BuLi, THF, −65 °C, 30 min; (ii) Me_3MCl (M = Si, Ge, Sn); (iii) 0.01 M H_2SO_4, acetone, H_2O

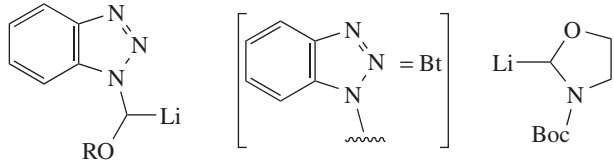
Acetals derived from glyoxylic esters can be deprotonated with LDA at −78 to −10 °C to provide enolates **450** ($R^1 = Et$[660], $R^1 = Me$[661,662]). The anion **450** ($R^1 = Et$) gave Michael addition by reaction with a α,β-butenolide, being used for the synthesis of 4-isoavenaciolide[660]. The addition of a similar intermediate ($R^1 = Me$) to carbonyl compounds, followed by dehydration and final hydrogenation, allowed the synthesis of methyl 2,2-dimethoxyalkanoates[661]. The alkylation of the anion **450** ($R^1 = Me$) allowed the direct preparation of the same type of alkanoates (Scheme 118)[662].



SCHEME 118. Reagents: (i) LDA, THF, −78 to −10 °C; (ii) R^2Hal

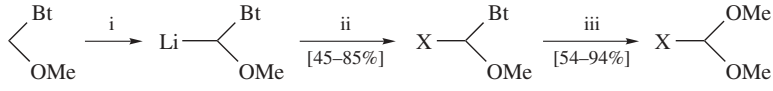
J. 2-Lithiohemiaminals and Aminals

(Benzotriazol-1-yl)alkoxymethyllithiums **451** and 2-lithiooxazolidines **452** are two types of acyllithium reagents which can be considered as protected formyl anions with hemiaminal structure.



(451) **(452)**

1-(Methoxymethyl)benzotriazole **453** and related alkoxy substituted derivatives can be prepared by reaction of 1-chloromethylbenzotriazole with the corresponding alkoxide[663]. The deprotonation of compound **453** with *n*-BuLi at −78 °C gave the anion **454**, which can be alkylated with alkyl bromides in 70–85% yield. It also reacts with other electrophiles, such as aldehydes, ketones, trimethylsilyl chloride and esters (Scheme 119)[664].



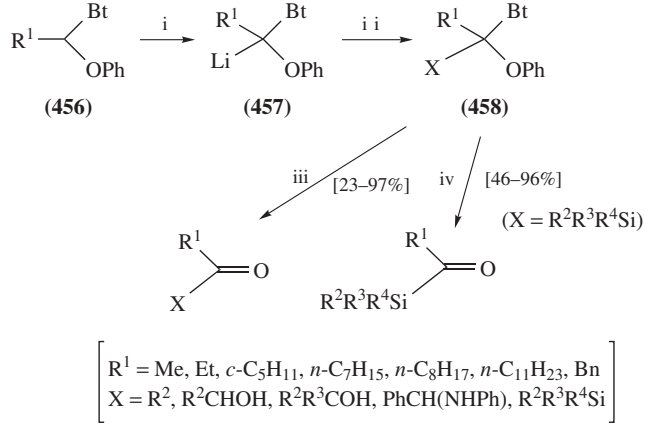
(453) **(454)** **(455)**

[X = R, RCHOH, R^1R^2COH, Me_3Si, PhCO]

SCHEME 119. Reagents: (i) *n*-BuLi, THF, −78 °C, 1 h; (ii) EX = RHal, RCHO, R^1R^2CO, Me_3SiCl, $PhCO_2Et$; (iii) MeOH, TsOH

The treatment of adducts **455** with methanol in the presence of *p*-toluenesulfonic acid gave the corresponding dimethyl acetals[663].

Similarly, 1-(phenoxyalkyl)benzotriazoles **456** can be lithiated to give the corresponding acyllithiums **457**, which have been used for the preparation of alkanoyl silanes and functionalized ketones (Scheme 120)[665]. Hydrolysis of adducts **458** was performed in refluxing aqueous ethanol (50%) containing 5% of sulfuric acid for 10 min. For acyl silanes, milder reaction conditions were used. When 1,4-dibromobutane was used as dielectrophile, alkyl, aryl, alkenyl and alkynyl 1,4-diketones were prepared in 74–86% yield[666].



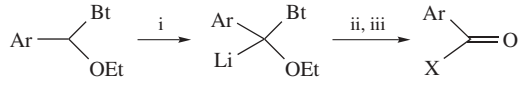
(456) **(457)** **(458)**

$$\left[\begin{array}{l} R^1 = \text{Me, Et, } c\text{-}C_5H_{11}, n\text{-}C_7H_{15}, n\text{-}C_8H_{17}, n\text{-}C_{11}H_{23}, \text{Bn} \\ X = R^2, R^2CHOH, R^2R^3COH, PhCH(NHPh), R^2R^3R^4Si \end{array}\right]$$

SCHEME 120. Reagents: (i) *n*-BuLi, THF, −78 °C, 2–5 min; (ii) EX = R^2Br, R^2CHO, R^2R^3CO, PhCH=NPh, $R^2R^3R^4SiCl$; (iii) EtOH, 5% H_2SO_4, reflux, 10 min; (iv) THF, 5 M HCl, reflux, 7 h

Aromatic and heteroaromatic aldehydes can be transformed into benzotriazole adducts **459** by reaction with benzotriazole and triethyl orthoformate in good yields. They can be deprotonated to the corresponding benzylic-type acyllithium equivalents **460** by means of *n*-BuLi at −78 °C in less than 2 min[667]. These benzotriazole-stabilized carbanions have been trapped with alkyl halides, aldehydes, ketones and imines, the resulting adducts being hydrolyzed in situ to the corresponding phenones by addition of diluted hydrochloric acid at room temperature for less than one hour (Scheme 121). Under a similar protocol aroyl-, heteroaroyl-, alkenoyl and alkynoyl silanes can be prepared in very good yields[668].

Alkynyl ketones can be prepared using the former useful methodology. Starting from propargyl aldehyde diethyl acetals and benzotriazole under toluene reflux, 1-(benzotriazol-1-yl) propargyl ethyl ethers were prepared in 83–84% yield. The deprotonation is very

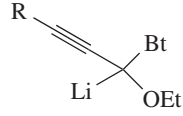


(459) **(460)**

[X = R^1, R^1CHOH, R^1R^2COH, $R^1CH(NHR^2)$]

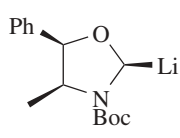
SCHEME 121. Reagents: (i) *n*-BuLi, THF, −78 °C, 2 min; (ii) EX = R^1Br, R^1CHO, R^1R^2CO, $R^1CH{=}NR^2$; (iii) H_2O, HCl, rt

fast, as in the case of the aryl substituted derivatives **459**. Subsequent reactions of anions **461** with alkyl halides, carbonyl compounds, imines, esters, trialkylsilyl chlorides, dialkyl carbonates and isocyanates followed by acid hydrolysis allowed the preparation of functionalized alkynyl ketones[669].

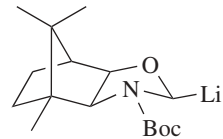


(461)

2-Lithiooxazolines **452** have been used as chiral formyllithiums. As chiral auxiliaries, (1*R*,2*S*)-norephedrine[654] and a camphor derived aminoalcohol[670] have been used to generate organolithiums **462** and **463** by tin–lithium transmetallation. These intermediates gave, after addition to aldehydes, mixtures of diastereomeric alcohols, which were oxidized to the corresponding ketones with PCC, reduced with $NaBH_4$ or reacted with Grignard compounds to give alcohols with >96% de. Final hydrolysis (to give the corresponding α-hydroxy aldehydes) followed by reduction gave 1,2-diols with >96% ee. When *N*-Boc-4,4-dimethyl-1,3-oxazolidine **464** was treated with *s*-BuLi in the presence of (−)-sparteine, the resulting anion reacted with benzaldehyde in the presence of $MgBr_2$ to give a 90/10 mixture of *syn/anti* adducts **465** (*syn*: 90% ee; *anti*: 88% ee)[671]. Final separation of diastereomers, protection of the alcohol functionality, Boc and aminoaminal deprotections and reduction gave the resulting diols (Scheme 122).

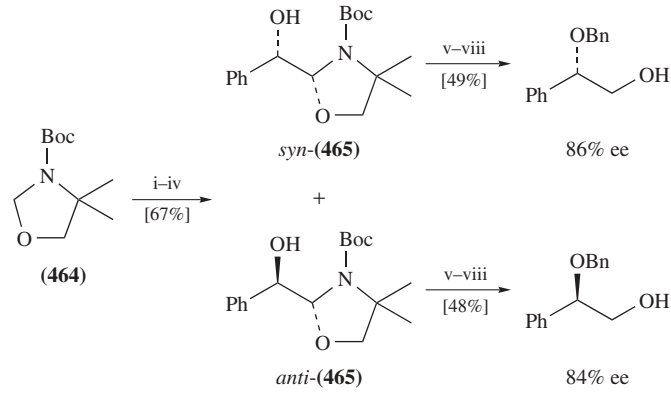


(462)

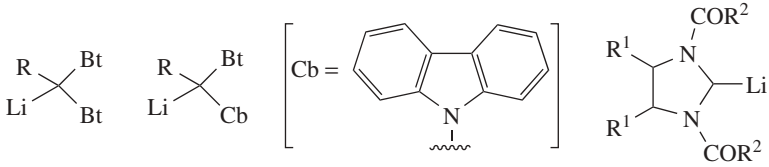


(463)

Bis(benzotriazol-1-yl) **466** and (benzotriazol-1-yl)(carbazol-9-yl)methyllithium **467** and *N*,*N*′-bisacylimidazolidines derived organolithium **468**, described by the Katritzky[672–675] and Coldham[676,677] groups, can be considered as 2-lithioaminal derivatives. Initial studies with benzotriazole-stabilized organolithiums **466** (R = Ph, *p*-tolyl[672], H[673]) obtained by deprotonation with LDA at −78 to 0 °C or with *n*-BuLi at −78 °C, followed by reaction with a great variety of electrophiles, gave the corresponding substituted products with good yields. However, the hydrolysis step was not successful under acidic conditions in many examples, indicating a lack of sufficient electronic assistance from one benzotriazolyl group to allow the departure of the other protonated benzotriazole. For those reasons, the



SCHEME 122. Reagents: (i) *s*-BuLi, (−)-sparteine, Et_2O, −78 °C; (ii) $MgBr_2$, −78 °C to rt; (iii) PhCHO, −78 °C, 3 h, then −78 °C to rt, 3 h; (iv) H_2O; (v) BnBr, NaH; (vi) TFA; (vii) THF, H_2O; (viii) $NaBH_4$

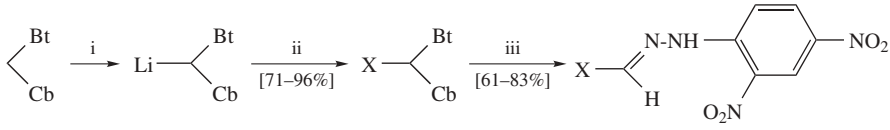


(466) **(467)** **(468)**

change to carbazole as a better electron donor to assist in the elimination of benzotriazole gave much better results in the synthetic application of intermediates **467** as formyl and acyl anions.

(Benzotriazol-1-yl)(carbazol-9-yl)methane **469** can be readily deprotonated with *n*-BuLi at −78 °C and reacted with different electrophiles to afford the corresponding adducts **470** (Scheme 123)[673]. Treatment of these adducts with concentrated sulfuric acid in THF/H_2O (2/1) in the presence of 2,4-dinitrophenylhydrazine gave the corresponding hydrazones **471**. The benzyl and *n*-butyl derivatives **467** (R = Bn, *n*-Bu) have been used as acyl anion intermediates, which reacted with alkyl halides, isocyanates, diphenyl disulfide, carbonyl compounds and trimethylsilyl chloride, as well as with cycloalkenones at the β-position[674]. Hydrolysis of the adducts with 0.9 M hydrochloric acid in THF at room temperature provided the corresponding carbonyl compounds in 51–89% yield, which can be easily separated from insoluble carbazole and benzotriazole by extraction with hexane. When the (benzotriazol-1-yl)(carbazol-9-yl)propyllithium bears a dialkylamino group at the β-position (see **467**, R = $R^1{}_2NCH_2$), these anions can be used as β-aminoacyl anions for the synthesis of β-aminoethyl ketones[675].

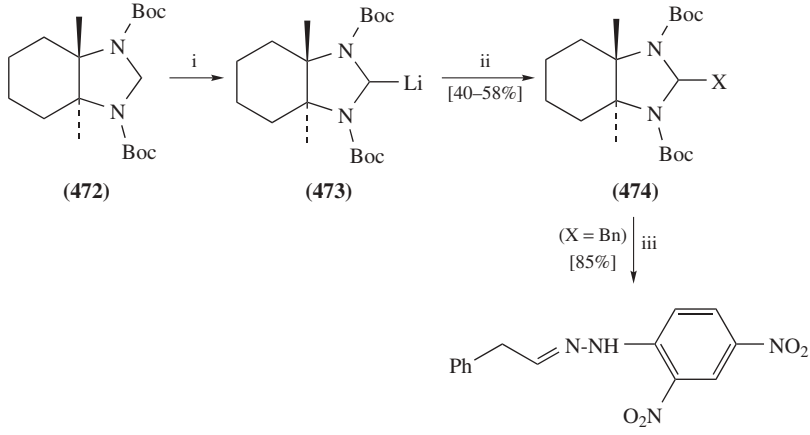
Imidazolidine-derived organolithium compounds **468** have been prepared by deprotonation of the corresponding *N*-acylated imidazolidines with two equivalents of *s*-BuLi at −78 °C. The best results have been obtained with the *trans*-1,2-diaminocyclohexane-derived imidazolidine **472**, so its anion **473** reacted with different electrophiles to give compounds **474** in moderated yields, which gave the expected hydrazones **471** as described above (Scheme 124)[676,677]. Other imidazolidines suffered deprotonation at the 4-position



(469) **(467)** (R = H) **(470)** **(471)**

[X = R, RCHOH, R_2COH, PhNHCS, PhNHCO, PhCO]

SCHEME 123. Reagents: (i) *n*-BuLi, THF, −78 °C, 2 h; (ii) EX = RHal, RCHO, R_2CO, PhNCS, PhNCO, $PhCO_2Et$; (iii) conc. H_2SO_4, THF/H_2O, 2,4-$(NO_2)_2C_6H_3NHNH_2$



(472) **(473)** **(474)**

[X = Me, Bn, CH_2=$CHCH_2$, PhNHCO, MeOCO, PhCO] **(471)**

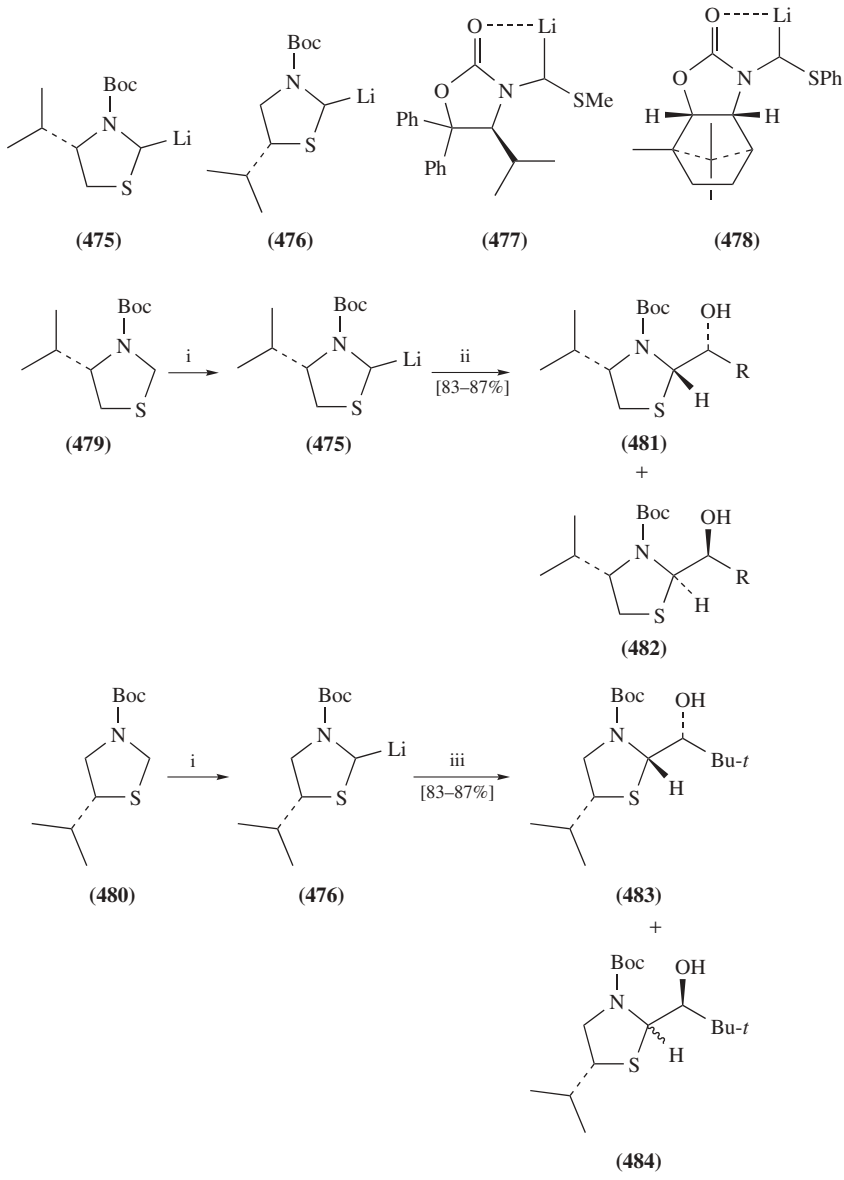
SCHEME 124. Reagents: (i) *s*-BuLi, THF, −78 °C, 30 min; (ii) EX = MeI, BnBr, CH_2=$CHCH_2Br$, PhNCO, MeOCOCl, PhCOCl; (iii) TFA, CH_2Cl_2, 0 °C, 2,4-$(NO_2)_2C_6H_3NHNH_2$

giving numerous byproducts. Using chiral imidazolidines and aldehydes as electrophiles, inseparable mixture of diastereomers was obtained[677].

K. 2-Lithioaminothioacetals

Chiral formyllithiums **475–478** have been prepared from the corresponding cyclic and acyclic *S*,*N*-acetals. *N*-Boc-Thiazolidines having an isopropyl group at the 4- or 5-position **479** or **480** were lithiated with *n*-BuLi at −78 °C and reacted with aldehydes to form only two of the four possible diastereomers with 40% or 70% diastereoselectivity for the major isomer **481** or **483**, respectively (compare with compounds **482** and **484**) (Scheme 125)[678].

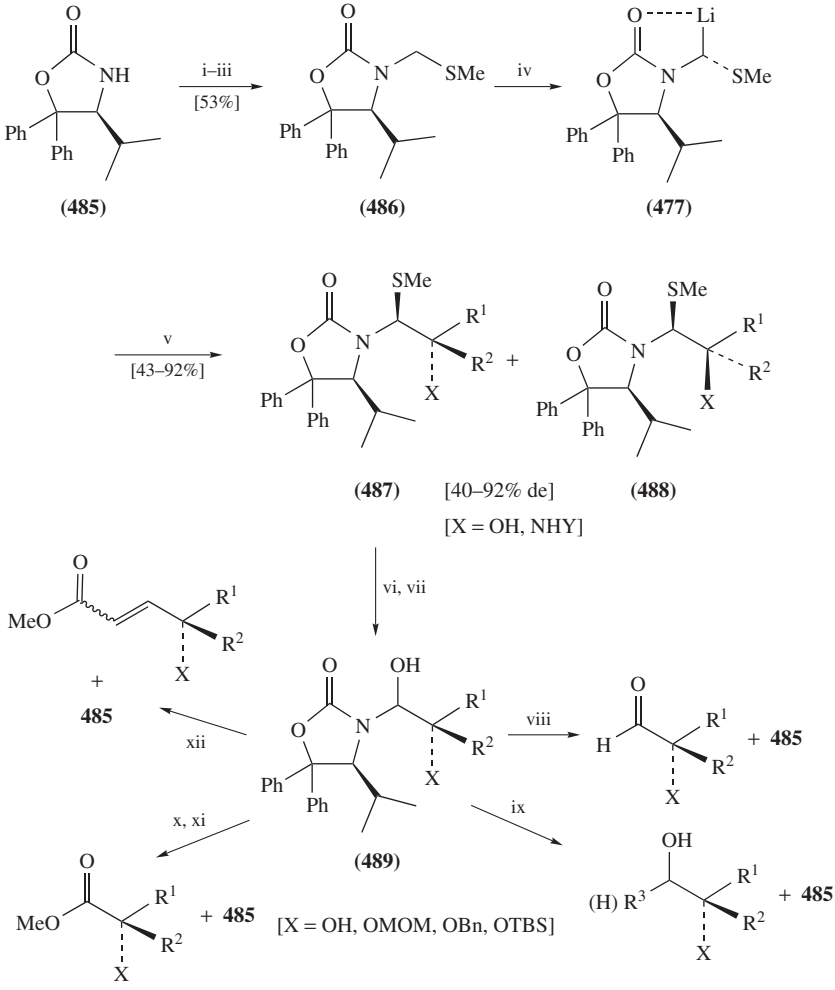
4-Isopropyl-5,5-diphenyloxazolidin-2-one **485** has been used as chiral auxiliary for the preparation of the acyclic amino thioacetal **486** which, after lithiation, gave high diastereoselective addition to aldehydes, imines and prochiral ketones[679–681] (Scheme 126). Computational, IR and NMR spectroscopic investigations on the chiral formyllithium **477** suggested its (*S*)-configuration[681]. Carbonyl compounds major adducts **487** (X = OH) (for minor diastereomers, see compounds **488**) or their protected derivatives (X = OMOM, OBn, OTBS) can be transformed into hemiaminals **489** by treatment with $Hg(O_2CCF_3)_2$ in a mixture of acetonitrile, THF and water during 5 min. These hemiaminals gave, upon



SCHEME 125. Reagents: (i) *n*-BuLi, THF, −78 °C; (ii) RCHO; (iii) *t*-BuCHO

addition of DBU, the corresponding aldehydes and the oxazolidinone **485**. Alternatively, they can be reduced to 1,2-diols and 2-aminoalcohols or oxidized to 2-hydroxy esters or, after reaction with Ph_3PCHCO_2Me, transformed into 4-hydroxy-2-alkenoates.

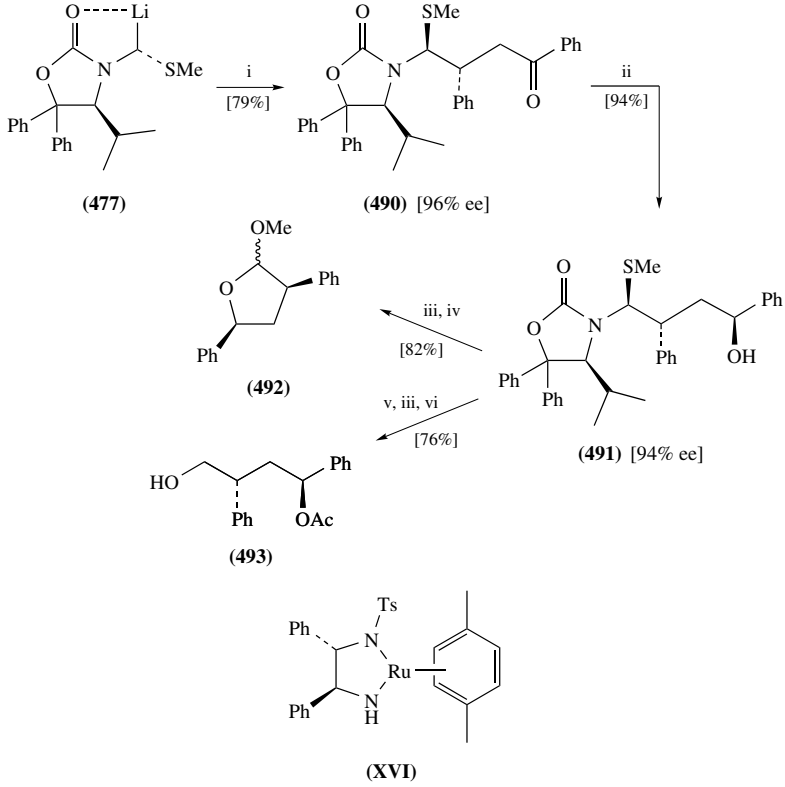
Michael addition of the anion **477** to chalcones, trityl enones and 2,6-di-(*tert*-butyl)-4-methoxyphenyl cinnamate took place exclusively with high diastereoselectivity[682] (Scheme



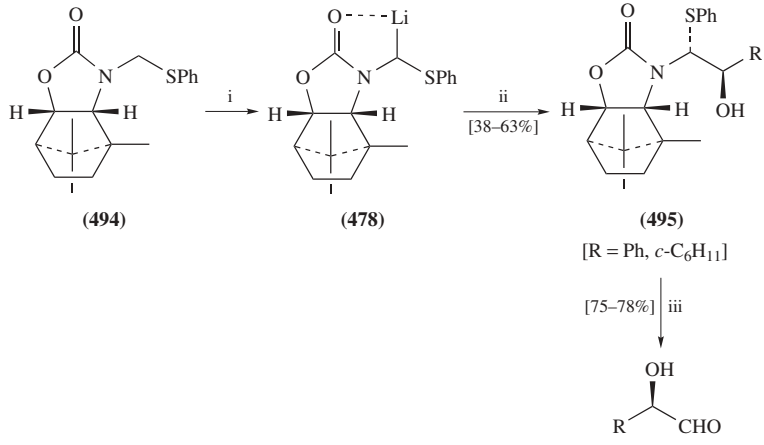
SCHEME 126. Reagents: (i) *n*-BuLi, THF, 0 °C; (ii) DMSO; (iii) $ClCH_2SMe$; (iv) *n*-BuLi, THF or Et_2O, −78 °C, 5 min; (v) EX = R^1R^2CO, $R^1CH{=}NY$ (Y = $POPh_2$, SO_2Tol-*p*, SO_2Mes), −100 to −78 °C, 20 min; (vi) protection; (vii) $Hg(O_2CCF_3)_2$, MeCN, THF, H_2O (2:2:1), rt, 5 min; (viii) DBU; (ix) $NaBH_4$, DBU or R^3MgX; (x) PCC; (xi) LiBr, DBU, MeOH; (xii) DBU, Ph_3PCHCO_2Me

127). However, 1,2-diaddition was observed in the case of α,β-unsaturated aldehydes and other ketones. The corresponding chalcone adduct **490** has been reduced to compound **491**, which was transformed into the cyclic acetal **492** and the 1,4-diol derivative **493**.

N-(Phenylsulfanylmethyl)oxazolidinones derived from camphor **494** can be lithiated with *n*-BuLi at −78 °C to give the chiral formyllithium equivalent **478**[683] (Scheme 128). This intermediate added to aldehydes in good yields, but lower stereoselectivity than compound **477**, to afford crystalline adducts, which allowed the isolation of the major diastereomer **495**. Hydrolysis of these adducts gave α-hydroxy aldehydes, which can be oxidized with PCC to the corresponding α-hydroxy acids.



SCHEME 127. Reagents: (i) (*E*)-PhCH=CHCOPh, −100 °C; (ii) complex (**XVI**); (iii) $Hg(O_2CCF_3)_2$; (iv) MeOH, H_2SO_4; (v) Ac_2O, DMAP; (vi) $NaBH_4$, DBU



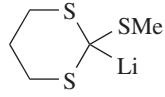
SCHEME 128. Reagents: (i) *n*-BuLi, THF, −78 °C; (ii) RCHO; (iii) $Hg(OAc)_2$, $CaCO_3$, HOAc, −78 °C

L. α-Lithioorthothioesters

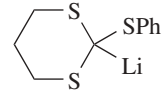
Tris-heterosubstituted organolithium compounds are considered as carboxyl anions and related synthons. Tris(methylsulfanyl)- and tris(phenylsulfanyl)methyllithium, **496** and **497**, and other acyclic tris(alkylsulfanyl)methyllithiums **498–500** and cyclic ones **501** and **502** have been described as sulfur-containing LiCXYZ compounds[12,684–687].

$LiC(SMe)_3$ $LiC(SPh)_3$ $LiC(SEt)_3$ $LiC(SPr\text{-}n)_3$ $LiC(SBn)_3$

(496) **(497)** **(498)** **(499)** **(500)**



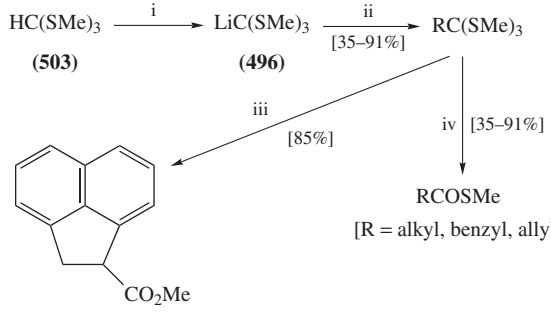
(501)



(502)

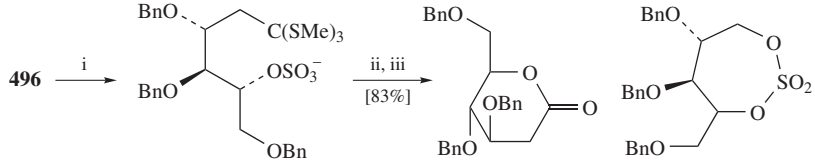
The lithiated trithioorthoformates **496–498** and **501** were described at the same time by Seebach[688] and were formed by deprotonation of the corresponding trithioorthoesters with *n*-BuLi at low temperature. Alternatively, this type of organolithium can be prepared from tetrathiocarbonates by sulfur–lithium exchange with *n*-BuLi[689,690]. The two first reagents **496** and **497** are very popular reagents in organic synthesis, whereas reagents **499–502** have scarcely been used. After reaction with electrophiles the deprotection is carried out mainly with mercury(II) salts[691].

Tris(methylsulfanyl)methane **503**[692] is deprotonated with *n*-BuLi in THF at −78 °C to give the intermediate **496**[688,693], which has been applied widely as carboxylate anion equivalent. This tris(methylsulfanyl)methyllithium **496** is stable at temperatures below −50 °C, decomposing at higher temperatures to provide tetrakis(methylsulfanyl)ethane. Starting from tetrakis(methylsulfanyl)methane, compound **496** can be generated by treatment with *n*-BuLi at −95 °C[688]. This anion can be alkylated with alkyl halides[694–697], such as primary and secondary alkyl chlorides, bromides and iodides (Scheme 129). 1-Bromoacenaphthene gave 1-[tris(methylsulfanyl)methyl]acenaphthene in 95% yield, a precursor of the plant growth regulator acenaphthene-1-carboxylic acid[696]. The deprotection of thermally unstable trithioorthoesters to methyl esters can be performed with mercury(II) chloride and mercury(II) oxide in aqueous methanol under reflux[698]. Thiol esters can be obtained by hydrolysis with 35% aqueous HBF_4 in DMSO or THF[694].



SCHEME 129. Reagents: (i) *n*-BuLi, THF, −78 °C; (ii) RHal, −78 °C to rt; (iii) HgO, $HgCl_2$, MeOH, H_2O, reflux (for R = 1-acenaphthenyl); (iv) 35% aq HBF_4, DMSO, 130 °C or THF, 67 °C

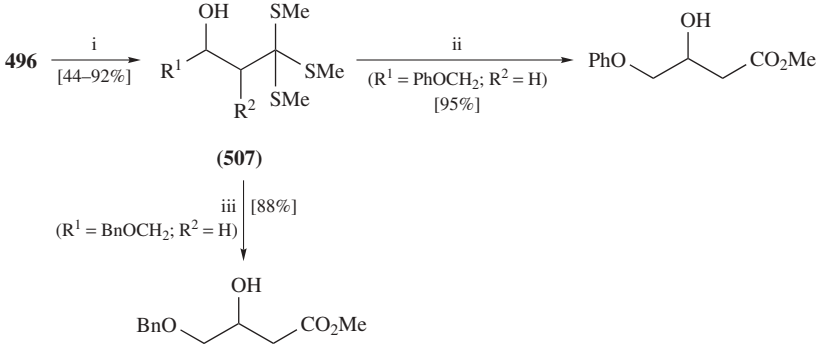
Pseudomonic acid analogues have been prepared using 1,8-diiodooctane and 1,9-dibromononane as electrophiles[695]. 2,3,5-Tri-*O*-benzyl-D-arabinitol 1,4-cyclic sulfate **504** has been used as electrophile for the alkylation of compound **496**, so intermediate **505** was deprotected with *N*-bromosuccinimide (NBS) to give the lactone **506**, a potential precursor of a shikimate analogue[162] (Scheme 130).



(505) **(506)** **(504)**

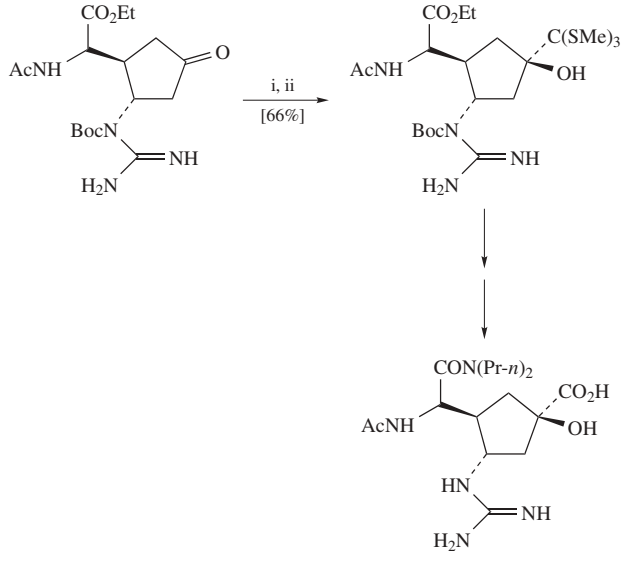
SCHEME 130. Reagents: (i) **504**, THF, −40 °C, 0.5 h; (ii) HSO_4; (iii) NBS, $Et_3NH_2CO_3$, MeCN, H_2O, 0 °C

For the alkylation of the organolithium intermediate **496** with epoxides[699,700] the best reaction conditions were the use of a mixture of THF/HMPA (5/1) at −45 °C[700]. Further deprotection of adducts **507** either with mercury(II) salts or NBS allows the synthesis of β-hydroxy esters in high yields (Scheme 131).



SCHEME 131. Reagents: (i) $R^1CH(O)CHR^2$, THF/HMPA (5/1), −70 to −45 °C, 30 min; (ii) $HgCl_2$, HgO, MeOH/H_2O (12/1); (iii) NBS, $NaHCO_3$, MeOH/H_2O (12/1)

The reaction of tris(methylsulfanyl)methyllithium (**496**) with carbonyl compounds can be directed to the synthesis of α-hydroxy carboxylic acid derivatives[701–708] and, in the case of cyclic ketones, for their ring expansion to give 1,2-ketothioacetal products[709–712] under copper(I) salts or acid-promoted regioselective rearrangement. The 1,2-addition to α,β-unsaturated ketones only was observed. Some applications are the preparation of a BCE ring model for the total synthesis of the quasinoidal antileukemia agent bruceantin[701], to the synthesis of 2-alkyltetronic acids[702], some inhibitors of prostatic steroid 5α-reductase[704] and inhibitors of influenza neuraminidases, such as 1-carboxy-1-hydroxy derivatives **508**[708] (Scheme 132). A protected α-hydroxy-β-homoarginine (prepared from arginine aldehyde[705]), polioxamic acid (prepared from L-threose aldehyde[707]) or a pantoic acid derivative (obtained from 3-hydroxy-2,2-dimethylpropanal[706]) are other examples of the addition of compound **496** to aldehydes.



(508)

SCHEME 132. Reagents: (i) **496**, THF, −78 °C; (ii) NH_4Cl

Acylation of tris(methylsulfanyl)methyllithium (**496**) has been performed with esters[713], lactones[714–716], ethyl chloroformate[689] and carbon disulfide[717]. A complete study on the reaction of the intermediate **496** with aromatic, heteroaromatic and aliphatic esters showed that α-keto trithioorthoesters **509** and α-keto dithioacetals **510** are formed[713] (Scheme 133). Compounds **509** were obtained mainly with a reagent/anion ratio of 1/1.25 at −95 °C for 5 min and subsequent addition of *N*-(methylsulfanyl)phthalimide to the reaction mixture.

$$RCO_2Me \xrightarrow{\text{i, ii}} \underset{\textbf{(509)}}{RCOC(SMe)_3} + \underset{\textbf{(510)}}{RCOCH(SMe)_2}$$

[82–100%]

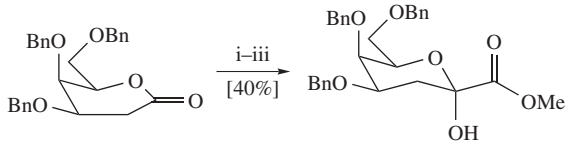
[R = H, *t*-Bu, *n*-C_9H_{19}, FCH_2, $MeOCH_2$, $CH(OMe)_2$, MeOCO, 4-ClC_6H_4, 2,5-$Cl_2C_6H_3$, 4-$MeOC_6H_4$, 2-furyl, 2-thienyl, 2-pyrrolyl, 3-pyridyl]

SCHEME 133. Reagents: (i) **496**, −95 °C, 5 min; (ii) *N*-(methylsulfanyl)phthalimide, −95 °C to rt

In the case of aldonolactones, different lithiated trithioorthoesters **496–498** and **501** were essayed. The intermediate **496** was the most efficient acyllithium, allowing the formation of methyl 2-aldulosonates after mercury(II)-promoted methanolysis. Scheme 134 illustrates the preparation of compound **511** from the corresponding lactone[714].

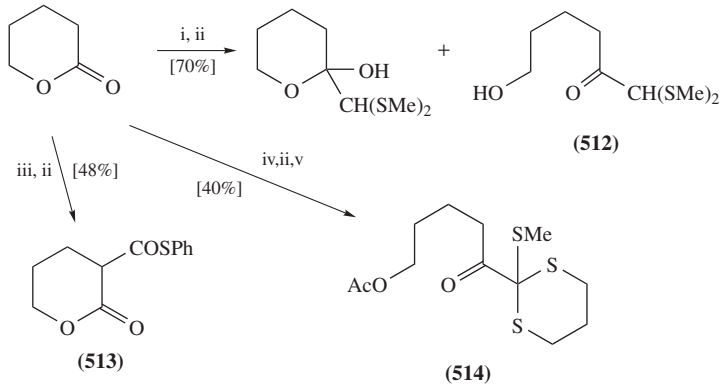
However, studies carried out with δ-valerolactone and organolithiums **496, 497** and **501** gave compounds **512–514**, respectively[715,716] (Scheme 135). Only intermediate **501** afforded the keto orthothioester without elimination of the methylsulfanyl group.

Addition of the anion **496** to a bicyclic cyclohexenone[701] gave 1,2-addition, but cyclohexenone[163] and 2-(trimethylsilylmethyl)propenal[718] gave mixtures of 1,2- and 1,4-addition products, whereas tris(phenylsulfanyl)methyllithium (**497**) gave exclusively



(511)

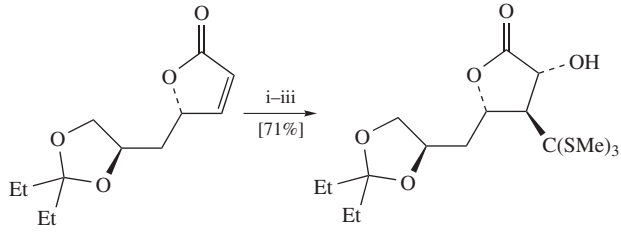
SCHEME 134. Reagents: (i) **496**, −78 to −20 °C; (ii) NH_4Cl; (iii) $HgCl_2$, HgO, 95% MeOH, rt



(512) **(513)** **(514)**

SCHEME 135. Reagents: (i) **496**, −78 to −20 °C; (ii) NH_4Cl; (iii) **497**, −78 °C; (iv) **501**, −78 to −20 °C; (v) Ac_2O, Py

conjugate addition to cyclohexenone[719]. However, for cyclopentenone[720] and 2,3,4,9-tetrahydro-1*H*-xanthene-1,9-dione[721], used in the synthesis of secalonic acids and other natural products, only 1,4-addition is observed at temperatures below −50 °C. α,β-Butenolides are good Michael acceptors and the intermediate enolates can be trapped with an electrophile, such as formaldehyde or methyl iodide, allowing the double functionalization at the β- and α-position, respectively. This methodology has been used with optically active α,β-butenolides in the synthesis of the antibiotic protolichesterinic acid[722]. Polyhydroxylated carboxylic acids[723], several fragments of the antibiotic amphotericin B, such as compound **516** (prepared from the butenolide **515**[724] as shown in Scheme 136) and chiral 1,4-diols[725] have been prepared using a final Raney-nickel reduction of the tris(methylsulfanyl)methyl moiety to a methyl group.



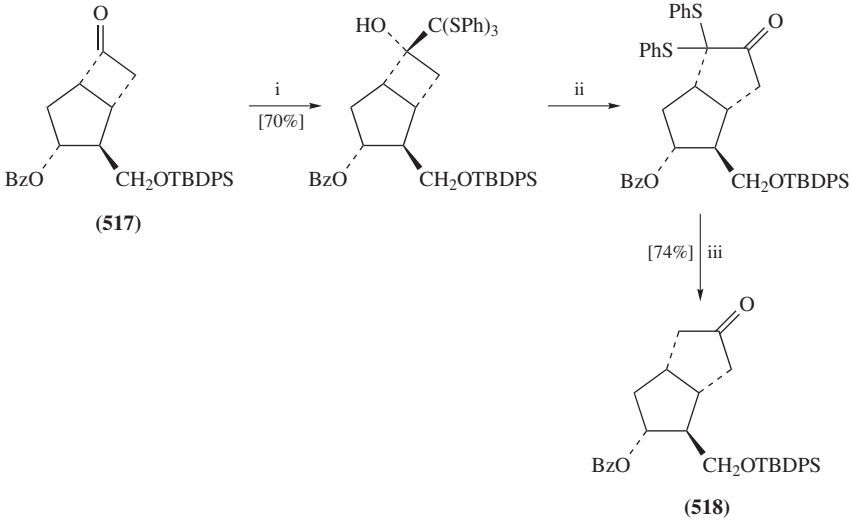
(515) **(516)**

SCHEME 136. Reagents: (i) **496**, −78 °C; (ii) NH_4Cl; (iii) LiHMDS, MoO_5•Py•HMPA, −78 °C

The addition to an arenetricarbonylchromium complex can be considered as a Michael-type reaction. In the case of (1-methoxynaphthalene)tricarbonylchromium an addition of the anion **496** took place to C5, whereas tris(phenylsulfanyl)methyllithium (**497**) failed[249].

Tris(phenylsulfanyl)methyllithium (**497**)[726] was prepared in the same way as for the corresponding methylsulfanyl derivative (**496**)[689–691] by deprotonation of tris(phenylsulfanyl) methane[727] with *n*-BuLi at −78 °C as well as from tetrakis(phenylsulfanyl)methane by sulfur–lithium exchange[690] or from diphenyl trithiocarbonate and phenyllithium[690]. It also decomposes to give the bis(phenylsulfanyl)carbene[689, 690, 728, 729]. This reagent is less reactive than compound **496** due to its bulkiness. It can be alkylated with primary alkyl and allyl halides[688–690, 730] or epoxides[688, 689], silylated with chlorotrimethylsilane[688, 689] and reacts also with disulfides[688, 689]. *N*-Tosylaziridines can be used as electrophiles, but the final hydrolysis of the corresponding adducts failed[731]. Deprotection to carboxylic acids[698, 718] or esters[732] can be performed with either mercury(II) chloride and mercury(II) oxide in methanol[698] or silver trifluoroacetate[718], as well as to thioesters[733]. In general, tris(phenylsulfanyl)methyl derivatives are more easily hydrolyzable than the corresponding tris(methylsulfanyl)methyl ones.

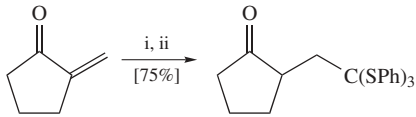
1,2-Addition of compound **497** to aliphatic, aromatic and α,β-unsaturated aldehydes[688, 689, 718, 734] gave the corresponding adducts, which can be hydrolyzed to α-hydroxy carboxylic esters by means of mercury(II) oxide in 50% aqueous tetrafluoroboric acid in the presence of an alcohol at room temperature[735]. However, cyclic ketone adducts have been used mostly as in the case of the tris(methylsulfanyl)methyllithium derivatives, in ring expansion rearrangements for the preparation of α,α-bis(phenylsulfanyl)cycloalkanones[710, 736] as illustrated in Scheme 137 for the synthesis of compound **518** from the ketone **517**, a carbacyclin precursor[736].



SCHEME 137. Reagents: (i) **497**, −78 °C; (ii) $HgCl_2$, DMF, −40 °C; (iii) Ra-Ni, EtOH, 50 °C

On the other hand, α,β-unsaturated ketones[732, 737–743] suffered conjugate addition providing γ-keto carboxylic acid methyl esters after mercury(II)-catalyzed methanolysis[732]. Michael adducts have been used for the generation of new carbanions, which can suffer new conjugate additions and cyclopropanations[737–743]. This conjugate addition

to α,β-unsaturated aldehydes, ketones and esters can be improved in the presence of chlorotrimethylsilane[744,745]. For instance, in the case of 2-methylenecyclopentanone, 24% of the Michael adduct **519** was obtained in the absence of chlorotrimethylsilane and 75% with this additive[745] (Scheme 138).

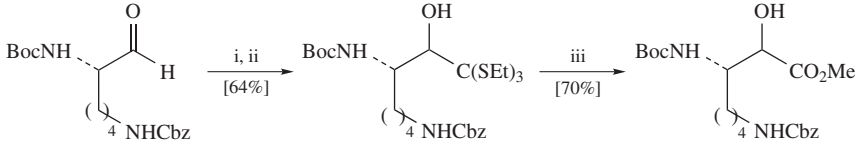


(519)

SCHEME 138. Reagents: (i) **497**, −78 °C, Me_3SiCl; (ii) HCl

Ethyl chloroformate[688,609] or carbon dioxide[691] can be used as carboxylating agents. However, δ-valerolactone reacted with the ethylsulfanyl intermediate **497** to give compound **513** (Scheme 135)[715,716].

Another lithiated trithioformate, such as the intermediate **498**, has been used for the synthesis of α-hydroxy esters by reaction with aldehydes and final deprotection, as mentioned for compound **497**[735]. The aldehyde **520** has been transformed into the hydroxy ester **521**, a key intermediate for the preparation of peptidyl α-keto esters[746] (Scheme 139).



(520) **(521)**

SCHEME 139. Reagents: (i) **498**, −78 °C; (ii) H_2O; (iii) $HgCl_2$, HgO, MeOH

The cyclic reagent **501** reacts with alkyl halides and carbonyl compounds in good yields[698]. In the case of α,β-unsaturated carbonyl compounds, 1,2-addition was mainly observed[698,747] and the addition to δ-valerolactone gave compound **514**[715,716] (Scheme 135). The conjugate addition has been studied with reagents **499–502** and cyclohexenone or chalcone, whereas 4-phenylbut-3-en-2-one and 4-methylpent-3-en-2-one gave 1,2-addition products[748].

IV. OTHER ACYLLITHIUM EQUIVALENTS

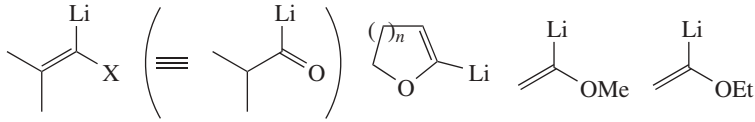
α-Heteroatom-substituted alkenyl-, dienyl- and allenyllithium derivatives **XIII–XV** (see Introduction) are important acyllithium equivalents widely used in organic synthesis. They must be generated at very low temperature and can be easily hydrolyzed, after reaction with electrophiles, to give the corresponding carbonyl compounds. Other acyllithium equivalents, such as cyanohydrins, α-aminonitriles and α-lithiated five-membered aromatic heterocycles, will not be considered because they have been far less used in synthetic organic chemistry.

A. α-Substituted Alkenyllithiums

1. Enol ethers

These acyllithium equivalents **522**[8,749–751] are usually derived from vinyl ethers, the corresponding thioethers or enamine derivatives being much less used. They react mainly

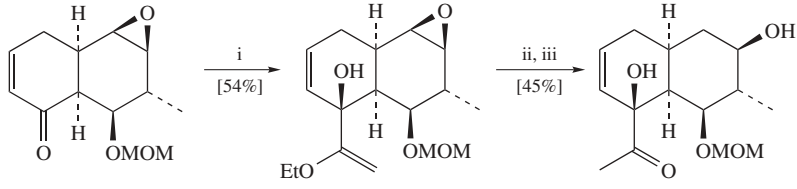
as nucleophilic sp^2-hybridized carbanions more than as electrophilic carbenoids. The cyclic oxygenated derivatives **523** have been less used as cyclic acyl anion equivalents than the acyclic compounds **522** (X = OR). They are prepared mainly by hydrogen–lithium and tin–lithium exchange at low temperature.



(522) **(523)** **(524)** **(525)**

The simplest α-lithiated acyclic vinyl ethers are 1-methoxy **524** and 1-ethoxyvinyllithium **525** (MVL and EVL, respectively). The former intermediate **524** was prepared by deprotonation of an excess of methoxy vinyl ether with *t*-BuLi at −60 °C in THF, followed by slow warming to 0 °C[752]. Several drawbacks to this preparation of MVL are: (a) methyl vinyl ether (MVE) is a gas, (b) some dilithioacetylene is produced by elimination of methanol and (c) an excess of MVE is present in the reaction medium. An alternative to the mentioned procedure is the use of tetrakis(α-methoxyvinyl)tin and *n*-BuLi at 0 °C, but this tin reagent has to be prepared from MVE and *t*-BuLi[753,754]. The first deprotonation of liquid ethoxy vinyl ether (EVE) was also performed with *t*-BuLi in pentane but in the presence of TMEDA[755]. The use of TMEDA can be avoided using the following reaction conditions: (a) *n*-BuLi at 0 °C[756], (b) an excess of *t*-BuLi[757] and (c) careful warming to −22 °C[758]. However, the resulting EVL solutions are contaminated with acetaldehyde enolate anion and ethylene coming from the deprotonation of THF. This problem can be overcome by using tetrahydropyran (THP) instead of THF and a slight excess of *t*-BuLi, followed by warming to −5 °C[759,760]. Another method uses *n*-BuLi/*t*-BuOK (the Lochmann–Schlosser base) and TMEDA in hexane or pentane at −20 °C, probably affording the potassium ethyl vinyl ether[761].

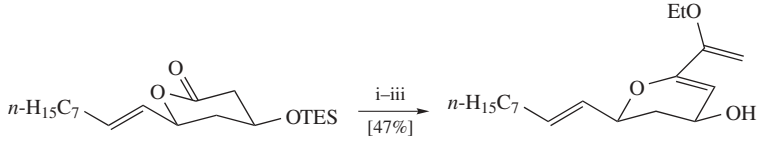
The alkylation of **524** and **525** has been carried out with primary iodides[752,762] and allyl bromides[752]. The reaction with epoxides requires the presence of $BF_3{\bullet}OEt_2$ as well as with oxetanes[763]. Reagents **524** and **525** react with aldehydes[752,755,764–766], ketones and enones[755,767–776] giving 1,2-addition products. In the case of highly enolizable enones, EVL has been treated with $CeCl_3$ to afford the corresponding 1,2-addition products[777]. Diastereoselective addition to chiral α-substituted aldehydes[778,779] and ketones[758,780–787] is illustrated in Scheme 140, which shows the diastereoselective addition of the intermediate **525** to the ketone **526** to give product **527**. After reduction and hydrolysis, it afforded the methyl ketone **528**, an intermediate in the synthesis of the 11-oxatricyclo[5.3.1.$0^{3,8}$] undec-5-ene unit of coloraducin (luminamicin)[787]. Diastereoselective addition of EVL (**525**) to (benzocyclobutenone)tricarbonylchromium(0) took place *anti* to the metal[788].



(526) **(527)** **(528)**

SCHEME 140. Reagents: (i) **525**, THF, −78 °C; (ii) $LiAlH_4$, Et_2O; (iii) HCl−H_2O

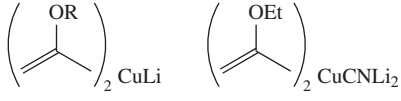
Acylation of MVL (**524**) or EVL (**525**) with lactones[774,789] or esters[752] afforded the corresponding mono or diaddition products, respectively. Scheme 141 shows the synthesis of compound **530**, an intermediate in the synthesis of the bicyclo[5.3.1]undecenone core of penostatin F starting from compound **529**[789]. Carboxylic acids and nitriles gave lower yields[752] than *N*,*N*-dimethyl carboxamides[759]. When Weinreb amides are used as electrophiles, $MgBr_2{\bullet}OEt_2$ has to be added to get good yields (61–73%) of 2-alkoxy enones[790].



(529) **(530)**

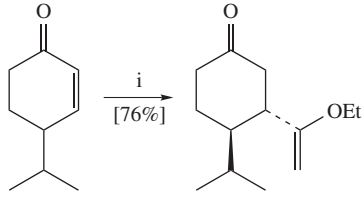
SCHEME 141. Reagents: (i) **525**, THF, −78 °C; (ii) $SOCl_2$, DMAP, CH_2Cl_2; (iii) TBAF, THF

Michael addition to α,β-unsaturated ketones can be performed with low-order cuprates **531** and **532** derived from intermediates **524** or **525**, respectively, and CuI or $CuI{\bullet}SMe_2$ (50–90%)[767,791–793]. In the case of hindered enones, a good 1,4-regioselectivity was achieved by addition of $BF_3{\bullet}OEt_2$ to the cuprate[794]. The high-order cuprate **533**, prepared by reaction of compound **525** with 2 equiv of $Me_2Cu(CN)Li_2$, also gives conjugate addition to 4-isopropylcyclohexenone **534** to give the *trans*-compound **535** (Scheme 142)[795]. On the other hand, 1,2-addition of compound **525** to enones also took place in the presence of $MgBr_2{\bullet}OEt_2$[796]. Conjugate addition of MVL (**524**) and EVL (**525**) has been observed with electrophilic alkenes such as acyl ylides[797], vinyl benzothiazoles[798], vinyl sulfones[799], *exo*-methylene cyclopentadienes[800,801], activated 2-vinylindoles[802] and η^6-arenechromiumtricarbonyl complexes[803].



(531) R = Me
(532) R = Et

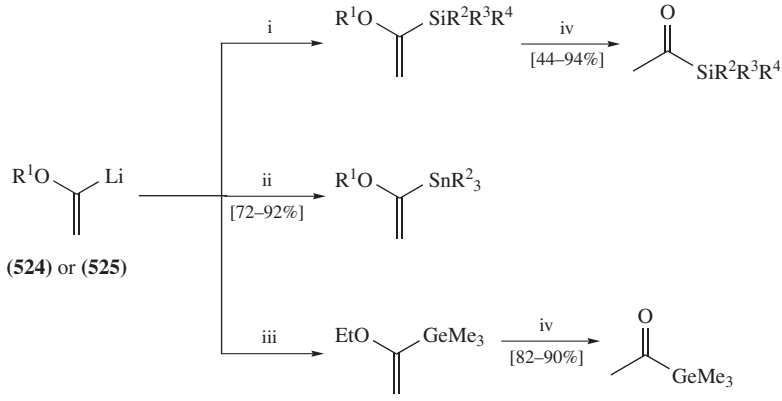
(533)



(534) **(535)**

SCHEME 142. Reagents: (i) **533**, THF, −78 °C

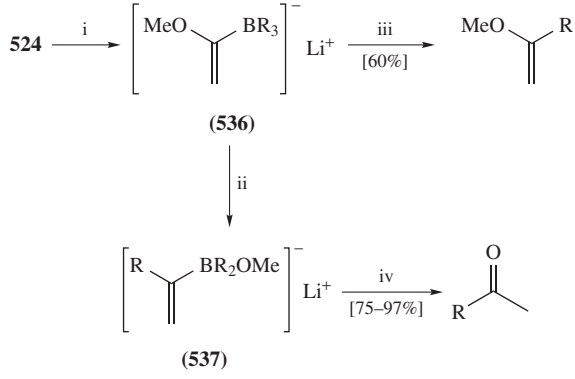
Acyl silanes[753,804–811] and germanes[812] can be prepared from MVL (**524**) or EVL (**525**) by reaction with silyl and germyl chlorides, respectively, followed by acid hydrolysis (Scheme 143). Vinyl stannanes are useful for the preparation of unsolvated MVL[753,754]



SCHEME 143. Reagents: (i) $ClSiR^2R^3R^4$; (ii) $ClSnR^2{}_3$; (iii) $ClGeMe_3$ (for $R^1 = Et$); (iv) HCl, H_2O

and for palladium-catalyzed reactions (Stille reaction) with acid chlorides[813], and aryl or vinyl halides and triflates[814–816]. Similar couplings can be carried out by transmetallation of EVL (**525**) with $ZnCl_2$ and aryl or vinyl halides (Negishi reaction)[817,818].

The reaction of MVL with trialkylboranes gave vinyl borate salts **536**, which suffer alkyl migration at room temperature to give salts **537**. These compounds can be transformed into vinyl ethers or methyl ketones by oxidation with hydrogen peroxide (Scheme 144)[819].

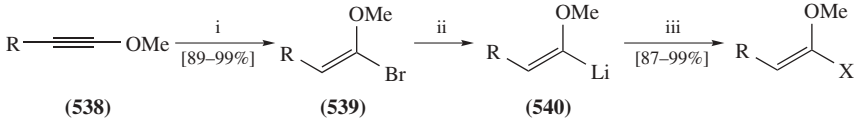


SCHEME 144. Reagents: (i) R_3B, −78 °C; (ii) rt; (iii) I_2; (iv) H_2O_2, NaOH

Subsequent hydrolysis of MVL (**524**) and EVL (**525**) adducts has been performed under a variety of mild acidic conditions such as dilute hydrochloric acid in methanol[752,767,790], THF[769,783,798,814], ethanol[803], ether[812], dioxane[780–782] or acetone[810,811,813], silver sulfate in aqueous sulfuric acid[755], 3 M perchloric acid in aqueous methanol[768], *p*-toluenesulfonic acid in aqueous acetone[801], methanol[796] or ethylene glycol[754], acetic acid in aqueous THF[762,785], trifluoroacetic acid[788], wet silica gel in benzene[791], 0.1 M oxalic acid in methanol[792] or $HgCl_2$–$CdCO_3$ in aqueous methanol–benzene[808] to provide methyl ketones. Other transformations of vinyl ethers are the reaction with NBS or NCS to produce α-halomethyl ketones[773,809] and the treatment with OsO_4 provided α-hydroxymethyl ketones[779–782,820]. Some applications of these reactions are key steps in the

synthesis of natural products such as the allopumiliotoxin A alkaloids 267A and 339B[783], three sesquiterpene lactones (thapsigargins)[779], terpenes silphinene[801] and α-cedrene[775,776] and everninomicin 13,384-1[792].

A new approach to β-alkyl substituted α-methoxy vinyllithiums **540** with *Z*-configuration involved the stereoselective metallation of α-bromo vinyl ethers **539**, prepared from acetylenes **538**, with *t*-BuLi at $-78\,^{\circ}C$ (Scheme 145)[821]. These anions react with different electrophiles to give the corresponding vinyl ethers in good yields. The β-isobutyl substituted derivative as cuprate has been added to an enone in the total synthesis of the anticancer natural product OSW-1[822].

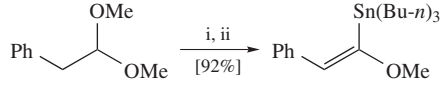


(538) **(539)** **(540)**

$$\begin{bmatrix} R = Me, Et, i\text{-}Bu, n\text{-}C_6H_{13}, CH_2{=}CHCH_2 \\ X = PhCHOH, BnOCO, Me_3Si, Me_3Sn \end{bmatrix}$$

SCHEME 145. Reagents: (i) Me_3SiBr, MeOH, CH_2Cl_2, $-40\,^{\circ}C$; (ii) *t*-BuLi, $-78\,^{\circ}C$; (iii) EX = PhCHO, $ClCO_2Bn$, Me_3SiCl, Me_3SnCl

In the case of a β-phenyl substituted α-methoxy vinyl anion, the acetal **541** has been treated with the Lochmann–Schlosser superbase to promote β-elimination followed by α-deprotonation. The corresponding anion has been trapped with tri-*n*-butylchlorostannane to give stereoselectively the stannane **542** (Scheme 146)[823].



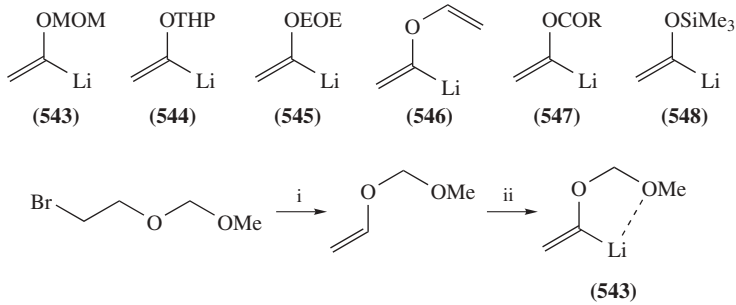
(541) **(542)**

SCHEME 146. Reagents: (i) *n*-BuLi, *t*-BuOK, THF, $-95\,^{\circ}C$; (ii) $n\text{-}Bu_3SnCl$

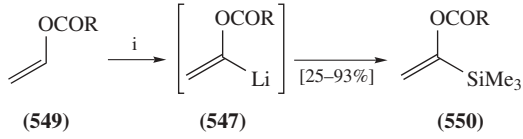
As potential alternatives to MVL (**524**) and EVL (**525**), other lithiated vinyl ethers such as lithiated methoxymethyl (**543**), tetrahydropyranyl (**544**) and ethoxyethyl (**545**) vinyl ethers and divinyl ether (**546**), acyl vinyl ethers (**547**) and silyl vinyl ether (**548**) have been described. The MOM and THP vinyl ethers are prepared by dehydrobromination of the corresponding 2-haloethyl ethers with *t*-BuOK or KOH[764,824–826]. These ethers undergo easy deprotonation, probably assisted by chelation of the oxygen atoms of the MOM and THP units, with *s*-BuLi[825,826] or *n*-BuLi[764] to provide anions **543** and **544** as shown in Scheme 147 for compound **543**. The resulting vinyllithiums **543** and **544** reacted with aldehydes[764,825,826] and ketones[827]. Ethoxyethyl vinyl ether and divinyl ether have also been prepared by dehydrobromination and dehydrochlorination with *t*-BuLi to afford anions **545**[824] and **546**[828], respectively.

Vinyl esters (**549**) have been deprotonated with LDA at $-78\,^{\circ}C$ and trapped with chlorotrimethylsilane or chlorotriethylsilane to give silylated enol esters **550** (Scheme 148)[829].

(Trimethylsilyloxy)vinyllithium **548** has been prepared by tin–lithium exchange from the vinylstannane **552**, which is generated from acetyltri-*n*-butyltin **551** (Scheme 149)[830]. This vinyllithium suffers a reverse Brook rearrangement to generate the alkoxide **553** used for the synthesis of acylsilanes[831].

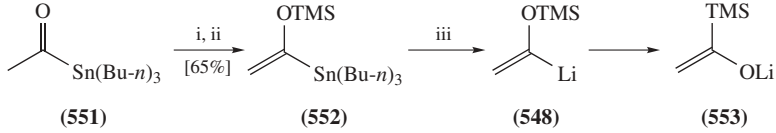


SCHEME 147. Reagents: (i) KOH, tris[2-(2-methoxyethoxy)ethyl]amine; (ii) *n*-BuLi or *s*-BuLi, −78 °C

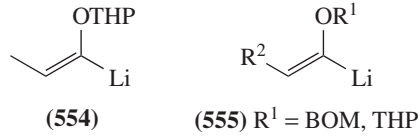


[R = *t*-Bu, $Me(CH_2)_3CHMe$, n-C_9H_{19}, Ph]

SCHEME 148. Reagents: (i) LDA, Me_3SiCl, −70 °C to rt



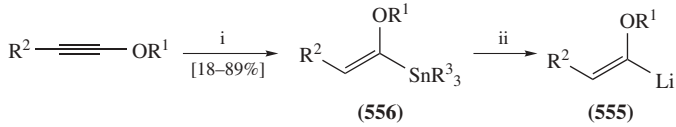
SCHEME 149. Reagents: (i) LDA, THF, −78 to 0 °C; (ii) Me_3SiCl, −78 °C to rt; (iii) *n*-BuLi



A β-substituted enol ether bearing a typical protecting group, such as tetrahydropyranyl in compound **554**, has been prepared by deprotonation with *s*-BuLi and trapped with MeI in 83% yield[832].

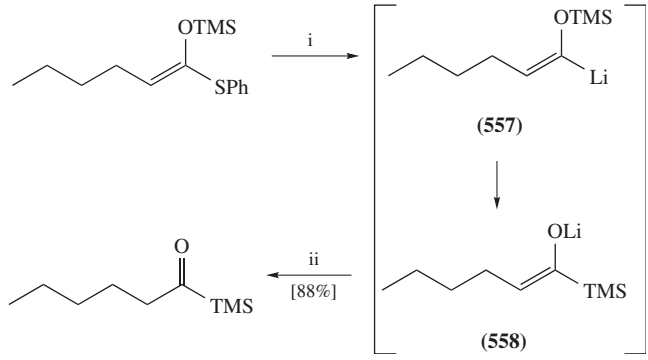
A general method for the synthesis of intermediates of type **555** has been described by Kocienski using stannylated precursors. Starting vinylstannanes **556** were prepared by palladium(0)-catalyzed hydrostannylation of 1-alkoxyalk-1-ynes. The transmetallation with *n*-BuLi provided the corresponding vinyllithiums **555** (Scheme 150)[833].

β-Substituted α-lithiated silyl enol ether **557** has been prepared by reductive lithiation of vinyl tellurides[834] and sulfides[835,836] with lithium 1-(dimethylamino)naphthalenide (LDMAN). This intermediate **557** gave, after inverse Brook rearrangement, the enolate **558** and after hydrolysis the corresponding acylsilane (Scheme 151).



[R^1 = Bn, THP; R^2 = *n*-Bu, *s*-Bu, *t*-Bu]

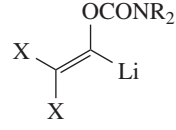
SCHEME 150. Reagents: (i) $R^3{}_3SnH$, $Pd(PPh_3)_4$, rt, 30 min; (ii) *n*-BuLi, THF, −78 °C



SCHEME 151. Reagents: (i) LDMAN, THF, −78 °C, 45 min; (ii) H_2O

2. Enol carbamates

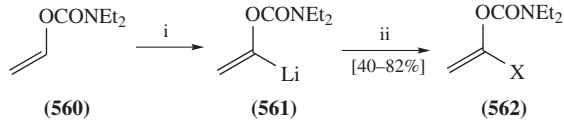
Lithiated enol carbamates **559** have been reported as complementary acyl anion equivalents of MVL (**524**) and EVL (**525**). Non-fluorinated enol carbamates have been prepared by *O*-carbamoylation of acetaldehyde lithium enolate (80–87% yield) or by quantitative addition of trimethylsilylamides to vinyl chloroformate[837].



(559) X = H, F, R

Lithiation of compound **560** with *s*-BuLi-TMEDA in THF at −78 °C following an inverse addition protocol provided the anion **561**. It reacts with primary alkyl iodides and triflates, silyl chlorides, diphenyl disulfide, epoxides, aldehydes, ketones, imines, acyl chlorides, isocyanates and sulfonyl fluorides to yield the expected compounds **562** (Scheme 152). The transmetallation of compound **561** with $ZnBr_2$ allowed the palladium-catalyzed cross-coupling reaction with aryl and vinyl bromides[837]. When the reaction was quenched with 1,2-dibromotetrafluoroethane, the corresponding bromide **562** (X = Br) is obtained[838].

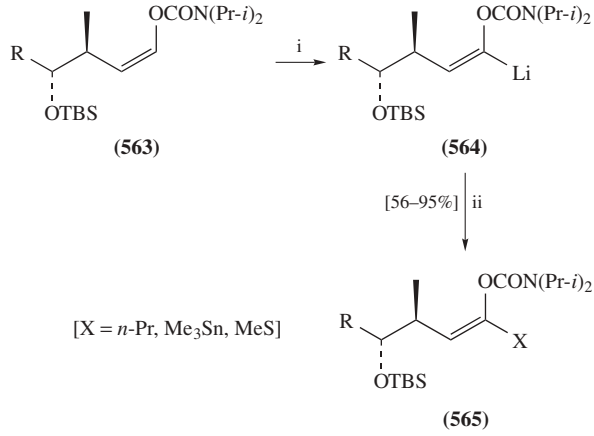
The substituted *N*,*N*-diisopropyl enol carbamates **563** were prepared by reaction of metallated allylic carbamates with aldehydes[839–843]. The stereoselective deprotonation of compound **563** can be performed with *t*-BuLi[841] or *n*-BuLi-TMEDA[839] in THF at −70 to −85 °C to give the lithio derivatives **564** (Scheme 153). These intermediates reacted with



(560) **(561)** **(562)**

[X = R, Me_3SiCH_2, R_3Si, PhS, $R^1R^2C(OH)CHR^3$, RCHOH, R^1R^2COH, PhCH(NHPh), PhCO, *t*-BuNHCO, *p*-$TolSO_2$, Br]

SCHEME 152. Reagents: (i) *s*-BuLi, TMEDA, THF, −78 °C; (ii) EX = RI, Me_3SiCH_2Tf, R_3SiCl, Ph_2S_2, epoxides (BF_3•OEt_2), RCHO, R^1R^2CO, PhCH=NPh, PhCOCl, *t*-BuNCO, *p*-$TolSO_2F$, CF_2BrCF_2Br

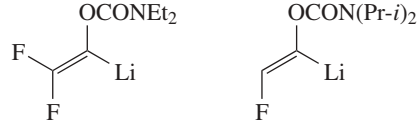


(563) **(564)** **(565)**

SCHEME 153. Reagents: (i) *n*-BuLi, TMEDA, THF, −78 °C; (ii) EX = *n*-PrI, Me_3SnCl, Me_2S_2

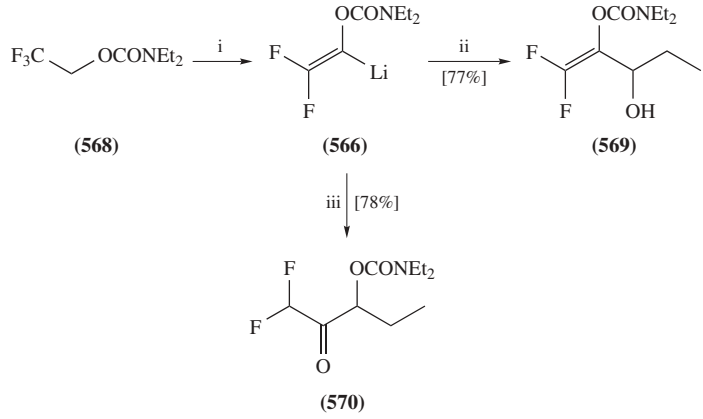
alkyl iodides, Me_3SnCl and dimethyl disulfide with retention of the configuration of the double bond to provide compounds **565**[839, 841]. However, hydrolysis of these compounds has not been performed yet.

Lithiated di- and monofluorinated enol carbamates **566**[844–847] and **567**[848] are fluorine-containing acyl anion equivalents, which allow the synthesis of α-fluorinated ketones.



(566) **(567)**

The difluorovinyllithium **566** was initially prepared by in situ dehydrofluorination–deprotonation of the *N*,*N*-diethyl carbamate derivative **568** with two equiv of LiTMP[845] or LDA[844, 845] (Scheme 154). This intermediate **566** showed lower reactivity than the corresponding defluorinated system **561**. Moderate to good yields were obtained with silicon, selenium and tin halides (38–80%)[844, 845, 847] and alkyl triflates (71–91%)[845], moderate reactivity being showed toward carbon dioxide and carbonyl compounds[844, 845, 847]. The reaction of intermediate **566** with aldehydes gave compound

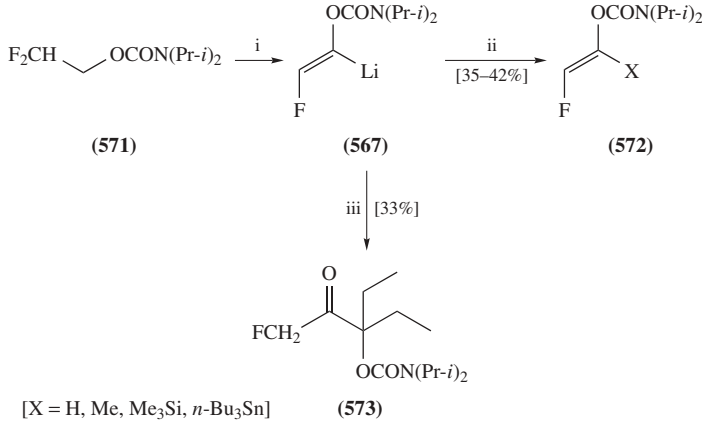


(568) **(566)** **(569)** **(570)**

SCHEME 154. Reagents: (i) LDA, THF, −78 °C, 1 h; (ii) EtCHO, 10 s; (iii) EtCHO, 2 h

569 after a very short reaction time (10 seconds), whereas after 2 hours compound **570** was isolated, resulting respectively from a direct trapping or a carbamoyl migration process[844].

Similarly, the *N*,*N*-diisopropyl carbamate **571** derived from difluoroethanol provided, after reaction with *t*-BuLi-TMEDA at −70 °C, the monofluorovinyllithium **567**[848] (Scheme 155). This reagent reacts with moderate reactivity with different electrophiles to afford compounds **572** giving, in the case of pentan-3-one, the corresponding compound **573**.



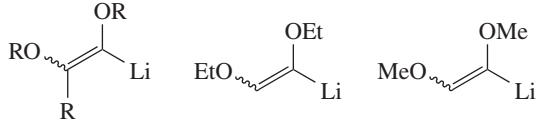
(571) **(567)** **(572)**

[X = H, Me, Me_3Si, *n*-Bu_3Sn] **(573)**

SCHEME 155. Reagents: (i) *t*-BuLi-TMEDA, THF, −78 °C; (ii) EX = NH_4Cl, MeI, Me_3SiCl, *n*-Bu_3SnCl; (iii) Et_2CO

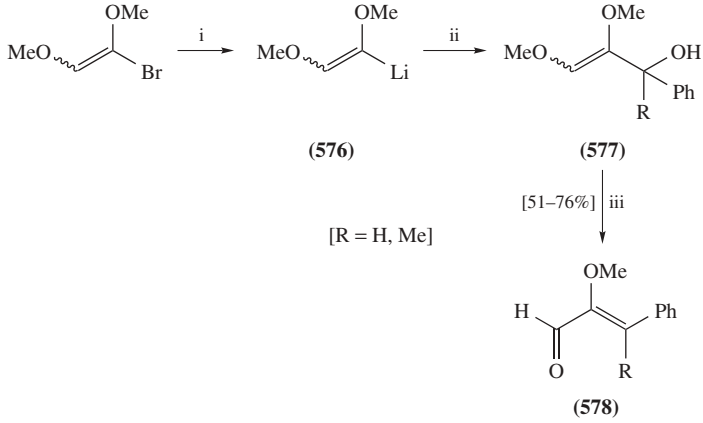
3. Other acyclic enol ethers

1,2-Dialkyloxyvinyllithiums **574** are another type of acyllithium equivalent which bear an alkoxy group at the β-position. They were initially prepared by bromine–lithium exchange from 1-bromo-1,2-diethoxyethene with *n*-BuLi in ether at −35 °C[849] and from 1-bromo-1,2-dimethoxyethene and *n*-BuLi in ether at −78 °C[850] to provide intermediates **575** and **576**, respectively as mixtures of *Z*/*E*-isomers.



(574) **(575)** **(576)**

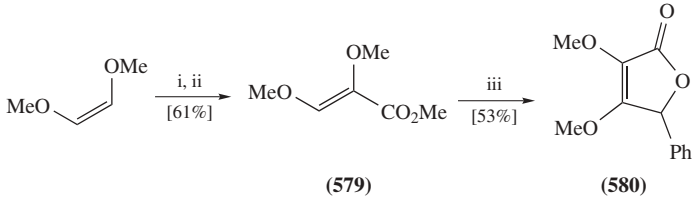
The reactivity of the organolithium compound **576** has been assayed with aldehydes and ketones to yield allylic alcohols **577** which, after hydrolysis, provide stereoselectively α-methoxy-α,β-unsaturated aldehydes **578**[850,851] (Scheme 156). The reaction of the anion **576** with trialkyl boranes generated borates, which have been used as intermediates in organic synthesis[852–855]. On the other hand, the reaction of the same intermediate with $M(CO)_6$ (M = Cr, W) gave the corresponding (*Z*)-1,2-dimethoxyvinylcarbene complexes[856].



(576) **(577)** **(578)**

SCHEME 156. Reagents: (i) *n*-BuLi, Et_2O, −78 °C; (ii) EX = PhCHO, PhCOMe; (iii) 6 M HCl, THE

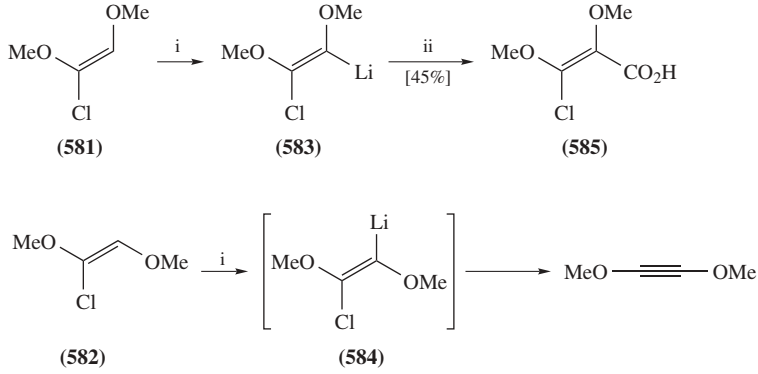
Starting from (*Z*)-1,2-dimethoxyethene, the *Z*-isomer of 1,2-dimethoxyvinyl anion was prepared by deprotonation with the Lochmann–Schlosser base at −78 °C, being trapped with methyl chloroformate to provide the acrylate **579**[857] (Scheme 157). This compound was further lithiated at the β-position to give a β-acyl vinyllithium[858] which, after reaction with benzaldehyde, was transformed into the α,β-butenolide **580**.



(579) **(580)**

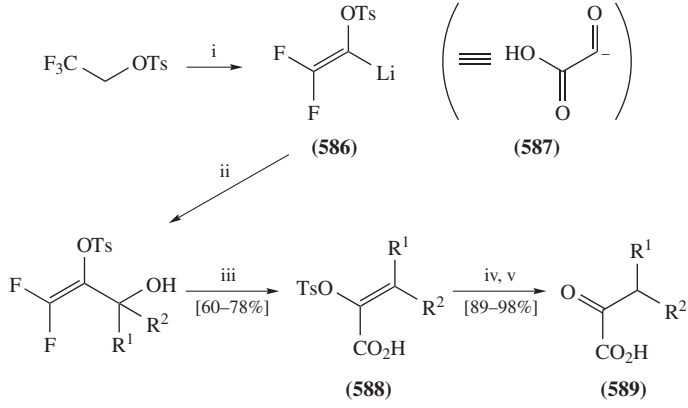
SCHEME 157. Reagents: (i) *n*-BuLi-*t*-BuOK, THF, −78 °C; (ii) $ClCO_2Me$; (iii) LDA, PhCHO, −90 °C

The lithiation of (*E*)- and (*Z*)-1,2-dimethoxy-1-chloroethene **581** and **582** with *s*-BuLi or *n*-BuLi at −100 °C gave anions **583** and **584**, respectively. However, only the (*E*)-isomer **583** could be trapped with carbon dioxide to give 2,3-dimethoxy-3-chloroacrylic acid (**585**)[859] (Scheme 158). In the case of compound **584**, the *anti* β-elimination occurred more easily than the *syn* one in intermediate **583** to give dimethoxyacetylene, which was hydrolyzed to give methyl methoxyacetate.



SCHEME 158. Reagents: (i) *n*-BuLi, THF, −100 °C; (ii) CO_2

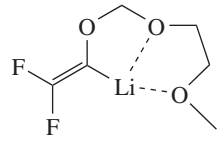
2,2-Difluoro-1-(tosyloxy)vinyllithium **586** has been employed as an acyl anion equivalent of the type **587**. This anion was prepared by treatment of 2,2,2-trifluoroethyl tosylate with two equiv of LDA at −78 °C[860] (Scheme 159). The reaction of intermediate **586** with carbonyl compounds, followed by acid hydrolysis, gave compounds **588** which, after basic treatment with sodium hydroxide, afforded α-keto acids **589**. The reaction of the intermediate **586** with boranes provided the corresponding borates, which have been used in the synthesis of fluorinated molecules[861].



SCHEME 159. Reagents: (i) LDA (2 equiv), THF, −78 °C; (ii) R^1R^2CO; (iii) 95% H_2SO_4; (iv) 10% aq NaOH; (v) HCl

Similarly, the difluorinated methoxyethoxymethyl derivative **590** has been prepared by treatment of MEM-protected trifluoroethanol with 2 equiv of LDA in THF at

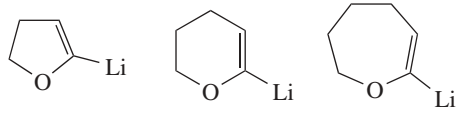
$-78\,^{\circ}C$[862–864]. This vinyllithium reagent reacted with different electrophiles in good yields except for alkylating reagents (44–94%). However, this reagent has not been used as acyl anion equivalent.



(590)

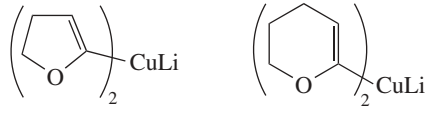
4. Cyclic vinyl ethers

α-Lithiodihydrofuran **591** and α-lithiodihydropyran **592** represent the simplest intermediates of this family of α-lithiated cycloalkenyl ethers acting as cyclic acyl anion equivalents. Other substituted analogues have been developed for specific syntheses of natural products mainly with spiroacetal units. There are several lithiation procedures for the preparation of these reagents: (a) deprotonation of dihydrofuran (DHF) and dihydropyran (DHP) with *t*-BuLi in pentane and a small amount of THF (2 equiv) at -10 to $0\,^{\circ}C$[865, 866] and (b) deprotonation of DHF and DHP with *n*-BuLi and a catalytic amount of TMEDA in hexane or pentane at $0\,^{\circ}C$ to room temperature[757, 867]. The resulting organolithiums **591** and **592** precipitated and can be isolated as the corresponding solids. Alternatively, compound **592** can be prepared by reaction of the corresponding α-stannyl derivative with *n*-BuLi in THF[868, 869]. The α-lithiated 2,3,4,5-tetrahydrooxepin **593** has been prepared by deprotonation of the corresponding heterocycle with *n*-BuLi in THF–benzene at room temperature for 3 days[870].



(591) **(592)** **(593)**

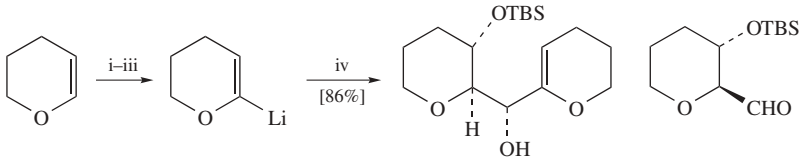
The alkylation of compounds **591** and **592** can be performed with primary alkyl bromides and iodides[824, 865, 866, 871–887]. This procedure, followed by different transformations of the alkylated products, has been applied extensively in organic synthesis. However, the alkylation with epoxides gave very poor yields with intermediates **591** and **592**, so they have to be transmetallated to low-order cuprates **594**[888] and **595**[889] in order to undergo reaction with these electrophiles in THF at 0 to $20\,^{\circ}C$.



(594) **(595)**

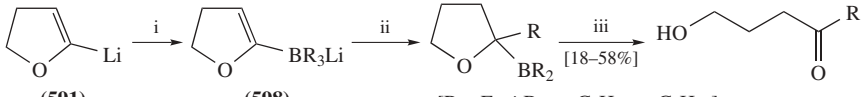
The reaction of organolithiums **591** and **592** with aldehydes and ketones took place at low temperatures (-78 to $0\,^{\circ}C$) to generate the corresponding alcohols (50–100% yield)[824, 865, 872, 873, 890–893]. Diastereoselective addition took place with chiral aldehydes,

so compound **592** reacted with the aldehyde **596** to give the product **597** as a 8:1 mixture of diastereomers[869, 894] (Scheme 160), as well as with chiral bicyclic ketones (norcamphor and fenchone)[895, 896]. The addition of cerium(III) chloride improved the diastereoselectivity and avoided enolization problems[896–898]. On the other hand, the use of THF–TMEDA as solvents increased the reactivity with hindered ketones[899]. In the case of α,β-unsaturated ketones[824, 865, 890, 892] and quinones[900], 1,2-addition reaction took place with organolithiums **591** and **592**. However, with a mixed cuprate derived from the lithium intermediate **592** and a copper acetylide, conjugate addition occurred with cyclohexenone affording the corresponding 1,4-addition product in 91% yield[865]. Conjugate addition has also been performed with the organolithium **592** and α,β-unsaturated sulfones[799].



SCHEME 160. Reagents: (i) *t*-BuLi, −78 °C; (ii) *n*-Bu_3SnCl; (iii) *n*-BuLi, −78 °C; (iv) **596**

The reaction of lithiated DHF and DHP with acylating agents, such as carbon dioxide, acyl chlorides or anhydrides, gave dialkylated alcohols (41–67% yields)[824, 890]. γ-Lactones reacted with the organolithium **592** to produce γ-hydroxy ketones[901]. *N*,*N*-Dialkylcarboxamides can be used as acylating reagents when THP is used as solvent instead of THF–pentane[759]. Imine adducts were obtained in moderate yields by using nitriles as electrophiles and hexane as solvent[802]. Heteroelectrophiles, such as silyl chlorides[873, 902–905], germanyl chlorides[904], stannyl chlorides[869, 873, 906] and disulfides[761, 824], generated the corresponding substituted derivatives. The reaction with trialkylboranes in THF at −78 °C provided stable lithium α-alkoxyvinylborates **598** which, by protonolysis and oxidative treatment, gave γ-hydroxy ketones[840] (Scheme 161).

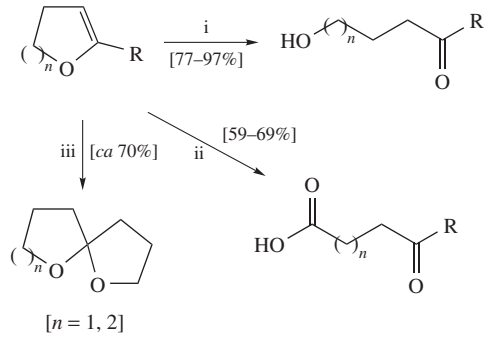


SCHEME 161. Reagents: (i) BR_3; (ii) AcOH or H_2O; (iii) H_2O_2, NaOH

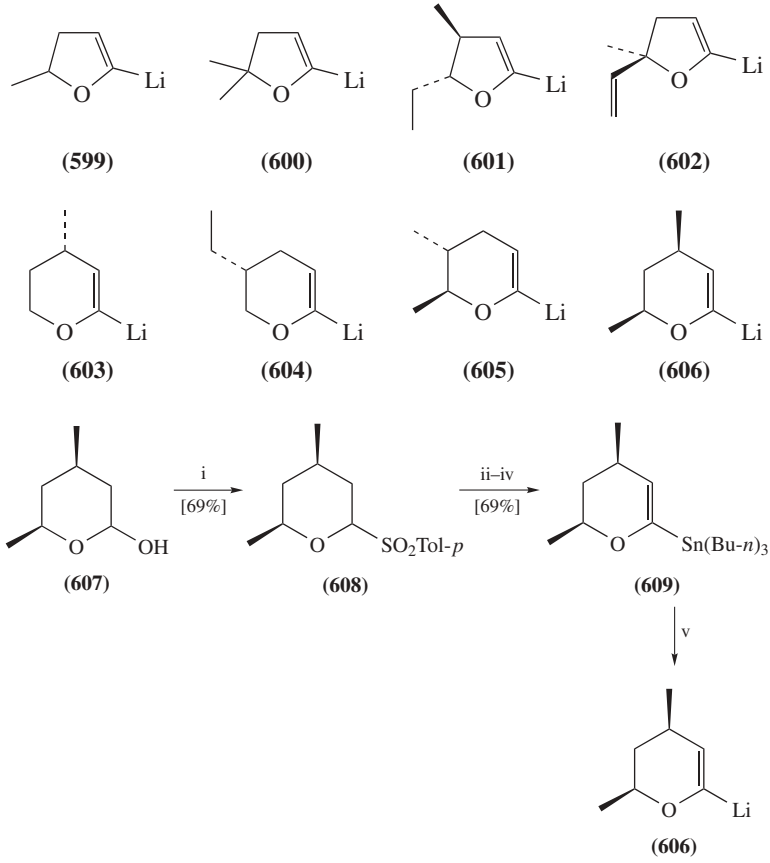
Hydrolysis of alkylated products and carbonyl compound adducts derived from α-lithiated DHF and DHP with 2 M HCl in THF at room temperature gave γ- and δ-hydroxy ketones, respectively[824, 865] (Scheme 162). Jones oxidation generated keto acids[866, 887] and when the R substituent bears an hydroxy group, cyclization occurred in the presence of pyridinium tosylate (PPTS) in CH_2Cl_2 or HCl in ether to provide spiroketals[875, 883, 894, 901].

Alkyl substituted α-lithiodihydrofurans **599–602** and α-lithiodihydropyrans **603–606** have been used for natural product synthesis. They are prepared by deprotonation of the corresponding DHF or DHP derivatives with *t*-BuLi in THF at −78 to 0 °C. Lithiated DHP **606** has been prepared by tin–lithium transmetallation starting from the hemiacetal **607**, by successive transformation into the sulfone **608**[907] and the stannane **609**[908] (Scheme 163).

The α-lithiated cyclic vinyl ethers **599** and **603** have been allowed to react with alkyl iodides[881, 886] and compounds **599, 600**[909, 910] and **606**[910] with carbonyl compounds.



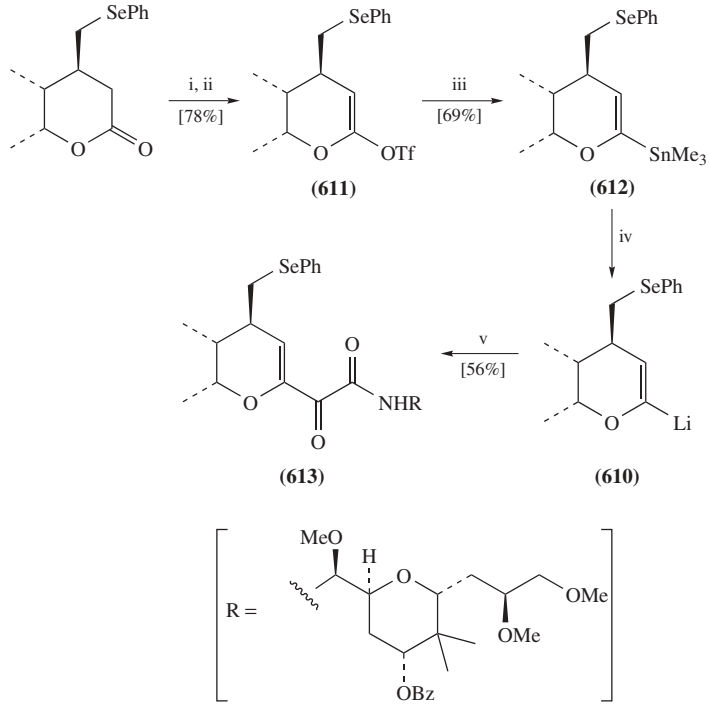
SCHEME 162. Reagents: (i) 2 M HCl, aq THF, rt; (ii) H_2CrO_4, 0 °C to rt; (iii) PPTS, CH_2Cl_2



SCHEME 163. Reagents: (i) *p*-TolSO_2H, $CaCl_2$; (ii) *n*-BuLi; (iii) *n*-Bu_3SnCl; (iv) DIPEA, $CHCl_3$, heat; (v) *n*-BuLi, THF, −78 °C

Cuprates derived from compound **604** and CuI[911,912] or from copper acetylide and compound **605**[913,914] underwent alkylation with epoxides.

The tin–lithium transmetallation of a α-(trimethylstannyl)dihydropyran has been used for the preparation of the α-lithiated DHP **610**, since the direct α-deprotonation of the corresponding selenium-containing dihydropyranyl system did not occur due to the preferential selenium–lithium exchange with *t*-BuLi. A selenium-containing lactone was transformed into the enol triflates **611** which, after palladium-catalyzed stannylation, generated the vinyl stannane **612**. Treatment of compound **612** with *n*-BuLi at −78 °C gave the vinyllithium **610** which, by reaction with a methyl oxamate, gave the keto amides **613**[915,916], a precursor of the insect toxin pederin (Scheme 164). This strategy cannot be used with dihydrofurans because the preparation of the corresponding triflate intermediates failed.

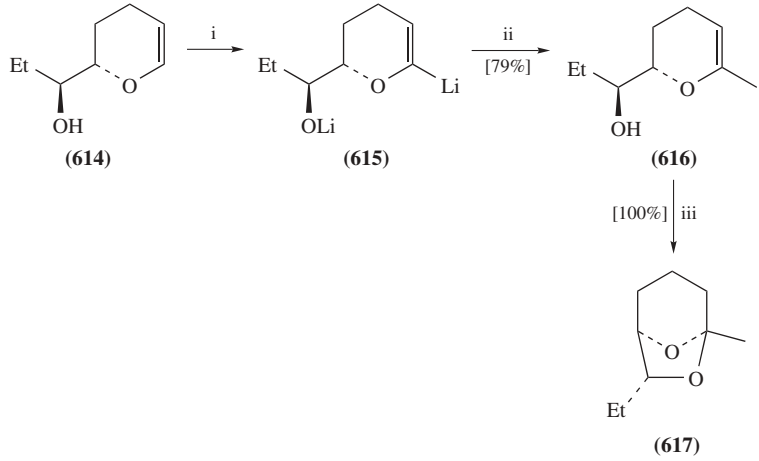


SCHEME 164. Reagents: (i) LiHMDS, −78 °C; (ii) $PhNTf_2$, −78 °C to rt; (iii) Me_6Sn_2, $Pd(PPh_3)_4$, LiCl, THF, reflux; (iv) *n*-BuLi, THF, −78 °C, 15 min; (v) $MeO_2CCONHR$, TMEDA, THF, −78 °C, 30 min

α-Lithiated DHFs have been used in the synthesis of natural products, so significant examples are: compound **599** for recifeiolide[885] and theaspirane[910], **600** for 20-hydroxyecdysone[909], **601** for rosaramycin[917], **602** for dactyloxene B/C[918,919] and grindelic acid[920,921]. THP derivatives include compound **603**, a precursor of premonensin B[881], **604** for talaromycin B[911,912], **605** for milbemycin β_3[913,914], **606** for jaspamide[843] and **610** for (+)-pederin[915,916].

For the synthesis of *exo*-brevicomin **617**, the acrolein dimer was transformed mainly into the *threo*-DHP **614** by addition of ethylmagnesium bromide and chromatographic

separation. The double deprotonation of compound **614** with *n*-BuLi-TMEDA gave the dianion **615**, which was methylated to give compound **616** and finally treated under acidic conditions to afford *exo*-brevicomin **617**[922,923] (Scheme 165). A similar strategy has been used for the synthesis of the sex pheromone of the Douglas–Fir Tussock moth[924].



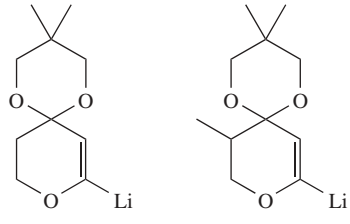
SCHEME 165. Reagents: (i) *n*-BuLi, TMEDA, hexane, 0 °C to rt; (ii) MeI, 0 °C to rt; (iii) TsOH

α-Lithiated dihydropyran ketals **618**[895,925,926] and **619**[926–928] can be considered not only acyl anions but also β-acyl vinyl anions[858] equivalents. They have been prepared by α-deprotonation of the corresponding DHP with *t*-BuLi in THF at −78 to 0 °C. The addition of these intermediates to aldehydes took place in good yields in the presence of HMPA[925–928]. This methodology has been applied to the total synthesis of phyllanthoside[925–927] and breynolide[928]. In the case of the intermediate **618**, its reaction with the ketone **620** in the presence of cerium(III) chloride gave a 4.6:1 mixture of the corresponding diastereomeric adducts (Scheme 166).

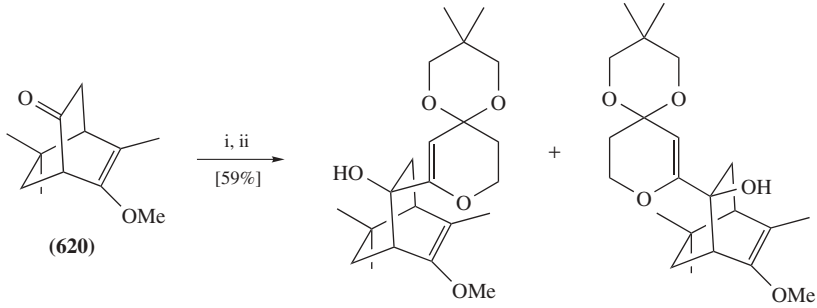
Several α-lithiated glycals and other α-lithiated DHFs and DHPs bearing oxygenated groups have been used widely in organic synthesis. 1-Alkoxy DHF anions **621** and **622** were prepared by deprotonation with an excess of *t*-BuLi and THF (3 equiv) in pentane[824,865]. In the case of compounds **623** and **624**, the same deprotonation conditions mentioned above were used[929]. Lithiated 1-methoxy substituted DHPs **625** and **626** were prepared in the same way as the corresponding DHF anions **621** and **622**[824,865]. When poor results were obtained using these metallation conditions (for oxygenated DHF and DHP derivatives), use of the Lochmann–Schlosser base (*n*-BuLi/*t*-BuOK) improved the yields. In general, these substrates are less acidic and deprotonation of the protecting groups, such as benzyl and TBS, competes with the α-lithiation. Better protecting groups are trityl[929], MOM[930,931] and TIPS or TBDPS[916,932–935].

Several α-lithiated glycols **627–633** have been prepared by deprotonation with an excess of *t*-BuLi and used in the synthesis of spiro bis-*C*,*C*-glycosides using cyclobutanone and cyclopentanone as electrophiles[935].

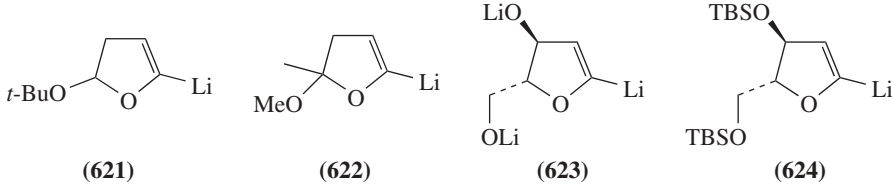
An alternative strategy for the generation of vinyllithiums derived from glucals and related TBS-protected DHPs involves the deprotonation with the Lochmann–Schlosser base followed by trapping the anion with *n*-Bu_3SnCl. Desilylation–deprotection with benzyl bromide and tin–lithium transmetallation gave the corresponding α-lithiated glucals[936]. The intermediate **636** has been prepared from compound **634** through the stannane **635**



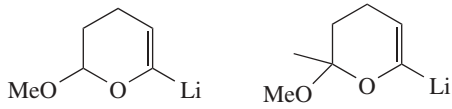
(618) **(619)**



SCHEME 166. Reagents: (i) **618**, $CeCl_3$, THF, DME, −78 °C to rt; (ii) NH_4Cl



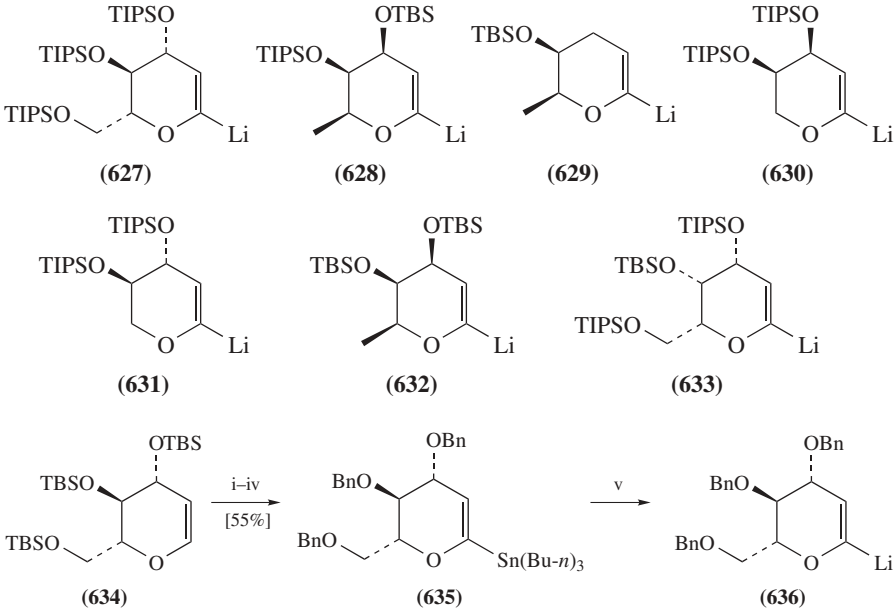
(621) **(622)** **(623)** **(624)**



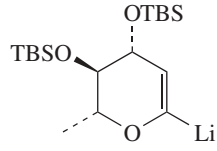
(625) **(626)**

(Scheme 167), following this Hanessian methodology, and allowed to react with a variety of electrophiles such as methyl iodide, TMSCl and carbonyl compounds to afford the corresponding adducts in good overall yields[936–939]. These transformations have been used for the synthesis of the polyether antibiotic (−)-calcimycin[930,931].

An example prepared by tin–lithium transmetallation is compound **637**, which reacts with enolizable ketones, after transmetallation with cerium(III) chloride[895]. This intermediate was transformed into the corresponding vinylzinc reagent and, after palladium(0)-catalyzed cross-coupling reactions with aryl iodides, was used in the synthesis of the antitumor antibiotic rineomycinone B^2 methyl ester[940,941]. The vinyllithium **627** has also been transformed into the corresponding vinyl iodide by stannylation followed by reaction with iodine. The arylation has been performed in this case by a palladium(0)-catalyzed



SCHEME 167. Reagents: (i) *n*-BuLi/*t*-BuOK, THF, −78 °C; (ii) *n*-Bu_3SnCl; (iii) TBAF, THF, rt; (iv) KH, BnBr; (v) *n*-BuLi, −78 °C

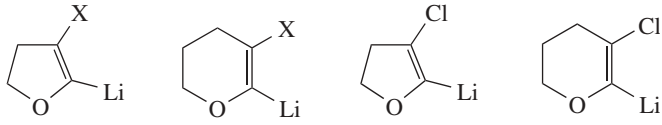


(637)

coupling protocol with arylzinc, arylboronic acids and arylstannanes to generate the corresponding C1-aryl glycals[933,942].

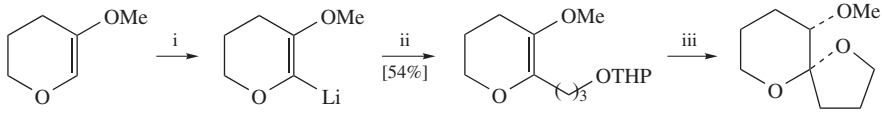
β-Heterosubstituted (X = Cl, OR, SO_2R) α-lithiated DHF and DHP derivatives of the type **638** and **639** were obtained by an easy deprotonation of the corresponding DHF and DHP precursors. The β-chloro derivatives **640**[943,944] and **641**[871,890] were prepared by deprotonation of 4-chloro-2,3-dihydrofuran and 5-chloro-3,4-dihydro-2*H*-pyran with *n*-BuLi in THF at −78 °C and at room temperature, respectively. Starting from 2-alkoxy-3-chlorotetrahydrofurans, compound **640** can be prepared by reaction with an excess of phenyllithium in ether at room temperature[945]. These β-chloro vinyllithiums reacted with alkyl iodides and carbonyl compounds in good yields (65–85%). The corresponding β-chlorovinyl metal carbene complexes have been prepared by reaction of compounds **640** and **641** with $Cr(CO)_6$ and used in benzoannulation reactions with alkynes[946].

For the synthesis of the α-lithiated 5-methoxy-3,4-dihydro-2*H*-pyran **642**, the deprotonation must be carried out with *n*-BuLi or *t*-BuLi at 0 to 50 °C in ether, DME or hexane[947,948]. For the preparation of hemiacetals[947,948] or spiroacetals[948], bifunctional electrophiles were used. Scheme 168 illustrates the preparation of the spiroacetal **644** from the alkylated product **643**[948].



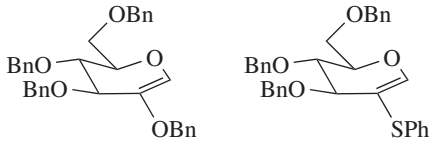
(638) **(639)** **(640)** **(641)**

[X = Cl, OR, SO_2R]



(642) **(643)** **(644)**

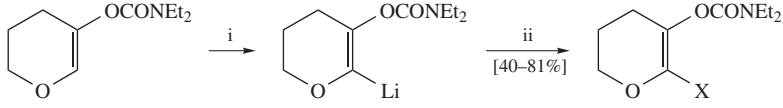
SCHEME 168. Reagents: (i) *n*-BuLi, THF, 0 to 50 °C; (ii) $I(CH_2)_3OTHP$; (iii) HCl, H_2O, THF



(645) **(646)**

β-Substituted glucals **645** and **646**, bearing a benzyloxy and a phenylsulfanyl group, have been deprotonated with the Lochmann–Schlosser base and LDA or *t*-BuLi, respectively. After reacting with electrophiles, these intermediates provide functionalized *C*-glucopyranosides[949].

The carbamate substituted DHP derivative **647** has been deprotonated with *t*-BuLi in THF at −78 °C to give the vinyllithium **648**[950] (Scheme 169). This reagent has been functionalized with a variety of electrophiles in good yields. The iodinated derivative **649** (X = I) underwent Suzuki–Miyaura couplings with arylboronic acids to afford the corresponding α-arylated DHPs.

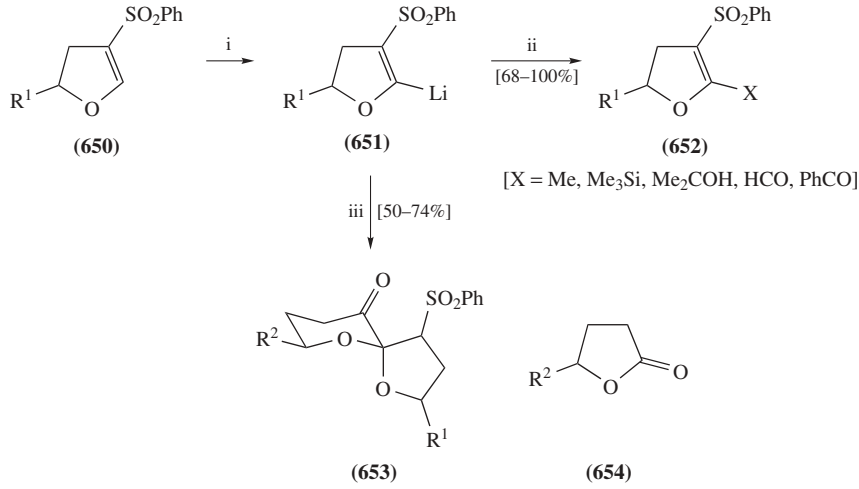


(647) **(648)** **(649)**

[X = ArCHOH, HCO, EtOCO, Me_2NCO, Me_3Si, PhS, PhSe, I]

SCHEME 169. Reagents: (i) *t*-BuLi, THF, −78 °C, 4 h; (ii) EX = ArCHO, DMF, $ClCO_2Et$, $ClCONMe_2$, Me_3SiCl, Ph_2S_2, Ph_2Se_2, I_2

Compounds **650**, DHFs substituted by a phenylsulfonyl group at the β-position, have been lithiated with *n*-BuLi in THF at −78 °C to provide intermediates **651**. They were allowed to react with different electrophiles in good yields leading to compounds **652**, and with γ-lactones **654** they gave dioxaspiro[4,5]decanes **653** as a mixture of diastereomers[951,952] (Scheme 170).



SCHEME 170. Reagents: (i) *n*-BuLi, THF, −78 °C; (ii) EX = MeI, Me_3SiCl, Me_2CO, HCO_2Et, $PhCO_2Me$, −78 °C; (iii) **654**

5. 1,4-Dioxene

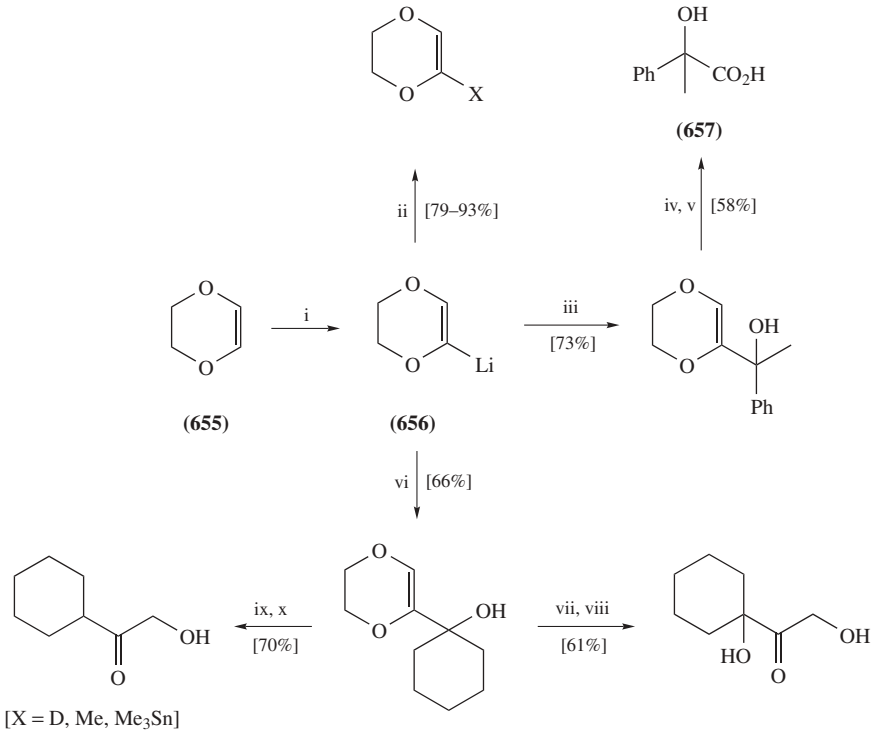
2-Lithio-5,6-dihydro-1,4-dioxene (**656**) was obtained by deprotonation of 1,4-dioxene (**655**) with *n*-BuLi at 0 °C[953] or *t*-BuLi at −30 to −20 °C[954] to give a white solid stable at room temperature for one day. Alternatively, *t*-BuLi at 0 °C in either dioxane–pentane (1:5)[953] or THF[955,956] can also be used. The intermediate **656** has been used as a α-hydroxymethyl acyl anion and as hydroxycarbonyl anion, undergoing alkylation, stannylation, aldol reactions and other transformations[953,957–963] (Scheme 171). In the case of acetophenone, (±)-atrolactic acid **657** was obtained after oxidation with PCC (to give an ester) and final hydrolysis. In addition to α-hydroxy acids (39–61%)[962], α,α′-dihydroxyketones (45–90%)[958,959] can be obtained by oxidation with MCPBA followed by reduction with $NaBH_4$, as well as α-hydroxymethyl ketones (40–85%)[954,958] by acidic hydrolysis and reduction with $LiAlH_4$. Aldol products have also been used for the synthesis of spirocyclopropane derivatives[964], substituted furans[965] and oxabicyclo[4.2.1]nonene systems[966].

Lithiated dioxene **656** reacted with $Mo(CO)_6$ and $Cr(CO)_6$ to form the corresponding carbenes, which reacted with acetylenes[955] and enynes[956], giving rise to aromatic compounds. For the ring opening of epoxides, the intermediate **656** has to be transformed into the corresponding low-order cuprate (either with CuI or $CuBr{\bullet}SMe_2$) and $BF_3{\bullet}OEt_2$ has to be added, as well as into a high-order cuprate with $CuCN{\bullet}LiCl$[967]. These cuprates react with enones, providing the corresponding 1,4-addition adducts (63–94%)[967,968].

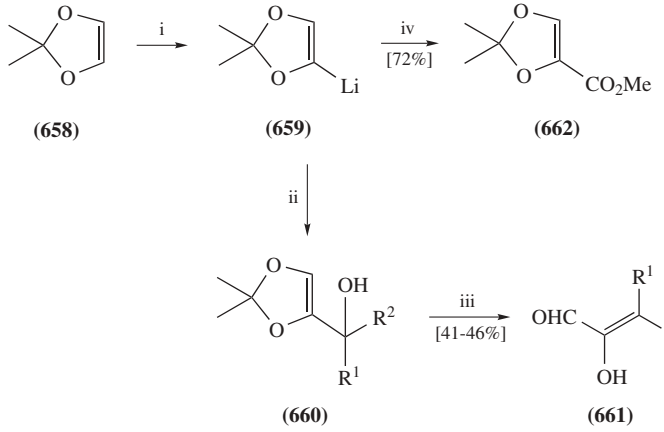
The dioxole **658** gave, after treatment with *t*-BuLi in THF at −78 °C, the related reagent **659**[857,969] (Scheme 172). This anion reacts with aldehydes and ketones to give adducts **660** which, after acidic hydrolysis, gave enols of α-oxo aldehydes **661**[969], reacting also with methyl chloroformate to yield the ester **662**[857].

6. Vinyl sulfides and selenides

Vinyllithiums bearing an alkyl or arylsulfanyl (**663**) and selanyl (**664**) group at the α-position can be used as acyl anion equivalents. The reaction of these intermediates

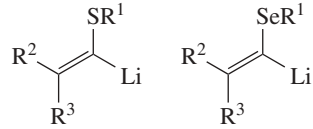


SCHEME 171. Reagents: (i) *t*-BuLi, THF, −30 to 0 °C; (ii) EX = D_2O, MeI, Me_3SnCl; (iii) PhCOMe; (iv) PCC; (v) NaOH; (vi) cyclohexanone; (vii) MCPBA; (viii) $NaBH_4$; (ix) SiO_2, oxalic acid; (x) $LiAlH_4$



SCHEME 172. Reagents: (i) *t*-BuLi, THF, −78 °C, 1 h; (ii) R^1R^2CO; (iii) HCl, H_2O; (iv) $ClCO_2Me$

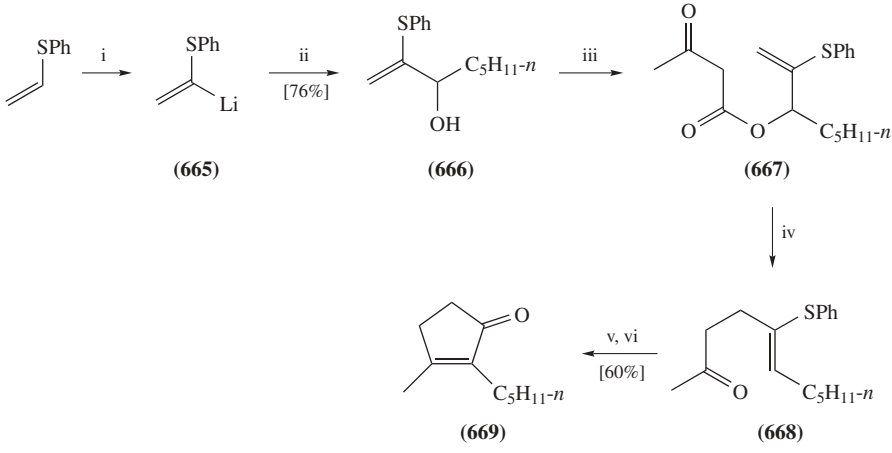
with electrophiles followed by mercury(II) salt treatment allowed the generation of a carbonyl group. The preparation of sulfur-containing vinyllithiums **663** can be performed by deprotonation of enol thioethers derived from aldehydes with *s*-BuLi[970], *n*-BuLi[971] or LDA in THF–HMPA (9:1)[972] and LDA in hexane[973] at temperatures ranging between −60 and −78 °C. However, using alkyllithiums, the corresponding products were invariably contaminated with compounds resulting from the addition of the alkyllithium to the vinyl phenyl sulfide. The last-mentioned metallation conditions (LDA in hexane at −78 °C) gave the best results without any by-products[974].



(663) **(664)**

Intermediates **663** can be prepared by tin–lithium transmetallation with *n*-BuLi from α-stannylated vinyl sulfides[974]. Starting from 1,1-bis(arylsulfanyl)ethenes, a reductive metallation with lithium naphthalenide at −70 °C is a very efficient approach to lithiated vinyl sulfides[975,976]. Other methods involved bromine–lithium exchange[977] or addition of methyl or phenyllithium to thioketenes[978]. A convenient method for the preparation of 1-(methylsulfanyl) and 1-(phenylsulfanyl) vinyllithiums was the treatment of 2-methoxyethyl sulfides with 2 equiv of *n*-BuLi–TMEDA at −30 °C[979].

Vinyllithiums of type **663** ($R^2 = R^3 = H$) reacted with primary alkyl bromides, carbonyl compounds, carbon dioxide, DMF, silyl chlorides, stannyl chlorides, disulfides and phenylselenyl bromide[142,970–979]. Scheme 173 shows the synthesis of dihydrojasmone **669** from the corresponding 1,4-diketone. α-(Phenylsulfanyl)vinyllithium **665**, prepared from phenyl vinyl thioether, reacted with hexanal and the corresponding adduct **666** was transformed into its acetoacetate. This ester **667** underwent a Carrol reaction to produce the ketone **668**, which was transformed into the cyclopentenone **669** by deprotection either

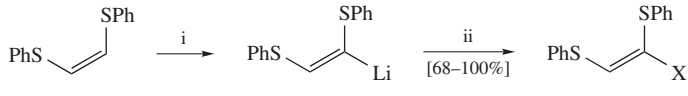


(665) **(666)** **(667)** **(668)** **(669)**

SCHEME 173. Reagents: (i) LDA, THF–HMPA, −60 °C, 30 min; (ii) *n*-$C_5H_{11}CHO$; (iii) diketene; (iv) $(i\text{-PrO})_3Al$ (cat.), 160 °C; (v) $TiCl_4$, MeCN or TFA; (vi) 2% NaOH, EtOH, heat

with $TiCl_4$ in aqueous acetonitrile or with trifluoroacetic acid, followed by aldol condensation under basic conditions[972]. On the other hand, vinyl sulfides can also be hydrolyzed with mercury(II) chloride in aqueous acetonitrile[970].

The β-substituted α-sulfur-containing vinyllithium **671** has been prepared from *cis*-1,2-bis(phenylsulfanyl)ethane **670** by means of either *t*-BuLi or LDA at $-78\,^{\circ}C$ in THF[980] (Scheme 174). This intermediate reacts with different electrophiles to give the expected products **672** in good yields.

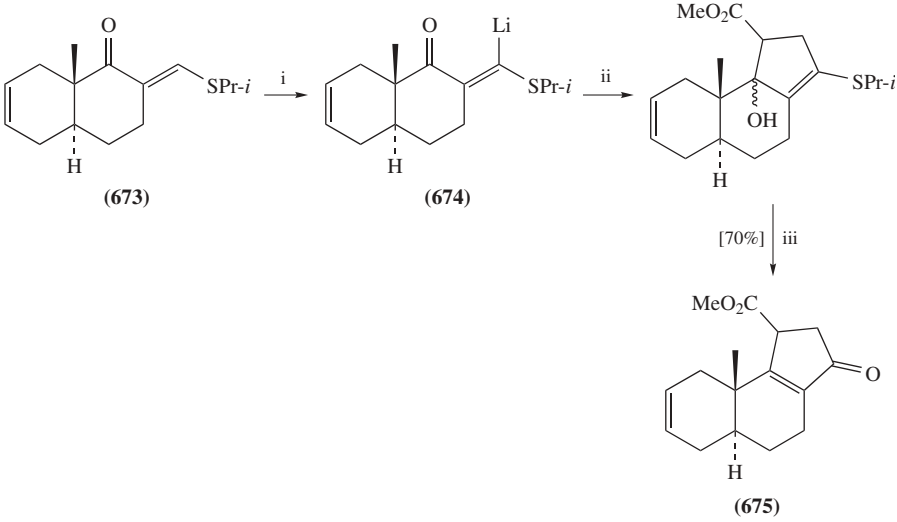


(670) **(671)** **(672)**

[X = D, Me, MeS, PhCHOH]

SCHEME 174. Reagents: (i) *t*-BuLi or LDA, THF, $-78\,^{\circ}C$; (ii) EX = MeOD, MeI, Me_2S_2, PhCHO

Other lithiated vinyl sulfides bearing a carbonyl group at the β-position have been used in organic synthesis mainly as β-acyl vinyl anion equivalents[858]. The 2-(isopropylsulfanylmethylene) derivative **673** has been deprotonated with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) to give the intermediate **674** which, after addition to methyl acrylate and final hydrolysis, afforded the cyclopentenone **675** in 70% overall yield[981] (Scheme 175).

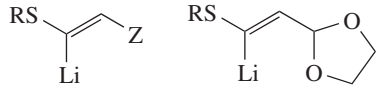


(673) **(674)** **(675)**

SCHEME 175. Reagents: (i) LTMP, THF, $-78\,^{\circ}C$, 1 h; (ii) $CH_2{=}CHCO_2Me$, $-78\,^{\circ}C$ to rt; (iii) 5% HCl, THF, rt

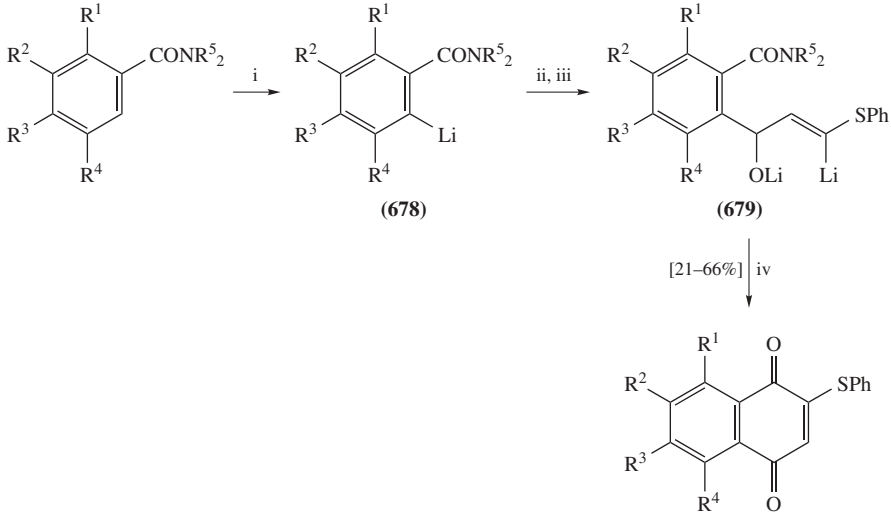
Other β-acyl vinyl anions such as β-lithiated β-sulfur-substituted acrylic acid unprotected derivatives **676** (Z = CO_2Li, CO_2R, CONLiR, $CONR_2$, CN) and the protected compound **677** have also been described[858].

For the synthesis of 1,4-naphthoquinones from benzamides, a tandem lithiation has been performed using intermediates **678** and **679**[982]. Intermediates **679** reacted with



(676) **(677)**

3-(phenylsulfanyl) acrolein and, after deprotonation of the vinyl sulfide moiety, the new organolithiums evolved underwent an intramolecular acylation followed by air oxidation to afford the expected benzoquinones (Scheme 176).



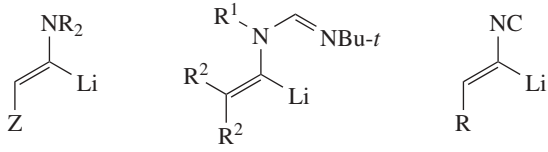
SCHEME 176. Reagents: (i) *s*-BuLi, TMEDA, THF, −78 °C; (ii) (*E*)-PhSCH=CHCHO, −78 °C, 2 h; (iii) *s*-BuLi, −78 °C to rt; (iv) NH_4Cl

Vinyl selenides have been lithiated at the α-position by LDA[983,984] at −78 °C in THF to give α-(arylselanyl)vinyllithiums **680**, α-(methylselanyl)vinyllithiums **681** being obtained by selenium–lithium transmetallation from 1,1-bis(methylselanyl)alkenes with *n*-BuLi in THF or *t*-BuLi in ether at −78 °C[985,986]. These intermediates reacted with alkyl halides, epoxides, carbonyl compounds and DMF[985], the final deprotection being performed by mercury(II) salts[986].

(680) **(681)**

7. Enamines

Enamines can be deprotonated with *n*-BuLi or *t*-BuLi if some stabilizing groups are present at the nitrogen or on the alkene. Some examples are β-amino acrylic acid derivatives **682**[987,988], which have also been employed as β-acyl vinyl anion equivalents[858].

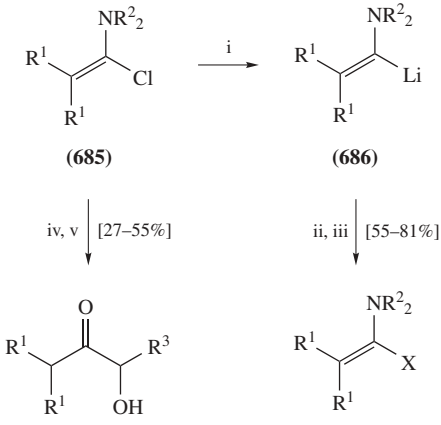


(682) **(683)** **(684)**

[Z = CO_2Et, $CONEt_2$, CN]

They are very unstable and must be generated at temperatures ranging between −100 and −120 °C, whereas lithiated amidines **683** can be kept in solution at −78 to −20 °C[989]. Lithiated isonitriles **684** are also very unstable species[990].

Simple enamines cannot be deprotonated directly at the α-position due to their low acidity, but starting from α-chloroenamines **685**, α-lithioenamines **686**[991] have been prepared by chlorine–lithium exchange using an arene-catalyzed lithiation[992]. The treatment of compounds **685** with an excess of lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) in THF at −90 °C allowed the preparation of intermediates **686**, which were trapped with a variety of electrophiles (Scheme 177). For aldol reactions, the arene-catalyzed lithiation has to be performed in the presence of aldehydes (Barbier conditions) at −40 °C. These adducts were transformed into α-hydroxy ketones after acid hydrolysis with hydrochloric acid or silica gel.



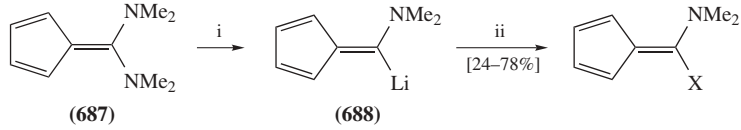
(685) **(686)**

[X = D, Me_3Si, CO_2H, *c*-$C_6H_{11}NHCO$, $PhCOCH_2CHPh$]

SCHEME 177. Reagents: (i) Li, DTBB (5 mol%), THF, −90 °C; (ii) EX = D_2O, Me_3SiCl, CO_2, *c*-$C_6H_{11}NCO$, PhCOCH=CHPh (BF_3•OEt_2); (iii) H_2O; (iv) Li, DTBB (5 mol%), R^3CHO, THF, −40 °C; (v) 2 M HCl or SiO_2

Stoichiometric lithium naphthalenide has been used for the lithiation of 6,6-bis(dimethylamino)fulvene **687**, generating at −78 °C the lithioenamine **688**, which has been used for the preparation of 6-aminofulvenes in moderate yields[993] (Scheme 178).

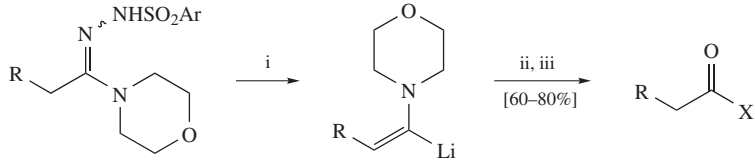
Treatment of 2,4,6-triisopropylbenzenesulfonyl derivatives **689** with *t*-BuLi gave the α-lithioenamines **690**[994], which reacted with different electrophiles to give the corresponding adducts finally transformed into ketones by easy hydrolysis (Scheme 179).



(687) **(688)**

[X = D, MeOCO, PhS, PhSe]

SCHEME 178. Reagents: (i) $LiC_{10}H_8$ (2.2 equiv), THF, −78 °C, 10 min; (ii) EX = D_2O, $CO(OMe)_2$, $PhSSO_2Ph$, Ph_2Se_2

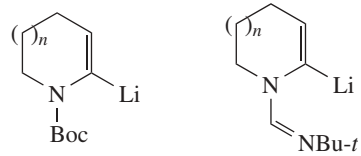


(689) **(690)**

[R = H, Ph; X = Me, $(CH_2)_5COH$]

SCHEME 179. Reagents: (i) *t*-BuLi (2 equiv), −78 to 10 °C, 5 min; (ii) EX = MeI, $(CH_2)_5CO$, −78 °C to rt; (iii) H_2O

Lithiated cyclic enamines **691**[995,996] and amidines **692**[989,997] have been prepared by deprotonation of the corresponding heterocycles with *t*-BuLi in THF at −78 °C, being allowed to react with several electrophiles. This methodology has been applied to the synthesis of pyrrolidine and piperidine derived compounds, intermediates **691** and **692** acting in these cases not as acyllithium equivalents.



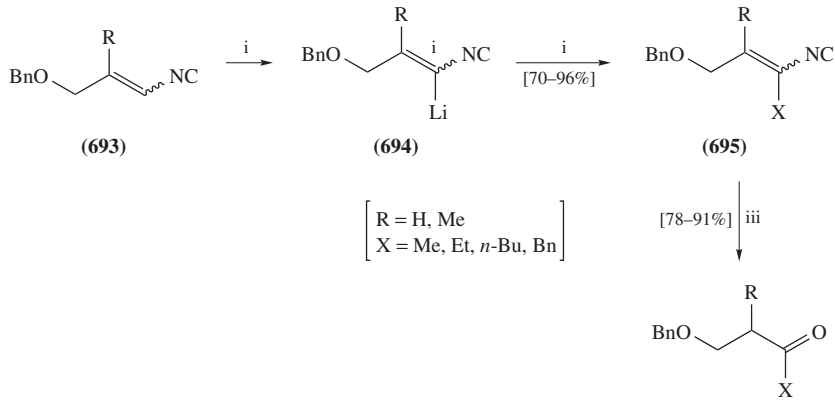
(691) [n = 0, 1] **(692)**

Vinyl isonitriles **693** can be deprotonated with LDA in THF at −78 °C to give the vinyllithium **694**, which has been used as a 3-hydroxypropanoyl anion equivalent. Intermediate **694** reacted with primary alkyl iodides and bromides to form alkylated products **695** and, after hydrolysis, the corresponding ketones, which can be submitted to hydrogenolysis, leading to β-hydroxyethyl ketones in good yields (66–90%)[998] (Scheme 180).

B. α-Substituted Dienyllithiums

In this section, the preparation and reactivity of α-lithiated dienyl and trienyl ethers as well as dienyl thioethers as acyl anion equivalents will be considered[749–751].

1-Methoxybuta-1,3-diene was initially lithiated with *t*-BuLi in THF at −78 °C and trapped with benzaldehyde to provide after hydrolysis α-crotonylbenzyl alcohol in 30% yield[752]. The efficient preparation of compound **696** was performed with *t*-BuLi at −78 °C



SCHEME 180. Reagents: (i) LDA, THF; (ii) EX = MeI, EtBr, *n*-BuBr, BnBr; (iii) conc. HCl, THF, 0 °C

(696) R = Me
(697) R = Et

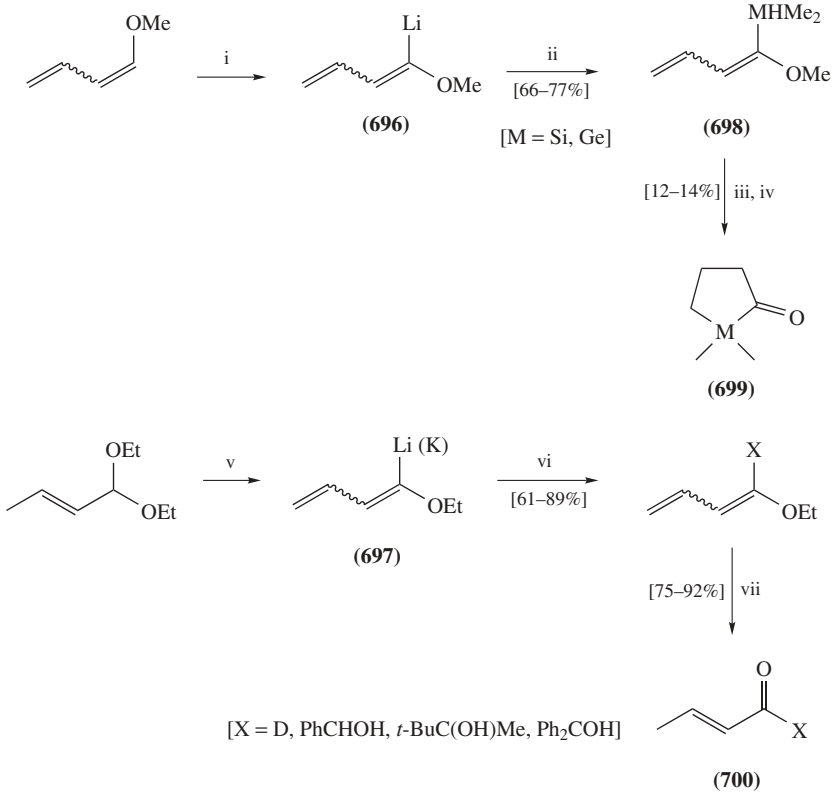
and slow warm-up to −20 °C[999, 1000]. For the preparation of the corresponding ethoxy derivative, 1,1-diethoxybut-2-ene was treated with two equiv of the superbase *s*-BuLi/*t*-BuLi (LICKOR base) at −95 °C in THF[1001]. These intermediates **696** and **697** have been employed in the synthesis as crotonyl anion equivalents.

α-Alkoxy dienyllithium **696** reacts with electrophiles such as silyl and germanyl chlorides to give compounds **698**. In the case of intermediate **697**, its reaction with carbonyl compounds followed by hydrolysis afforded the corresponding α,β-unsaturated ketones **700** (Scheme 181). Sila- and germacyclopentan-2-ones **699** have been prepared from compounds **698**[999].

By reaction of the dienal **701** with the dienyl anion **697** and subsequent hydrolysis, the triene **702** was obtained. This enone **702** underwent intramolecular Diels–Alder reaction to give the *trans*-fused tetrahydroindanone **703**[1002] (Scheme 182).

The intermediate **697** has been used in the synthesis of a captodative bis-diene **704** which, after heating, underwent intramolecular cycloaddition to provide a 2:1 mixture of adducts **705** and **706** (Scheme 183)[1003].

α-Ethoxybutadienylboronic esters **707** have been prepared by reaction of compound **697** with triisopropylborate followed by treatment with 2,2-dimethylpropane-1,3-diol. These boronic esters **707** have been arylated under palladium(0) catalysis to give, after hydrolysis, the corresponding phenones[1004] (Scheme 184). When trialkylboranes were used as electrophiles the corresponding borates are obtained which, by treatment with water and THF, led to the corresponding 1-ethoxy-1-alkylbutadienes **708**, and by treatment with $BF_3 \cdot OEt_2$ to enones[1005]. (*Z*)-1-Methoxy and phenoxybutadienes have also been metallated with *n*-BuLi/*t*-BuOK with retention of the configuration, giving the corresponding anions[1006].

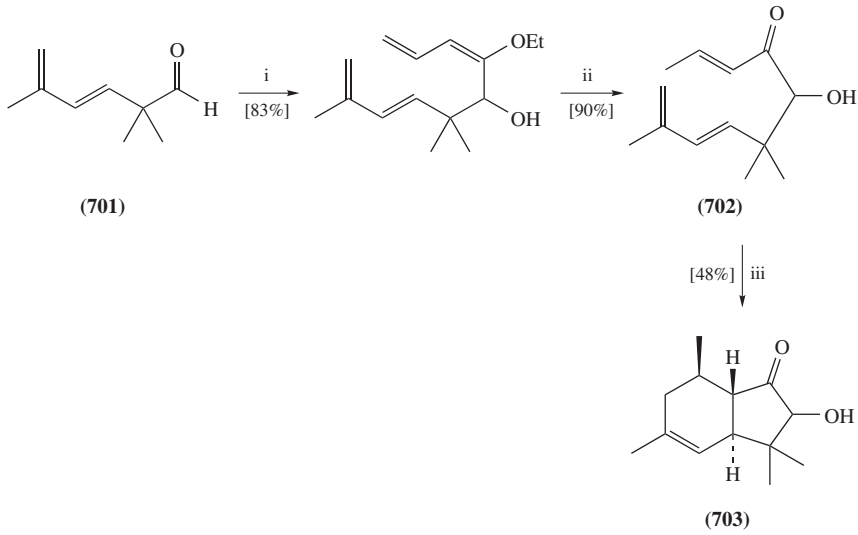


SCHEME 181. Reagents: (i) *t*-BuLi, THF, −78 to −20 °C; (ii) EX = Me_2MHCl (M = Si, Ge); (iii) H_2PtCl_6; (iv) 2 M HCl; (v) *s*-BuLi, *t*-BuOK (2 equiv), THF, −95 °C, 2 h; (vi) EX = D_2O, PhCHO, *t*-BuCOMe, Ph_2CO; (vii) 0.02 M HCl, MeOH/H_2O (4:1)

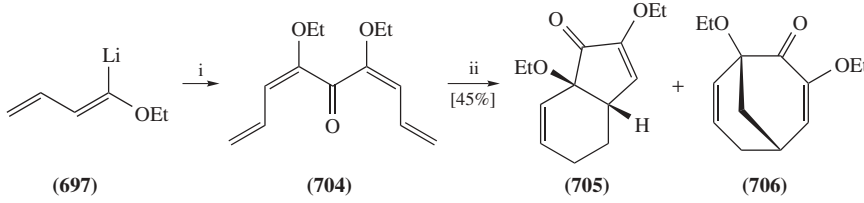
Isoprenyl derivatives **709** (1:3 mixture of *Z*/*E* diastereomers) underwent metallation with *t*-BuLi to give the dienyllithium **710** which, after trapping with Me_3MCl (M = Si, Ge, Sn), afforded the corresponding derivatives **711**[1000] (Scheme 185). The (*E*)-isomer seems to be destroyed in the reaction, since it is not isomerized to the (*Z*)-diene and does not remain in the reaction mixture. However, the hydrolysis of isoprenyl ethers **711** with 0.2 M HCl in a mixture of acetone and water gave mixtures of the expected conjugated and unconjugated enones.

1-Metallated 1-ethoxy-1,3-dienes **697** and **712**, obtained from the corresponding acetals by means of the LICKOR base, have been treated with alkyl halides, epoxides, carbonyl compounds, carbon dioxide and carboxylic esters affording (*E*)-1-substituted 1-ethoxy-1,3-dienes and, after hydrolysis, α,β-unsaturated carbonyl compounds[1007–1010] (Scheme 186). Intermediates **697** and **712** have been transformed into the corresponding vinyl stannanes, which were submitted to Stille couplings with iodobenzene and benzoyl chloride[823].

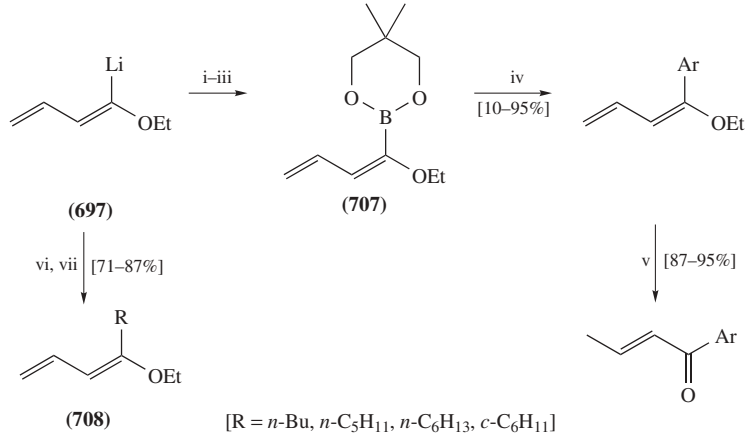
Lithiated 1-alkoxydienes substituted at the terminal position, **713** and **714**, bearing a methoxy or a MOMO group, have been prepared by α-deprotonation with *s*-BuLi in THF



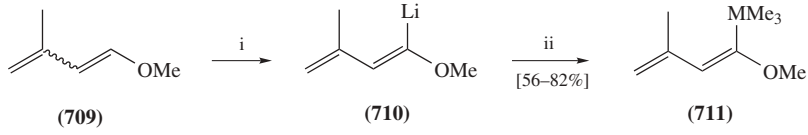
SCHEME 182. Reagents: (i) **697**, THF, −95 °C; (ii) Amberlyst-15, $CHCl_3$; (iii) PhMe, heat



SCHEME 183. Reagents: (i) $(EtO)_2CO$, THF, −90 °C; (ii) PhMe, reflux, 22 h



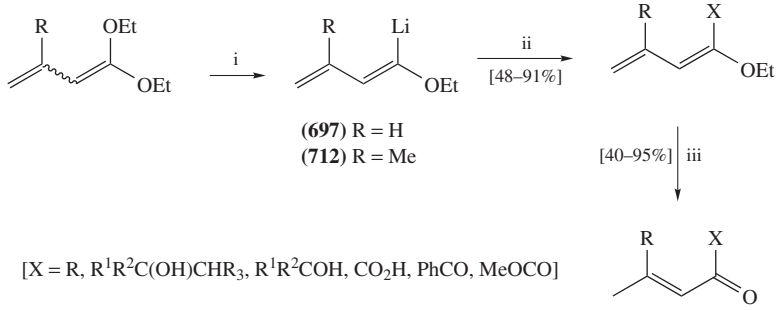
SCHEME 184. Reagents: (i) $B(OPr\text{-}i)_3$; (ii) H_2O; (iii) $Me_2C(CH_2OH)_2$; (iv) ArX, Pd(0); (v) Amberlyst-15; (vi) BR_3, THF, −95 °C; (vii) H_2O-THF, −95 °C



(709) **(710)** **(711)**

[M = Si, Ge, Sn]

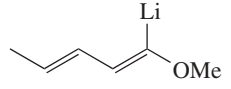
SCHEME 185. Reagents: (i) *t*-BuLi, THF, −78 to −20 °C, 30 min; (ii) Me_3MCl (M = Si, Ge, Sn), −78 °C



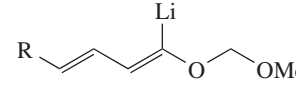
(697) R = H
(712) R = Me

SCHEME 186. Reagents: (i) *s*-BuLi/*t*-BuOK, THF, −95 °C; (ii) EX = RHal, epoxides, R^1R^2CO, CO_2, $PhCO_2Et$, $(MeO)_2CO$; (iii) 0.02 M HCl, MeOH, H_2O or Amberlyst-15, $CHCl_3$ or 0.02 M HCl, THF, H_2O

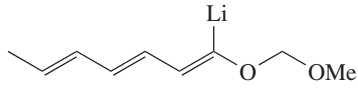
at −78 °C for 1.5 hours[1011]. The unsubstituted MOM derivative **714** (R = H) can also be metallated under the previously mentioned conditions. The α-lithiated triene **715** has been generated by means of *n*-BuLi in DME containing TMEDA (1 equiv) at −78 °C for 2 hours, whereas the lithiation of methoxytriene failed under these reaction conditions. All these reagents have been trapped only with TMSCl to give the corresponding silylated dienyl and trienyl derivatives in good yields (68–90%) and with (1*Z*,3*E*)- or (1*Z*,3*E*,5*E*)-configuration.



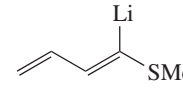
(713)



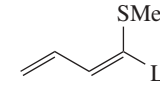
(714) R = H, Me, *i*-Pr, *i*-Bu



(715)



(*E*-716)

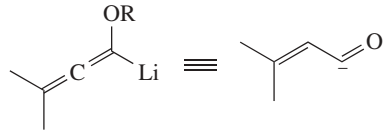


(*Z*-716)

The deprotonation of 1-(methylsulfanyl)buta-1,3-diene cannot be performed with *n*-BuLi, but the Lochmann–Schlosser base, followed by addition of lithium bromide, afforded stereospecifically dienyllithiums (*E*)-**716** and (*Z*)-**716**[1006, 1012]. These intermediates are configurationally stable below −20 °C[1013] but they have not been further used as crotonyl anion equivalents.

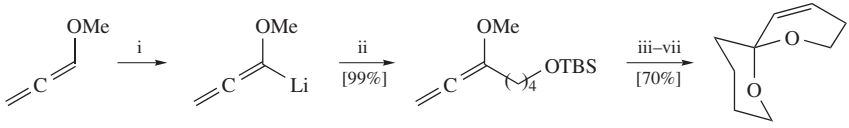
C. α-Substituted Allenyllithiums

In this section, α-lithiated 1-alkoxyallenes **717** will be mainly considered as α,β-unsaturated acyl anions[749–751,1013]. The lithiation of 1-methoxyallene (**718**) took place easily with *n*-BuLi at −30 to −40 °C, and the resulting allenyllithium **719** is stable at −30 °C for several days[1014,1015] (Scheme 187). The starting allene can be prepared from propargyl alcohol by methylation and isomerization with 0.1 equiv of *t*-BuOK[1014,1015]. Alternatively, lower temperatures (−78 °C)[1016], the use of a mixture of THF and hexane as solvent[1017] and the substitution of *n*-BuLi by MeLi[1018] are minor variants for the preparation of compound **719**. NMR and IR spectroscopy as well as *ab initio* model calculations proved that compound **719** exists as a 1,3-bridged structure **A** instead of the oxygenated coordinated structure **B**[1019].



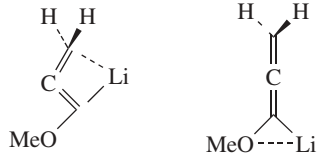
(717)

The reactivity of 1-methoxyallenyllithium **719** is higher in THF solution because the more reactive dimer is formed, this intermediate acting as an acryloyl anion equivalent. The alkylation of intermediate **719** was performed initially in THF–ether[1014], giving better yields in THF[1017,1020–1025], and works with primary alkyl halides. The product **720**, resulting from the alkylation of 1-methoxyallenyllithium with *O*-silylated 4-iodobutan-1-ol, has been used for the synthesis of 1,7-dioxaspiro[5.5]undec-4-ene **721**[1021] (Scheme 187). As this scheme shows, after alkylation at C1, a second deprotonation–alkylation at C3 with an epoxide was performed in this convergent synthesis. This type of spiro compounds are precursors for the synthesis of natural products such as talaromycins A and B[1017,1021] and lacrimin A[1023,1024].



(718) **(719)** **(720)** **(721)**

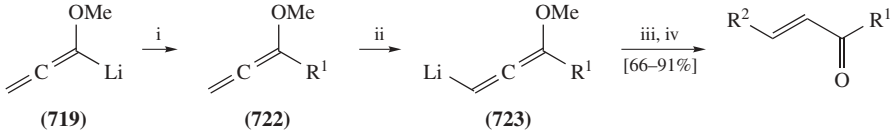
SCHEME 187. Reagents: (i) *n*-BuLi, THF-hexane, −25 °C, 30 min; (ii) $I(CH_2)_4OTBS$, −25 °C, 4 h; (iii) *t*-BuLi, THF-hexane, −50 °C, 45 min; (iv) ethylene oxide; (v) TBAF, THF, rt; (vi) PPTS, MeOH; (vii) I_2



A **(719)** **B**

For the synthesis of α,β-unsaturated ketones, a similar dilithiation–dialkylation process with alkyl halides at C1 and C3 was performed with excellent overall yields[1026]

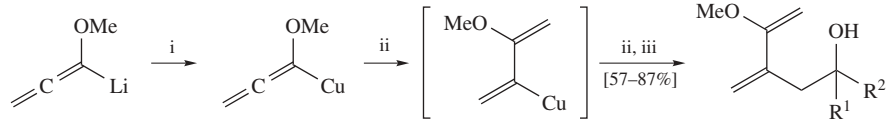
(Scheme 188). The resulting 1-methoxy-3-lithioallene **723** (prepared from the intermediate **719** through compound **722**) can be trapped with a variety of electrophiles[1026–1029] **719** acting in all these cases as a α- and γ-acyl anion equivalent. 1-Substituted-1-methoxyallenes can be rearranged with good stereoselectivity to (*E*)-1-substituted-2-methoxybutadienes by means of pyridinium *p*-toluenesulfonate (PPTS) (39–53%)[1025]. Alkylation of the allenyllithium **719** with oxirane took place in ether at −50 °C in 72% yield[1030]. Arylations of α-lithiomethoxyallene can be carried out with aryl iodides under palladium(0) catalysis[1031] and using the corresponding allenyl zincate[756].



(719) **(722)** **(723)**

SCHEME 188. Reagents: (i) R^1X; (ii) *n*-BuLi; (iii) R^2X; (iv) aq. 5% H_2SO_4

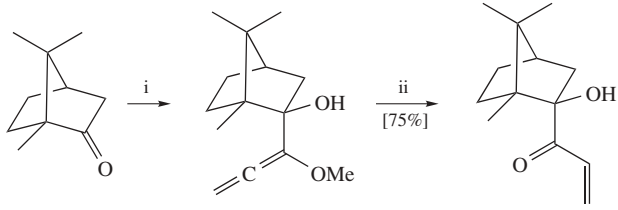
In the case of the allenyl copper intermediate **724**, its alkylation with (iodomethyl)zinc iodide and carbonyl compounds afforded dienes **725**[1032] (Scheme 189).



(719) **(724)** **(725)**

SCHEME 189. Reagents: (i) CuI•2LiCl, −30 °C; (ii) ICH_2ZnI; (iii) R^1R^2CO

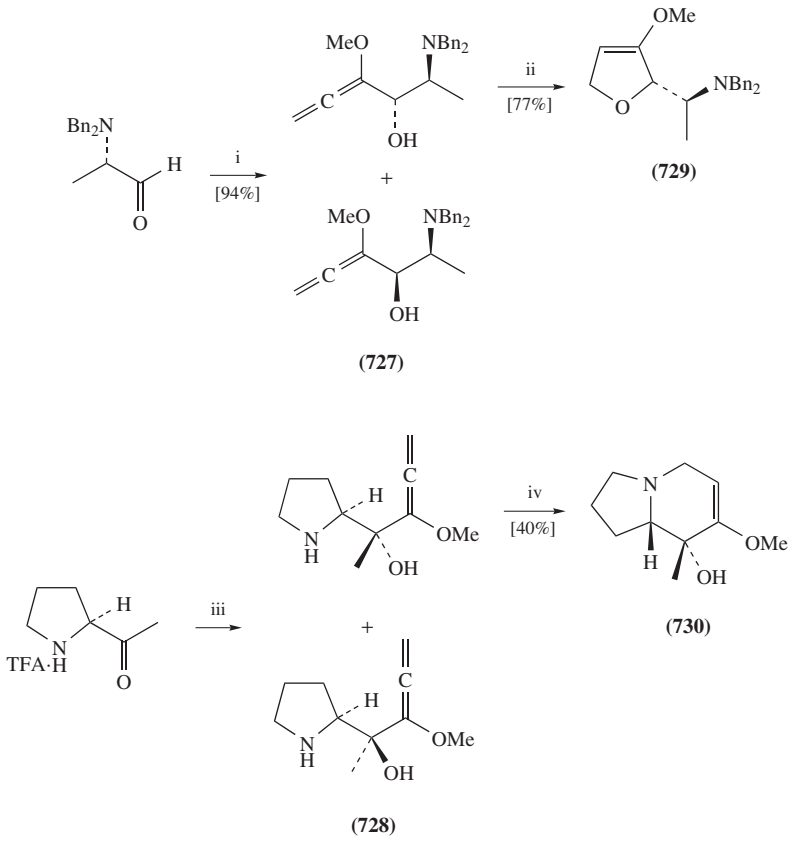
Carbonyl compounds have also been used as electrophiles with the intermediate **719** to afford α-allenic alcohols[758, 783, 788, 1016, 1030, 1033–1051] and, after hydrolysis, the corresponding hydroxy enones[1034, 1037–1051]. The chiral acrylate equivalent *endo*-2-acryloylisoborneol (**726**), used in metal-free Diels–Alder reactions, has been prepared by reaction of (+)-camphor with compound **719**[1039] (Scheme 190).



(726)

SCHEME 190. Reagents: (i) **719**, TMEDA, THF, −30 °C; (ii) 1 M HCl

1,2-Addition of intermediate **719** to protected α-amino aldehydes[1035, 1041, 1042] gave the corresponding adducts, for instance compounds **727**[1035] in good *anti*-diastereoselectivity (95:5) according to the Felkin–Anh model (Scheme 191). Chiral α-amino ketones[758, 783, 1043, 1045] also underwent diastereoselective addition of compound **719** to provide the

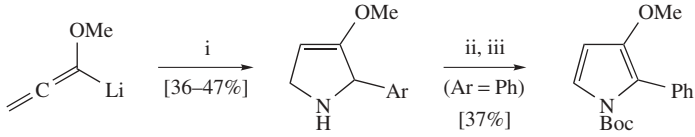


SCHEME 191. Reagents: (i) **719**, ether, −78 °C; (ii) *t*-BuOK; (iii) **719** (3 equiv); (iv) TsOH, MeCN

expected adducts **728**[783] (Scheme 191). In both examples the corresponding major diastereomers have been cyclized, in the case of **727** with a catalytic amount of *t*-BuOK giving rise to the formation of the 2,5-dihydrofuran **729**[1034], and in the case of **728** to give the octahydroindolizine **730**[783] with *p*-toluenesulfonic acid.

α-Hydroxyallenes obtained by addition of **719** to carbonyl compounds can also be used for the synthesis of different compounds, such as tetrasubstituted furans[1046], spiroalkanones[1047], 5-hydroxy-5-vinylcyclopent-2-en-1-ones[1045], α-hydroxy esters via ozonolysis[1041], the AB taxane ring system[1037], tetralone derivatives[1040], 1,3-indanediones[788], hydroxy-substituted tetronic acid derivatives[1048], helical spirocycles[1044], dihydrofuranones[1049], polyquinanes[1050] and the cytotoxic styryllactone (+)-goniodiol[1051].

The [3 + 2] cyclization methodology for the construction of 2,5-dihydrofurans **729**[1034] has been applied to the synthesis of chiral 2,5-dihydropyrrole derivatives by using chiral imines as electrophiles[1052]. This methodology has been applied to the synthesis of the chiral pyrrolidine (−)-detoxinine[1052]. When in situ generated *N*-trimethylsilyl imines were allowed to react with compound **719**, 3-pyrrolines **731** were obtained[1053]. The corresponding protected dihydropyrrole derivative **731** (Ar = Ph) was oxidized to the corresponding pyrrole **732** by means of MnO_2[1053] (Scheme 192).

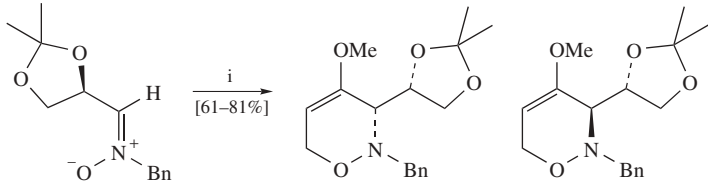


(719) **(731)** **(732)**

SCHEME 192. Reagents: (i) LiHMDS, ArCHO; (ii) Boc_2O, DMAP; (iii) MnO_2

In the case of silylated imines derived from aliphatic aldehydes[1053] and *N*-tosylimines[1054], the corresponding adducts must be cyclized by using a catalytic amount of silver nitrate. The addition of compound **719** to hydrazones in ether at $-25\,^{\circ}C$ for 16 hours gave α-allenyl hydrazines[1055–1057]. However, when the reaction was performed under the same reaction conditions, but in THF instead of ether, the corresponding 3-pyrrolines were obtained[1057]. When SAMP hydrazones are used, enantiopure pyrrolines can be prepared[1055, 1056].

When nitrones were used as electrophiles, the intermediate **719** gave 3,6-dihydro-2*H*-1,2-oxazines through a [3 + 3] cyclization process[1058, 1059]. Thus, starting from the (*R*)-glyceraldehyde-derived nitrone **733** and working in THF, the 1,2-oxazine *syn*-**734** was formed with excellent diastereoselectivity (96%) (Scheme 193). The complexation of compound **733** with Et_2AlCl in ether gave the compound *anti*-**734** in 94% de. These two diastereomers could be obtained in enantiomerically pure form and used for the synthesis of polyhydroxylated pyrrolidines. Chiral cyclic nitrones and intermediate **719** gave also bicyclic 1,2-oxazines with excellent diastereoselectivity, after cyclization of the corresponding adducts by simple stirring in dilute CH_2Cl_2 solution[1060]. These 1,2-oxazines gave enantiopure pyrrolidines after hydrogenolysis.



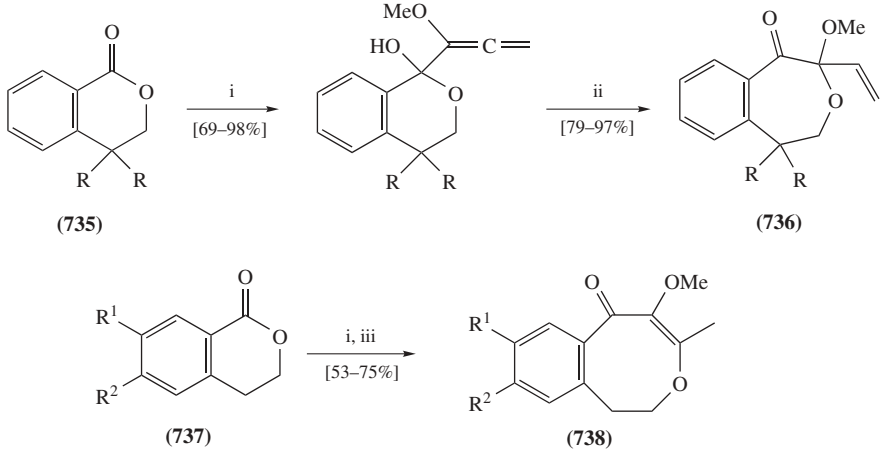
(733) (*syn*-**734**) (*anti*-**734**)

SCHEME 193. Reagents: (i) **719**, THF, $-78\,^{\circ}C$

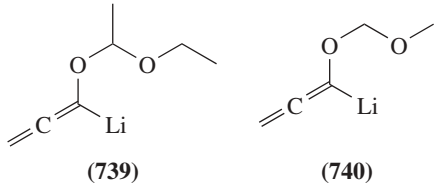
Seven-membered cyclic ethers **736** have been prepared by palladium(0)-catalyzed ring expansion of the adducts resulting from the addition of the intermediate **719** to 4,4-dialkylisochromanones **735**[1061]. However, when isochromanones **737** were used as electrophiles, the resulting adducts afforded the corresponding eight-membered cyclic ethers **738** after aqueous work-up (Scheme 194).

1-Methoxyallenyllithium **719** has been trapped with heteronucleophiles including chlorotrimethylsilane (50%)[1029], chlorotrimethyltin (61%)[1035], dimethyl disulfide (75%)[1033] and iodine (95%)[1018].

Related ethoxyethyl[805, 1062–1065] and methoxymethyl[827, 1066–1082] allenyllithiums **739** and **740**, respectively, can be prepared by deprotonation of the corresponding allenyl ethers with *n*-BuLi in THF or THF–ether (1:1), respectively, at -78 to $-95\,^{\circ}C$. The anion **739** was trapped with silyl chlorides to generate allenyl silanes which, upon hydrolysis (0.1 M H_2SO_4 in aqueous THF or 2 M HCl in acetone), gave the corresponding silyl

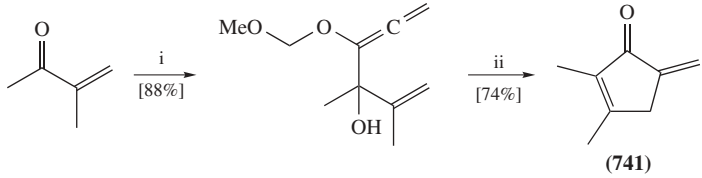


SCHEME 194. Reagents: (i) **719**, THF, −30 °C; (ii) $Pd(PPh_3)_4$, P(Tol-*o*)$_3$, THF, reflux; (iii) H_2O



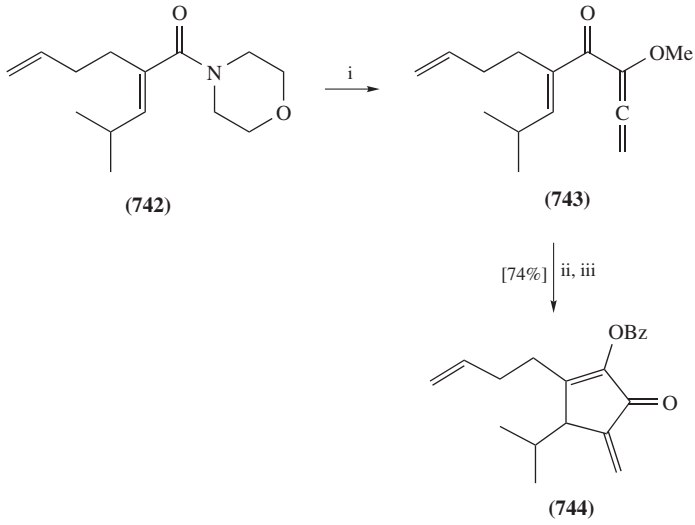
enones (29–84%)[805, 1063]. The anion **739** was trapped with trimethylstannyl chloride in 83% yield and was hydrolyzed to the corresponding acylstannane[1065].

1-(Methoxymethoxy)allenyllithium **740** has been used in cationic cyclopentannulation reactions (a variant of the Nazarov cycloaddition) for the synthesis of cyclopentenones[827, 1066–1082]. When α,β-unsaturated ketones[827, 1066–1075] were used as electrophiles, the corresponding 1,2-adducts gave, upon acid-catalyzed rearrangement (BF_3•OEt_2 or TFAA-2,6-lutidine), the corresponding α-methylenecyclopentenones. Scheme 195 illustrates the synthesis of the fungal antibiotic methylenomycin B (**741**) from 3-methyl-3-buten-2-one[1069]. Methylenomycin A[827, 1068, 1069, 1071] and xanthocidin[1073] have also been prepared using this methodology.



SCHEME 195. Reagents: (i) **740** (4 equiv), THF, ether, −78 °C; (ii) TFAA (3 equiv), 2,6-lutidine, CH_2Cl_2, −20 °C

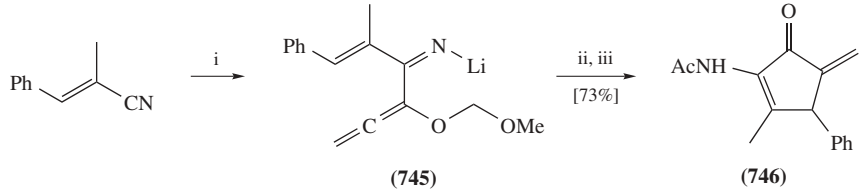
The second variant of this method uses α,β-unsaturated Weinreb amides as electrophiles[1066, 1076, 1077]. The 1,2-addition of compound **740** to the amide **742** gave the ketone **743**, which underwent spontaneous Nazarov cyclization upon work-up[1077]



SCHEME 196. Reagents: (i) **740**, THF, −78 °C; (ii) AcOH; (iii) PhCOCl, Et_3N

(Scheme 196). The obtained cyclopentenone **744** is a key intermediate used in the formal total synthesis of roseophilin[1077].

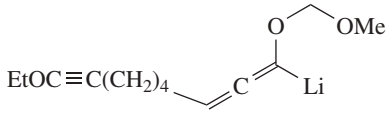
The third variant employed an α,β-unsaturated nitrile as electrophile[1078]. The addition of compound **740** to α-methylcinnamonitrile at −78 °C led to the formation of a lithioimine **745**, which was quenched with saturated $(NH_4)H_2PO_4$ to give, after electrocyclization of the imine, the α-aminocyclopentenone **746**, after acetylation (Scheme 197).



SCHEME 197. Reagents: (i) **740**, THF, −78 °C, 1 h; (ii) $(NH_4)H_2PO_4$; (iii) Ac_2O, Py, DMAP

Other 3-substituted 1-lithio-1-(methoxymethoxy)allenes such as compounds **747–749** have been used in the synthesis of cyclopentenones. The intermediate **747** and an amide have been used for the synthesis of Δ^7-10-chloro-15-deoxy PGA1 ethyl ester[1079] and, by reaction with a trifluoromethyl dienone, for the synthesis of 15-deoxy-12-hydroxy-10-(trifluoromethyl)- Δ^7 PGA1 ethyl ester[1080]. A combination of allenyllithiums **740, 748** and **749** with amides allowed the parallel chemical synthesis of cyclopentenones[1081].

For the convergent synthesis of α-alkylidene α-hydroxycyclopentenones **752**, the α-methylcinnamamide **750** was allowed to react with the allenyllithium **740** giving, after in situ γ-deprotonation, the intermediate **751**. This dianion can be trapped with different electrophiles to afford the corresponding products **752**, after acidic hydrolysis[1082] (Scheme 198). When an ethyl enone was used instead of an amide, α-ethylcyclopentenones were prepared following the same methodology (55–79% yield)[1082].



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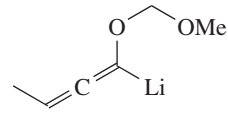

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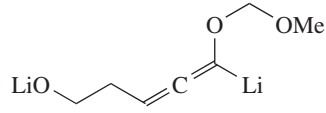

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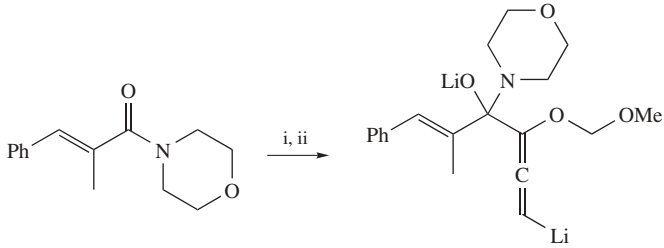

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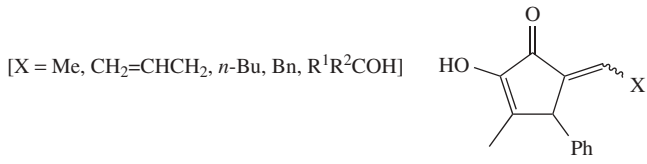


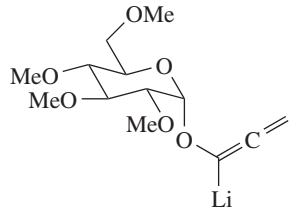
[X = Me, CH_2=$CHCH_2$, *n*-Bu, Bn, R^1R^2COH]

(752)

SCHEME 198. Reagents: (i) **740**, THF, −78 °C, 30 min; (ii) *s*-BuLi, −78 °C, 20 min; (iii) EX = MeI, CH_2=$CHCH_2Cl$, *n*-BuBr, BnBr, R^1R^2CO, −78 to −30 °C; (iv) aq HCl

Asymmetric cyclopentannelations have been performed with the amide **742** and chiral allenyllithiums **753–756** bearing sugar-derived chiral auxiliaries to give α-hydroxy-α'-methylene cyclopentenones in 61–82% ee[1083]. Camphor-derived intermediate **757** was proved to be the best for the asymmetric synthesis of cyclopentenones in 69–85% ee[1077, 1084, 1085]. This strategy has been used for the enantiospecific total synthesis of roseophilin[1084]. The γ-substituted chiral allenyllithium **759** reacted with amides, giving alkylidene α-hydroxycyclopentenones with high ee (92–96%) and with (*Z*)-configuration

on the exocyclic alkene[1085]. However, the diastereomer **758** gave lower ee. The chiral carbamate-derived allenyllithium **760** gave a 98% of chirality transfer in the cyclopentannelation with amides and ketones[1086].



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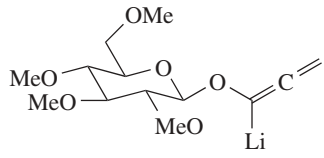

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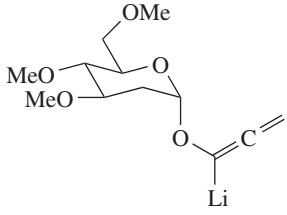

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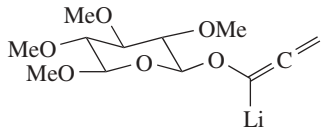

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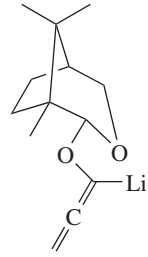

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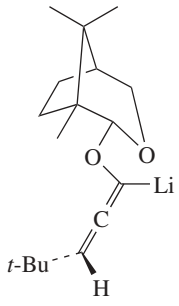

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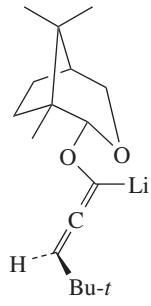

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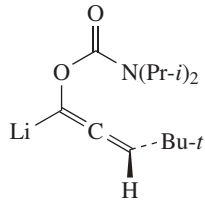
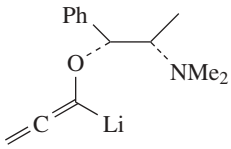


(760)

Other previously described chiral allenyllithiums derived from aminoalcohols **761–764**, menthol **765** and sugars **766–768**[1087–1089] have been prepared by deprotonation with *n*-BuLi in ether at −40 °C for 15 min. They reacted with carbonyl compounds giving, after hydrolysis, enantioenriched α-hydroxy ketones.

The diacetone glucose **767** was the best reagent and has been used in the synthesis of the allenic alcohol **769** (92% de) which, after protection of the hydroxy group and final hydrolysis, afforded the unsaturated ketol derivative **770** (Scheme 199). This compound **770** is a key intermediate in the total synthesis of the cytotoxic styryl lactone (+)-goniodiol[1051,1089].



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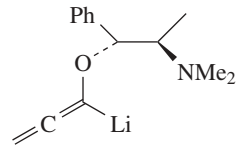

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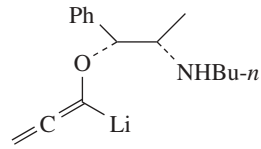

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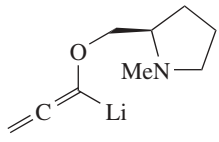

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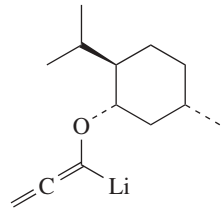

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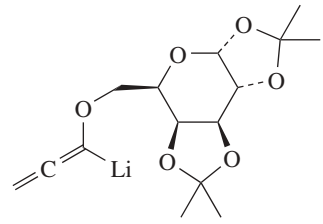

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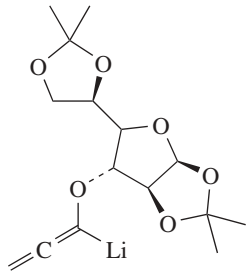

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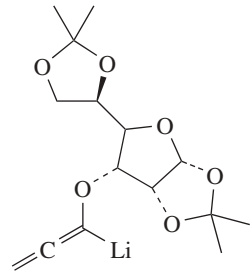


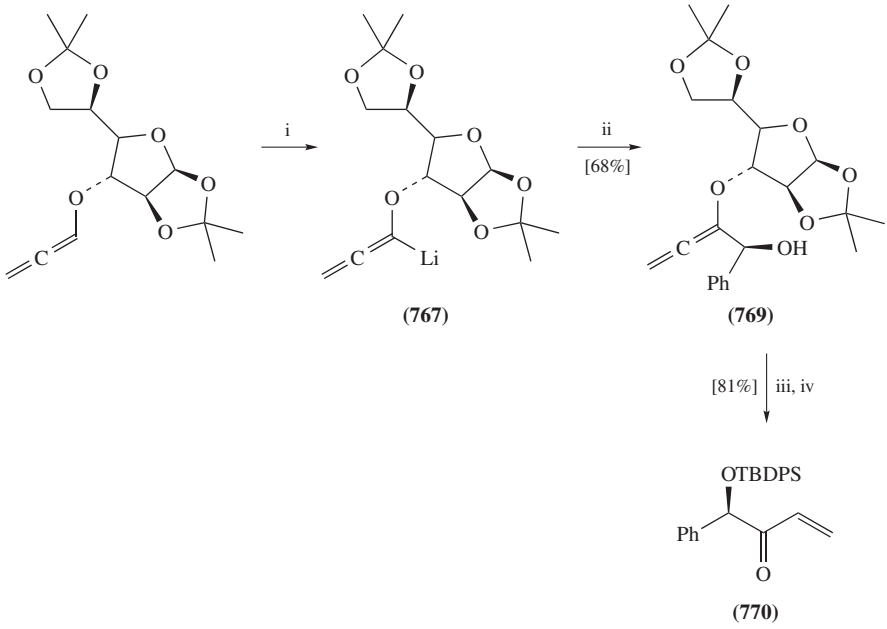
(768)

Allenyl trialkylsilyl ethers **771** can be α-deprotonated with *t*-BuLi in THF at $-78\,^{\circ}C$ to give the allenyllithiums **772**[1090, 1091]. They underwent reverse Brook rearrangement to afford the silaacrolein enolates **773**, which react with aldehydes and ketones to yield the α,β-unsaturated acyl silanes **774** (Scheme 200). For enolizable aldehydes transmetallation with $ZnCl_2$–TMEDA, and $MgBr_2$ for ketones, provided better yields.

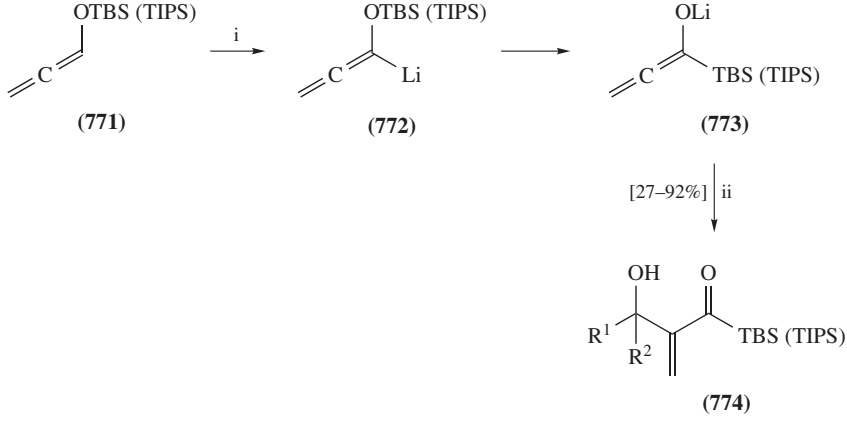
Allenyl sulfides have been converted into their α-lithio derivatives by deprotonation with *n*-BuLi in THF at $-78\,^{\circ}C$[1092] or in the presence of TMEDA[1093, 1094]. For example, compound **775** reacted with isobutylene oxide to give compound **776**, after cyclization (Scheme 201). This dihydropyran **776** was transformed into atlantone **777**, as a mixture of Z/E diastereomers, by treatment with $HgCl_2$ in wet acetonitrile[1092].

The α-lithiated allenyl phenyl sulfide **778**[1093] and other 3,3-dialkylated derivatives **779**[1094] have been used for the preparation of α-(phenylsulfanyl)enones[1093] and highly substituted 2,2-dihydrooxoles[1094].

α-Lithiated cumulenyl ethers and thioethers **781** can be generated by treatment of acetylenic bis-ethers and thioethers **780** with *n*-BuLi in ether at -20 to $-50\,^{\circ}C$[1095, 1096] (Scheme 202). They underwent reaction with different electrophiles to give cumulenic ethers **782** as a mixture of Z/E isomers.

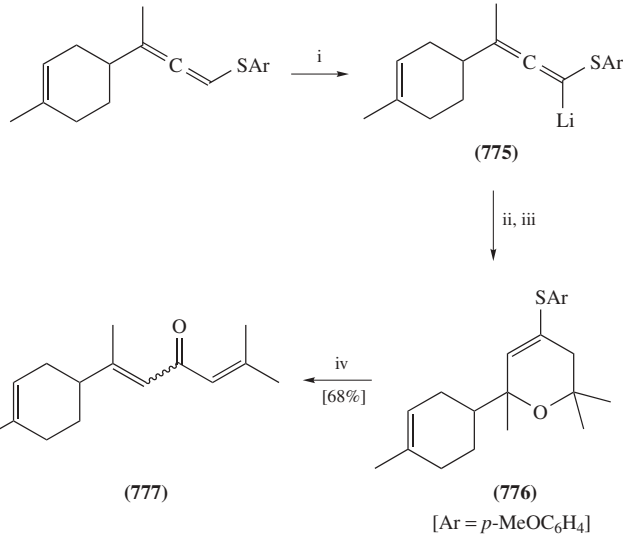


SCHEME 199. Reagents. (i) *n*-BuLi, ether, −40 °C, 15 min; (ii) PhCHO; (iii) TBDPSCl, DMAP; (iv) TFA

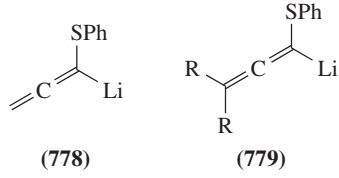


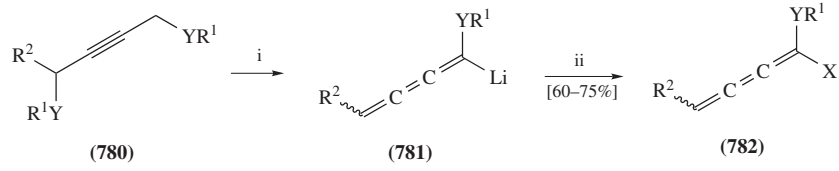
SCHEME 200. Reagents: (i) *t*-BuLi, THF, −78 °C; (ii) R^1R^2CO, −78 °C

Dimethylated cumulenyllithium **783** has been prepared by deprotonation of the corresponding cumulenyl methyl ether with *n*-BuLi in ether or THF at −30 °C. These anions reacted with aldehydes and ketones to produce the corresponding adducts (55–90% yield)[1097]. However, due to the instability of these types of compounds, they have not been used in organic synthesis as acyllithium equivalents.



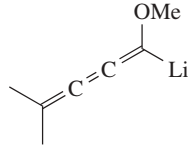
SCHEME 201. Reagents: (i) *n*-BuLi, THF, −78 °C; (ii) isobutylene oxide; (iii) TsOH; (iv) $HgCl_2$





R^1 = Et, *t*-Bu
R^2 = H, Me, *i*-Pr, *n*-C_5H_{11}
X = H, D, Me, Me_2COH
Y = O, S

SCHEME 202. Reagents: (i) *n*-BuLi (2 equiv), ether, −40 °C; (ii) EX = H_2O, D_2O, MeI, Me_2CO



(783)

V. CONCLUSIONS

This chapter has shown how extensive and intense the search for acyllithiums and their synthetic equivalents as umpoled reagents has been during the last approximately forty years. The widespread use of a vast array of these reagents in organic synthesis has become a classical strategy for carbon–carbon forming reactions leading to 1,2-bifunctional products. Among them, the 'dithiane route' remains as one of the most used methodologies in natural product synthesis. The enantioselective reaction of chiral formyl- and acyllithiums is still a challenging subject of study for asymmetric synthesis.

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CHAPTER 4

Intramolecular carbolithiation reactions

FRANCISCO J. FAÑANÁS

Instituto Universitario de Química Organometálica ''Enrique Moles'', Unidad Asociada al CSIC, Universidad de Oviedo, C/Julián Clavería, 8, E-33006 Oviedo, Spain
Fax: +34 98 510 3446; e-mail: fjfv@uniovi.es

and

ROBERTO SANZ

Departamento de Química, Facultad de Ciencias, Universidad de Burgos, Plaza Missael Bañuelos s/n, E-09001 Burgos, Spain
e-mail: rsd@ubu.es

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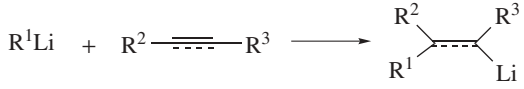
I. INTRODUCTION

Reactions which result in the addition of a carbon–lithium bond of an organolithium **1** across an unactivated carbon–carbon multiple bond **2**, leading to a new organolithium **3**, are called carbolithiation reactions (equation 1)[1]. So, although the addition of organolithiums to polarized C=X bonds is one of the most used method of making carbon–carbon bonds, this kind of reaction will not be treated in this chapter. In that way, we refer to carbolithiation reactions when the attacked carbon–carbon multiple bond is non-polarized or weakly polarized. In the intermolecular case the carbometallation ability of **1** must be higher than that of **3** to prevent the formation of polymers by its continued reaction[2]; however, in the intramolecular version, where entropy factors are favourable, the starting organolithium and the product could have similar reactivities.



(1)

(1) **(2)** **(3)**

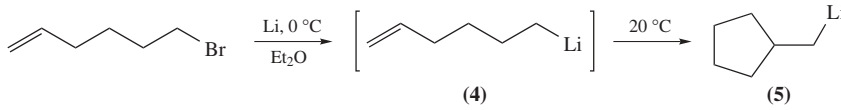
Consequently, the intramolecular carbolithiation reaction of organolithiums onto an unactivated olefinic or acetylenic bond has emerged as a useful methodology for the preparation of cyclopentylmethyllithium derivatives, their heterocyclic analogues and, less effectively, the corresponding six-membered rings. This kind of cyclization reaction could be considered as a group within a more general type of reaction called 'anionic cyclization reactions', which includes processes that involve the attack of an organolithium

on an electrophile within the same molecule. These anionic cyclization reactions onto carbonyl, esters, amides, nitriles, epoxides, alkyl halides etc., first developed by Parham and Bradsher[3], and those of stabilized nucleophiles, such as enolates, fall outside the scope of this chapter. Also, the cyclization reaction of organolithiums onto activated alkenes, like unsaturated esters, ketones or amides, will not be covered[4], though electron-poor alkenes are in general too susceptible to direct attack by alkyllithiums to be useful as traps in cyclization reactions. After an overview of general aspects of intramolecular carbolithiation reactions, we shall then consider in this chapter the more recent advances in this field[5]. With this objective we have divided the topic according to the hybridization of the carbon atom that bears the negative charge (sp^3 or sp^2) and to the character of the multiple bond being carbometallated (double or triple). Also, within each section we will consider especially heteroatom-substituted organolithiums because, although this methodology allows the efficient preparation of heterocyclic systems, it has received less attention.

II. GENERAL ASPECTS OF INTRAMOLECULAR CARBOLITHIATION REACTIONS

A. First Examples

In the late 1960s Drozd and coworkers reported that 5-hexenyllithium **4**, which was prepared from 1-bromo-5-hexene by reaction with lithium metal, undergoes an isomerization to cyclopentylmethyllithium **5** at room temperature, but few details were given in these short communications (Scheme 1)[6].



(4) (5)

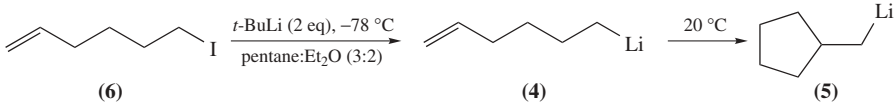
SCHEME 1

This result was confirmed and extended by Oliver and coworkers in a series of reports dealing with the intramolecular attack of a variety of organometallics[7] (Al, Mg, Li, Zn, etc.) onto unactivated alkenes. When **4** was prepared from di(5-hexenyl)mercury, it cyclized to **5** in less than 1 h at 25 °C in diethyl ether and these cyclization reactions were thought to be promoted by metal–alkene complexation[8], that required metals bearing empty orbitals. Moreover, the rate of cyclization is highly solvent-dependent: at 25 °C **4** takes 8 days to cyclize in pentane, 96 h in benzene and less than an hour in diethyl ether.

Despite that the regioselective cyclization of 5-hexenyllithiums could be synthetically useful, in those years there was no real development of this methodology[9], probably due to the lack of a convenient and efficient procedure for the preparation of unsaturated alkyllithiums and to the conventional belief that simple alkenes are not thought of as sites of nucleophilic attack. Moreover, this was a period when radical cyclizations and radical cascade reactions came to the fore[10], and 5-hexenyl substrates were used as probes for radical intermediates in reactions suspected of proceeding via single-electron transfer (SET).

It was in 1985 when Bailey and coworkers[11], in the course of a mechanistic study of the lithium–halogen exchange reaction, reignited interest in anionic cyclization reactions of organolithiums onto alkenes as a synthetic method for forming carbocycles. They showed that the iodine–lithium exchange of primary alkyl iodides like **6** with *t*-BuLi at −78 °C did not proceed via radical intermediates and they studied the kinetics of isomerization of 5-hexenyllithium **4** to **5** by ^{1}H NMR. This conversion is a clean first-order process characterized by $\Delta H^{\ddagger} = 11.8$ kcal mol^{-1} and $\Delta S^{\ddagger} = -30$ eu, and so the rate of

rearrangement is a strong function of temperature: **4** is indefinitely stable at −78 °C, but it cyclizes to **5** upon warming to room temperature ($t_{1/2} \sim 5.5$ min at 23 °C). However, the conversion of **4** to **5** is very much slower (by a factor of 10^8–10^{10}) than the 5-*exo* closure of the 5-hexenyl radical, which is known to cyclize rapidly ($k \sim 10^5$ s^{-1} at 0 °C)[12] in essentially quantitative yield to the cyclopentylmethyl radical (Scheme 2).

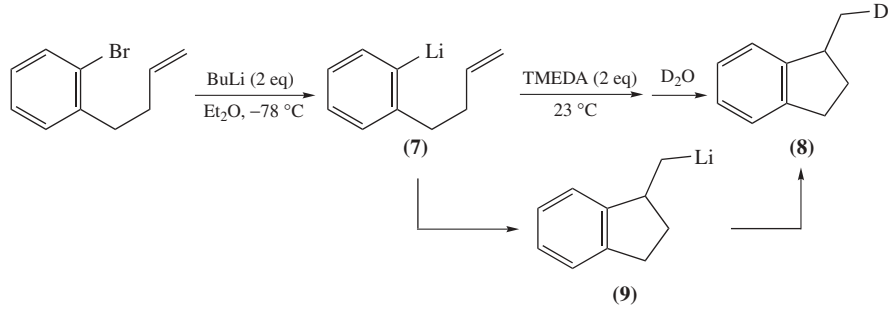


(6) **(4)** **(5)**

SCHEME 2

It is important to note that although organolithiums are often (as here) represented as monomeric, they are in fact aggregates whose degree of association may be affected by such factors as solvent, concentration and temperature[13].

Parallel work in those years showed that both vinyl- and aryllithium cyclization reactions onto alkenes are successful despite that an energetically less favourable sp^2 to sp^3 carbanion transformation would be required in this case. The first example of an aryllithium carbolithiation reaction was due to Woolsey and coworkers[14], who reported that the phenyllithium derivative **7** with a *o*-(3-butenyl) moiety cyclizes at room temperature in diethyl ether/TMEDA giving rise, after deuteriolysis, to 1-deuteriomethylindane **8** (Scheme 3). Organolithium **7** is generated by bromine–lithium exchange at −78 °C and is stable at this temperature. Cyclization reaction was negligible indeed at −78 °C in THF and only takes place with a convenient rate at higher temperatures to afford primary alkyllithium **9**.

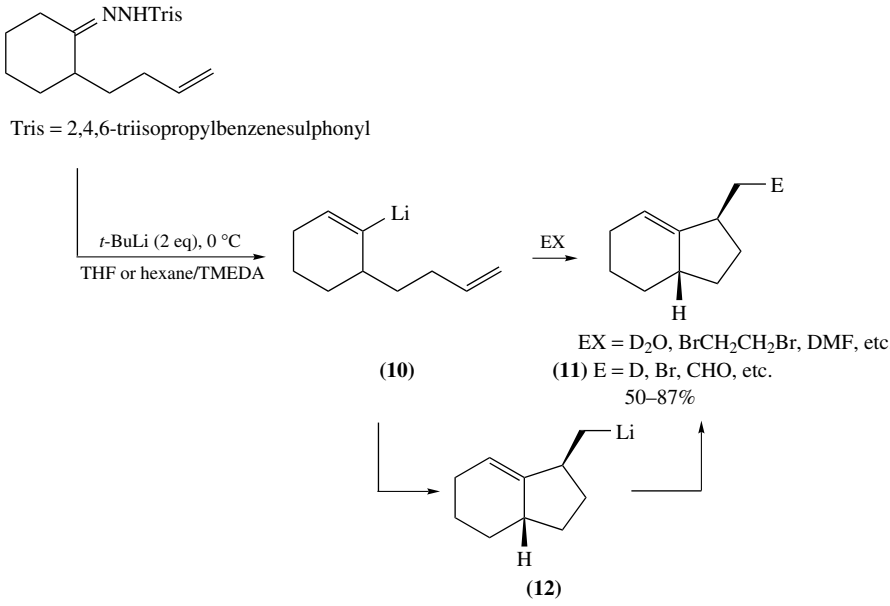


(7) **(8)** **(9)**

SCHEME 3

The first vinyllithium carbolithiation reaction was reported by Chamberlin and Bloom[15], who showed that Shapiro-derived organolithium **10** cyclized onto a terminal alkene giving stereoselectively (>50:1) bicyclic compounds **11**, after treatment with electrophiles (Scheme 4). The intermediate alkyllithiums **12** are generated via a 5-*exo-trig* cyclization reaction from **10**, which undergo the carbolithiation reaction at approximately the same rate as reported by Bailey for the simple parent compound 5-hexenyllithium, i.e. with a half-life of a few minutes at 0 °C.

Although all these carbolithiation reactions are thermodynamically favourable processes since they produce a carbon–carbon σ-bond (bond energy *ca* 88 kcal mol^{-1};



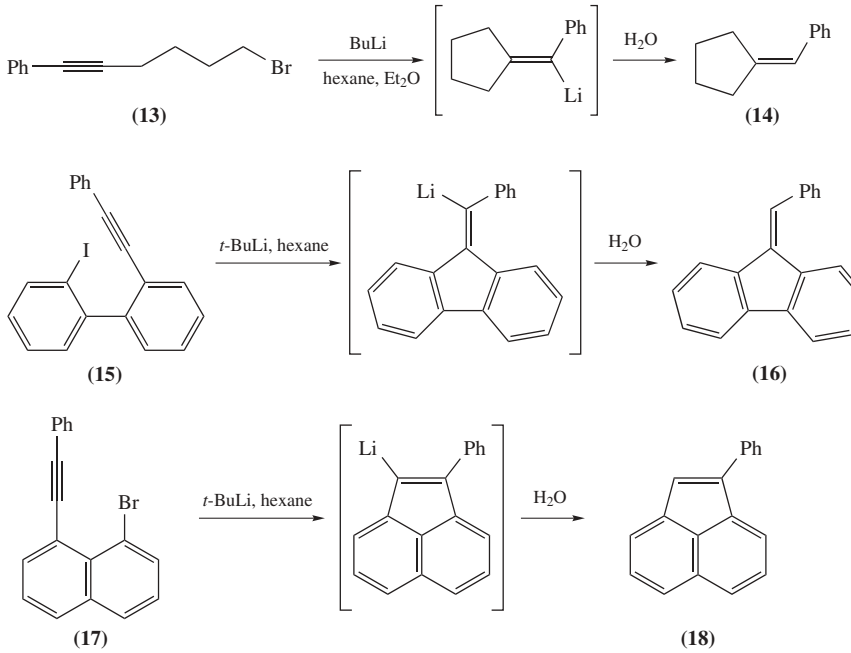
SCHEME 4

370 kJ mol^{-1}) at the expense of a π-bond (bond energy *ca* 60 kcal mol^{-1}; 250 kJ mol^{-1}), in many cases the isomerizations are sluggish at room temperature. Fortunately, the presence of lithiophilic Lewis bases such as THF or TMEDA serve to increase the rate of the cyclization reactions.

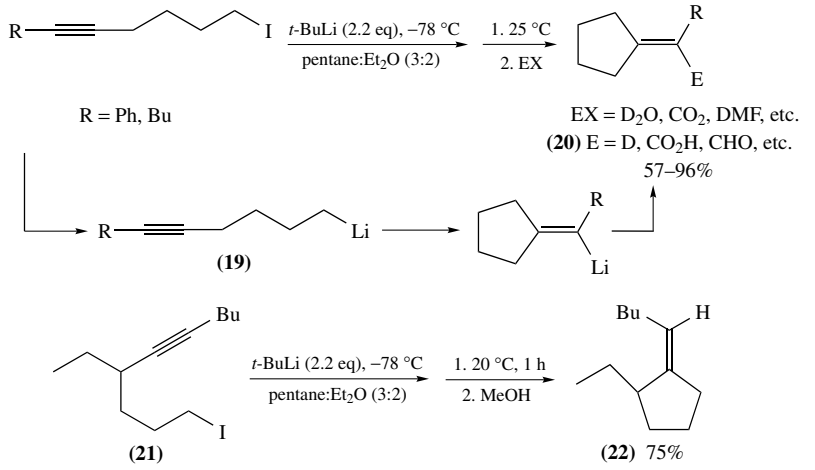
On the other hand, the first cyclization reactions of organolithiums onto alkynes are also known since the 1960s. Kandil and Dessy[16] as well as Ward[17] illustrated how both 5-*exo* (**13** to **14** and **15** to **16**) and 5-*endo* (**17** to **18**) closures are possible for this kind of substrates (Scheme 5). However, at that time, it was not clear how much of the product was due to participation of radicals in the mechanism.

In 1989 Bailey and coworkers cleanly generated 5-hexynyllithiums **19**, derived from the corresponding iodides by a non-radical-mediated halogen–lithium exchange at $-78\,^{\circ}$C, and showed that they isomerize to exocyclic vinyllithium derivatives which may be trapped with electrophiles to afford functionalized cyclopentylidene-containing products **20**, via a regiospecific 5-*exo-dig* ring closure (Scheme 6). These intramolecular carbolithiation reactions are *syn*-stereospecific processes as was demonstrated with iodide **21**, which upon iodine–lithium exchange and further cyclization gives rise to isomerically pure (*Z*)-alkene **22** with no trace of the *E* isomer (Scheme 6)[18].

The kinetics of the cyclization reaction of 5-hexynyllithiums **19** was also studied showing that (6-phenyl-5-hexynyl)lithium (**19**, R = Ph) has a half-life of *ca* 6 min at $-50.6\,^{\circ}$C, whereas cyclization reaction of 5-decynyllithium (**19**, R = Bu) is some 10^6 times slower. The rather dramatic increase in the rate of cyclization on going from an alkyl-substituted 5-hexyn-1-yllithium to a phenyl-substituted substrate is most likely a consequence of a reduction in $\Delta H^{\ddagger}$ due to stabilization of the incipient vinyllithium product by the phenyl group[19]. It is also interesting to note that the 5-*exo-dig* cyclization reaction of **19** (R = Bu) is slower than the corresponding 5-*exo-trig* carbolithiation reaction of 5-hexenyllithium.



SCHEME 5



SCHEME 6

B. Stereoselectivity and Mechanism

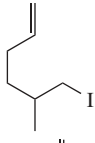
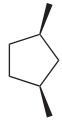
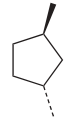
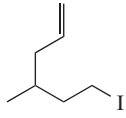
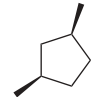
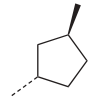
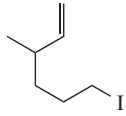
1. Anionic vs. radical cyclization reaction

One general aspect to consider about intramolecular carbolithiation reactions is the fact that the isomerizations of unsaturated organolithiums could, in principle, proceed via

radical cyclizations. To solve this controversy the method for the generation of the starting organolithium might not involve radical intermediates or, alternatively, if its formation takes place via single-electron transfer processes, the capture of the second electron must be faster than the radical cyclization reaction. For instance, in contrast with primary alkyl iodides, the bromine–lithium interchange reaction between an alkyllithium and a primary alkyl bromide is an outer-sphere process involving single-electron transfer (SET)[20], and cyclizations of alkyl bromide-derived organolithiums may proceed with significant contribution from radical pathways[21]. Also, the formation of phenyllithium derivative **7** (Scheme 3) with lithium naphthalene in THF at −78 °C afforded 52% of 1-methylindane in 1 h. So, under these conditions, the cyclization reaction is of a radical nature, and this halogen–lithium exchange probably takes place, to some degree, via a single-electron transfer. Lack of cyclization at −78 °C using BuLi suggests that radicals do not intervene in this case and the cyclization at 23 °C is a true carbolithiation reaction.

Organolithium cyclization reactions have important advantages over the corresponding radical cyclizations as it should be possible to functionalize the initially formed cyclization product by reaction with electrophiles, whereas it is not generally possible to trap the corresponding radical intermediate. Moreover, they are much more stereoselective than the analogous radical-mediated cyclization reactions with regard to stereogenic centres within the newly formed ring. As shown in Table 1, the cyclization of substituted 5-hexenyllithiums is a totally regiospecific 5-*exo-trig* process that leads to a disubstituted cyclopentane derivative[22]. The major isomer produced upon cyclization is the same as that generated in the kinetically controlled isomerization of an analogously substituted 5-hexenyl radical[23]. Significantly, the cyclization reaction of substituted 5-hexenyllithiums is much more stereoselective than the corresponding radical-mediated isomerizations. This stereochemical contrast between radical and anionic cyclizations provides a useful test of the mechanism and can be used to elucidate the course of reactions whose mechanism is ambiguous.

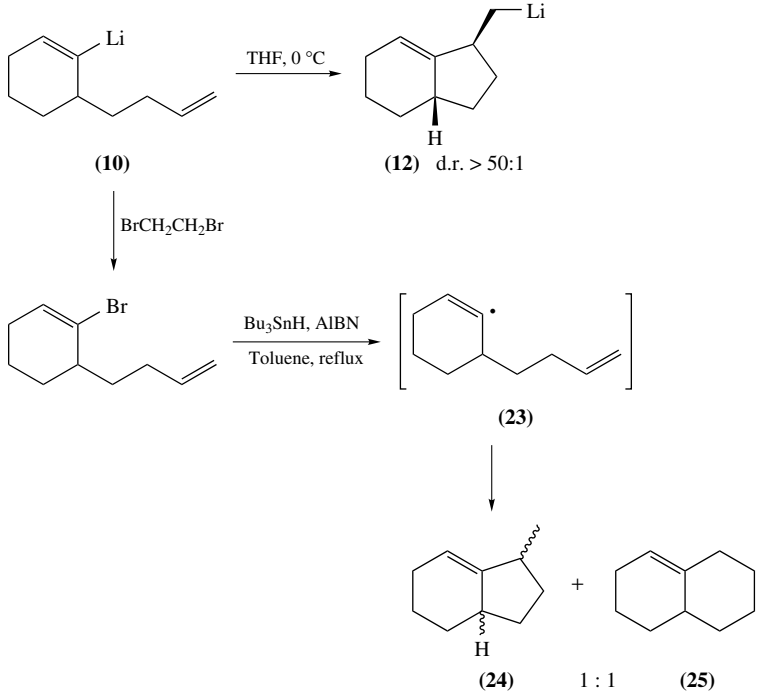
TABLE 1. Stereoselectivity for carbolithiation vs. radical cyclization of 5-hexenyllithiums or radicals

Starting material	*cis*-Product	*trans*-Product	Ratio (organolithium cyclization) [a] *cis*/*trans*	Ratio (radical cyclization) [b] *cis*/*trans*
			1:10	1:1.8
			10:1	2.5:1
			1:12	1:5

[a] Conditions: 1) *t*-BuLi (2 eq), pentane: Et_2O, −78 °C; 2) TMEDA (2.2 eq), −78 °C; 3) −78 to 20 °C; 4) MeOH.
[b] Conditions: Bu_3SnH, benzene, 80 °C.

Although lithiophilic Lewis bases such as THF, TMEDA and PMDTA have been found to increase the rate of cyclization of substituted 5-hexen-1-yllithiums, such additives do not reduce the high stereoselectivity of these processes[22].

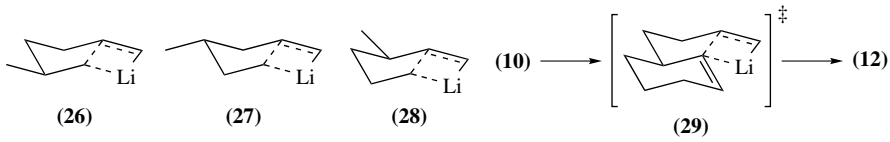
In the case of the vinyllithium carbolithiation described by Chamberlin and Bloom (Scheme 4) there is no mechanistic ambiguity; the cyclization is certainly anionic because the organolithium is generated by the Shapiro reaction. However, it is interesting to note the contrast in regio- and stereoselectivity with the related cyclization of radical **23**, that was also studied by these authors (Scheme 7). Trapping of vinyllithium **10** with dibromoethane afforded a vinyl bromide, which on treatment with Bu_3SnH under thermal initiation conditions gives a 1:1 mixture of the 5-*exo*- and 6-*endo*-products **24** and **25**, the first of them being a 3:1 mixture of diastereoisomers. This result clearly shows that the radical cyclization reaction is less regio- and stereoselective than the corresponding anionic process and eliminates the possibility that the observed vinyllithium cyclization might proceed through a transient radical intermediate.



SCHEME 7

2. Mechanism

The observed regioselectivities and stereoselectivities of the intramolecular addition of a carbon–lithium bond to an unactivated alkene (Table 1) could be rationalized by recourse to a transition-state model that resembles a cyclohexane chair in which substituents preferentially occupy pseudo-equatorial positions (structures **26–28**). The same model is proposed to explain the modest selectivities in the analogous radical cyclizations (Scheme 8).



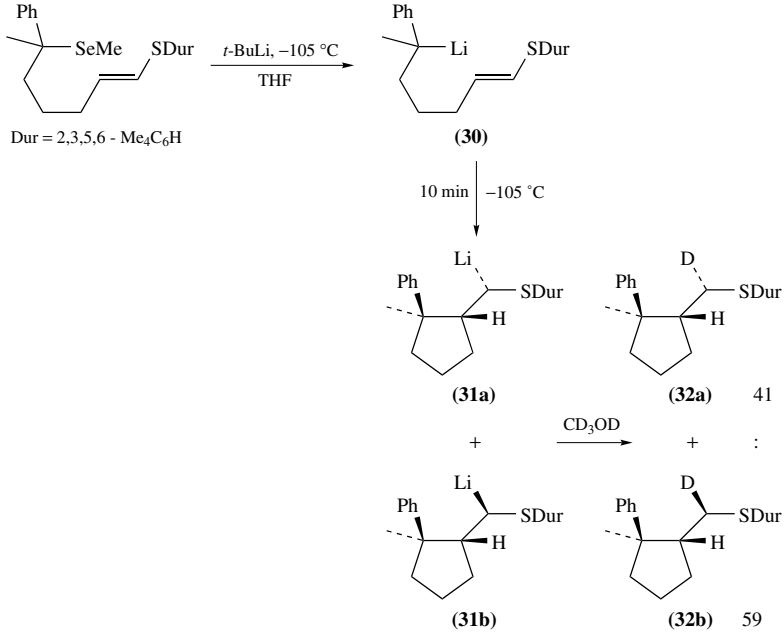
SCHEME 8

Chamberlin and coworkers proposed a similar chair-like transition state **29** to account for the stereoselectivity of the carbolithiation reaction of vinyllithium **10** to **12**[24]. The observed diastereoselectivity is consistent with a four-centre transition state where a preferred coplanar approach of the carbon–lithium bond to the double bond would give the obtained major product (Scheme 8).

As early as 1974, it was suggested by Oliver and Dolzine that the cyclization reaction of 5-hexenyl organometallics was promoted by an interaction between the lithium atom and the carbon–carbon double bond[7b]. *Ab initio* molecular orbital calculations carried out by Bailey and coworkers[22] reveal that the high degree of stereocontrol and the total regiospecificity that characterizes the intramolecular carbolithiation reactions is a consequence of an energetically favourable coordination of the lithium atom of the substrate with the remote π-bond, leading to a rigid cyclohexane chair-like transition state in which a substituent occupies a pseudo-equatorial position. As a consequence of this, the stereochemical outcome of the cyclization reactions may be anticipated, to a reasonable approximation, by reference to the conformational energy of a substituent in the cyclohexane system. Finally, the key to the high stereoselectivity of these reactions, relative to their radical counterparts, is their late, product-like transition state.

These theoretical studies were given real credibility when Hoffmann and Rölle showed that the lithium carbon–carbon double-bond interaction can be observed by heteronuclear coupling in the NMR spectrum of 5-hexenyllithium[25].

Another aspect of the mechanism of intramolecular carbolithiation reactions deals with the mode of addition of carbon and lithium across the carbon–carbon multiple bond. Whereas the carbolithiation reaction of triple bonds has been clearly demonstrated to be a *syn*-stereospecific process (see Scheme 6), though the generated vinyllithium derivatives could be geometrically unstable leading to mixtures of (*E/Z*) isomers, the stereochemistry of the addition to a carbon–carbon double bond is not completely probed. In order to test this, the new lithium-bearing carbon must be stereogenic, but this fact is not evident because, as discussed below, carbolithiation reactions usually fail if the product is a secondary organolithium. This problem was solved by Hoffmann and coworkers[26], who carried out the intramolecular carbolithiation reaction of the vinyl durylsulphide benzyllithium **30**, generated by selenium–lithium exchange in THF. The cyclization gives rise to a configurationally stable[27] α-durylthioalkyllithium compound **31** which can be trapped with electrophiles. The *ca* 1:1 mixture of products **32** indicates that the cyclization reaction in the presence of THF is non-stereospecific regarding the newly formed lithium-bearing stereocentre. The fact that the time between the carbolithiation and trapping reactions has no influence on the diastereoisomer ratio of **32a:32b** indicates that the α-durylthioalkyllithium compounds **31a** and **31b** are configurationally stable under the reaction conditions and so the diastereoisomer ratio is kinetically controlled (Scheme 9). Although the cyclization of the *Z*-isomer of **30** seems to be stereospecific in line with a concerted *syn*-addition of carbon and lithium to the double bond, this result does not prove that the mechanism is concerted and the experiments with *E*-**30** suggest that the carbolithiation reaction of vinyl sulphides could proceed in a non-concerted fashion, in which collapse of an ion pair determines the configuration of the lithium-bearing centre at the migration terminus.

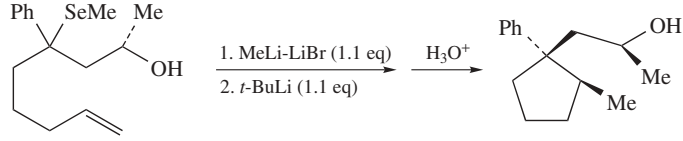


SCHEME 9

3. Control of absolute stereoselectivity

Control of absolute stereoselectivity in the intramolecular carbolithiation reactions is not a completely solved subject and several approaches have been used:

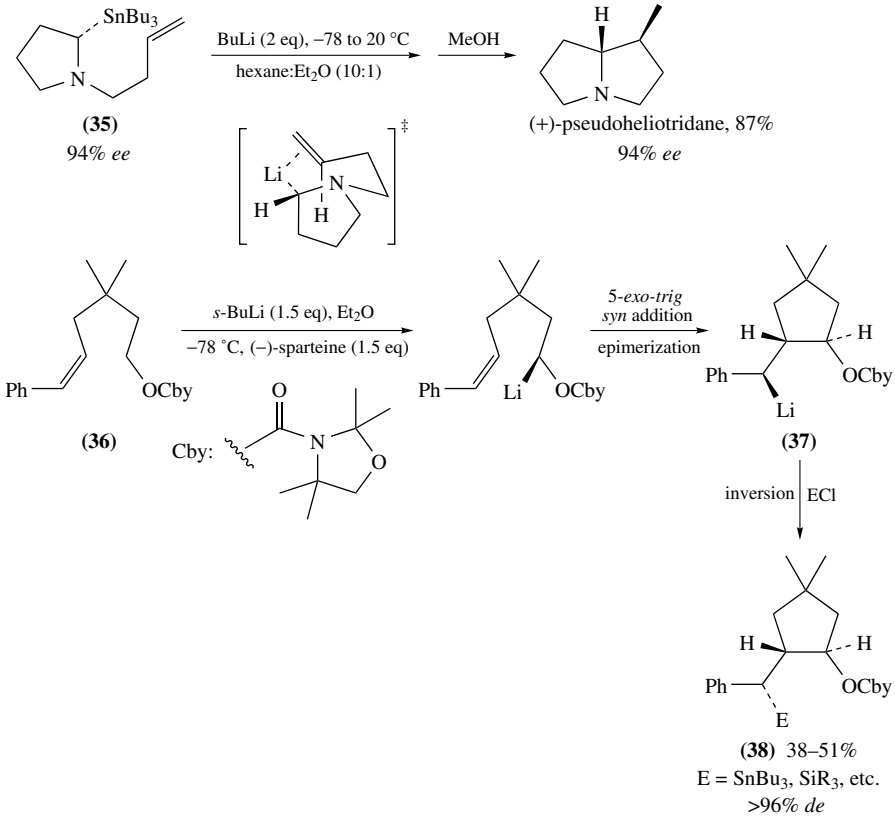
a. A 'chiral auxiliary' approach with the presence of an exocyclic stereocentre of defined configuration in the starting substrate to direct the cyclization. The first example of this strategy was reported by Krief and Bousbaa, who synthesized an optically active arylcyclopentane derivative **34** by carbocyclization of the alkenylbenzyllithium derived from selenide **33** by selenium–lithium exchange. The presence of a chiral alkoxy group in a suitable position allows high control of the relative stereochemistry and very high stereofacial differentiation, though the 'auxiliary' centre could only be removed by a long and not very efficient sequence of reactions (Scheme 10)[28].



SCHEME 10

b. A 'chiral substrate' approach with the use of a configurationally defined and stable organolithium starting material, usually generated by stereospecific tin–lithium exchange

or by enantioselective deprotonation. The first report of a carbolithiation reaction onto alkenes in which the carbanion is generated at a chiral centre in enantiomerically pure form is due to Coldham and coworkers. The use of a stereochemically defined and configurationally stable α-amino-organolithium formed by tin–lithium exchange from an almost enantiomerically pure stannane **35** allows the synthesis of (+)-pseudoheliotridane with complete stereocontrol. The cyclization reaction takes place with retention of configuration at the lithium atom-bearing carbanion centre and without loss of enantiomeric excess, showing that the carbolithiation reaction to the five-membered ring is more rapid than racemization. Only one diastereoisomer is formed, as expected from related intramolecular carbolithiation reaction with the preference for reaction via a chair-like conformation (Scheme 11)[29].

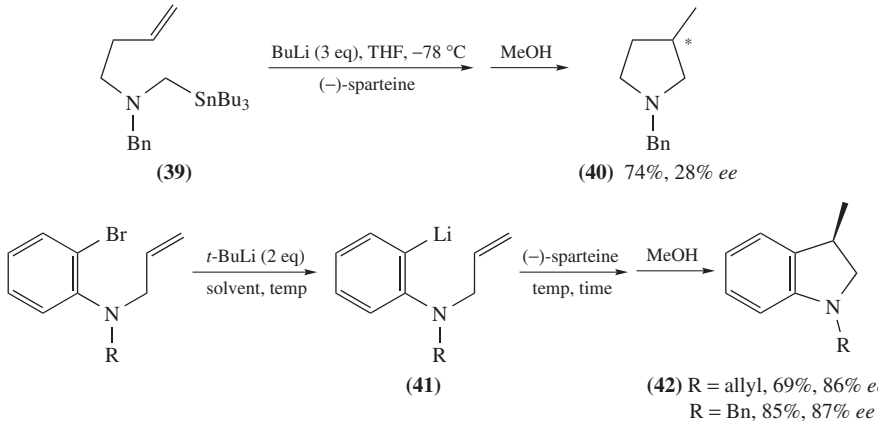


SCHEME 11

On the basis that a wide variety of (*S*)-configurated (α-carbamoyloxy)alkyllithium derivatives are accessible by (−)-sparteine-mediated deprotonation[30], Hoppe and coworkers have described the synthesis of enantiomerically and diastereomerically pure cyclopentanols **38** by asymmetric cyclocarbolithiation reaction of 5-alkenyl carbamates like **36**. Its deprotonation with *s*-BuLi/(−)-sparteine gives a chiral organolithium which cyclizes to benzyllithium **37** via 5-*exo*-*trig* and again with retention of configuration at the carbanionic

centre. The reaction of **37** with electrophiles takes place with inversion of the configuration giving rise to compounds **38** in moderate yields. A *syn*-addition of the starting chiral organolithium to the alkene followed by an epimerization at the benzylic centre, that affords the thermodynamically more stable epimer **37**, is proposed and supported by the fact that the sequences of reactions starting from the (*E*)-**36** lead to the same diastereoisomers (Scheme 11)[31].

c. A 'chiral ligand' approach with the use of an external ligand like (−)-sparteine to confer enantiofacial selectivity in cyclizations of achiral olefinic organolithiums. This ability to discriminate between the enantiotopic faces of an unactivated carbon–carbon double bond tethered to a formally carbanionic centre considerably extends the synthetic utility of intramolecular carbolithiation reaction as a route to carbocyclic and heterocyclic compounds. The first example of an enantioselective carbolithiation process with (−)-sparteine was reported by Marek, Normant and coworkers[32], who carried out the intermolecular asymmetric carbolithiation of cinnamyl derivatives. With respect to the intramolecular version, the first example using this methodology was due to Coldham and coworkers, who described the enantioselective preparation of 1-benzyl-3-methylpyrrolidine **40** from the achiral α-amino-organolithium derived from stannane **39** (Scheme 12)[33]. However, low levels of enantiomeric excess (<30%) were found with these substrates. More recently, Bailey and Mealy[34] as well as Groth and Sanz[35] independently reported that indolines **42** could be prepared by this methodology in an enantioselective manner if the 5-*exo-trig* carbolithiation reaction of organolithium **41**, generated by bromine–lithium exchange, is carried out in the presence of (−)-sparteine. They also observed that when the reaction was conducted in non-polar solvents like toluene or cumene, nearly 90% *ee* was reached. However, the use of THF as solvent gave rise to almost racemic products (Scheme 12). The fact that facial selection at the olefin is not effected by a chiral carbanionic centre, in contrast to other sparteine-mediated reactions, mainly reported by Hoppe and coworkers (see Scheme 11), but exclusively by a chiral lithium–sparteine complex, considerably extends the synthetic utility of anionic cyclization as a route to cyclic compounds.



(39)

(40) 74%, 28% *ee*

(41)

(42) R = allyl, 69%, 86% *ee*
R = Bn, 85%, 87% *ee*

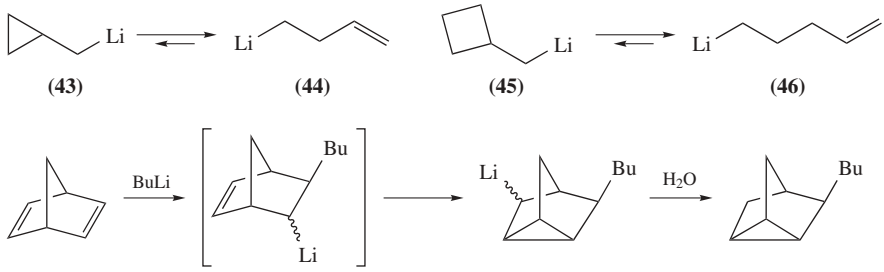
SCHEME 12

C. Scope and Limitations

1. Ring size

Without careful design of the starting material it is not usually possible to form three- and four-membered rings by intramolecular carbolithiation reaction onto carbon–carbon

double bonds because organolithium compounds bearing a three- or four-membered ring adjacent to the carbon–lithium bond undergo rapid ring-opening to give 3-butenyllithium or 4-pentenyllithium derivatives, respectively. Cyclopropylmethyllithium **43** and cyclobutylmethyllithium **45** undergo ring opening to 3-butenyllithium **44** and 4-pentenyllithium **46** (Scheme 13). The kinetics of the ring opening of **45** has been studied by Bailey and coworkers[36] in a solvent system composed of isooctane–dibutyl ether (3:2 by volume) finding $t_{1/2}$ *ca* 3 min for the cleavage of **45** at 0 °C. However, there are some isolated examples of three- or four-membered ring-forming carbolithiation reactions. Wittig and Offen reported in 1960 that the organolithium **47** generated by intermolecular addition of BuLi to norbornadiene undergoes a 3-*exo-trig* intramolecular carbolithiation reaction to afford after protonation compound **48** (Scheme 13)[37].



(43) **(44)** **(45)** **(46)**

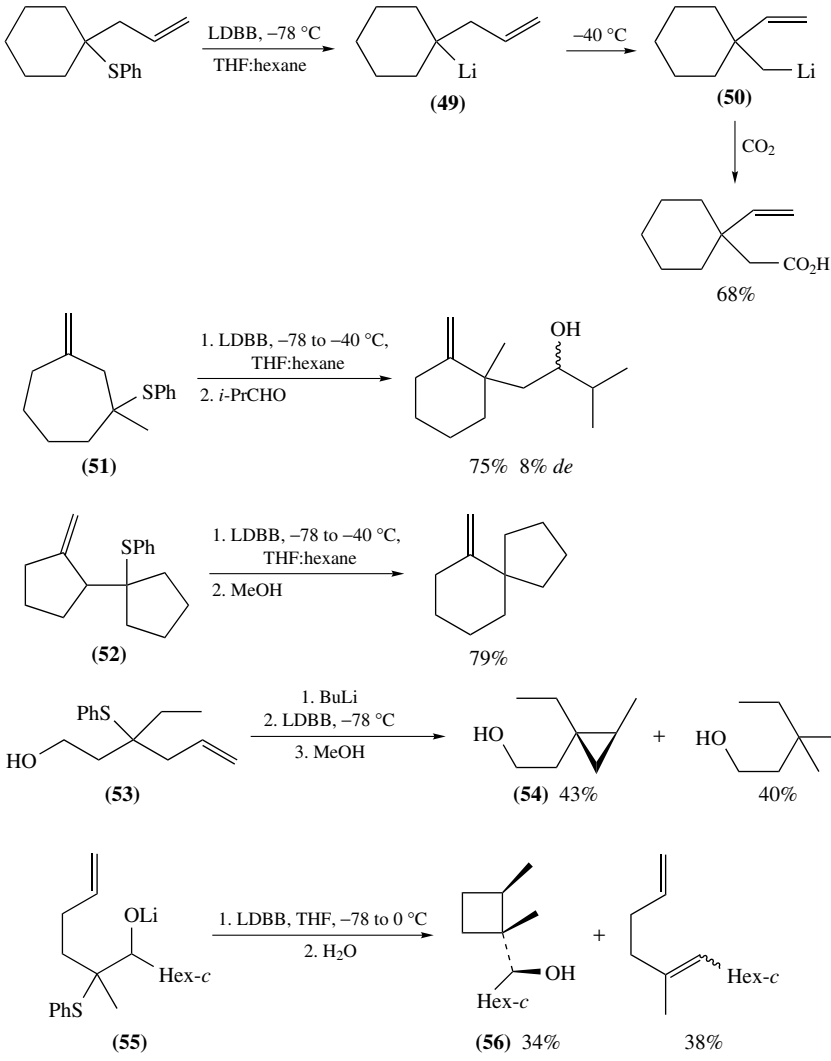
(47) **(48)** 30%

SCHEME 13

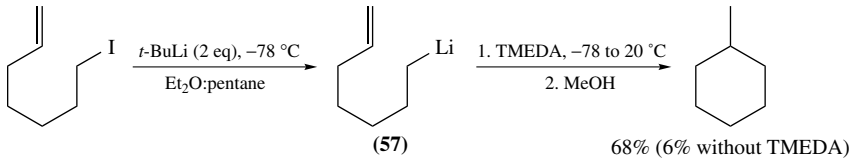
From simple acyclic organolithium compounds, three- and four-membered rings can usually be generated only as transient intermediates. Cohen and Mudryk have used the rearrangements of secondary and tertiary homoallyllithiums as **49**, prepared by reductive lithiation, to less substituted homoallyllithiums **50** via intermediate (cyclopropylcarbinyl) lithiums[38]. By the use of appropriate reactants like **51** or **52**, ring contractions and expansions can be the results of such rearrangements. A very considerable acceleration of the rearrangement of a tertiary homoallyllithium, derived from sulphide **53**, that bears a CH_2CH_2OLi substituent on the lithium-bearing carbon atom, has been attributed to a coordination of the oxyanion to the lithium ion associated with carbon. The stereochemistry of the intermediate (cyclopropylcarbinyl)lithium, which can be detected by the isolation of cyclopropyl derivative **54**, is consistent with this explanation (Scheme 14). Similar chemistry was also reported from these authors for the generation, rearrangements and synthetic uses of bishomoallyllithiums, though their 1,3-vinyl rearrangements via cyclobutylcarbinyllithiums are less facile than the corresponding 1,2-vinyl rearrangements of homoallyllithiums[39]. Cyclobutyl derivative **56** could be isolated in moderate yield from the 4-*exo-trig* carbolithiation reaction of the tertiary organolithium derived from sulphide **55** (Scheme 14).

As discussed later, some examples for the formation of three- and four-membered ring products have been reported from substituted alkenes that generate more stabilized organolithium compounds after cyclization.

Cyclization reactions of a 6-*exo-trig* nature are possible, but are much slower than the 5-*exo-trig* ones, and require the presence of TMEDA and higher temperatures, but they would not reach completion. So 6-heptenyllithium **57**, derived from 7-iodo-1-heptene, isomerizes at room temperature in moderate yield to afford methylcyclohexane (Scheme 15)[40].



SCHEME 14

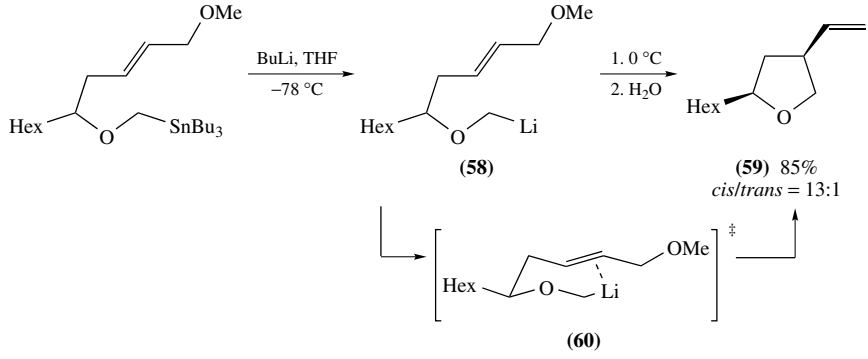


SCHEME 15

On the other hand, as discussed below in the case of acetylenic organolithiums 4-, 5- and 6-*exo-dig* cyclization reactions are possible with appropriate substitution of the triple bond.

2. Substitution of the unsaturated carbon–carbon bond

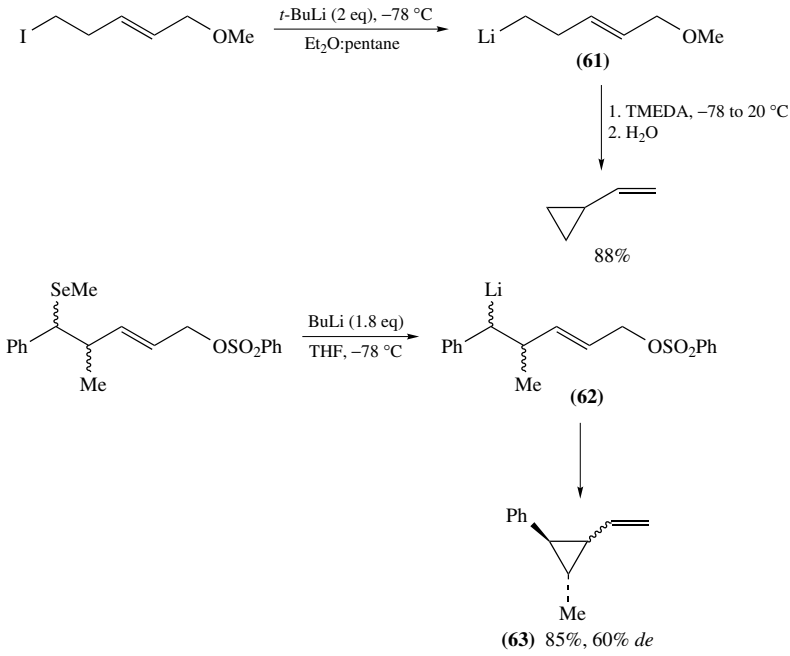
The major drawback of the carbolithiation reactions of olefinic organolithiums is that they are limited to terminal double bonds (i.e. the alkenyl trap may only be monosubstituted or 1,1-disubstituted); this is a key point of divergence from radical cyclizations in which the formation of tertiary radicals is common. However, it has been possible to obtain cyclized products for 1,2-disubstituted olefins when the formed alkyllithium product is substituted with a leaving group in a β-position leading to an elimination reaction of the organolithium. This strategy was first used by Broka and coworkers[41] in the anionic cyclization reaction of α-alkoxy organolithiums as a stereoselective route to tetrahydrofurans. Tin–lithium exchange on an appropriate homoallylic tributylstannylmethyl ether generates the corresponding organolithium **58**, which cyclizes in a highly *cis*-selective way upon warming to 0 °C to afford substituted tetrahydrofuran **59**. The presence of a leaving group at the distal allylic position enhances not only the yield of cyclic product but the stereoselectivity as well. Again, a cyclohexane chair-like transition state (**60**) could be considered to predict the stereoselectivity (Scheme 16). The failure of anions in which the double bond bears an alkyl substituent instead of the methoxymethyl group to cyclize is significant, since it argues against the possible involvement of radical intermediates in the successful cyclizations.



SCHEME 16

Cyclopropane derivatives can be obtained by 3-*exo-trig* cyclization reactions when the resulting cyclopropylmethyllithium can undergo this kind of elimination reaction. Bailey and Tao have prepared vinylcyclopropane in 88% yield by this methodology from the primary organolithium **61**, generated by low-temperature lithium–iodine exchange (Scheme 17)[42]. Also, benzyl selenides like **62** bearing a γ-alkenyl-ε-sulphonyloxy side chain react with BuLi to produce, via the corresponding benzyllithiums, 1-aryl-2-vinyl cyclopropanes **63** with moderate stereoselectivity (Scheme 17)[43].

The ease of these cyclization reactions may be due to the fact that, in the transition state, anionic character can be partially displaced onto oxygen. Independently of the mechanism of these processes which also could be considered as intramolecular S_N' cyclization reactions, this useful trick has been used sometimes for the synthesis of vinylcyclopentanes, vinyl tetrahydrofurans and pyrrolidines, as described above.

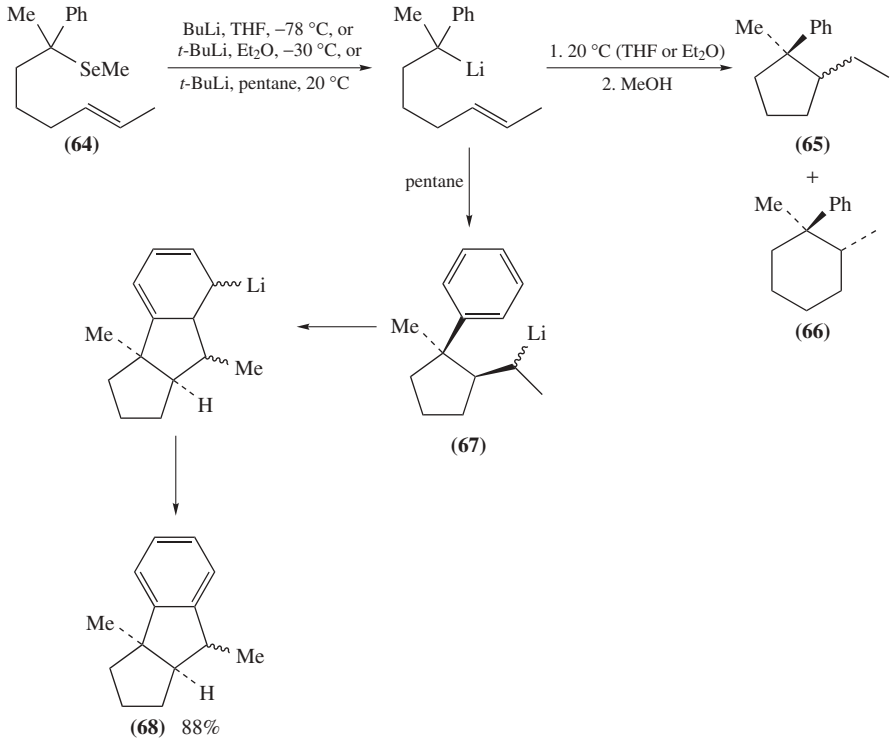


SCHEME 17

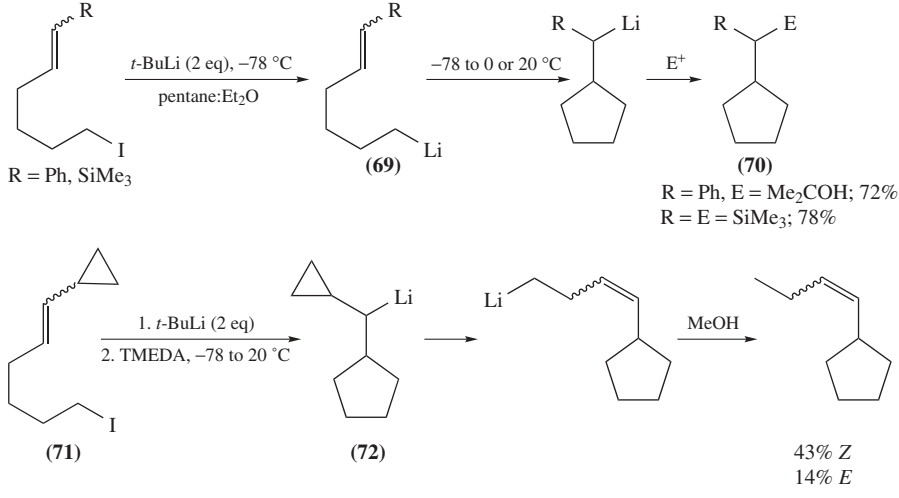
Nevertheless, Krief and coworkers have reported that tertiary benzyllithiums are able to add, though in low yield, to an α,β-dialkyl substituted carbon–carbon double bond. Selenide **64** gives, after selenium–lithium exchange, variable mixtures of 5-*exo*- and 6-*endo*-products **65** and **66** depending upon the solvent used (THF or diethyl ether). Moreover, if cyclization of **64** is carried out in pentane, a cyclopent(*a*)indene derivative **68** can be obtained in very good yield and its formation requires a highly unfavourable addition to a 1,2-disubstituted alkene, followed by attack of the secondary organolithium **67** on the aromatic ring with further re-aromatization by a loss of lithium hydride (Scheme 18)[44]. Attempts to carbolithiate onto a trisubstituted double bond were unsuccessful and only intermolecular metallation of ethylene, generated from THF, was observed.

In this context Bailey and Gavaskar have described that terminally substituted 5-hexenyllithiums bearing a moderately activating phenyl or trimethylsilyl group cleanly undergo a totally regiospecific 5-*exo*-cyclization reaction. Thus, organolithiums **69** afford, after functionalization with electrophiles, products **70** in good yields (Scheme 19)[45]. The ease with which such terminally substituted 5-hexenyllithiums undergo ring closure is a consequence of the ability of the substituents to stabilize the resulting organolithium and interestingly, for R = Ph, the addition to the *E* alkene is faster than to the *Z* isomer. As discussed below, we have recently reported that a tributyltin-substituted alkene is able to be intramolecularly carbolithiated by a *N*-(2-lithioallyl)amine.

On the other hand, cyclization of 6-cyclopropyl-5-hexenyllithium, derived from iodide **71**, is accompanied by ring opening of the three-membered ring in the intermediate organolithium **72**. However, in this case it is not possible to functionalize the putative 3-butenyllithium intermediate, probably due to competing protonation by solvent (Scheme 19)[45].

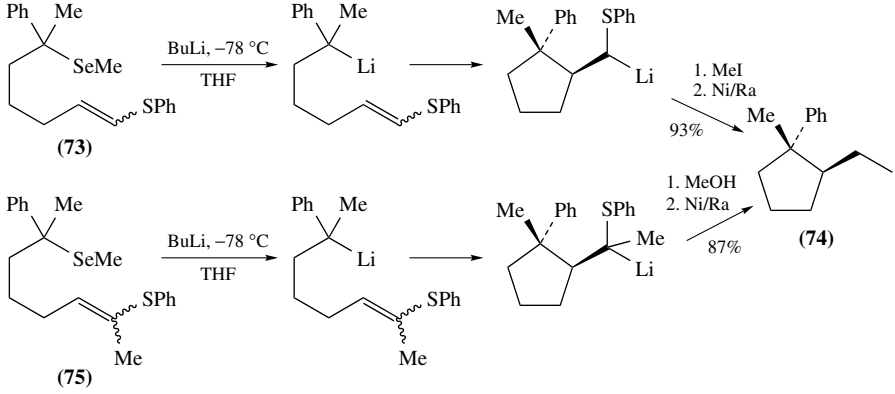


SCHEME 18



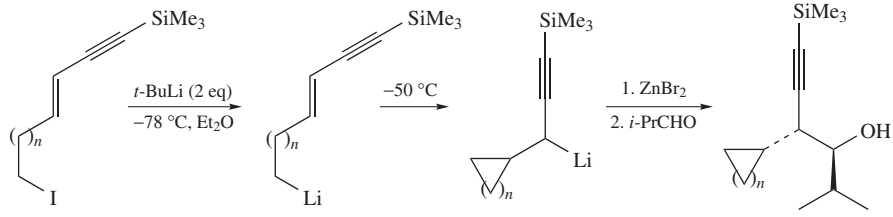
SCHEME 19

Krief and coworkers have also shown that vinyl sulphides are useful traps for the intramolecular carbolithiation reactions. Interestingly, as the sulphide substituent can be reductively removed, the cyclization reactions of benzyllithiums derived from **73** and **75** are synthetically equivalents to cyclizations onto disubstituted double bonds, giving rise by complementary routes to compound **74** (Scheme 20)[46]. Like the corresponding carbolithiation reactions onto monosubstituted alkenes they are highly stereoselective but dependent on the solvent used, i.e. the derivatives in which the methyl- and the phenylthio groups are *cis* (THF) or *trans* (pentane) one to the other are selectively formed.



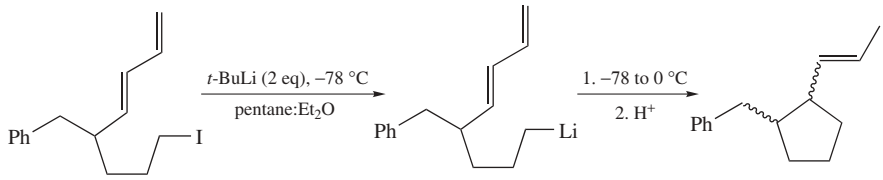
SCHEME 20

Other 1,2-disubstituted alkenes that can be carbolithiated are those substituted by alkynyl and alkenyl groups. Normant and Marek reported that the intramolecular carbolithiation reaction of silylated enynes **76** is easily accomplished at low temperature by iodine–lithium exchange giving rise to cyclized organolithiums **77**. The regioselectivity of the reactions of these propargyllithium species is controlled by transmetallation to the corresponding organozinc derivatives. In this way, functionalized three-, four- and five-membered rings **78** can be obtained in modest to good yields and with high diastereoselectivity (Scheme 21)[47].



SCHEME 21

Also, dienes can act as traps for organolithium cyclizations as showed by Cooke and Huang by the efficient formation of **80** as a mixture of ring substitution and olefin isomers



(79) **(80)** 94%

SCHEME 22

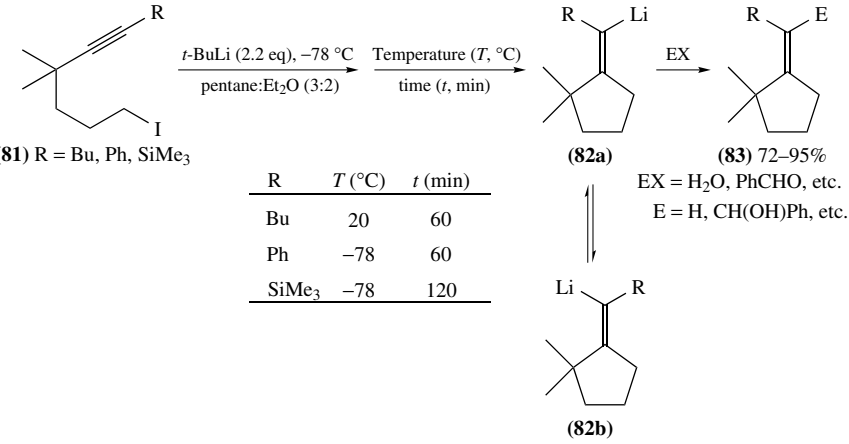
from the alkyllithium generated from iodide **79**. This successful intramolecular diene addition is significant insomuch as alkyllithium additions to unactivated dienes usually result in polymer formation (Scheme 22)[48].

On the other hand, for the carbolithiation reaction of alkynes an obvious limitation is that terminal alkynes are always deprotonated by organolithium reagents. Moreover, in some cases disubstituted ones are not readily carbolithiated if other reaction pathways, such as deprotonations of propargylic positions, occur more readily. While *endo-trig* cyclization reactions are rare for organolithiums, *endo-dig* ones are in general more favourable. However, it is impossible for the *endo-dig* cyclization reactions to proceed via the usual *syn*-carbolithiation mechanism because this would generate a *trans*-double bond in the ring. With silyl or aryl stabilizing substituents on the triple bond, it was also possible to make four- and six-membered rings by *exo-dig* cyclization reactions.

As shown in Scheme 6, these intramolecular carbolithiation reactions of alkynes are *syn*-stereospecific processes and so iodine–lithium exchange on iodides **81** gives rise to isomerically pure (*Z*)-vinyllithiums **82a** that may be functionalized to yield stereoisomerically pure products **83**. However, whereas alkyl-substituted vinyllithium intermediates are configurationally stable at room temperature, the corresponding aryl- or trimethylsilyl-substituted ones are less geometrically stable, yielding a mixture of vinyllithiums **82a** and **82b**. Hence the ratio of cyclic isomers produced upon carbolithiation reaction of phenyl- or trimethylsilyl-substituted 5-hexynyllithiums was found to be strongly dependent on the temperature at which the reaction was carried out and careful control of the conditions is needed in order to get good selectivities (Scheme 23)[49].

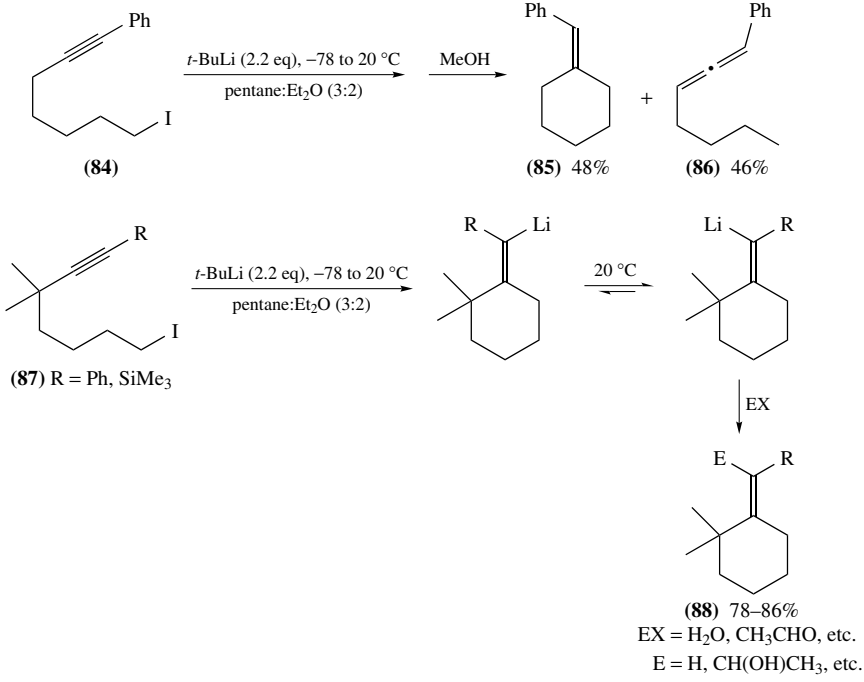
The 6-*exo-dig* cyclization mode was also tested by Bailey and Ovaska, by treatment of iodide **84** with *t*-BuLi and quench of the reaction mixture after warming to 20 °C. A 1:1 mixture of benzylidenecyclohexane **85** and allene **86** was obtained. It seems that ring closure of phenyl-substituted 6-heptynyllithiums and prototropic rearrangement leading to allenes are competitive processes at the elevated temperature needed for a 6-*exo* carbolithiation reaction (Scheme 24). Six-membered rings such as **88** could only be formed in high yield when the propargylic positions of the alkyne are blocked, like in iodides **87**, to avoid allene formation. However, the temperatures required to effect cyclization (20 °C) cause the isomerization of the first-formed *Z*-vinyllithium to the corresponding *E* isomer[50].

With silyl or phenyl stabilizing substituents (but not with alkyl) it is also possible to prepare four-membered rings by 4-*exo-dig* cyclization reactions. As shown in Scheme 25, unsubstituted cyclobutane derivatives **90** are formed in high yields from iodides **89** after reaction with *t*-BuLi and further warming to room temperature. The stereochemistry of the cyclization of phenyl- and trimethylsilyl-substituted 4-pentynyllithiums was tested employing iodides **91** bearing *gem*-dimethyl substituents at the propargylic position. The cyclization of these compounds was found to be a stereoselective *syn*-process when care was taken to carry out the carbolithiation reaction at a temperature low enough to preclude



R	*T* (°C)	*t* (min)
Bu	20	60
Ph	−78	60
$SiMe_3$	−78	120

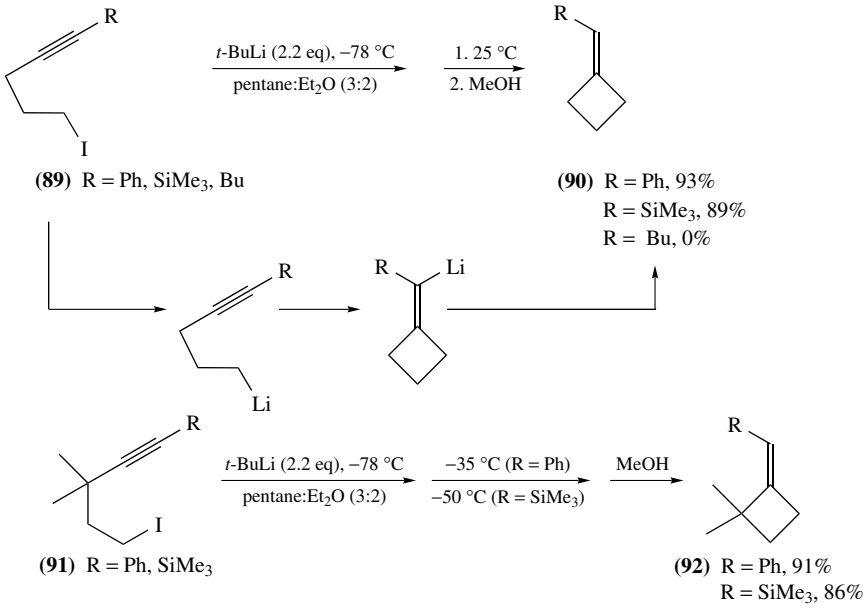
SCHEME 23



SCHEME 24

cis–trans isomerization of the vinyllithium products, and so isomerically pure compounds **92** could be isolated in good yields (Scheme 25)[49,50].

With convenient methods available for the generation of unsaturated organolithiums without the involvement of radical intermediates and a theoretical basis for predicting



SCHEME 25

the stereochemical outcome of these anionic cyclization reactions, the intramolecular carbolithiation reaction of olefinic organolithiums has been developed as a synthetic method to provide a regiospecific and highly stereoselective route to five-membered carbocycles[51] and heterocycles[52].

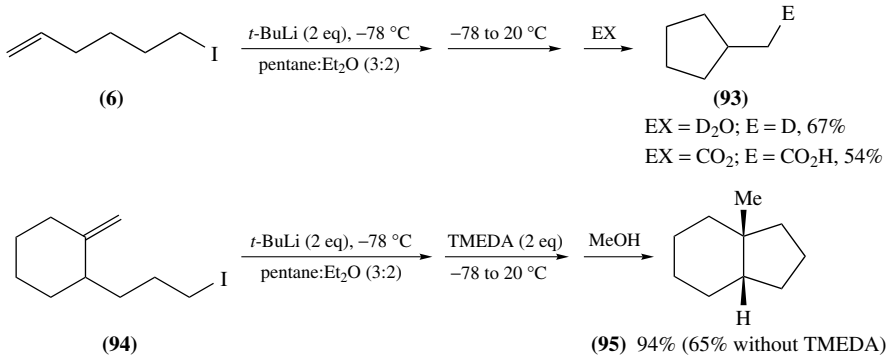
III. CARBOLITHIATION REACTION OF UNSATURATED ALKYLLITHIUMS

A. Cyclization Reaction of Olefinic Alkyllithiums

5-Hexenyllithiums undergo regiospecific 5-*exo-trig* cyclization reactions giving the corresponding cyclopentylmethyllithium derivatives. This section has been divided on the basis of the method used for the generation of the starting alkyllithium derivative.

1. Halogen–lithium exchange-derived alkyllithiums

The halogen–lithium exchange is the most general method to generate primary alkyllithiums. Iodoalkanes are the best substrates and optimum conditions involve the use of two equivalents of *t*-BuLi at $-78\,^{\circ}C$ in a solvent system such as 3:2 pentane:diethyl ether. However, organolithiums generated under these conditions often contain a small amount of hydrocarbon formally derived from reduction of the halide due to a partial elimination of HI from the *t*-BuI by-product. In contrast to the clean iodine–lithium exchange, the use of analogous bromides results in messy reactions and alkyl chlorides are essentially inert when treated with *t*-BuLi at $-78\,^{\circ}C$. As we have discussed in Scheme 2, carbolithiation reaction of 5-hexenyllithium takes place efficiently at room temperature and the intermediate cyclopentylmethyllithium can be trapped with electrophiles delivering methylcyclopentane derivatives **93**. To get good yields of functionalized products,



SCHEME 26

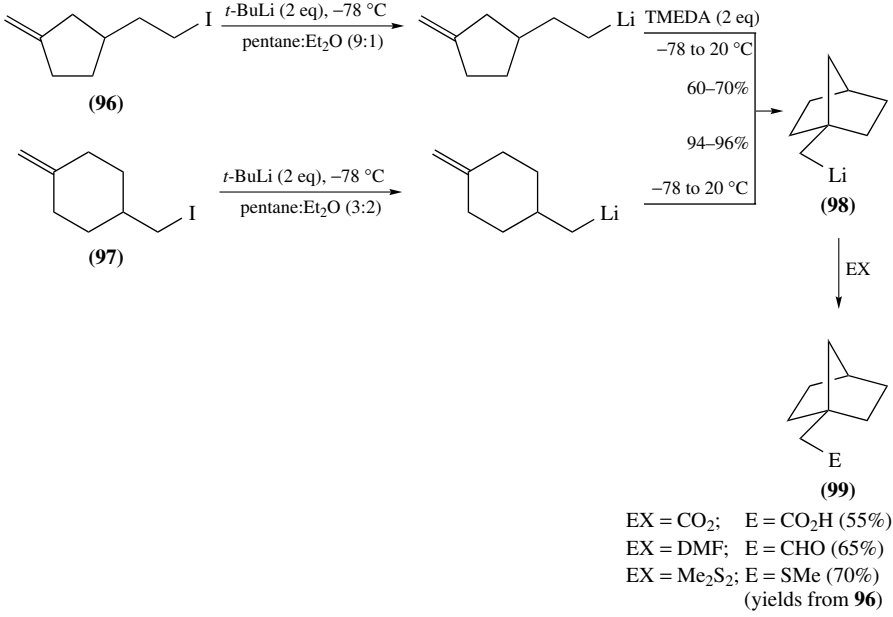
excessive reaction times are undesirable due to partial hydrolysis of the intermediate organolithium by the solvent (Scheme 26)[40].

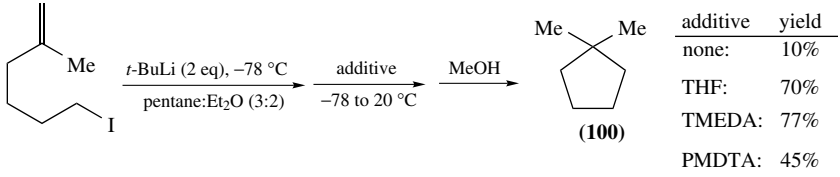
The cyclization reactions of 1,1-disubstituted olefin-containing substrates like **94** are sluggish at room temperature but they are facilitated by the addition of 2 equiv of TMEDA to the reaction mixture. As an example, **95** is formed in 65% yield without TMEDA, but 95% in its presence (Scheme 26).

Bailey and coworkers have also reported that anionic cyclization of 2-(3-methylenecyclopentyl)ethyllithium, derived from iodide **96**, provides a convenient route to 1-substituted bicyclo[2.2.1]heptanes **99** via a 5-*exo-trig* carbolithiation reaction, which requires the presence of TMEDA and produces (1-norbornylmethyl)lithium **98**[53]. A couple of years later these authors described an alternative way of generating the same organolithium **98** starting from iodide **97** via a 5-*exo-trig* cyclization of 1-(lithiomethyl)-4-methylenecyclohexane[54]. While formation of **98** from **96** is sluggish and moderate yields are obtained, it could be obtained almost quantitatively from **97** and the presence of TMEDA is not required (Scheme 27).

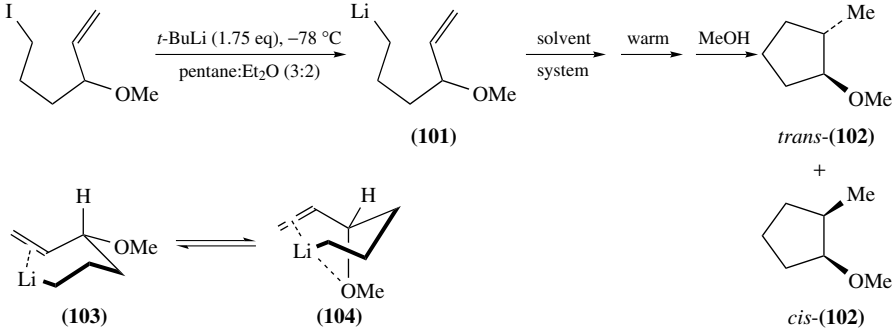
Lithiophilic Lewis bases are also necessary for the formation of **100** via a 5-*exo-trig* carbolithiation reaction of a 1,1-disubstituted olefin. The relative efficacy of additives like THF, TMEDA or PMDTA has been studied by these authors (Scheme 27)[22].

Although these Lewis bases have been found to increase the rate of cyclization of substituted 5-hexenyllithiums, the high stereoselectivities characteristic of the anionic cyclization are not adversely affected[22]. However, the cyclization of (4-methoxy-5-hexenyl)lithium **101**, which was prepared by iodine–lithium exchange from the corresponding iodide, gives rise to *cis*- and *trans*-1-methoxy-2-methylcyclopentanes **102**. Its isomeric ratio has been found to be dramatically dependent on the solvent system in which the carbolithiation reaction is conducted. The behaviour of **101** in pentane:diethyl ether is analogous to that of 4-alkyl-substituted 5-hexenyllithiums and the *trans*-selective nature of the cyclization is accommodated by a chair-like transition state **103** in which the 4-methoxy substituent preferentially occupies a pseudo-equatorial position. The stereochemistry of the isomerization of **101** is reversed in the presence of THF or TMEDA, and this *cis*-selective cyclization is rationalized by the transition state **104** which is stabilized via intramolecular coordination of the lithium atom with the proximal oxygen atom of the ether moiety. Bailey and coworkers tentatively propose that the Lewis base additives could sequester the lithium iodide generated in the initial exchange reaction favouring the intramolecular lithium–oxygen interaction (Scheme 28)[55].



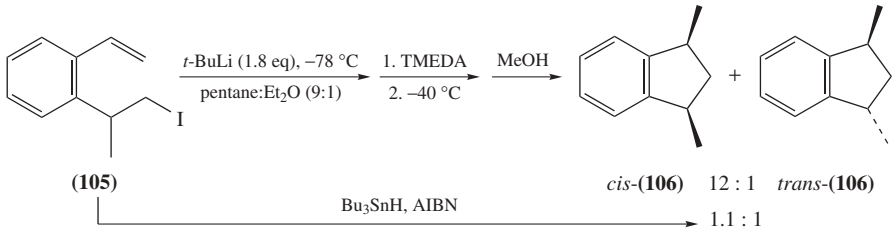


SCHEME 27



SCHEME 28

Another example in which the stereochemistry of the carbolithiation reaction is not easily predicted is shown in Scheme 29. In the course of investigations for the preparation of 1,3-dimethylindans via a radical-mediated cyclization or intramolecular carbolithiation reaction, Bailey and coworkers showed that whereas 2-(2-iodo-1-methylethyl)styrene **105** gives an almost equimolar mixture of *cis*- and *trans*-isomers of 1,3-dimethylindan **106** under treatment with a radical source, the corresponding intramolecular carbolithiation reaction is highly *cis*-selective (Scheme 29)[56]. As shown in Table 1 and Scheme 8, the cyclization of 2-substituted-5-hexenyllithiums usually takes place in a *trans*-selective way. The factors responsible for this unexpected *cis*-selective cyclization reaction were investigated computationally and the results of this analysis showed that the computed activation free energy for cyclization from the lower energy intramolecularly coordinated ground state (a *trans*-complex) to the *cis*-product via a *cis*-transition state is 0.69 kcal mol^{-1} favoured over the corresponding cyclization via a *trans*-transition state to a *trans*-product.

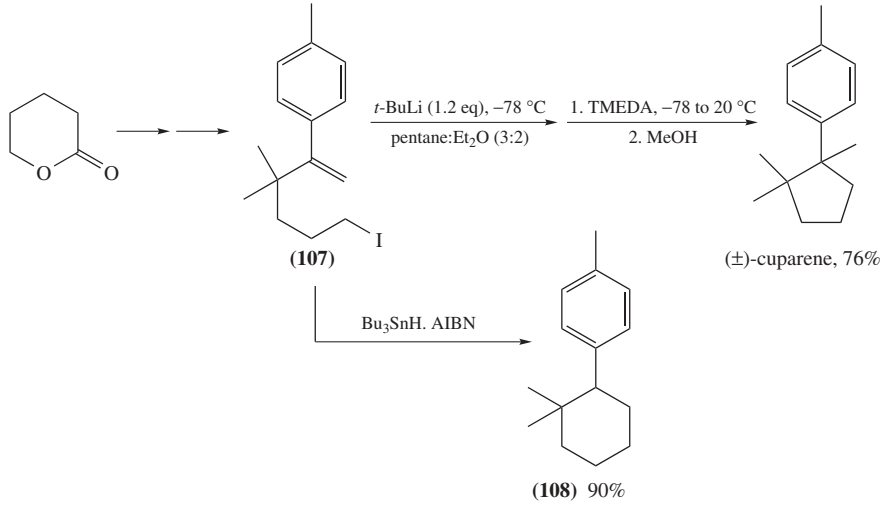


SCHEME 29

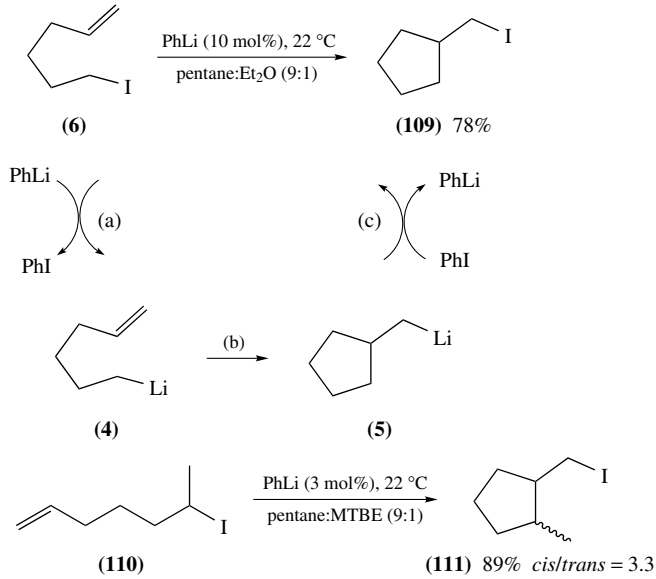
The naturally occurring sesquiterpene (±)-cuparene which contains two contiguous quaternary centres has also been prepared by Bailey and Khanolkar from iodide **107**, easily available from δ-valerolactone. The standard conditions for the iodine–lithium exchange have to be modified in order to avoid intermolecular addition of a second molecule of *t*-BuLi to the styrene double bond. The exclusively 5-*exo*-isomerization observed for the intramolecular carbolithiation reaction again contrasts with the radical mediated cyclization of **107** that proceeds via the 6-*endo-trig* mode to give **108** in very good yield and serves to highlight the often complementary behaviour of these two ways of ring closure (Scheme 30)[57].

Bailey and Carson have suggested that the reversible nature of the iodine–lithium exchange may be exploited to effect clean isomerization of 6-iodo-1-hexene (**6**) to (iodomethyl)cyclopentane **109** upon treatment of the unsaturated alkyl iodide with a catalytic amount of phenyllithium[58]. This novel cycloisomerization apparently involves three discrete steps as illustrated in the catalytic cycle shown in Scheme 31: (a) reversible exchange between the iodide precursor and phenyllithium, (b) irreversible cyclization and (c) regeneration of phenyllithium by iodine–lithium exchange. Interestingly, a secondary iodide like **110** is converted to its cyclic isomer **111** in good yield (Scheme 31). The process seems to be general and several 5-hexenyl iodides, including primary, secondary, tertiary or aryl, may be transformed into their cyclic isomers in the presence of a catalytic quantity of phenyllithium[59].

The mechanism of these transformations seems to be substrate-dependent and only the cycloisomerization of aryl and primary iodides was thought to proceed as shown in Scheme 31. The stereoselectivity of the isomerization of **110** to **111** is better accommodated with the intermediacy of 1-methyl-5-hexenyl radical[59]. Later, it was proposed that the isomerization of **6** to **109** also proceeds via a radical-mediated atom transfer process initiated by homolytic fragmentation of an ate-complex intermediate **112** (Scheme 32)[60].

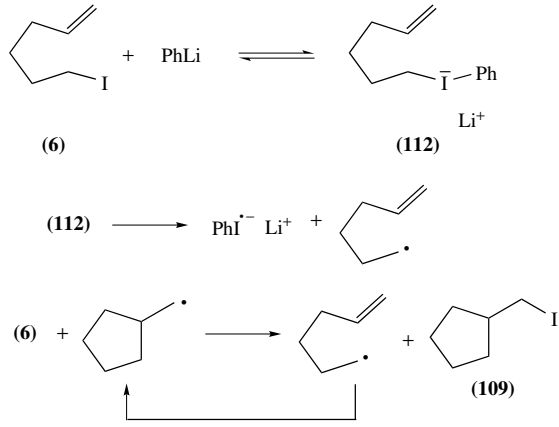


SCHEME 30

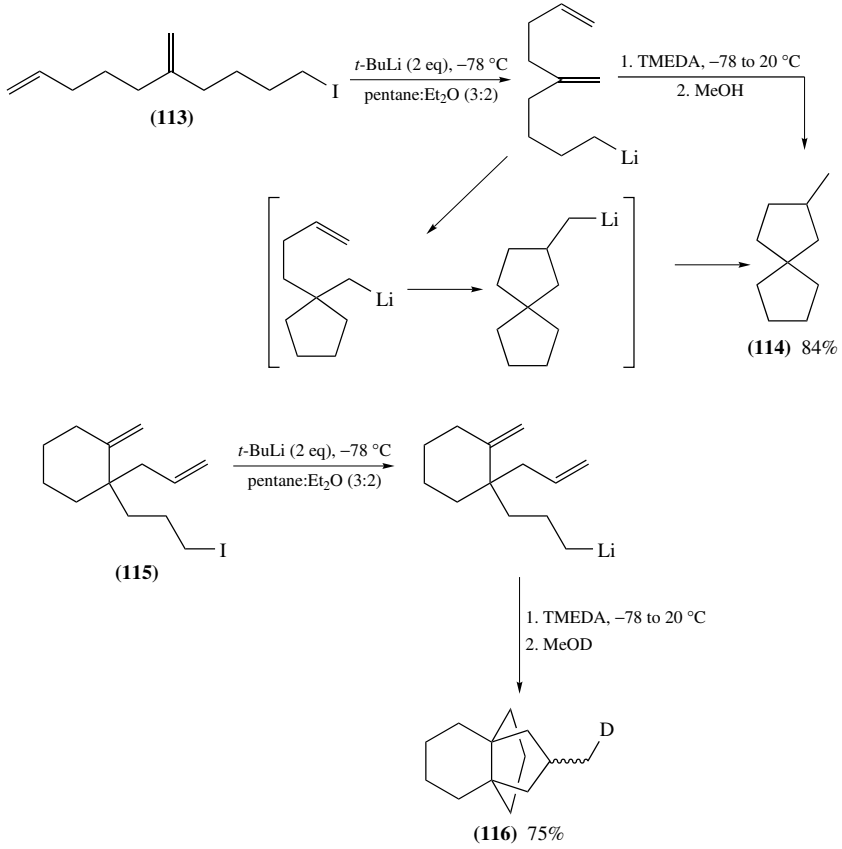


SCHEME 31

The stereocontrol inherent in the totally regiospecific 5-*exo-trig* isomerizations of substituted 5-hexenyllithiums may be exploited for the stereoselective synthesis of bicyclic systems by tandem cyclization of acyclic diolefinic alkyllithiums. To date, this strategy has not been widely applied, and the first examples were reported by Bailey and Rossi who were able to cyclize the organolithiums derived from iodides **113** and **115** in the presence of TMEDA to afford the polycarbocyclic products **114** and **116** (Scheme 33)[61].



SCHEME 32



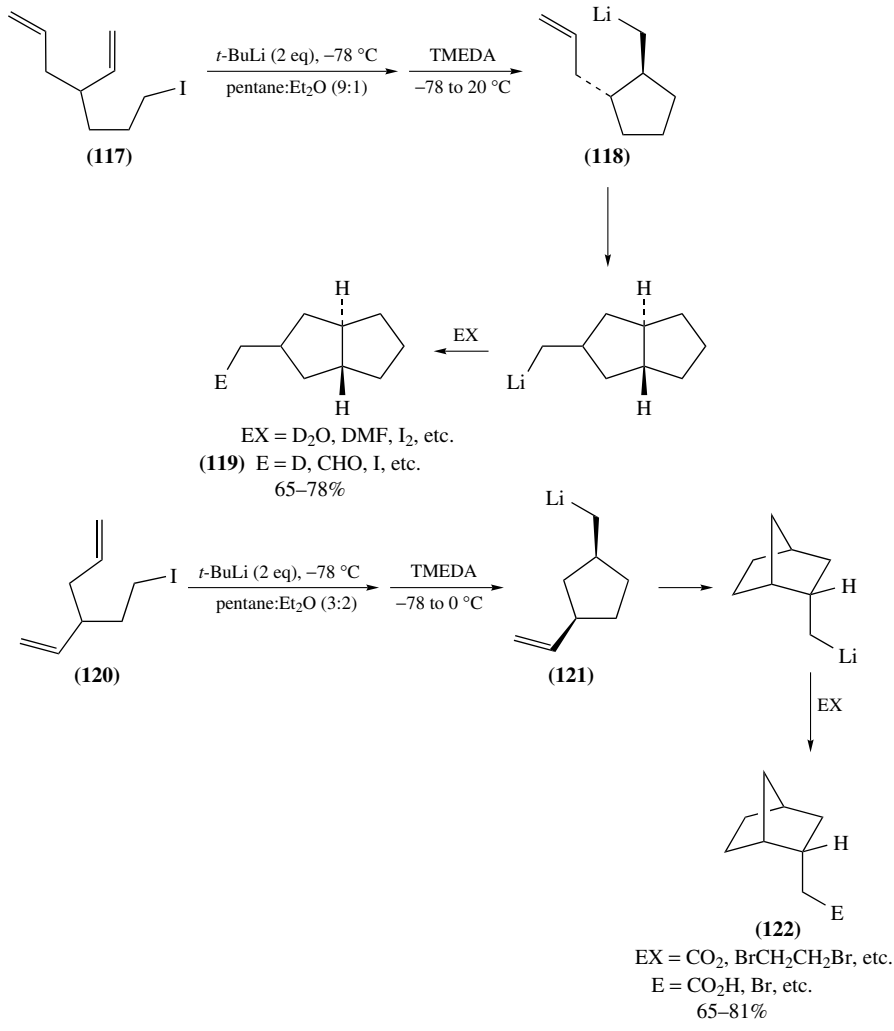
SCHEME 33

Cascade carbolithiation reactions can be stereoselective as shown by these authors in Scheme 34[62]. First, (4-allyl-5-hexenyl)lithium derived from iodide **117** isomerizes to afford a cyclopentane incorporating a *trans*-disposed 5-hexenyllithium moiety **118**, which on subsequent cyclization would deliver a *trans*-fused bicyclo[3.3.0]octane skeleton, 6.1–6.4 kcal mol^{-1} less stable than its *cis*-isomer. Despite this fact, 3-functionalized-*trans*-bicyclo[3.3.0]octane derivatives **119** are obtained in useful yields carrying out the initial iodine–lithium exchange in a 9:1 mixture of pentane:diethyl ether to minimize quench of the reactive organolithium intermediates prior to the trapping with electrophiles (Scheme 34). The ease with which the relatively inaccessible *trans*-bicyclo[3.3.0]octane skeleton is prepared by this methodology indicates that the initial stereoselective isomerization of (4-allyl-5-hexenyl)lithium to **118** is apparently operationally irreversible and kinetically controlled and the facility of the second carbolithiation reaction is an indication of the favourable thermodynamics associated with such isomerizations. On the other hand, *endo*-2-substituted bicyclo[2.2.1]heptanes **122** are readily prepared by tandem cyclization reactions of (3-ethenyl-5-hexenyl)lithium, derived from iodide **120**. Consideration of the chair-like transition state for the carbolithiation reaction of a 3-substituted 5-hexenyllithium suggests that the *cis*-product **121** should be formed with a high degree of stereocontrol upon monocyclization of (3-ethenyl-5-hexenyl)lithium and in fact the bicyclo[2.2.1]heptane system is generated diastereoselectively (*endo/exo ca* 50/1) (Scheme 34). Consequently, tandem anionic cyclization reactions provide a convenient and selective route to a variety of molecular frameworks that are not readily available by other approaches.

2. Selenium–lithium exchange-derived alkyllithiums

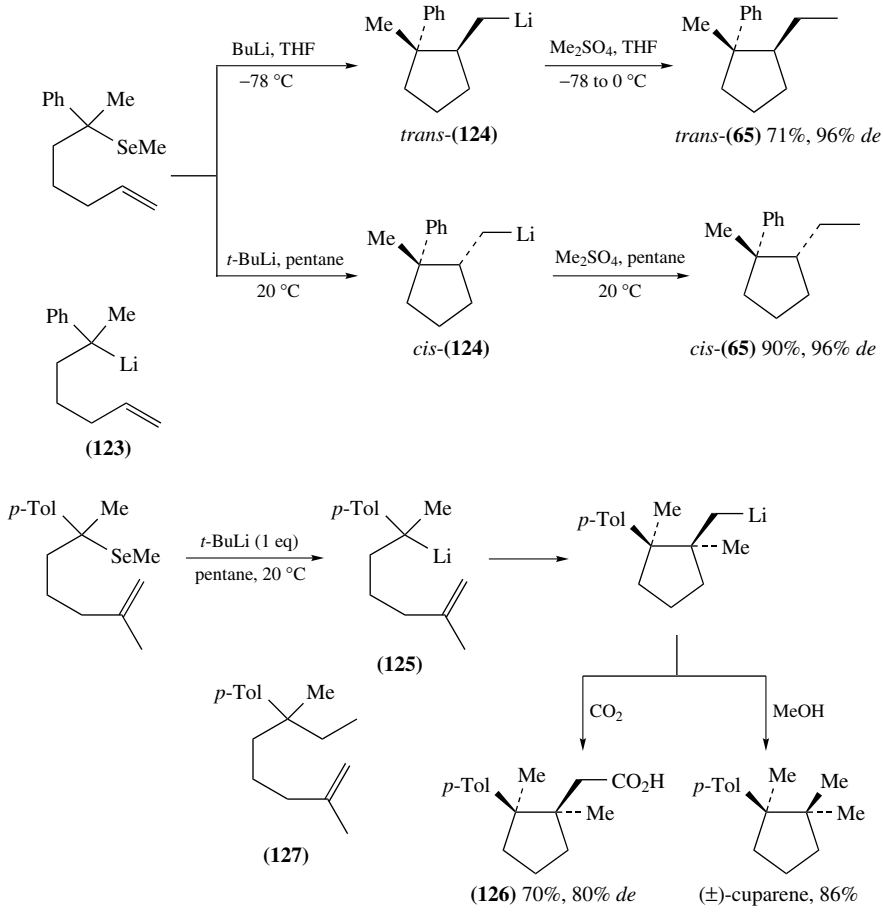
Since Krief and Barbeaux reported that benzyl selenides are very good precursors of benzyllithiums[63], these authors have described several examples that show the high propensity of these organolithiums to add to unactivated carbon–carbon double bonds. In 1987 they described that the parent ω-alkenylbenzyllithium **123**, generated by selenium–lithium exchange from the corresponding tertiary selenide, rearranges diastereoselectively (>20:1) in THF to the corresponding cyclopentylmethyllithium *trans*-**124**, which after hydrolysis leads to *trans*-1,2-dimethyl-1-phenylcyclopentane. Moreover, the stereocontrol depends upon the reaction conditions (nature of the solvent and temperature of the reaction). Thus, changing from THF and −78 °C to pentane and 20 °C completely reverses the selectivity from *trans*- to *cis*-diastereoisomer (Scheme 35)[64]. As shown in Scheme 18, this reaction cannot be extended to the synthesis of 2-ethyl-1-methyl-1-phenylcyclopentane **65** from selenide **64** owing to the high propensity of the intermediate organolithium to further react across the carbon–carbon double bond of the aromatic ring. An alternative route to **65** was accomplished by trapping organolithium intermediates **124** with methylating agents, dimethyl sulphate being the best option (Scheme 35)[65]. These authors also showed that cyclopentanes with two contiguous quaternary centres are accessible by this methodology, and so (±)-cuparene is synthesized in a straightforward way from benzyllithium **125**. This strategy uses a different disconnection from the one followed by Bailey and coworkers (see Scheme 30). In this case, the use of *t*-BuLi as base and pentane as solvent seem to be crucial for a successful reaction. When THF is used as solvent, formation of compounds **125** and **127**, derived from an addition of ethylene, is also produced. The isolation of acid **126** upon carbonation of the intermediate cyclized organolithium shows the diastereoselectivity of the process (Scheme 35)[66].

Krief and Barbeaux have also applied the selenium–lithium exchange methodology to some cascade carbolithiation reactions as shown in Scheme 36[67]. The 1,1-(bismethylseleno) derivative **128** undergoes a selenium–lithium exchange at −78 °C giving



SCHEME 34

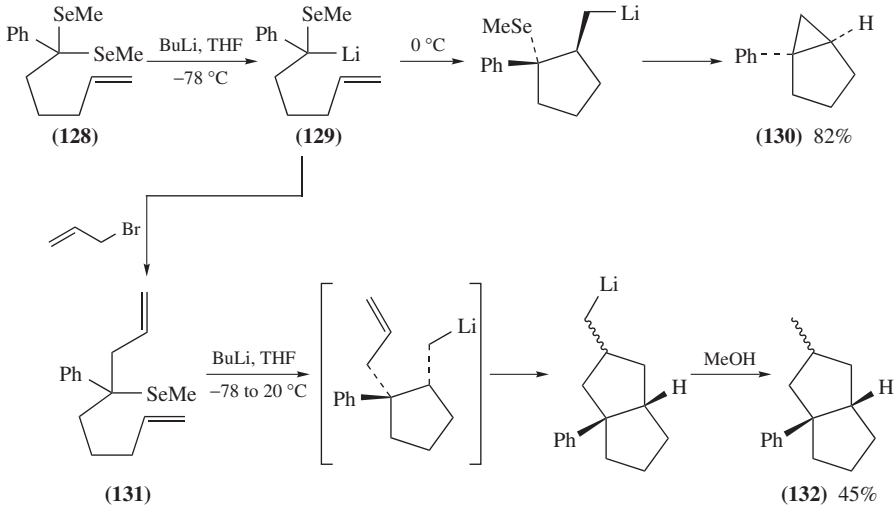
rise to tertiary benzylic anion **129**, which can be trapped with electrophiles (allylation affords product **131**). If **129** is warmed to 0 °C, 1-phenylbicyclo[3.1.0]hexane **130** is obtained in very good yield and its formation involves a 5-*exo* carbolithiation reaction and the subsequent intramolecular displacement of the selenium moiety. On the other hand, selenium–lithium exchange on **131** initiates a tandem cyclization process which involves two successive 5-*exo* cyclizations giving rise, after hydrolysis, to bicyclic compound **132** as a 75/25 mixture of diastereoisomers (Scheme 36).



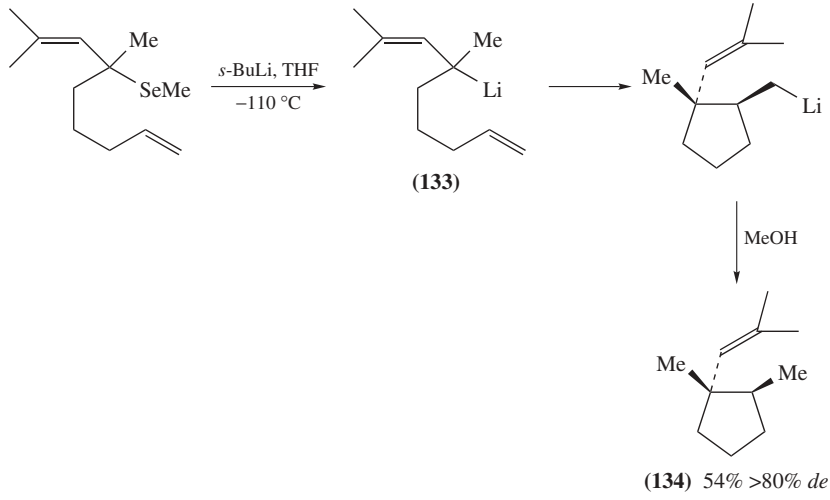
SCHEME 35

Krief and coworkers have extended this methodology to the corresponding allyllithiums showing that ω-alkenyllithiums as **133**, generated from the corresponding selenide, rapidly cyclize to produce, after hydrolysis, 1-methyl-2-vinylcyclopentanes **134** with high regio- and stereocontrol. The stereochemistry of the product proved again to be highly dependent upon the nature of the solvent (in diethyl ether at $-30\,^{\circ}C$ **134** was obtained in 40% yield but >99% *de*) (Scheme 37)[68].

1-Methoxybenzyllithiums bearing a suitably positioned carbon–carbon double bond like **135** possess a high propensity to produce stereoselectively the *cis*-isomer of cyclopentylmethyllithium derivative **136** that can be further functionalized with electrophiles, affording in good yields compounds **137**. The high stereocontrol of the cyclization, observed in all the solvents used, is probably due to the squeezing of the lithium cation, in the transition state, between the methoxy group and the carbon–carbon double bond. Moreover, this process



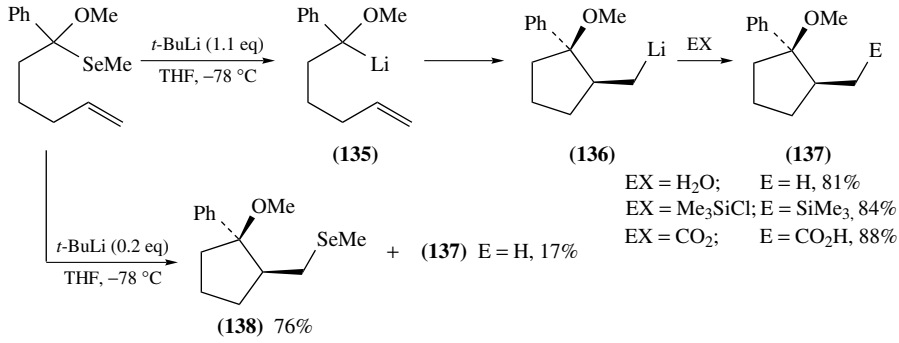
SCHEME 36



SCHEME 37

can be made catalytic in *t*-BuLi, due to the fact that intermediate **136** is able to cleave the selenium–carbon bond of the starting selenide, producing at the same time **138** and **135**. At the end, **138** is obtained in 76% yield besides 17% of **137** (E = H) corresponding to the amount of *t*-BuLi used in the reaction (Scheme 38)[69].

In this field, Krief and coworkers have also reported that the ω-styrenylbenzyllithium derived from 1,6-diphenyl-6-(methylseleno)-1-heptene **139** and butyllithiums provides after methanolysis *cis*- or *trans*-2-benzyl-1-methyl-1-phenylcyclopentane **140** with very

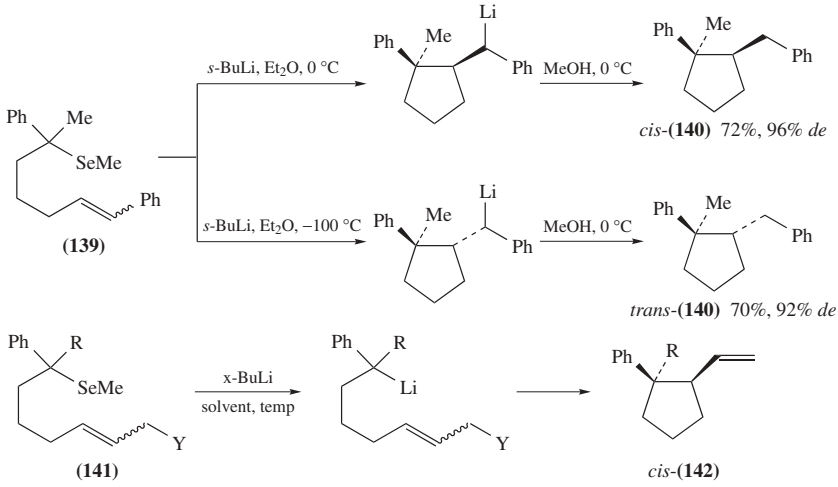


SCHEME 38

high stereocontrol. The compound bearing these two groups in *trans*-position is produced when the reaction is carried out in THF at $-78\,^{\circ}C$ or in diethyl ether at $-100\,^{\circ}C$, whereas its diastereoisomer is generated if the reaction is performed in diethyl ether at $0\,^{\circ}C$. In diethyl ether the ratio of stereoisomers changes continuously between $0\,^{\circ}C$ and $-100\,^{\circ}C$. These reactions occur under kinetic control in the whole range of temperature studied from $-100\,^{\circ}C$ to $0\,^{\circ}C$, since the same ratio of stereoisomers is obtained when the reaction performed at $-100\,^{\circ}C$ and is then quenched with MeOD either at that temperature or at $0\,^{\circ}C$ (Scheme 39)[70]. On the other hand, benzyl selenides bearing a side chain possessing in suitable position an allylic ether like **141** react with butyllithiums and produce, via the corresponding benzyllithiums, 1-aryl-2-vinylcyclopentanes such as **142**. The stereochemistry at the cyclopentane derivatives is controlled by the solvent and leads to the same stereocontrol as shown in Scheme 35; the aryl and the alkenyl chains (alkyl in compound **140**) are *cis* in pentane and *trans* in THF, starting from tertiary benzyllithiums. As discussed above, this cyclization reaction could involve a carbometallation reaction followed by a β-elimination of the alkoxide moiety or a S_N'-type reaction which can be concerted or not (Scheme 39)[71].

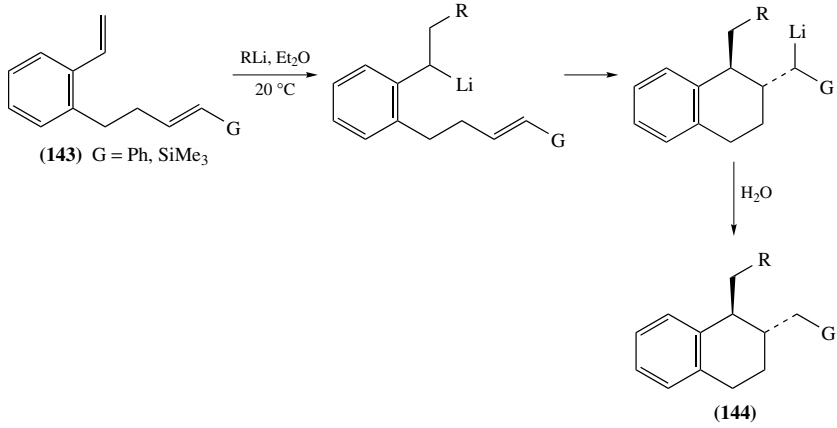
3. Alkyllithiums prepared by intermolecular carbolithiation reactions

Taylor and Wei have reported that styrene and 2-substituted styrenes undergo efficient addition and addition–trapping reactions with a range of organolithium reagents[72] and when the addition–carbolithiation reactions are carried out in the presence of (−)-sparteine, moderate *ee* can be obtained[73]. These authors have also explored the possibility of performing tandem intermolecular–intramolecular carbolithiation reactions to afford a variety of cyclized compounds. First, styrenes bearing unsaturated side chains at the 2-position like **143** undergo regioselective carbolithiation reaction of the styrene unit followed by 6-*exo-trig* cyclization to produce 1,2-disubstituted tetralins **144**. Only examples with moderately activated alkene traps, like styrenyl or vinylsilanes, were reported and the *trans*-stereoselectivity of the process also depends on the alkene moiety (Scheme 40)[74]. Later, these authors extended this strategy to the preparation of silacyclopentanes using vinyl silanes **145** as starting products. Regioselective intermolecular addition of BuLi promotes further intramolecular carbolithiation reaction onto the same kind of alkene-traps described above. In this case, moderate *trans*-selectivities were obtained in the cyclization step affording compounds **146** (Scheme 40)[75].



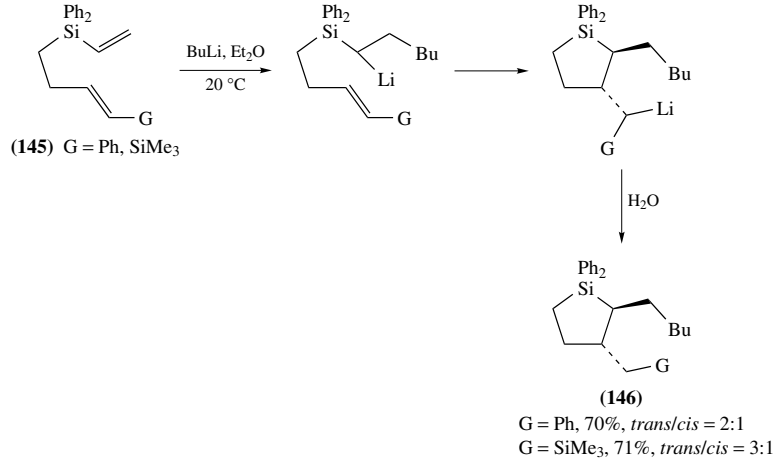
R	Y	*x*-	Solvent	Temp (°C)	Yield (%)	*cis*/*trans*
Me	OMe	*n*-	THF	−78	85	2/98
Me	OMe	*t*-	pentane	22	88	98/2
Me	OMEM	*n*-	THF	−78	83	3/97
Me	OMEM	*t*-	pentane	22	83	93/7
H	OMe	*t*-	pentane	22	76	97/3

SCHEME 39



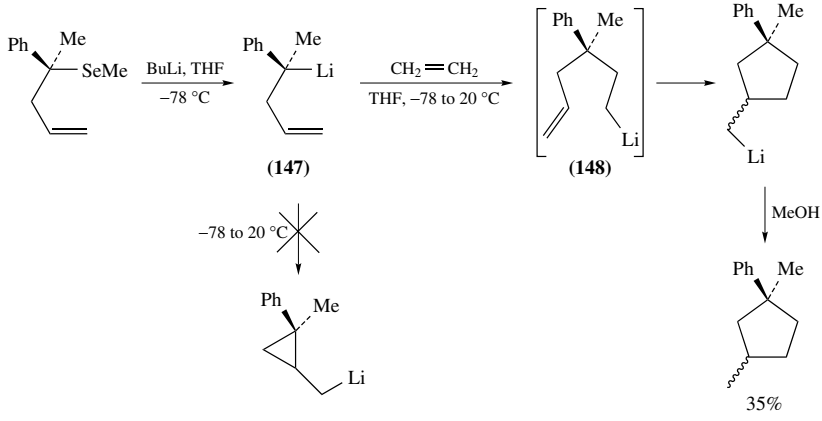
R	G	Yield (%)
Bu	Ph	71 (*trans*/*cis* = 2.2:1)
Bu	$SiMe_3$	75
Hex	$SiMe_3$	71

SCHEME 40



SCHEME 40. (*continued*)

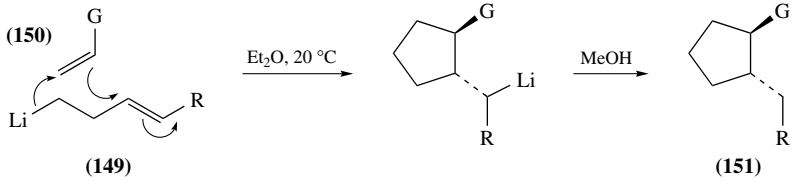
Trying to carry out 3-*exo* carbolithiation reactions with the tertiary benzyllithium **147**, generated by selenium–lithium exchange, Krief and Barbeaux have reported[66] an isolated example of the reaction of this homoallylic lithium reagent with ethylene and further intramolecular carbolithiation reaction of intermediate **148** onto the suitably positioned carbon–carbon double bond. The resulting 1,3-dimethyl-1-phenylcyclopentane was isolated in modest yield and as a 1:1 mixture of diastereoisomers (Scheme 41).



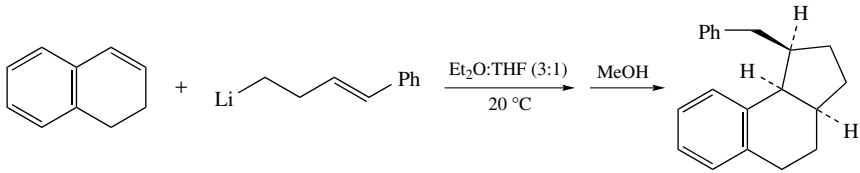
SCHEME 41

Taylor and Wei have also developed a versatile method for the synthesis of cyclopentanes employing readily available organolithium compounds as difunctional, conjunctive reagents. This strategy represents an anionic [3 + 2] approach to substituted cyclopentanes. The reactions of lithiated alkenes **149** with 'activated' alkenes **150** afford cyclopentane derivatives **151** in reasonable yield and, in some cases, with excellent stereocontrol. The alkenes **150** must be added over extended times to minimize polymerization processes. The

low stereoselectivity observed in the reaction of styrene (**150**, G = Ph) and **149** (R = Ph) is tentatively explained by a π-stacking effect, which provides added stabilization for the corresponding *cis*-isomer of **151**. These reactions can also be carried out on disubstituted alkenes, and thus reaction of **149** (R = Ph) with 1,2-dihydronaphthalene produces tricycle compound **152** as the only isolable product, though minor diastereomeric impurities were also detected. The *cis,cis* stereochemistry of **152** presumably again reflects a π-stacking effect (Scheme 42)[76].



G	R	Yield (%)	*trans/cis*
Ph	Ph	52	50:50
Ph	$SiPh_3$	45	100:0
$SiMe_3$	Ph	52	100:0



SCHEME 42

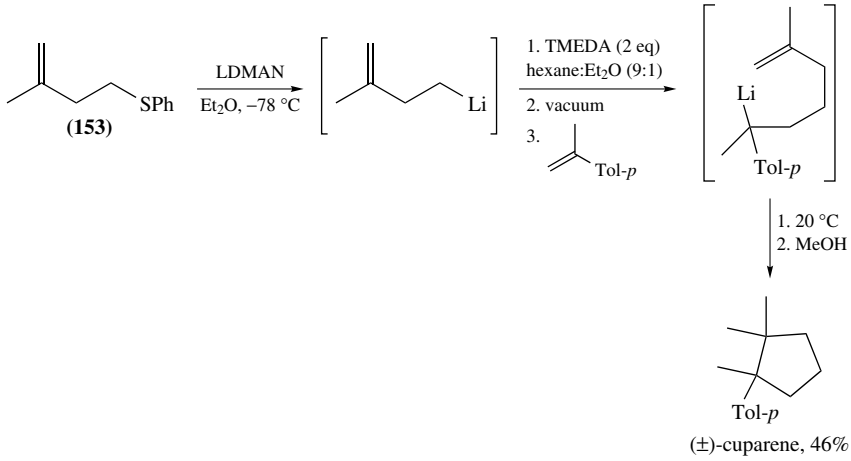
In this context Cohen and coworkers have reported that a homoallyllithium, generated by reductive lithiation (see below) from phenyl thioether **153**, adds to α-methylstyrene and the resulting benzyllithium is able to cyclize, giving rise to sesquiterpene (±)–cuparene (Scheme 43)[77].

4. Alkyllithiums prepared by deprotonation

As shown in Scheme 11, Hoppe and coworkers have accomplished the first enantioselective intramolecular carbolithiation reaction of alkenes by fusion of the concepts of the intramolecular carbolithiation reaction and the asymmetric deprotonation. The efficiency of this method has been demonstrated by the extension to other substrates by these and other authors[78]. However, this topic has been excellently reviewed by Hoppe and Christoph in Chapter 17 of Vol. 1 of *The Chemistry of Organolithium Compounds* and therefore it will not be treated in this chapter.

5. Alkyllithiums prepared by reductive lithiation

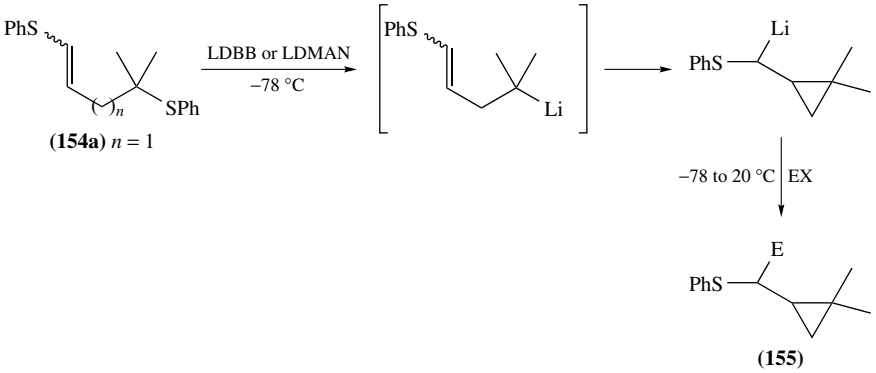
a. Reductive lithiation of phenyl thioethers. The vast majority of intramolecular carbolithiation reactions of olefinic alkyllithiums has been carried out from primary or



SCHEME 43

benzylic tertiary organolithiums, probably due to the fact that unstabilized secondary and tertiary organolithiums cannot be produced by the halogen–lithium or selenium–lithium exchange. However, the reductive lithiation of phenyl thioethers with aromatic radical-anions, such as lithium 1-(*N*,*N*-dimethylamino)naphthalene (LDMAN) and lithium 4,4′-di-*tert*-butylbiphenyl (LDBB), is a useful method of organolithium production[79] and, unlike the conventional method of organolithium preparation, the less stable the organolithium the greater the ease of its generation by reductive lithiation. In Scheme 14 it has been shown that olefinic homoallyllithiums and bishomoallyllithiums, generated by this method, undergo in some cases rearrangements via cyclopropylcarbinyllithium and cyclobutylcarbinyllithium intermediates, respectively. In this context, Cohen and coworkers have described that the reductive lithiation of 1,4- or 1,5-bis(phenylthio)-1-alkenes such as **154a** and **154b**, respectively, takes place regiospecifically at the phenylthio group, which is attached to the sp^3 carbon atom, and the resulting carbanions undergo intramolecular carbolithiation reaction onto the vinyl sulphide group, usually at $-78\,^{\circ}C$, leading to cyclopropyl **155** and cyclobutyl **156** derivatives. In the formation of four-membered rings in which the open-chain carbanion is primary or in which it is tertiary but with an additional alkyl group at the vinyl terminus bearing the phenylthio group, slightly elevated temperatures are required for cyclization of the carbanion whereas alkyl substitution at the proximal vinyl terminus inhibits the cyclization reaction (Scheme 44)[80].

More recently, Cohen and coworkers have shown that the reductive lithiation of phenyl thioethers allows virtually any kind of organolithium to be generated. Furthermore, allylic or homoallylic alkoxide groups on the alkene moiety greatly accelerate the reactions and lead in most cases to completely stereoselective cyclizations at $-78\,^{\circ}C$. Moreover, the cyclization products contain the useful alcohol function in addition to the lithiomethyl group. The cyclization reaction of **157** (R = Me) is one of the first examples of a 5-*exo* tertiary carbanionic cyclization and it occurs at a far lower temperature than that at which such cyclizations are usually performed. The high *trans*-selectivity in the cyclization reaction of the secondary organolithium derived from **157** (R = H) is consistent with a carbolithiation process. In both cases functionalized cyclopentane derivatives **158** are obtained in excellent yields (Scheme 45). One of the main advantages of the use of reductive lithiation is that it allows the generation of organolithium compounds in THF, and so the cyclization reactions of primary alkyllithiums occur at lower temperatures

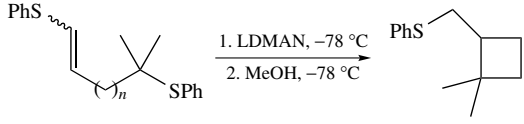


(154a) $n = 1$

(155)

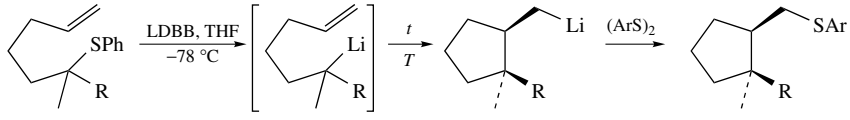
EX = H_2O; E = H, 87%

EX = *c*-HexCHO; E = *c*-HexCH(OH), 93%



(154b) $n = 2$ **(156)** 75%

SCHEME 44



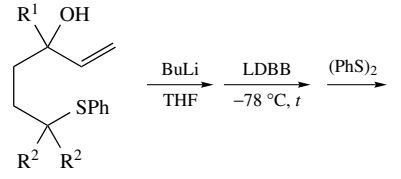
(157)

R = H; T = −78 °C; t = 10 min

R = Me; T = −45 °C; t = 2 h

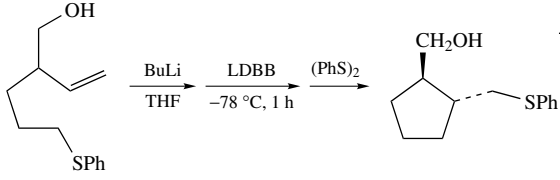
(158) R = H, 89% (*trans*/*cis* = 40:1)

R = Me, 94%



(159) **(160)**

R^1	R^2	t	Yield (%)
H	H	12 h	73
Me	H	12 h	81
H	Me	1 h	86
Me	Me	1 h	80



(161) **(162)** 64%

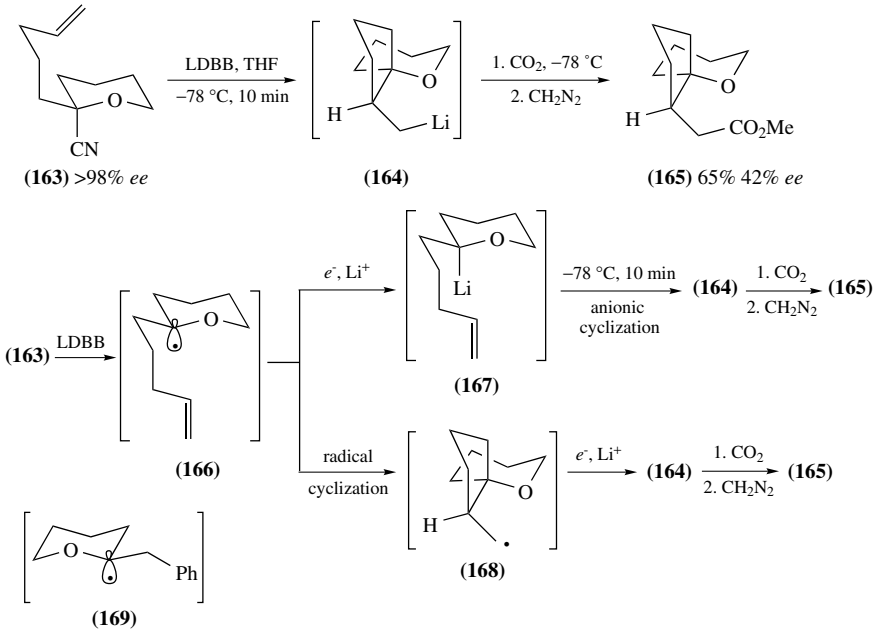
SCHEME 45

(−30 °C). Also, the presence of a lithium alkoxide group allows the cyclization of primary as well as tertiary alkyllithiums at temperatures as low as −78 °C. Thus, cyclopentanol derivatives **160** are easily obtained from alcohols **159** in very high yields and as single diastereoisomers (Scheme 45). As shown with thioether **161**, when the alkoxide group is placed in a homoallylic position, the reaction is even more effective and cyclized product **162** is formed in good yield at −78 °C in 1 h (Scheme 45)[81].

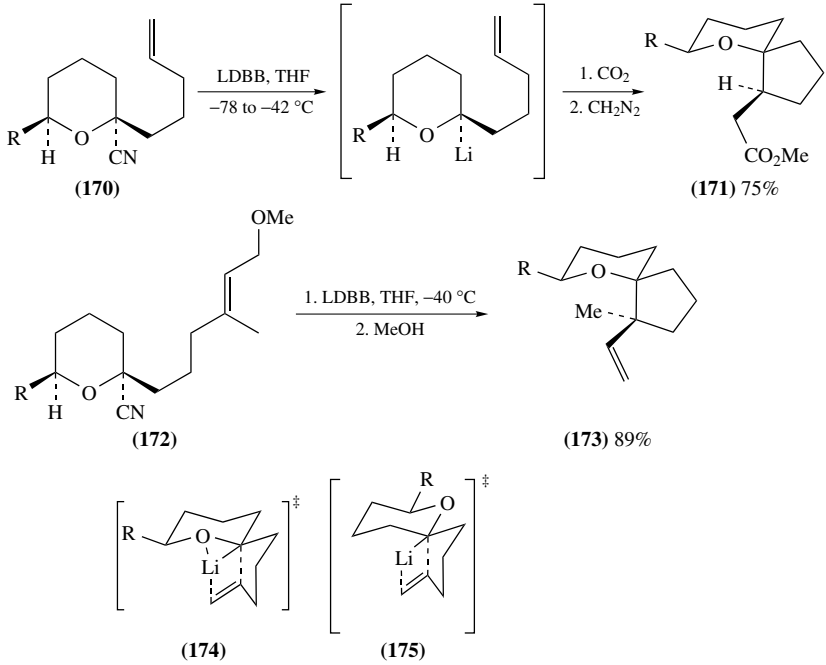
b. Reductive lithiation of nitriles. Nitriles can be alkylated efficiently to introduce functionalized alkyl chains and tertiary nitriles can be reductively cleaved to form alkyllithium reagents[82] that can cyclize in the presence of an internal olefin. Rychnovsky and coworkers have reported that optically pure nitrile **163** gives rise, upon treatment with LDBB and further reaction of the intermediate organolithium **164** with CO_2 and esterification, to cyclic product **165** as a single diastereoisomer in 42% *ee*. The cyclization reaction of **163** en route to **165** can be rationalized either as a radical or as an anionic cyclization. These two mechanistic possibilities are illustrated in Scheme 46. In both pathways, nitrile **163** is reduced to radical **166** that is the key branch point in each pathway. In the carbolithiation mechanism, the racemization of this radical will compete with reduction to the organolithium **167**, which is configurationally stable at −78 °C in THF, and the subsequent cyclization takes place with retention of configuration. Thus, in the carbolithiation pathway the *ee* of **165** is determined by the *ee* of **167**. However, the fact that the cyclization of **163** is complete in 10 min at −78 °C might suggest a radical cyclization, many of which are known to be very rapid, over the corresponding anionic cyclizations. Again, the racemization of the starting radical competes with its cyclization. The cyclized radical **168** would then be reduced to give alkyllithium reagent **164**. In this case, the *ee* of **165** would be determined by competition between recemization and cyclization of the starting radical. A radical clock reaction would help to distinguish between both pathways. Due to the fact that the starting radical is the only point in either mechanism where racemization would be likely, the *ee* of **165** is a direct measure of the life-time of the radical under the reaction conditions. Using the optical purity of **165** and the measured rate of racemization of radical **169**, structurally similar to **166**, gives an estimated life-time for radical **166** too brief to allow a radical cyclization, and thus it proceeds through an anionic pathway (Scheme 46)[83].

Having proved that reductive decyanation cyclizations take place through an anionic rather than a radical cyclization, these authors have shown that spirocyclic rings are easily prepared from 2-cyanotetrahydropyrans. A diastereoselective version of the previous cyclization is outlined in Scheme 47. Addition of nitrile **170** to excess LDBB leads to an axial alkyllithium intermediate that cyclizes onto the alkene with retention of the configuration. Carboxylation and treatment with diazomethane produced the spirocyclic ester **171** as a single diastereoisomer. Reductive cyclization onto a trisubstituted alkene has the potential to form two adjacent quaternary centres and this possibility was investigated with nitrile **172**. Its treatment with LDBB at −40 °C in THF produces spirocycle **173** in 89% yield as a single diastereoisomer. This surprisingly efficient cyclization generates two new quaternary stereocentres with complete stereoselectivity (Scheme 47). The stereochemical outcome of these cyclization reactions in which the diastereoisomer with the alkyl chain *cis* to the THP oxygen atom is formed exclusively has been rationalized on the basis of a model like **174**, with the alkene *cis* to the oxygen atom. This transition state should be favoured over **175** because it allows continuous coordination of the Li atom with the oxygen atom, whereas cyclization to the disfavoured *trans*-product requires that the strong Li−O dative bond be lost along the reaction coordinate (Scheme 47)[84].

These authors have also established that the tertiary alkyllithium, derived from optically pure acyclic precursor **176**, cyclizes onto a methoxy allyl ether moiety via an intramolecular S_N2' mechanism. Oxidation of the alkene product to the carboxylic acid **177** and

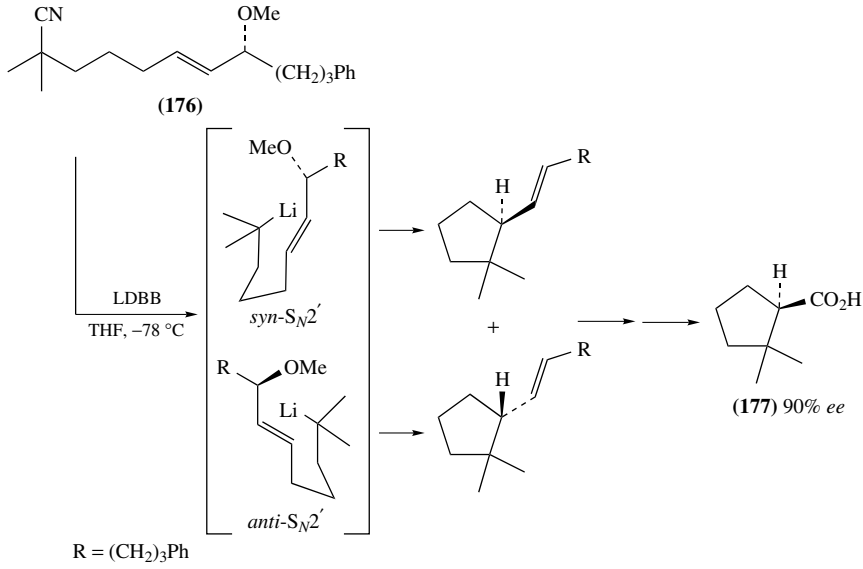


SCHEME 46



SCHEME 47

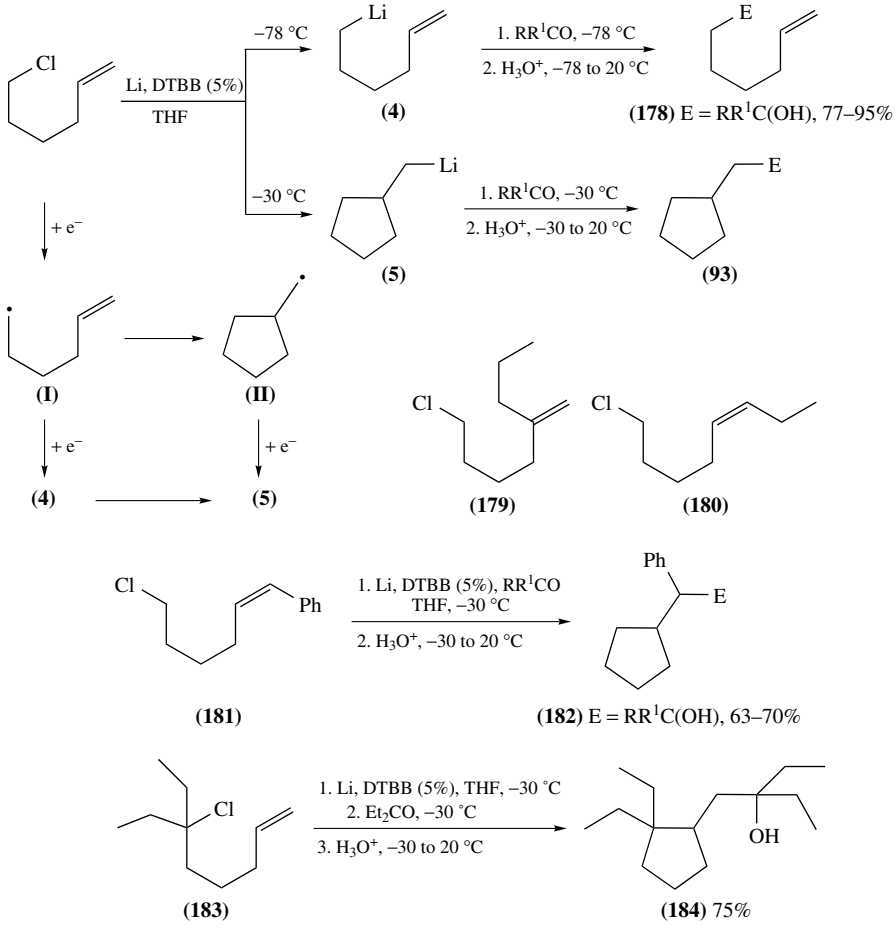
further derivatization provided the absolute configuration and the *syn*-preference of the cyclization reaction. Thus, in a conformationally unbiased system alkyllithium cyclizations onto methoxy alkenes prefer the *syn* S_N2' cyclization pathway with approximately a 96% stereochemical preference (Scheme 48)[85].



SCHEME 48

c. Reductive lithiation of chlorides. Yus and coworkers have developed a methodology ('arene-catalyzed lithiation') that allows one to carry out chlorine–lithium exchange under mild reaction conditions by using an excess of lithium powder and a catalytic amount of an arene (naphthalene and 4, 4′-di-*tert*-butylbiphenyl being the most commonly used)[86]. Recently, they have applied this strategy to the generation of unsaturated organolithium compounds by chlorine–lithium exchange in order to study their possible intramolecular carbolithiation reactions[87]. The reaction of 6-chloro-l-hexene with lithium powder and a catalytic amount of DTBB (5 mol%) in THF at $-78\,^{\circ}C$ leads to 5-hexenyllithium **4**, which is trapped with different carbonylic compounds to afford products **178**. However, when this reaction is carried out at $-30\,^{\circ}C$, cyclopentylmethyllithium **5** is generated, which by reaction with the same electrophiles as for **4** gives compounds **93** (Scheme 49). Concerning the possible mechanism of the reaction and considering the single-electron transfer nature of this kind of lithiation, these authors propose that a radical **I** is initially formed, which could either cyclize to a new radical **II** or take a second electron giving the carbanion **4**. Since the cyclization of the radical is more rapid than that of the carbanion, once the radical **I** is formed at $-78\,^{\circ}C$ it is converted rapidly to the anion **4** whereas at $-30\,^{\circ}C$ cyclization of **4** to **5** probably occurs. However, the other possible pathway at $-30\,^{\circ}C$, i.e. radical cyclization of **I** to **II** and further reduction to **5**, cannot be completely ruled out (Scheme 49). This cyclization reaction does not take place with chloride **180** bearing a terminally alkyl-substituted double bond and in the case of cinnamyl derivative **181** an exclusively 5-*exo* cyclization takes place to afford compounds **182**. These facts support the anionic mechanism, but the failure of the supposed carbolithiation reaction in the case of chloride **179** is not consistent because similar organolithiums generated by

iodine–lithium exchange undergo cyclization. Therefore, it is difficult to decide between the radical or anionic nature of these processes with the examples described in the literature. Regardless of the mechanism of these cyclization reactions, these authors have shown that this methodology also works with secondary and tertiary chlorides. For instance, tertiary chloride **183** gives rise to functionalized cyclized derivative **184** upon metallation with Li-DTBB at −30 °C (Scheme 49).



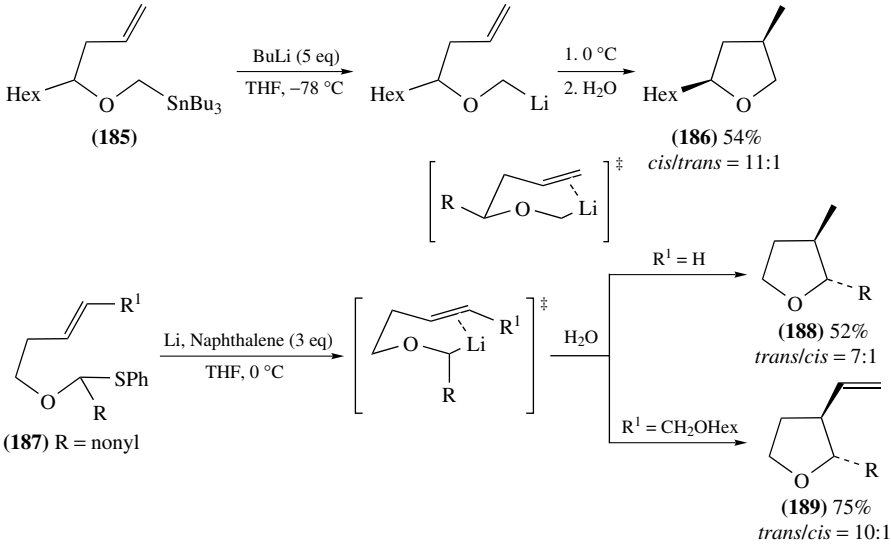
SCHEME 49

B. Cyclization Reaction of Heteroatom-substituted Olefinic Alkyllithiums

1. Oxygen-substituted alkyllithiums

The formation of tetrahydrofurans by intramolecular carbolithiation reaction of α-alkoxyorganolithiums was pioneered by Broka and coworkers[41]. They used tin–lithium exchange on the homoallylic tributylstannylmethyl ether **185** to generate the corresponding organolithium, which on warming undergoes anionic cyclization to afford

cis-2,4-disubstituted tetrahydrofuran **186**. A large excess of BuLi (5 eq) must be used in order to avoid stannylation of the cyclized organolithium by the $SnBu_4$ produced in the initial tin–lithium exchange (Scheme 50). A useful variant of this method, which employs allylic ethers as cyclization terminators, has been shown in Scheme 16. The stereochemical outcome of these cyclizations is similar to that which would be reasonably expected for the corresponding radical-mediated process, although the degree of selectivity is unusually high. This stereoselectivity may be taken to imply a chair-like transition state.

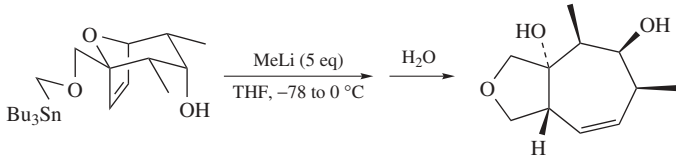


SCHEME 50

In an effort to increase the versatility of this method, these authors have examined alternative strategies for the generation of α-alkoxyorganolithiums. Using reductive lithiation of *O*,*S*-thioacetals **187** with lithium naphthalene, they have shown that 2,3-disubstituted tetrahydrofurans **188** and **189** could be prepared with good *trans*-stereoselectivity, explained through an analogous transition state. Again, when the trap is an allylic ether the yield and the selectivity increase (Scheme 50)[88]. Although due to the reductive nature of the method for the generation of organolithium it seems plausible that these cyclization reactions could be radical-mediated, the high *trans*-selectivity contrasts with the *cis* selectivity of the corresponding radical reactions and this fact is strong evidence in favour of a carbolithiation process.

In a synthetic application of this methodology Lautens and Kumanovic have prepared bicyclo[5.3.0] decenes as **191**, that contain up to five contiguous stereocentres, on treatment of oxabicyclo[3.2.1] substrates such as **190** with excess of MeLi (to avoid stannane reincorporation) (Scheme 51)[89]. These authors have also applied the same reaction to the analogous α-thioorganolithium, giving the corresponding tetrahydrothiophene derivative also in good yield.

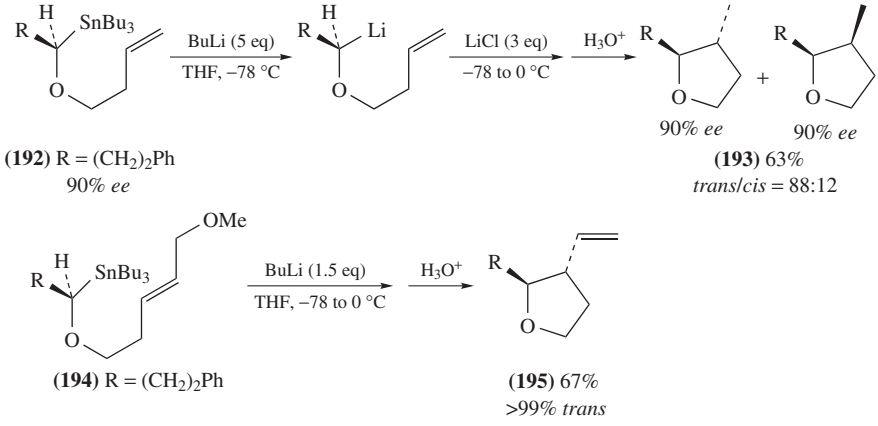
Nakai and coworkers[90] have demonstrated that the carbanion cyclization of enantioenriched α-(homoallyloxy)alkyllithiums, prepared from the corresponding stannanes **192**, proceeds with complete retention of configuration at the lithium-atom-bearing carbon centre. The obtained tetrahydrofurans **193** are formed with high *trans*-selectivity and without losing the enantiomeric purity. This means that the lithium might coordinate to the



(190) **(191)** 85%

SCHEME 51

olefinic bond in the transition state and hence the cyclization takes place in a carbolithiative way (Scheme 52). Without the addition of lithium halide, the yield drops considerably probably due to a competitive interaction of the lithium with the ether oxygen, which is minimized by the lithium salt. Again a subsequent β-elimination reaction is responsible for the cyclization on stannane **194**, which leads to 2,3-disubstituted tetrahydrofuran **195** with good yields and a high level of *trans*-diastereoselectivity (Scheme 52).



(192) R = $(CH_2)_2$Ph
90% *ee*

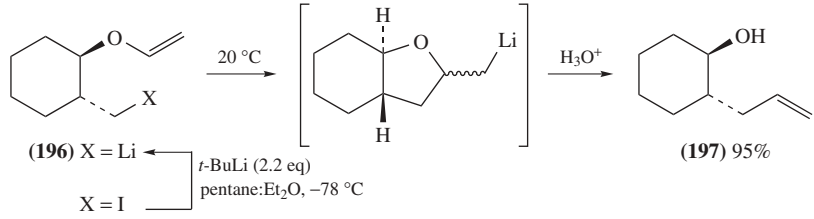
(193) 63%
trans/*cis* = 88:12

(194) R = $(CH_2)_2$Ph

(195) 67%
>99% *trans*

SCHEME 52

On the other hand, olefinic γ-alkoxyorganolithiums like 4-oxa-5-hexenylithium **196** (X = Li), which may be prepared from *trans*-1-iodomethyl-2-vinyloxycyclohexane **196** (X = I) by iodine–lithium exchange, cyclize on warming to room temperature to a transient tetrahydrofuran derivative, but this undergoes rapid β-elimination to the *trans*-2-allylcyclohexanol **197**, after hydrolysis. The overall transformation is equivalent to a [1,4]-Wittig rearrangement (Scheme 53)[91].



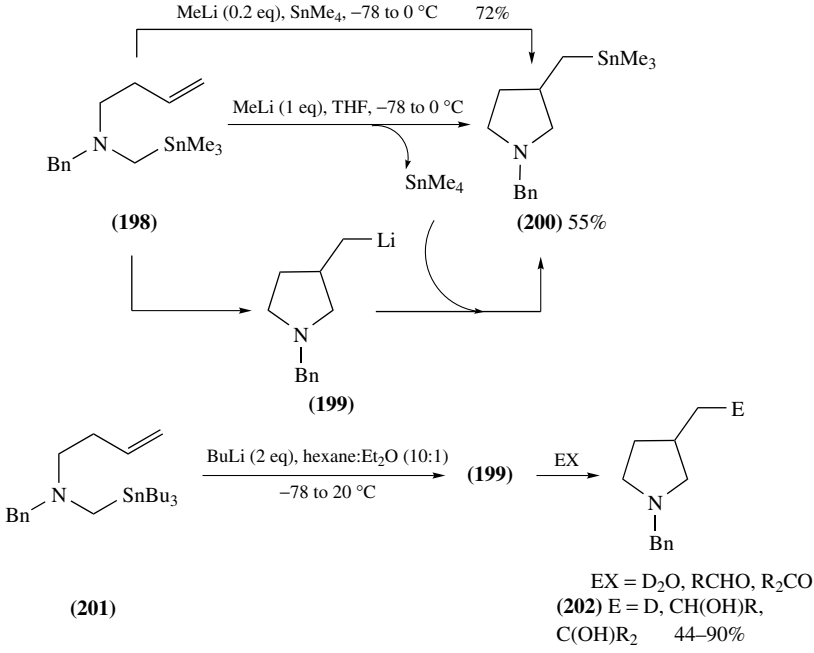
(196) X = Li
X = I

(197) 95%

SCHEME 53

2. Nitrogen-substituted alkyllithiums

The preparation of pyrrolidines by carbolithiation reaction of *N*-homoallyl α-amino-organolithium compounds has been extensively studied in the past ten years by Coldham and coworkers, who have used the tin–lithium exchange method for the generation of the organolithiums. For instance, aminomethylstannane **198** gives rise to pyrrolidine **200** probably by way of the lithiomethyl intermediate **199**. The overall transformation of **198** into **200** is a rearrangement and can be promoted with only 0.2 eq of MeLi in the presence of $SnMe_4$ even in better yield than the stoichiometric case (Scheme 54)[92].

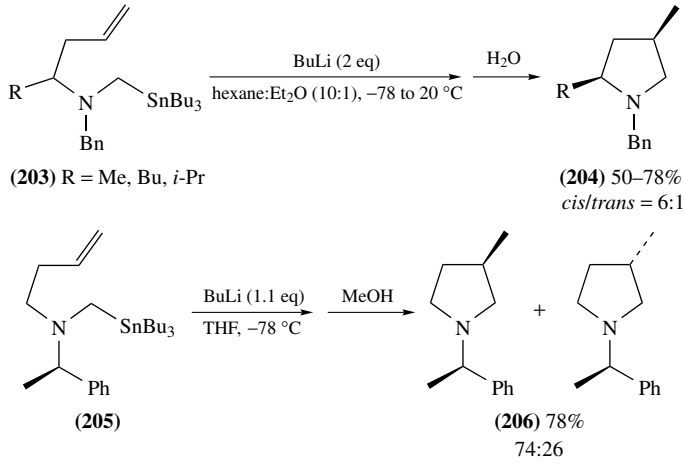


SCHEME 54

In contrast, the use of the tributylstannane **201** allows the preparation of a variety of 3-substituted pyrrolidines **202**, by treatment of the same organolithium intermediate **199** with different electrophiles (Scheme 54)[93].

When similar α-substituted homoallylic amines **203** are used as substrates, the cyclization of the corresponding α-amino-organolithiums results in the formation of 2,4-disubstituted pyrrolidines **204** with high selectivities in favour of the *cis*-isomers. In THF only the *cis*-isomer of **204** (R = Me) was detected, but the yield is significantly lower than in hexane:diethyl ether (Scheme 55). Using the 'chiral auxiliary' approach to control the stereoselectivity, these authors have investigated the behaviour of homoallylamine **205** bearing an α-methylbenzyl chiral auxiliary on the nitrogen atom. However, only a modest 48% *de* was obtained in the expected 3-substituted pyrrolidine **206**. The addition of a chiral ligand like (−)-sparteine in THF causes a small but significant increase in the ratio of diastereoisomers (58% *de*)[33].

In the same context, α-aminomethylstannanes with pendant allylic ethers **207** are converted, on treatment with BuLi, to 3-alkenylpyrrolidines **208** in good yields (Scheme 56)[94].

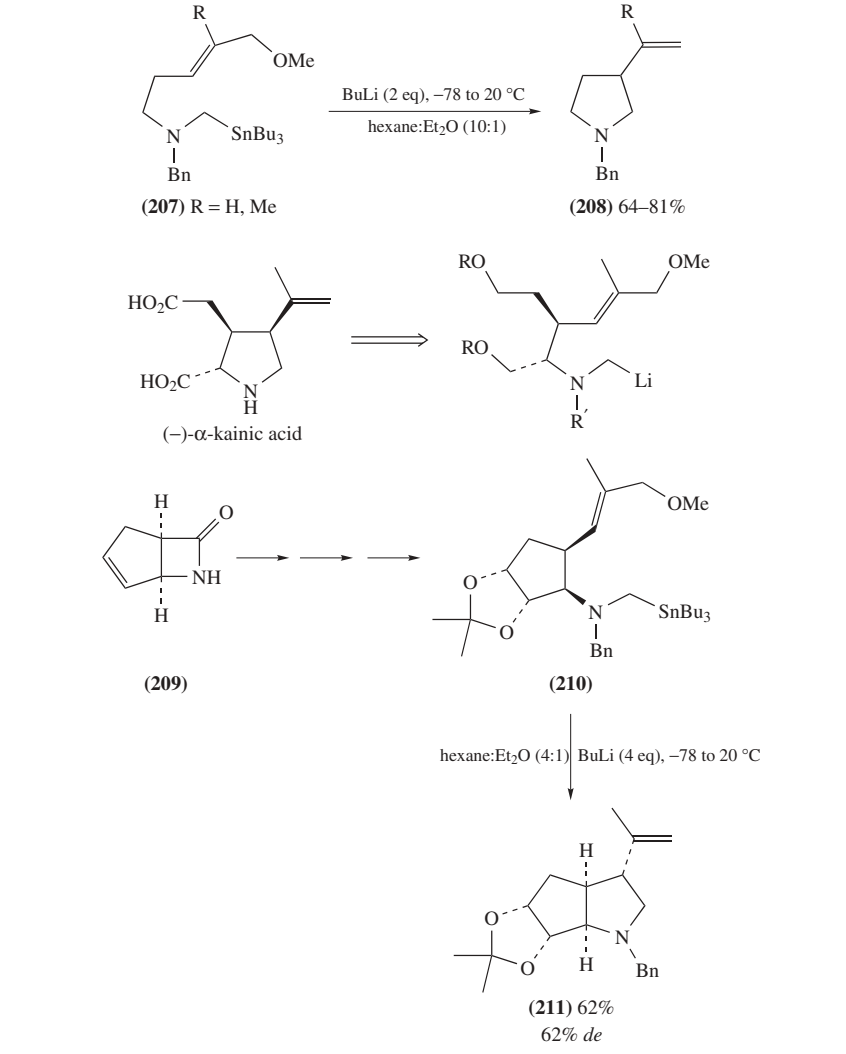


SCHEME 55

This methodology has been applied to the synthesis of an advanced intermediate **211** related to the natural product (−)-α-kainic acid. The required stannane **210** was prepared in several steps from β-lactam **209**. Disappointingly, the major diastereoisomer (with respect to the new stereogenic centre) of the desired pyrrolidine **211** was not the expected one for similar cyclizations and has not the required stereochemistry across C-3 and C-4 for the synthesis of kainic acid (Scheme 56)[95]. Attempts to alter the stereoselectivity by changing the solvent were unsuccessful. The authors reasoned that if the intramolecular carbolithiation reaction takes place through a six-membered chair-shaped transition state, then different conformations must be preferred for the two different cyclizations leading to the *cis*-and *trans*-diastereoisomers of **211**.

The pyrrolizidine nucleus is also affordable by intramolecular carbolithiation reaction starting from stannane **212**. After transmetallation, cyclization and trapping with electrophiles the pyrrolizidines **213** were isolated as their picrate salts, as an inseparable (3:1) mixture of diastereoisomers. The preference for a chair-shaped transition state, with a *cis*-fused 1-azabicyclo[3.3.0]octane ring system, suggests that the major diastereoisomer would be the first, though this was not completely ascertained (Scheme 57)[96].

This methodology of tin–lithium exchange and intramolecular carbolithiation reaction has been used to construct the three nitrogen-positional isomers of the azabicyclo[2.2.1]heptane ring system. Functionalized 7-azabicyclo[2.2.1]heptanes **215** are accessed from either diastereoisomer of a 2,5-disubstituted pyrrolidine like **214** (Scheme 58)[97]. The 2-azabicyclo[2.2.1]heptane ring system **218** is formed stereoselectively in low yield by a tandem cyclization from stannane **216**, together with the *cis*-2-vinyl-4-methylpyrrolidine **217** derived from monocyclization. The second cyclization is not very effective, probably due to intramolecular chelation of the alkyllithium by the nitrogen lone pair. Fortunately, better yields of the 2-aza ring system can be obtained using an alternative approach from a 2-tributylstannyl-4-allylpyrrolidine **219**, despite the *trans*-arrangement of the tin (and, hence, lithium) and the allyl moiety (Scheme 58)[98]. The 1-azabicyclo[2.2.1]heptane system can be conveniently accessed from piperidinyl stannane **220**, which upon transmetallation and carbolithiation reactions affords the picrate salt **221** in good yield. In this case the addition of TMEDA is necessary to promote the cyclization step (Scheme 58)[98].



(207) R = H, Me

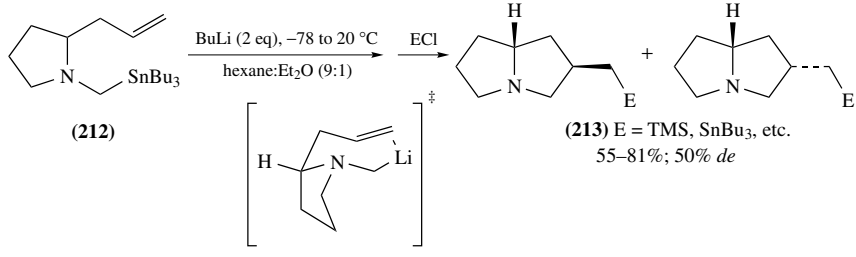
(208) 64–81%

(209)

(210)

(211) 62%
62% *de*

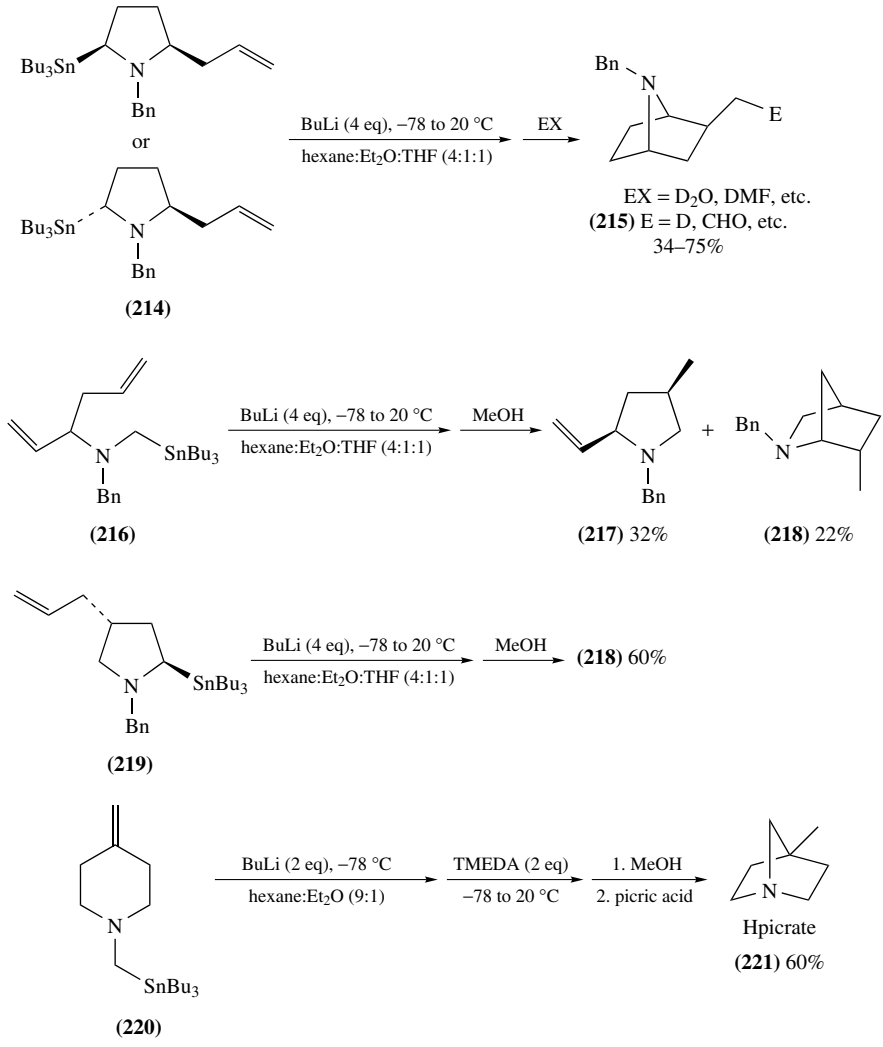
SCHEME 56



(212)

(213) E = TMS, $SnBu_3$, etc.
55–81%; 50% *de*

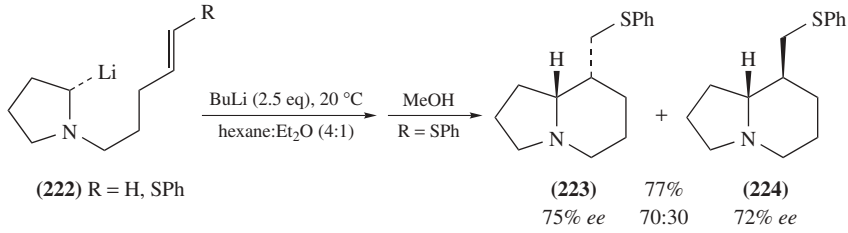
SCHEME 57



SCHEME 58

As shown in Scheme 11, the use of a stereochemically defined and configurationally stable α-amino-organolithium allows the synthesis, via 5-*exo* carbolithiation reaction, of a compound with complete stereocontrol. The corresponding cyclization to synthesize indolizidine derivatives was complicated by competitive racemization of the chiral organolithium **222** (R = H) prior to the slow 6-*exo* cyclization step. This problem of racemization is partially resolved on increasing the rate of the carbolithiation reaction by using a phenylthio-substituted alkene as the electrophilic tether. In that way octahydroindolizidines **223** and **224** were obtained as a 70:30 isomeric mixture and with good *ee* (75

and 72%, respectively). Racemic **224** is exclusively formed in the presence of TMEDA. A coordination of TMEDA to the lithium atom probably increases the rate of racemization of the organolithium species and alters the preferred conformation of the transition state for cyclization (Scheme 59)[99].

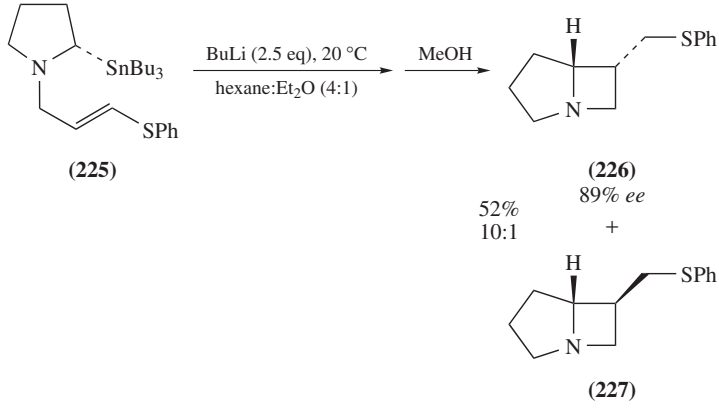


(222) R = H, SPh

(223) 77% **(224)**
75% *ee* 70:30 72% *ee*

SCHEME 59

Coldham and coworkers have also described a 4-*exo-trig* intramolecular carbolithiation reaction in similar starting compounds. Whereas the cyclization fails when a phenylthio substituent is not present in the stannane **225**, its presence leads to a moderately successful cyclization to 1-azabicyclo[3.2.0]heptane derivatives **226** and **227**. The moderate yield is due to the fact that the tin–lithium exchange competes with deprotonation of the substrate at the vinylic position. Nevertheless, the cyclization reaction takes place with a high diastereoselectivity in favour of the isomer **226**. The high enantiomeric excess found in the major isomer reflects that the cyclization reaction is much more rapid than the epimerization of the intermediate organolithium, though these authors have not been able to determine if cyclization has occurred with retention of configuration (Scheme 60)[100]. Again, the cyclization reaction of **225** was sensitive to the solvent, the addition of TMEDA gave similar yield and diastereoselectivity, but with reduced enantioselectivity. Moreover, although in THF transmetallation and carbolithiation reactions were extremely rapid at −78 °C and the yield was higher, no diastereisomeric excess was observed and **226** and **227** were formed in low *ee* (14–24%).



(225)

(226)
89% *ee*
52%
10:1
+

(227)

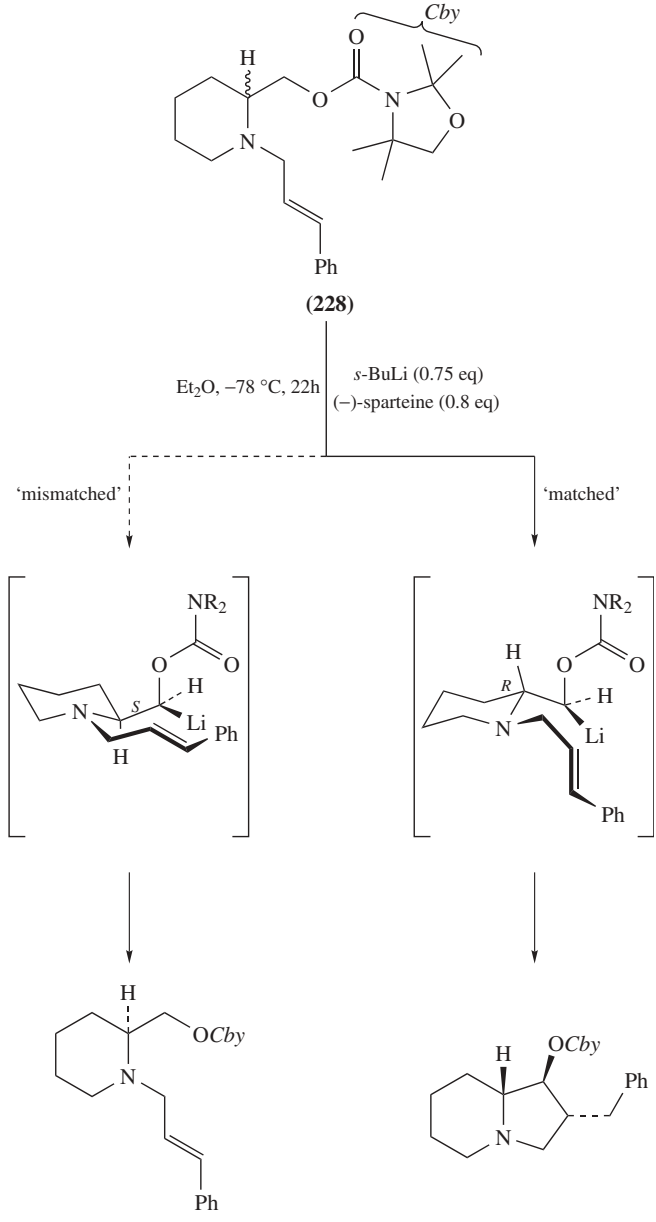
SCHEME 60

The technique of asymmetric deprotonation in the presence of (−)-sparteine to give configurationally defined α-carbamoyloxyorganolithiums has been used by Hoppe and coworkers, as shown in Scheme 11. Enantio-enriched 1-oxy-2-benzyl-substituted indolizidines **229** with functionalized side chains were easily prepared from racemic 2-(carbamoyloxy)methyl-*N*-cinnamylpiperidine **228**. The key steps are a kinetic resolution and a stereospecific and diastereoselective intramolecular carbolithiation reaction under the action of the recoverable auxiliary (−)-sparteine. Asymmetric deprotonation of **228** results in a 'matched' [(*R*)-**228**-Li] and 'mismatched' [(*S*)-**228**-Li] pair of organolithiums, that are kinetically resolved into indolizidine **229** by cyclization and recovered (*S*)-**228** (Scheme 61)[101]. These authors have extended this methodology to prepare highly enantio-enriched 3,4-divinylpyrrolidines by enantioselective (−)-sparteine-mediated lithiation and subsequent intramolecular anionic cyclization onto allylic chlorides[102].

Under particular conditions, organolithiums tethered to aromatic rings may cyclize, apparently by nucleophilic addition of the organolithium to the π-system of the aromatic ring[103]. Prior to the intensive investigation by Clayden and coworkers few isolated examples had been reported[104]. Since 1998, it has been established that in the case of aromatic amides, de-aromatizing anionic cyclization reaction is a common pattern of reactivity in *N*-benzyl naphthamides[105] and in *N*-benzyl benzamides[106]. As depicted in Scheme 62, after lithiation and addition of HMPA, *N*-*tert*-butyl-*N*-benzyl-1-naphthamide **230** and *N*-*tert*-butyl-1-benzamide **233** undergo a de-aromatizing cyclization reaction that leads to the enolates **231** and **234**, which can be quenched, usually stereoselectively, with electrophiles to give de-aromatized products **232**, **235** and **236**. The last two bicyclic cyclohexadiene derivatives are formed due to the fact that enolate **234** reacts both α and γ to the amide carbonyl group, leading to variable mixture of regioisomers. The diastereoselectivity of the reaction with the electrophiles appears to depend on their steric bulk. In some cases the lithiation does not occur first α to the nitrogen, but *ortho* to the amide, in which case an anion translocation is required so the cyclization can proceed[107].

Clayden and coworkers have also reported that substituted *N*-benzylbenzamides **237**, including those bearing electron-withdrawing, electron-donating, or conjugating groups, become lithiated, also with LDA, and cyclize to give, after aqueous quench and deprotection, a range of partially saturated isoindolones **238** as single regio- and stereoisomers (Scheme 63)[108]. In this context, *N*-benzyl *p*-anisamide **237** (R = *p*-OMe), on lithiation with *t*-BuLi in the presence of HMPA, undergoes a stereoselective anionic cyclization reaction with loss of aromaticity to give a bicyclic enone **239**, which may be converted in nine steps to (±)-kainic acid (Scheme 63)[109]. Moreover, chiral lithium amide bases are able to deprotonate **237** in an enantioselective way to yield an enantiomerically enriched benzylic organolithium compound, which undergoes de-aromatizing cyclization reactions to yield isoindolone **239** with moderate *ee*. Further transformations allowed one to synthesize enantiomerically pure (−)-kainic acid (Scheme 63)[110]. Related naphthamide starting materials have been used by these authors to prepare a known non-natural member of the aryl kainoid family having potent biological activity[111]. The use of 1-naphthamides with a chiral phenylglycinol auxiliary on the nitrogen allows asymmetric de-aromatizing anionic cyclizations[112].

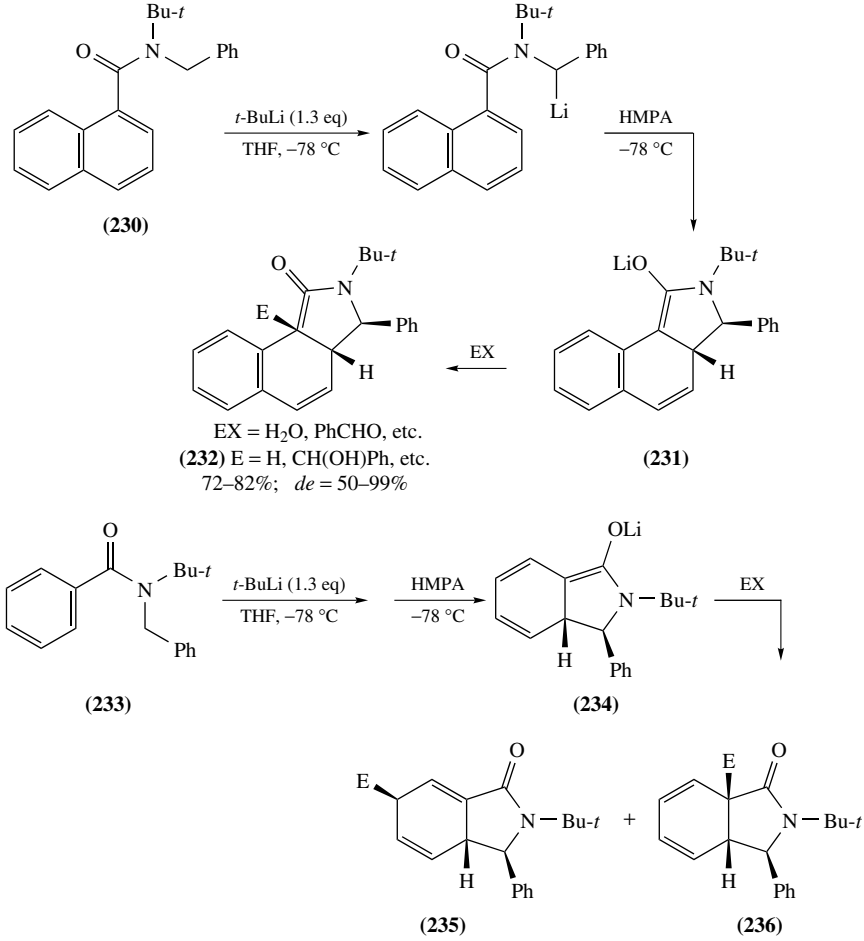
In search for alternative groups to be lithiated α to the nitrogen, these authors have reported that 1-naphthamides bearing *N*-allyl group **240**, on treatment with *t*-BuLi and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) as a safer substitute for HMPA, cyclizes to give a mixture of products, five-membered lactams **241** and mainly seven-membered lactams **242**. The latter are the first example of the synthesis of a seven-membered ring by an intramolecular carbolithiation reaction. An allyl anion, generated by DMPU-promoted anion translocation from the *ortho* to the α position, is proposed to be responsible for the formation of two different isomers (Scheme 64)[113].



(*S*-228) 46%
63% *ee*

(229) 34%
96% *de*; 95% *ee*

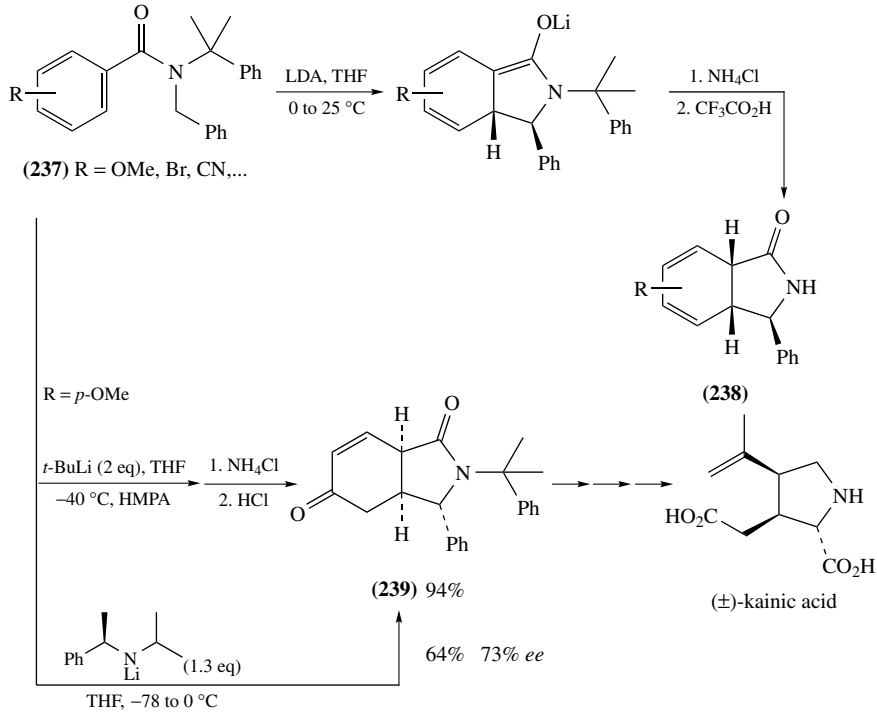
SCHEME 61



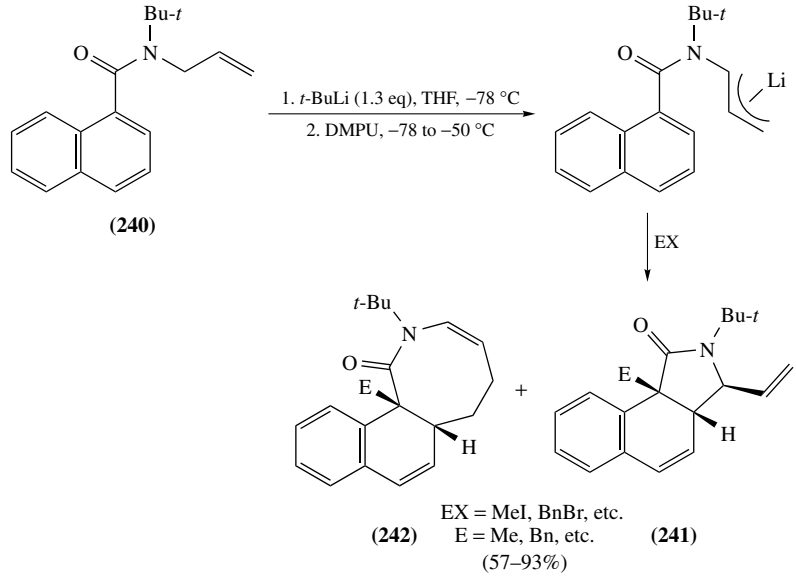
SCHEME 62

Unstabilized organolithiums like oxa-and aza-tethered γ-lithiopropylnaphthalenes, generated by tin–lithium exchange from stannanes **243**, are also able to cyclize by nucleophilic addition of the organolithium to an activated naphthalene ring. The resulting benzyllithiums react stereoselectively with electrophiles to give de-aromatized tricyclic products **244** with structural similarity to the arylnaphthalene lignans (Scheme 65)[114]. Without the oxazoline activating substituent, similar reactions lead to products derived from [2,3]-Wittig rearrangements.

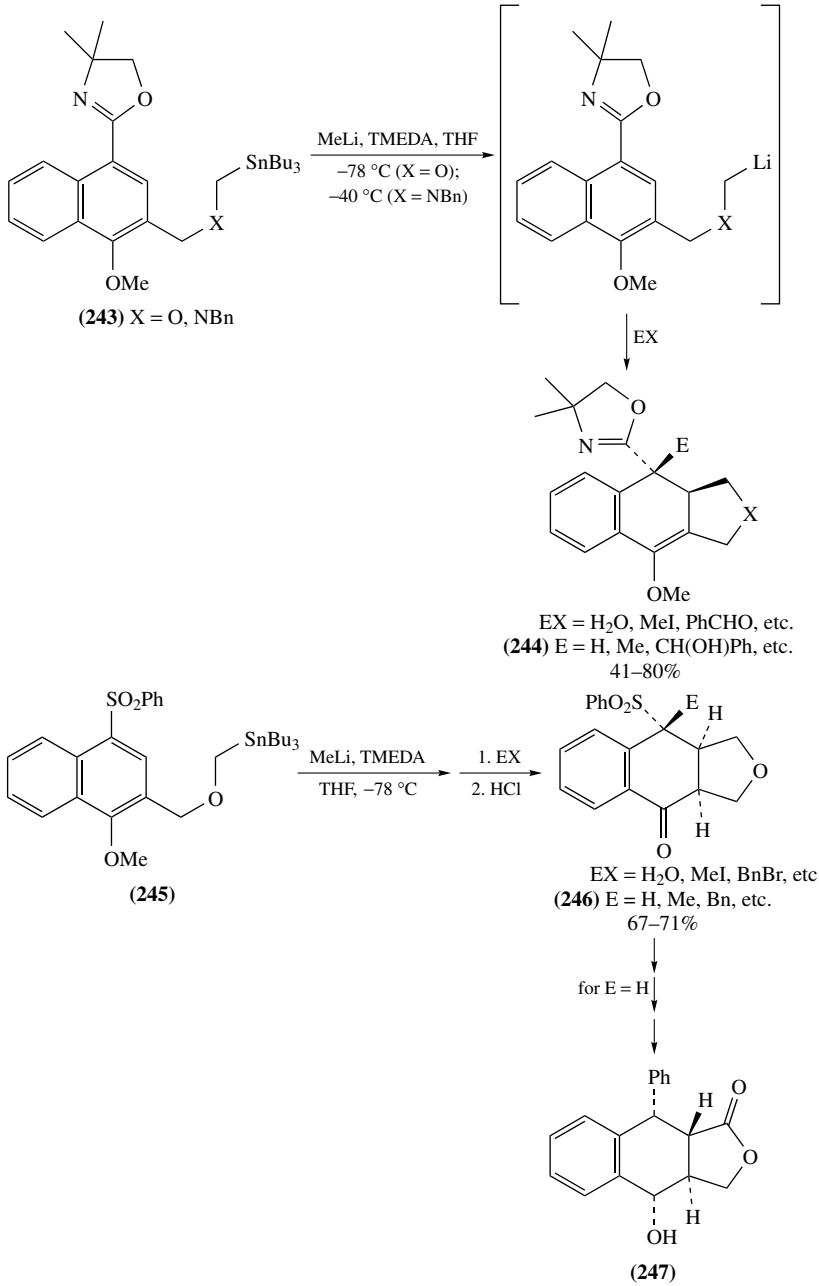
Also, the phenylsulphonyl group is able to promote the de-aromatizing cyclization of tethered organolithiums onto aromatic rings. In the same conditions as described above, sulphone **245** cyclizes to **246**, creating a new tetrahydrofuran ring. Both the cyclization and the subsequent electrophilic quenching take place with high levels of diastereoselectivity.



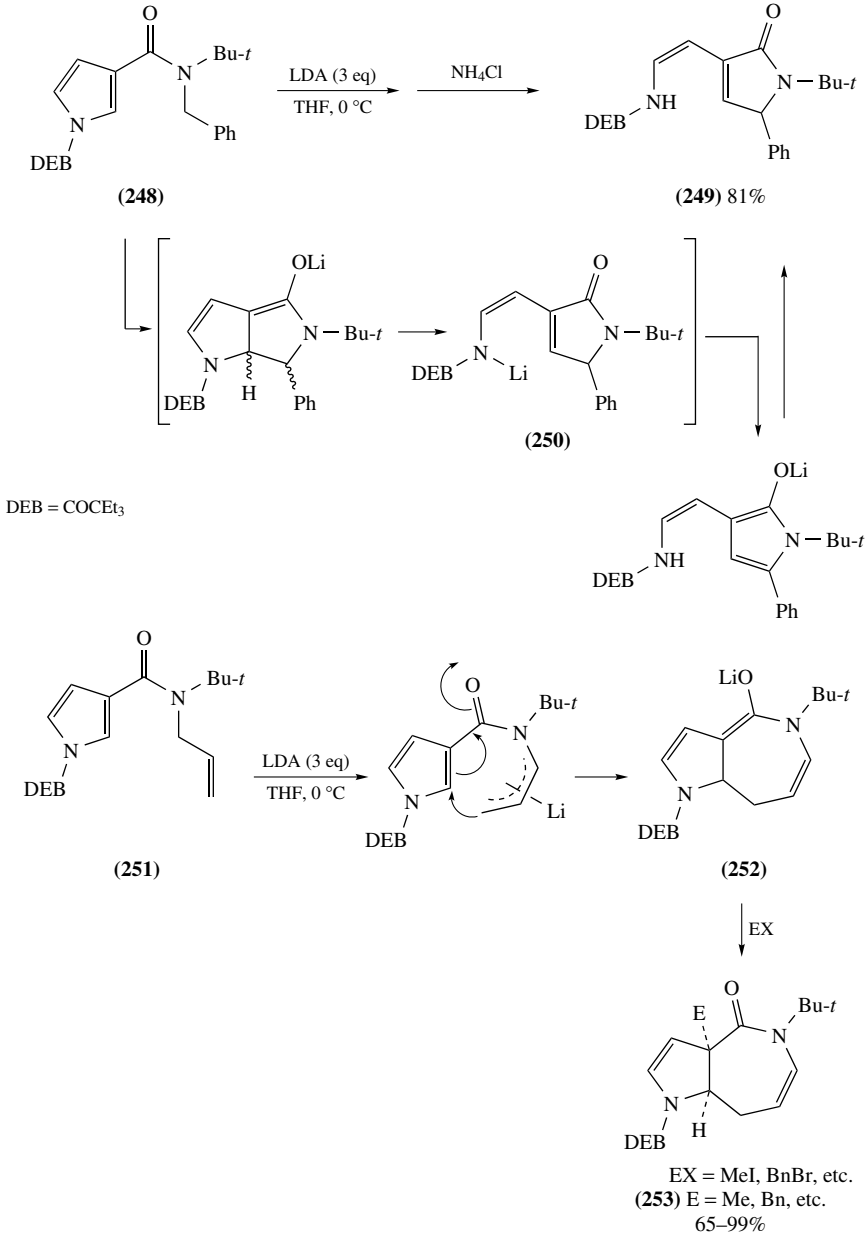
SCHEME 63



SCHEME 64


N
O
SnBu3
X
OMe
(243) X = O, NBn
MeLi, TMEDA, THF
–78 °C (X = O);
–40 °C (X = NBn)
Li
EX
E
EX = H2O, MeI, PhCHO, etc.
(244) E = H, Me, CH(OH)Ph, etc.
41–80%
SO2Ph
(245)
MeLi, TMEDA
THF, –78 °C
1. EX
2. HCl
PhO2S
H
EX = H2O, MeI, BnBr, etc.
(246) E = H, Me, Bn, etc.
67–71%
for E = H
Ph
OH
(247)

SCHEME 65

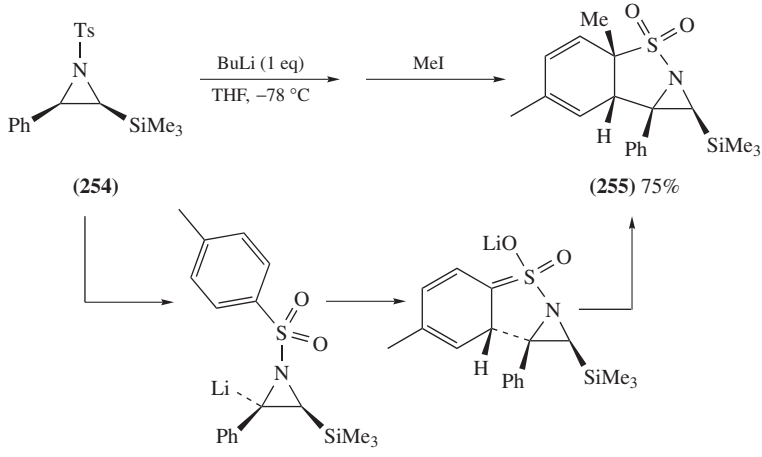

O
Bu-t
N
Ph
DEB
LDA (3 eq)
THF, 0 °C
NH4Cl
NH
OLi
Li
H
(248)
(249) 81%
(250)
DEB = COCEt3
(251)
(252)
EX
E
EX = MeI, BnBr, etc.
(253) E = Me, Bn, etc.
65–99%

SCHEME 66

The sulphonyl group can be removed and a nine-step sequence was developed to synthesize **247**, a close structural analogue of podophyllotoxin (Scheme 65)[115].

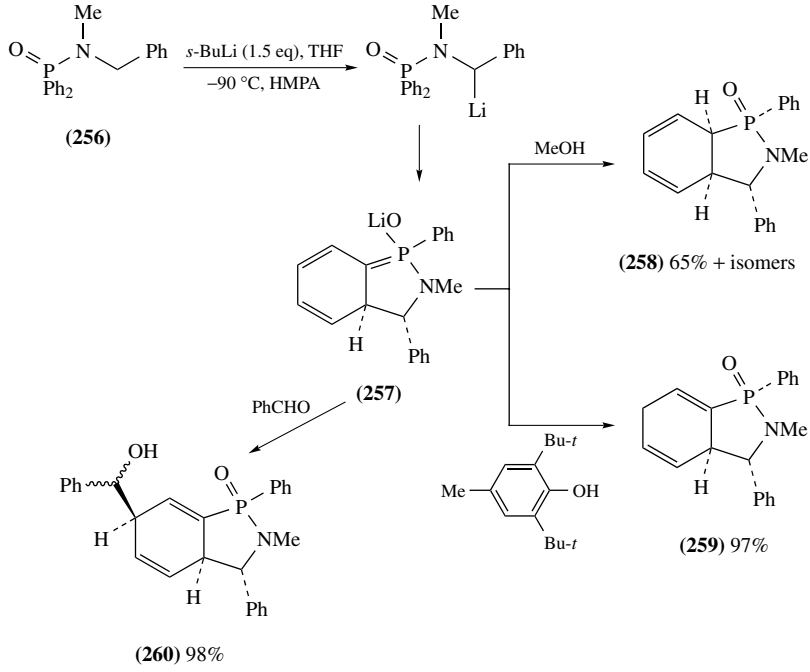
Despite its electron-rich nature, a pyrrole ring is susceptible to intramolecular attack by organolithiums. Thus, metallation of *N*-benzylpyrrolecarboxamide **248** with LDA in THF at 0 °C, subsequent evolution and final hydrolysis yield 3-(aminovinyl)pyrrolinone derivative **249**. Initial cyclization is accompanied by ring opening of the original pyrrole, giving rise to an amide **250** which must undergo an intramolecular proton transfer to give a new extended enolate that is finally protonated (Scheme 66). On the other hand, a similar reaction with *N*-allyl pyrrolecarboxamide **251** affords the 7,5-fused pyrroloazepinone **253**. After cyclization of the allyl anion, protonation of enolate **252** mainly gives the *cis*-fused 7,5-ring system, along with a small amount of the *trans*-**253** (E = H), whereas alkylation yields essentially the *cis*-isomer (Scheme 66)[116].

Similar examples of de-aromatizing anionic cyclization reactions have also been described by other authors. Aggarwal and Ferrara have reported that *cis*-aziridine **254**, on treatment with BuLi followed by quenching with iodomethane, gives the tricyclic aziridine **255** as a single diastereoisomer. This product probably arises from deprotonation of the benzylic carbon followed by intramolecular nucleophilic addition of the anion on the tosyl ring and subsequent methylation (Scheme 67)[117].



SCHEME 67

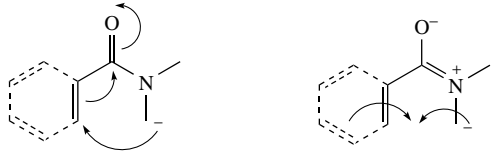
López-Ortiz and coworkers have described the first de-aromatizing reaction of a phenyl ring promoted by a phosphinamide group like in **256**. After deprotonation of the α-hydrogen to the nitrogen atom with *s*-BuLi, the intermediate lithium species undergoes an intramolecular attack on the aromatic ring leading to anionic de-aromatized cycloadduct **257**. While the protonation with methanol preferably occurs at the α-position to the phosphorus, affording benzazaphosphol derivatives **258**, 2,6-di-*t*-butyl-4-methylphenol protonates the γ-position, giving rise to isomeric derivatives **259** with excellent yields, regio and stereoselectivities (Scheme 68)[118]. These processes have been optimized by analysing the effects of metallation, quenching times, additives, the nature of the electrophiles used and the alkyl substituent linked to the nitrogen atom of the phosphinamide[119]. For example, functionalized tetrahydrobenzo[*c*][1,2]-1λ^5-azaphosphole **260** could be prepared in high yield and regio- and diastereoselectivity by reaction of **257** with benzaldehyde. In a similar



SCHEME 68

fashion, these authors have also reported the nucleophilic naphthalene de-aromatization of *N*-alkyl-*N*-benzyl(dinaphthyl)phosphinamides[120].

With respect to the mechanism of these anionic cyclizations of benzamides and phosphinamides, two possibilities can be envisaged, as illustrated with model system **261**: (i) a 5-*endo-trig* intramolecular Michael-type nucleophilic attack of the carbanionic centre to the *ortho* position of the electron-deficient aromatic ring, and (ii) a disrotatory electrocyclic ring-closure of the 2-azapentadienyl-like dipolar resonance structure **262** (Scheme 69). Although Clayden and coworkers have reported some stereochemical evidence consistent with the interpretation as a 6-electron disrotatory ring closure[121], recent experiments reported by these authors for the 5-*endo-trig* cyclizations of lithiated acrylamide derivatives[122] and *ab initio* calculations carried out by López-Ortiz, González and coworkers[123] argue in favour of the nucleophilic addition of the carbanionic centre to the electron-de-activated carbon–carbon double bond.



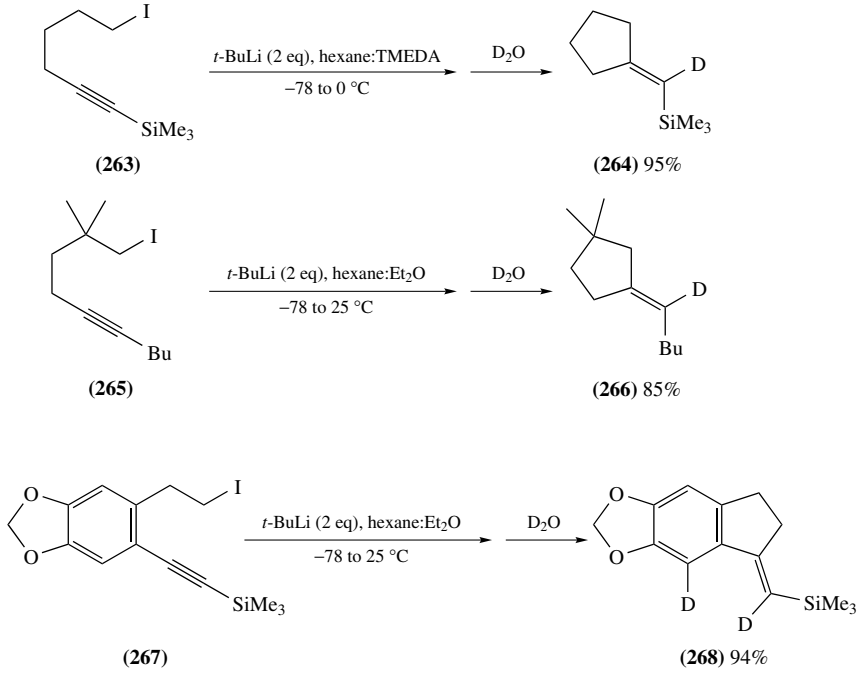
(261)
Ionic 5-*endo-trig* cyclization

(262)
Electrocyclic ring closure

SCHEME 69

C. Cyclization Reaction of Acetylenic Alkyllithiums

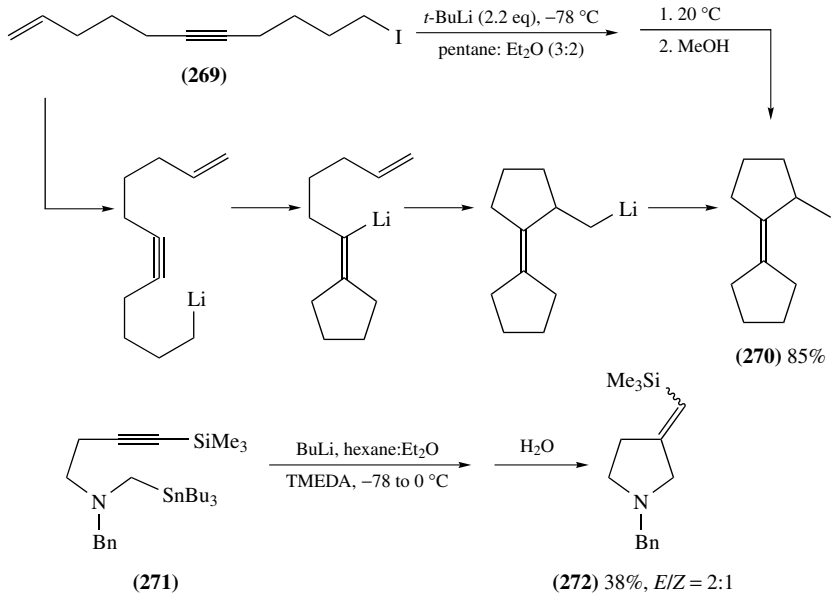
In 1967, Ward reported that treatment of 6-bromo-1-phenyl-1-hexyne **13** with BuLi at room temperature and subsequent hydrolysis gave mainly benzylidenecyclopentane **14** (Scheme 5)[17]. As has been demonstrated[124], bromine–lithium interchange between an alkyllithium and a primary alkyl bromide proceeds, at least in part, via single-electron transfer to give reactive alkyl radicals and so this cyclization reaction probably takes place through the intermediacy of free radicals. Since the iodine–lithium exchange of analogous substrates is, in contrast, an inner-sphere process that does not involve radical intermediates when conducted under appropriate conditions[125], 5-hexynyllithiums can be prepared from acetylenic iodides and can undergo intramolecular carbolithiation reactions that, as has been shown in Schemes 6 and 23, are *syn*-stereospecific processes. Several authors such as Negishi, Bailey and Coldham have generalized this kind of cyclization reaction to different systems, showing the synthetic potential of this methodology. Thus, Negishi and coworkers have described that different alkynes bearing a lithium atom at the δ-position, derived from iodides **263**, **265** and **267**, can cyclize in a stereoselective manner to give exocyclic alkenes containing five-membered carbocycles, as **264**, **266** and **268**, in high yields (Scheme 70)[126]. In the conversion of **267** into **268**, the use of 2 equivalents of *t*-BuLi, as in the other cases, led to the incorporation of the second deuterium atom on the benzene ring and anticipated stereoisomerization of the resulting 1-silyl-1-alkenyllithium[127].



SCHEME 70

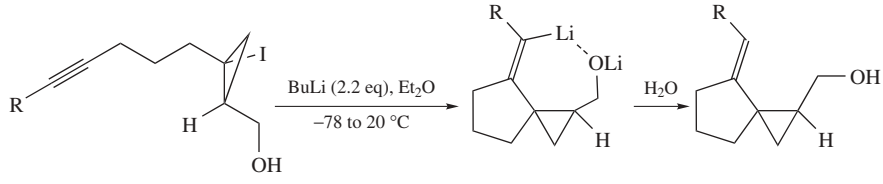
In the same context, Bailey and Ovaska have described a tandem cyclization of an enynyl alkyllithium generated by low-temperature iodine–lithium exchange on iodide **269**. Two sequential 5-*exo* cyclization reactions when warmed to room temperature afford

2-methyl-1-cyclopentylidenecyclopentane **270** in good yield (Scheme 71)[128]. Using a similar strategy, Coldham and coworkers have synthesized 3-vinylpyrrolidine **272**, obtained as a mixture of diastereoisomers, by anionic cyclization of the alkynyl stannane **271** (Scheme 71)[94].



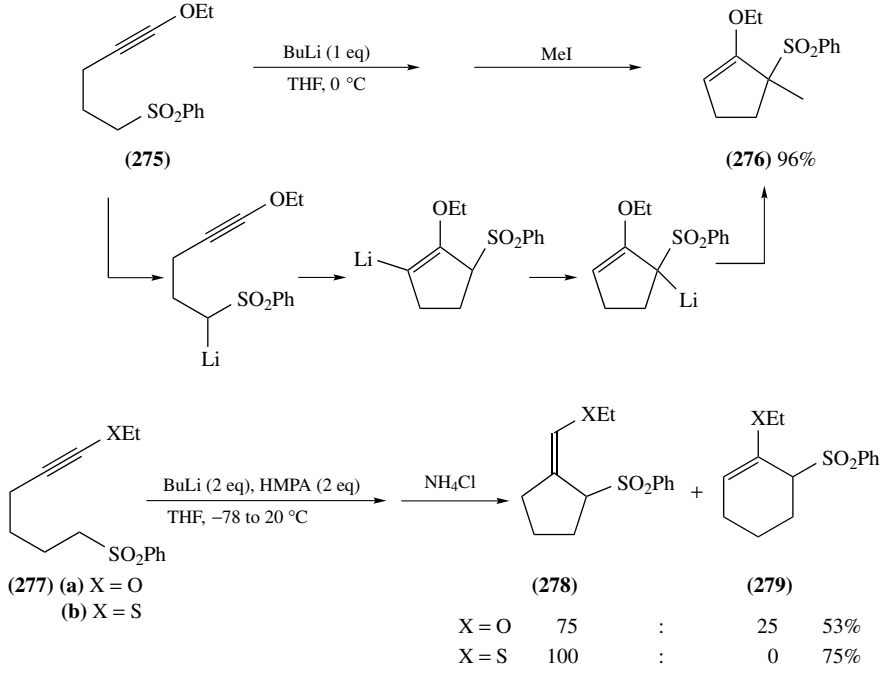
SCHEME 71

Piers and Coish have described how cyclopropyllithiums derived from substituted iodocyclopropanes **273** carbolithiate onto alkynes bearing an activating group like silyl, germyl or phenyl to afford functionalized spiro[2.4]heptanes **274**. Although room temperature was needed for the cyclization reaction, the intermediate alkenyllithiums resulted to be configurationally stable, probably due to an intramolecular coordination with the alkoxide group (Scheme 72)[129].



SCHEME 72

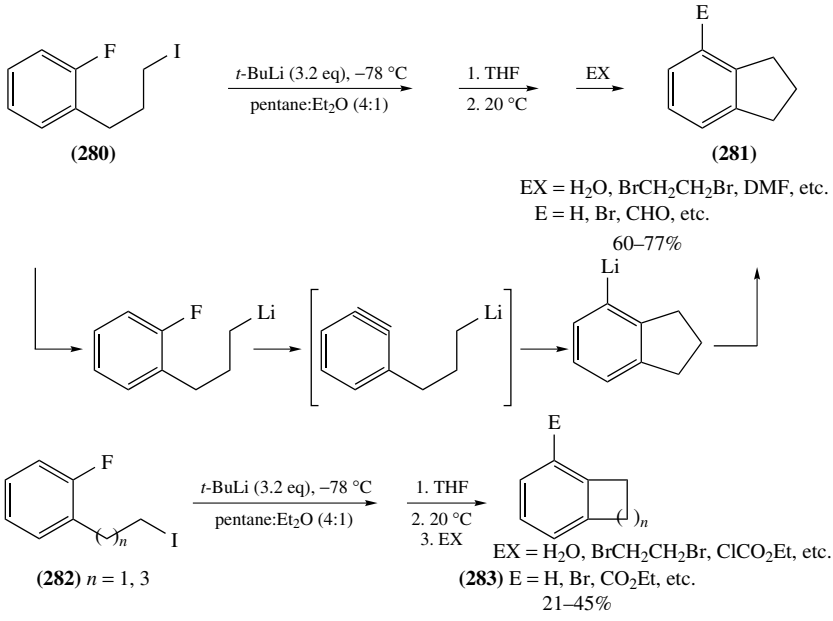
Although *exo-dig* cyclization reactions are in general more favourable for the carbolithiation reaction of acetylenic alkyllithiums, 5-*endo-dig* anionic ones do occur. Funk and coworkers have reported that ynol ethers and thioethers can be carbolithiated by stabilized carbanions[130]. So when they attempted the α-methylation of sulphone **275**, cyclized enol ether **276** was isolated in excellent yield. Its formation could be accounted by a *trans*-carbometallation of the alkoxyacetylene moiety by the α-phenylsulphonyl anion to afford a vinyl anion, which translocates to a thermodynamically preferred α-phenylsulphonyl anion. Regiospecific methylation of this allyl anion furnishes the cyclopentenyl sulphone **276** (Scheme 73). The *trans*-stereoselectivity can be understood, considering that the *endo-dig* cyclization reactions cannot proceed via the usual *syn*-carbolithiation mode because this would place a *trans* double bond in the ring. The regioselectivity of the cyclization reactions of alkoxyacetylene **277a** and alkylthioacetylene **277b** is also shown in Scheme 73. Anionic cyclization of the latter is completely regioselective to afford the 5-*exo* product **278** (X = S). However, for **277a**, the preference for nucleophilic addition at the α-carbon of the alkoxyacetylene moiety to yield **279** (X = O) is insufficient to overcome a kinetically favoured attack at the β-carbon leading to the smaller ring **278** (X = O) (Scheme 73). The stereochemistry of compounds **278** appears to arise by an unexplained *trans* carbolithiation reaction, perhaps due to O−Li coordination. Moreover, this cyclization reaction is not restricted to sulphone-stabilized carbanions and phosphorus ylides. Ester and ketone enolates also cyclize onto alkoxyacetylenes.



SCHEME 73

In light of the facile 5-*exo-dig* carbolithiation reaction of simple acetylenic alkyllithiums, Bailey and Longstaff have studied the analogous 5-*exo* cyclization of a benzyne-tethered alkyllithium. Regioselectively 4-functionalized indanes **281** have been prepared

from 1-fluoro-2-(3-iodopropyl)benzene **280** in good yields through the cascade sequence shown in Scheme 74. This sequence implies: (i) iodine–lithium exchange, (ii) regioselective abstraction of the *ortho* proton to the fluorine atom, (iii) loss of lithium fluoride to deliver a benzyne intermediate and (iv) intramolecular attack of the tethered organolithium to the strained 1,2-dehydrobenzene moiety to afford 4-indanyllithium. Careful control of the reaction conditions is necessary to obtain good results, since it is imperative that the initial iodine–lithium exchange is conducted in the absence of THF and this solvent is, however, needed to produce the *ortho* lithiation[131].



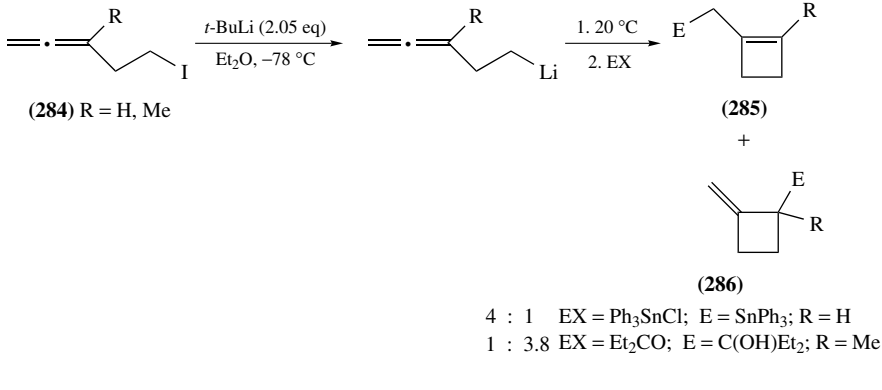
SCHEME 74

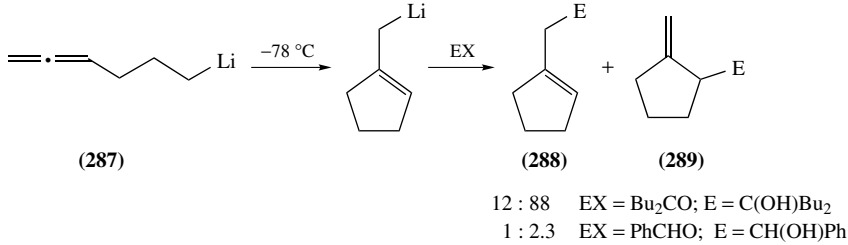
These authors have extended this reaction to the preparation of 3-substituted benzocyclobutenes **283** ($n = 1$) and 5-substituted tetralins **283** ($n = 3$) from α-(2-fluorophenyl)-ω-iodoalkanes **282**. In a similar way as described above, the processes involve generation and cyclization of benzyne-tethered alkyllithiums via 4-*exo* or 6-*exo*, though in these cases the yields are significantly lower (Scheme 74)[132].

D. Cyclization Reaction of Allenic Alkyllithiums

3,4-Pentadienyllithium reagents obtained from allenes **284** by metal–halogen exchange undergo at room temperature facile 4-*exo* cyclization reactions to the isomeric 1-cyclobutenylmethyllithium derivatives, which on treatment with electrophiles afford regioisomeric cyclobutenes **285** and **286** in variable ratios (Scheme 75)[133]. Probably the product benefits from allylic stabilization overcoming the four-membered ring formation. On the other hand, γ-allenyllithiums like **287** undergo a 5-*exo-dig* cyclization at $-78\,^{\circ}C$, giving rise, after trapping with electrophiles, to compounds **288** and **289** with moderate allylic regioselectivity (Scheme 75)[134]. These results show that the intramolecular complexation of the more remote double bond with the lithium centre

in β- and γ-allenyllithiums should be more favourable than the coordination to the closer double bond, probably due to strain considerations. On the other hand, a competitive intramolecular 1,5-proton-transfer process, that forms an internally lithiated allene, takes place on the corresponding δ-allenyllithiums and the carbolithiation reaction is therefore less efficient. However, the portion of the reaction involving cyclization proceeds by formation of the new carbon–carbon bond to the near allenic carbon, in accord with the generally established facility for five- over six-ring formation.





SCHEME 75

IV. CARBOLITHIATION REACTION OF UNSATURATED VINYLLITHIUMS AND ARYLLITHIUMS

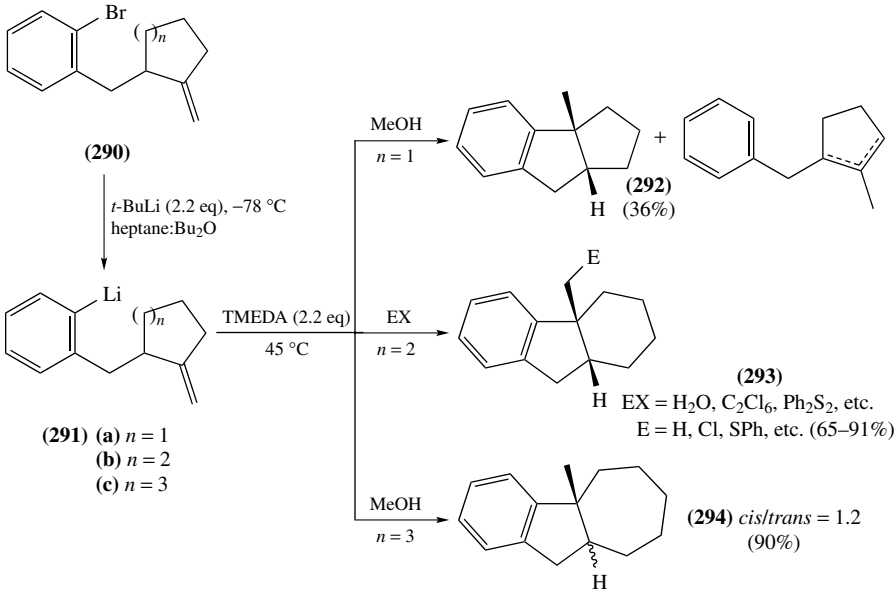
A. Cyclization Reaction of Olefinic Vinyllithiums and Aryllithiums

Although an energetically less favourable sp^2 to sp^3 carbanion transformation is involved in these processes, both aryllithium and vinyllithium cyclizations onto alkenes are successful. Moreover, cyclization reactions of vinyllithiums, rather than alkyllithiums, would also incorporate additional functionality (an alkene) into the product, allowing the preparation of alkylidenecycloalkanes with control of the alkene stereochemistry.

1. Olefinic aryllithiums

The first report of an aryllithum carbolithiation reaction is due to Woolsey and coworkers[14], who reported the cyclization reaction of *o*-(3-butenyl)bromobenzene via the aryllithium derivative (Scheme 3). More recently, Bailey and coworkers have studied the carbolithiation reaction of aryllithiums tethered to a methylenecycloalkane **291** (Scheme

76)[135], generated from bromides **290** by a low-temperature bromine–lithium exchange in a mixture of heptane:dibutyl ether (9:1 v/v). Although these cyclization reactions have been found to be kinetically slow, they result to be thermodynamically favourable and proceed at a useful rate at 45 °C in a regiospecific 5-*exo* mode. When the methylenecycloalkane is six-membered, the cyclization reaction affords stereoisomerically pure *cis*-fused products **293** providing a highly stereoselective route to 4a-substituted *cis*-hexahydrofluorenes. However, the aryllithiums **291a** and **291c** were somewhat less well-behaved under the same reaction conditions. Thus, although the methylenecyclopentane derivative **291a** cyclizes stereoselectively in an exclusively 5-*exo* fashion to afford **292**, formation of an allyllithium by abstraction of an allylic proton from the substrate effectively competes with the ring-closure. On the other hand, when the methylenecycloalkane moiety is seven-membered as in **291c**, the cyclization reaction is efficient but less stereoselective than the analogous process on five- and six-membered rings and octahydro-5a-methylcyclohepta[*a*]indene **294** is obtained as an approximately 55:45 mixture of *cis*- and *trans*-isomers. The stereochemical outcome found for the cyclization reaction of **291a** and **291b** is enforced by the geometry of the transition state for the ring-closure and the conformational constraints of these substrates. Hence coordination of the lithium atom with the methylene π-bond exocyclic to a tethered cyclopentane or cyclohexane ring can only take place on the face that is *syn*-disposed to the aryl substituent (Scheme 76).

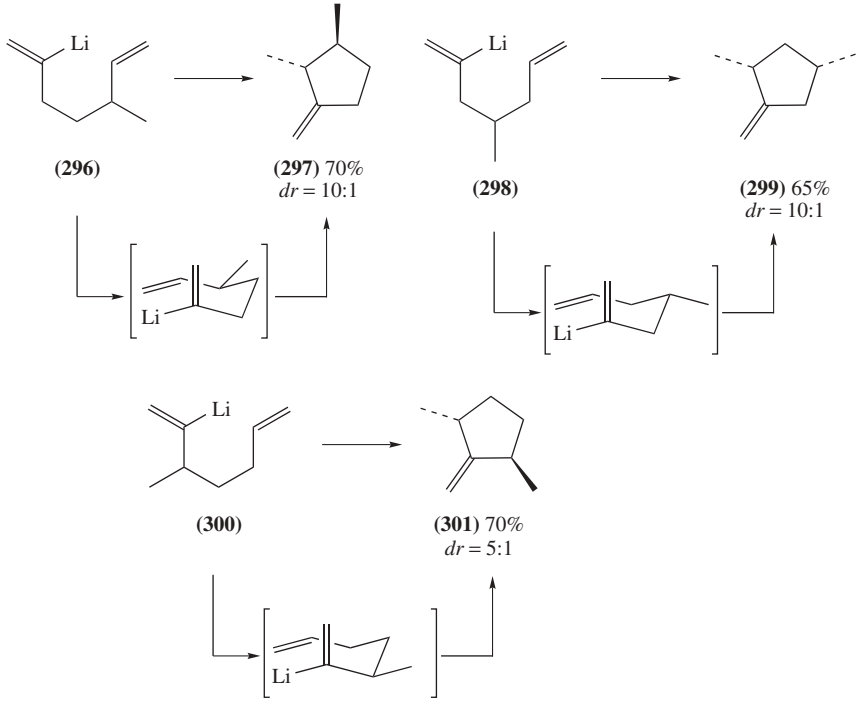


SCHEME 76

2. Olefinic vinyllithiums

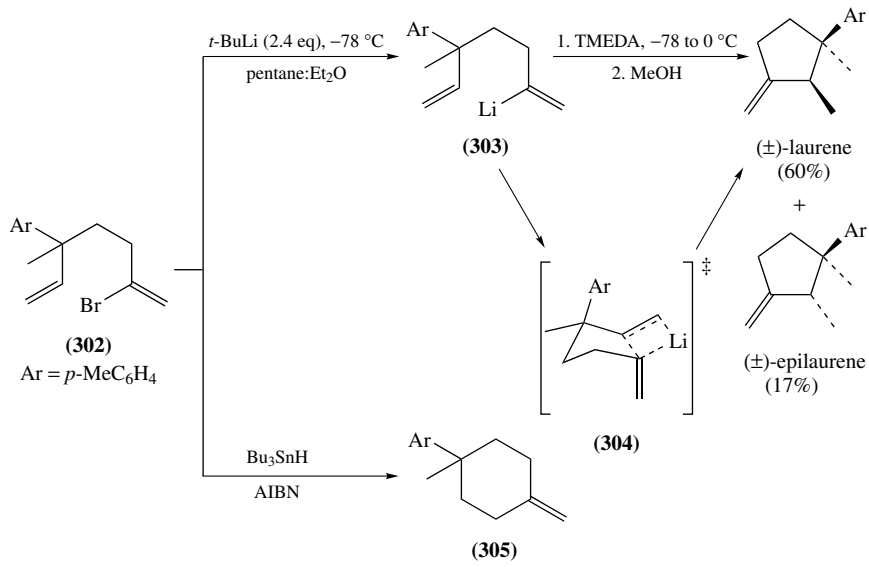
The first vinyllithium carbolithiation reaction was reported by Chamberlin and Bloom[15], who showed that vinyllithium reagents derived from ketone trisylhydrazones undergo anionic cyclization reactions to give functionalized cyclopentanes (Scheme 4). These authors have also shown that 5-, 4- and 3-alkyl-substituted 2-lithio-1,6-heptadienes like

296, **298** and **300**, respectively, generated from the corresponding trisylhydrazones, stereoselectively undergo intramolecular carbolithiation reaction. In each case there is a strong tendency for the formation of one of two possible product diastereoisomers **297**, **299** and **301**, respectively. The observed selectivity of methylenecyclopentane formation can be rationalized once again by coplanar four-centre transition states, for which the conformations with 'equatorial-like' substituents are favoured over conformations with 'axial-like' substituents (Scheme 77)[24].



SCHEME 77

The diastereoselectivity in this kind of vinyllithium cyclization reaction is only moderate if the stereogenic centre present in the substrate is a quaternary one instead of tertiary. So, Bailey and coworkers have reported that the closure of anion **303**, generated by low-temperature bromine–lithium exchange on bromide **302**, takes place with a moderate 55% *de* leading to a mixture of (±)-laurene and (±)-epilaurene (Scheme 78)[136]. The transition state **304** leading to the major isomer has a pseudo-axial aryl group and a pseudo-equatorial methyl, and the fact that the diastereoselectivity of these cyclization reactions may be predicted, at least qualitatively, by analysis of the conformational behaviour of chair-like transition states using a cyclohexane model offers new approaches to the synthesis of complex molecules by this methodology. Again, the analogous radical cyclization reaction of bromide **302** was carried out for comparison purposes and it takes place in a 6-*endo* fashion, giving methylenecyclohexane **305** and showing the complementarity and differences between radical and anionic cyclization reactions.

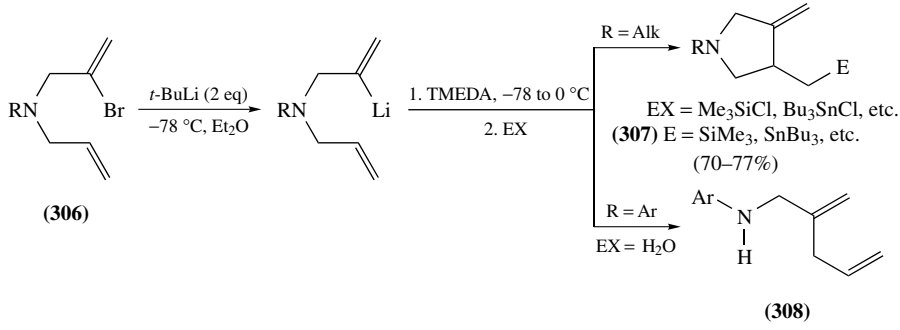


SCHEME 78

B. Cyclization Reaction of Heteroatom-substituted Olefinic Vinyllithiums and Aryllithiums

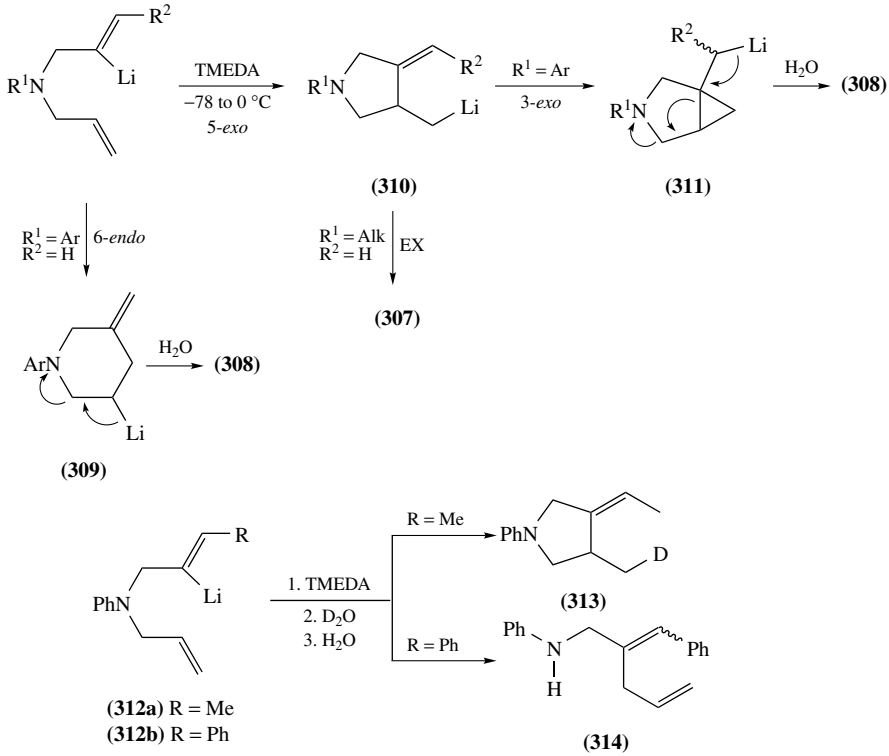
1. Heteroatom-substituted olefinic vinyllithiums

Our research group has been interested in recent years in the synthetic applications of *N*-allyl-*N*-2-lithioallyl amines, which are easily generated by bromine–lithium exchange in diethyl ether at low temperature from the corresponding *N*-allyl-*N*-2-bromoallyl amines **306**. These organolithium derivatives undergo a 5-*exo* carbolithiation reaction in the presence of TMEDA affording 3-functionalized-4-methylenepyrrolidines **307** in good yields. However, if the *N*-substituent is aromatic, the major products are the secondary amines **308** (Scheme 79)[137].



SCHEME 79

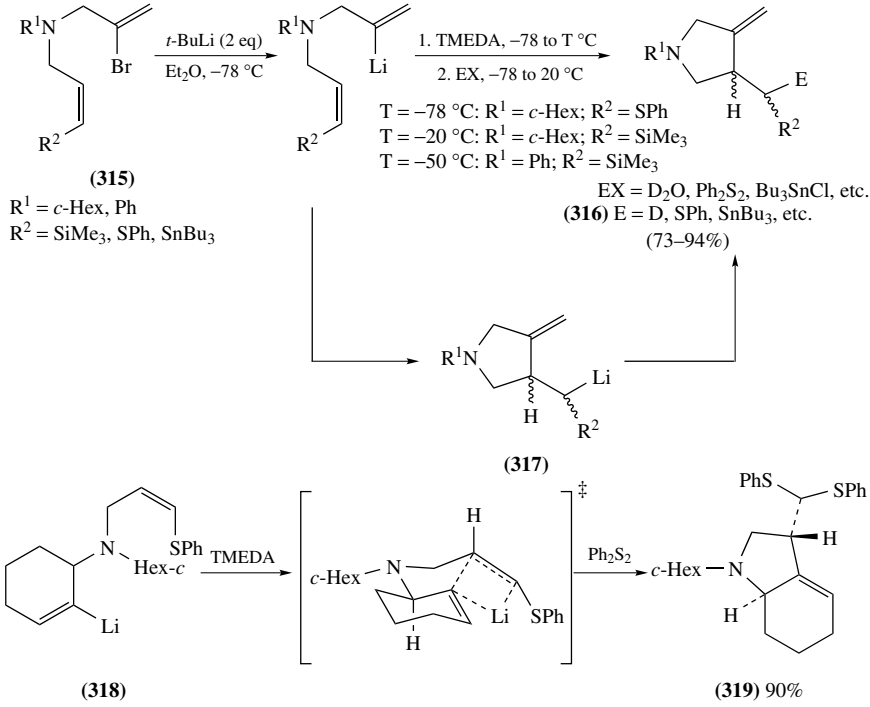
Although we have initially proposed that amine **308** is formed by a 6-*endo* ring closure followed by an irreversible β-elimination (Scheme 80), recently we have determined that amine **308** actually comes from a 5-*exo* carbolithiation reaction and further rearrangement via a cyclopropyl derivative[138]. Thus, treatment of *N*-2-lithioallyl amine **312a** with TMEDA affords exclusively the deuteriomethylpyrrolidine **313** derived from a 5-*exo* cyclization reaction, whereas organolithium **312b** gives rise selectively to the secondary amine **314** (Scheme 80). If the *N*-pentenylamines were formed by a 6-*endo* ring-closure affording intermediates **309**, this process would be essentially unaffected by a methyl group at the terminal position of the double bond such as **312a**. The no-formation of the secondary amine in this case suggests that the rearrangement proceeds via the cyclopropane pathway, i.e. a 3-*exo* cyclization reaction on lithiomethylpyrrolidine **310**, that affords intermediate **311**, followed by rapid and irreversible fragmentation to the lithium amide of **308**. Moreover, in the case of **312b** the exclusive formation of secondary amine **314** also supports the 5-*exo* followed by 3-*exo* due to the extra stabilization of **311** (R^2 = Ph) imposed by the benzylic character of this intermediate anion.



SCHEME 80

In this context we have recently reported that *N*-2-bromoallyl-*N*-(3-functionalized) allylamines **315** undergo, after formation of the corresponding vinyllithiums, intramolecular carbolithiation processes giving rise to functionalized methylenepyrrolidines **316** in good yields. We have shown that a moderately activating group at the terminal position of the double bond favours the cyclization reaction and we have presented the first

example of an intramolecular carbolithiation reaction onto a tributylstannyl-substituted olefin (Scheme 81)[139]. In those cases in which the E and R^2 groups are different, compounds **316** are obtained as an approximately 2:1 mixture of diastereoisomers, probably due to the configurational lability of organolithiums **317** at the temperature required to effect the cyclization. These intermediates are formed at different temperatures depending on the R^1 and R^2 groups. As an example, for the starting amine with R^1 = *c*-Hex and R^2 = SPh the carbolithiation reaction takes place at −78 °C, a much lower temperature than that observed for unsubstituted amines (R^2 = H, see Scheme 79). Moreover, with *N*-2-lithio-2-cyclohexenyl amine **318**, diastereoselective formation of hexahydroindole derivative **319** takes place efficiently, probably via a transition state similar to the one proposed by Chamberlin for the synthesis of related methylenecyclopentane derivatives (Scheme 81).

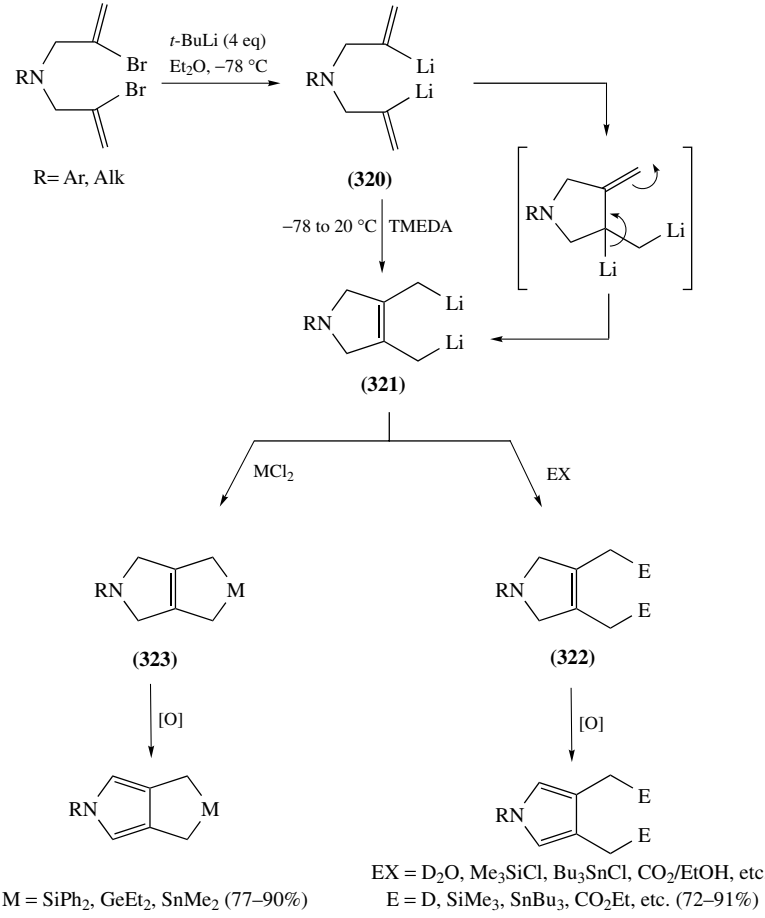


SCHEME 81

As we have already discussed, only terminal olefins and 1,2-disubstituted alkenes in which the initially formed alkyllithium product is substituted with a leaving group in a β-position or is stabilized by a moderately activating group are useful substrates for carbolithiation reactions. Despite this fact, our group has developed in recent years the intramolecular carbolithiation reaction of lithiated double bonds[140], a conceptually new process that expands the scope of this kind of reaction. Initially, we described how *N*,*N*-bis(2-lithioallyl)amines **320**, derived from easily prepared *N*,*N*-bis(2-bromoallyl)amines, cyclize efficiently to afford 3,4-bis(lithiomethyl)dihydropyrroles **321**, which could be trapped with electrophiles leading to functionalized *N*-heterocycles **322** in good yields (Scheme 82). This result could be explained by assuming an intramolecular carbolithiation reaction of

one vinyllithium moiety by the other one, affording a dilithiated methylenepyrrolidine intermediate, which could undergo an allylic rearrangement to give dilithiated compounds **321**. The overall transformation represents a cycloisomerization of vinyllithium to allyllithium moieties with formation of a new carbon–carbon double bond.

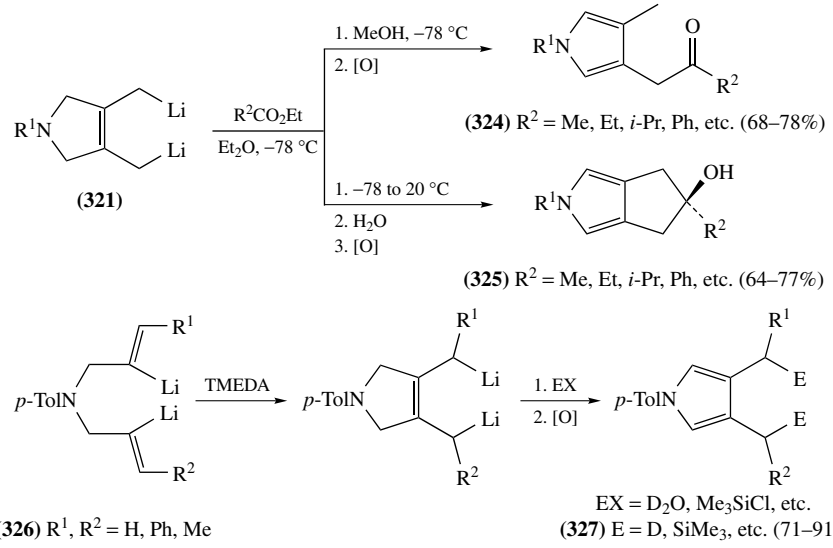
To extend the synthetic scope of this new reaction, we have carried out the functionalization of the new 1,4-dilithiated derivatives **321** with different electrophiles. The obtained dihydropyrrole derivatives **322** or **323** could be easily oxidized to the corresponding 3,4-difunctionalized pyrroles, which present a pattern of substitution difficult to achieve by conventional methods (Scheme 82)[141].



SCHEME 82

More recently, we have also described a new and unexpected reactivity of these 1,4-dianions **321** with carboxylic esters. Depending on the reaction conditions it is possible to obtain selectively β, γ-unsaturated ketones **324** or bicyclic cyclopentenol derivatives **325** (Scheme 83). In this work we have also shown additional evidence that support the carbolithiation reaction pathway for these transformations. Thus, *N*,*N*-bis(2-lithioallyl)amines

326, with different substituents at the terminal positions of the double bonds, undergo cyclization reaction affording new dilithiated compounds, which after treatment with electrophiles and oxidative workup give rise to the pyrrole derivatives **327**. The cyclization process occurs when at least one of these R^1 or R^2 groups is H or Ph. In the case of $R^1 = R^2 =$ Me the reaction fails, as expected for alkyl-substituted olefins in carbolithiation reactions (Scheme 83)[142].

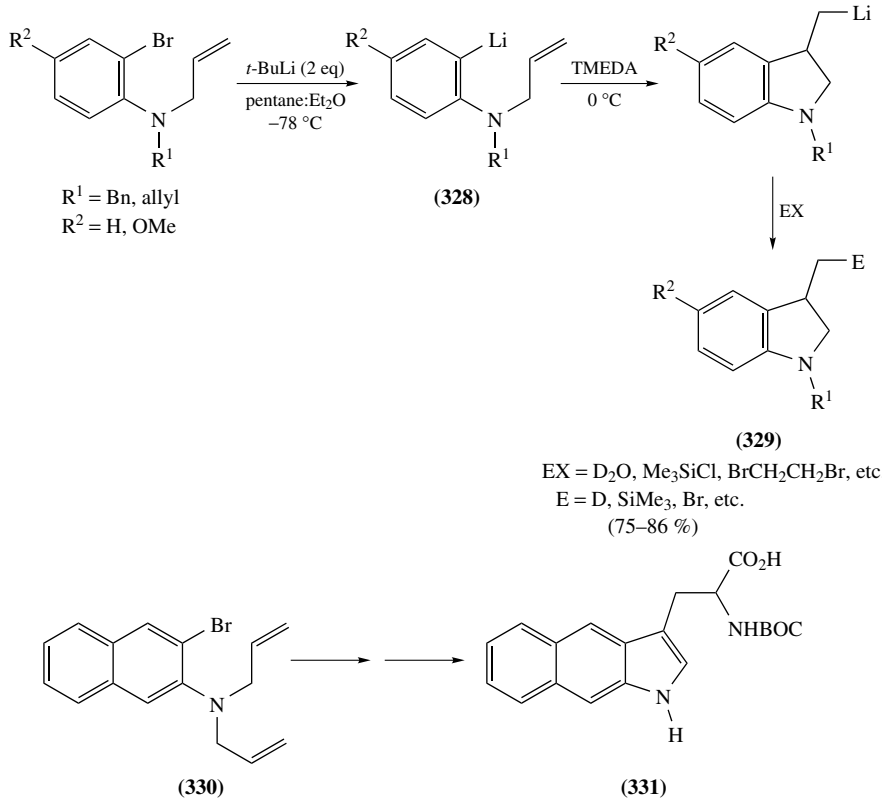


SCHEME 83

2. Heteroatom-substituted olefinic aryllithiums

With respect to aryllithiums, Liebeskind and Zhang[143] as well as Bailey and Jiang[144] simultaneously published the intramolecular carbolithiation of *N*-allyl-2-lithioanilines **328** that affords 3-lithiomethyl indolines. The starting organolithiums were generated from the corresponding aryl bromides by bromine–lithium exchange and the resulting cyclized anions could be trapped with electrophiles leading to 3-functionalized indolines **329** (Scheme 84). A similar approach was used in the synthesis of BOC protected benzo[*f*] tryptophan **331**[145], employing naphthalene derivative **330** as starting material (Scheme 84).

More recently, Bailey and Mealy[34] as well as Groth and Sanz[35] independently reported that these indolines **329** could be prepared by this methodology in an enantioselective manner if the cyclization step of **328** is carried out in the presence of a chiral ligand like (−)-sparteine (Scheme 85, see also Scheme 12). The chiral ligand shows the most pronounced effect in apolar donor solvents like toluene, though the use of pure diethyl ether generally produces only a slight decrease in the enantioselectivity. These results show that it is possible to effect enantiofacially selective cycloisomerization of an achiral olefinic organolithium by conducting the carbolithiation reaction of the achiral starting substrate in the presence of (−)-sparteine. Bailey and coworkers have also studied the effect of ligand structure on the asymmetric cyclization reaction of 2-(*N*,*N*-diallylamino)phenyllithium **328** (R^1 = allyl; R^2 = H). Although none of the ligands tested in their study affords 1-allyl-3-methylindoline **329** (R^1 = allyl; R^2 = E = H) in significantly higher *ee* than previously observed for this cyclization reaction in the presence

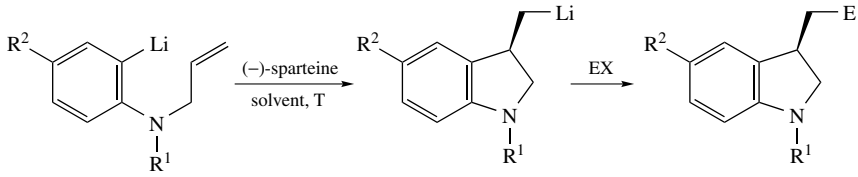


SCHEME 84

of (−)-sparteine, three structurally unrelated ligands, **332a**, **332b** and **332c**, which are available in either enantiomeric form, approach the efficiency of sparteine in this reaction. The *N*,*O*-dimethylpseudoephedrine ligand (**332a**) is a particularly effective surrogate for sparteine, affording 1-allyl-3-methylindoline in good yield and high *ee* (Scheme 85)[146].

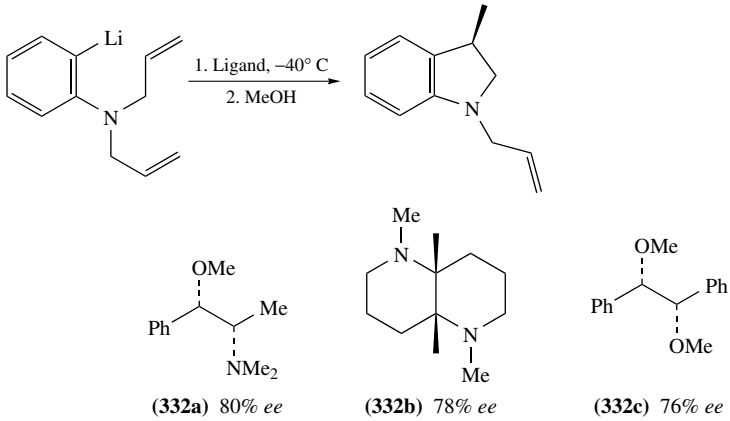
In this context, it has been observed that dilithio derivative **333** cyclizes in the presence of TMEDA to give a dilithiated indoline that may be differentially functionalized by sequential addition of electrophiles, affording 1,3-disubstituted indolines **334** (Scheme 86)[147]. This cyclization reaction also proceeds in an enantioselective way when it is carried out in the presence of the pseudoephedrine ligand **332a**. However, (−)-sparteine is in this case not able to promote the carbolithiation step, showing that the substrate structure may have a pronounced effect on the ability of a given ligand to facilitate the cyclization reaction.

An alternative to generate 2-lithioaniline derivatives uses 2-fluoroanilines as starting materials, and so, reaction of 2-fluoro- or 3-fluoro-*N*,*N*-diallylanilines **335** with different alkyllithiums (3 equivalents) lead to 3,4-disubstituted indolines **336** (Scheme 87)[148]. The overall transformation probably involves *ortho*-lithiation and loss of lithium fluoride, affording a benzyne intermediate, which regioselectively undergoes intermolecular addition of the alkyllithium, giving rise to a 2-lithioaniline **337**. This organolithium cyclizes



(328) (*R*)-**(329)**

R^1	R^2	E	Solvent	*T* (°C)	Yield (%)	*ee* (%)
Bn	H	Br	toluene	–90	70	85
Bn	OBn	Br	toluene	–78	68	85
Bn	F	H	toluene	–90	80	90
Allyl	H	H	pentane:Et_2O	–40	69	86
Allyl	H	H	Et_2O	–40	91	78

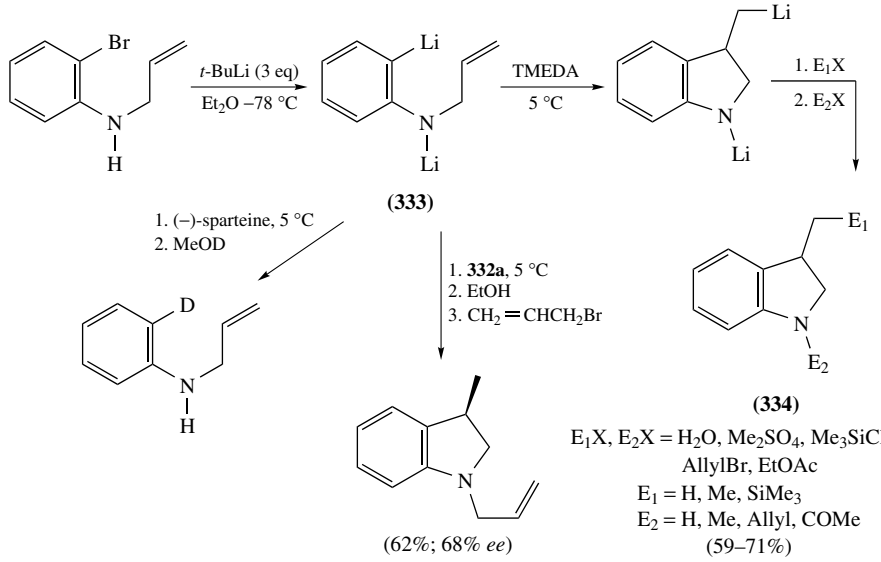


(332a) 80% *ee* **(332b)** 78% *ee* **(332c)** 76% *ee*

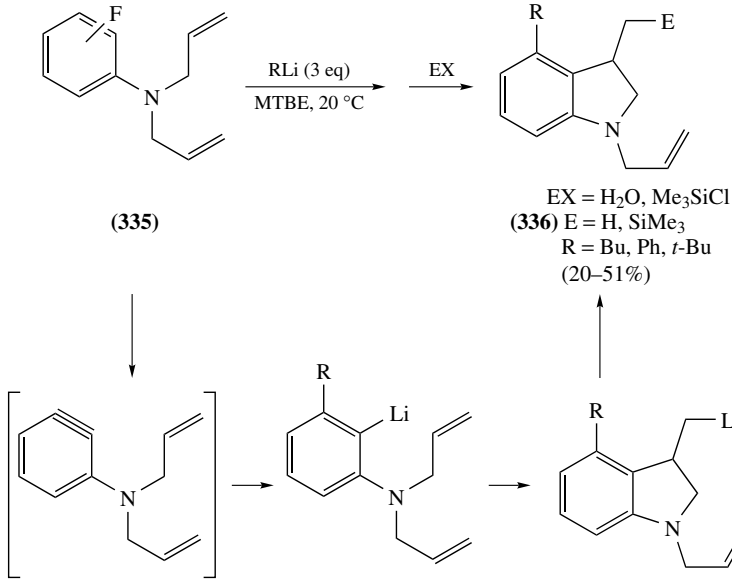
SCHEME 85

via a 5-*exo-trig* process to a lithiomethylindoline, which on treatment with electrophiles allows the isolation of indolines **336** in moderate yields.

In our group we have also developed the carbolithiation reaction of lithiated double bonds by aryllithium species. Thus, treatment of different *N*-2-bromoallyl-2-bromoanilines **338** with *t*-BuLi affords the corresponding dianions, which upon the addition of TMEDA and further treatment with electrophiles lead to the isolation of functionalized indoles **339** (Scheme 88). The formation of the indole nucleus could be explained via carbolithiation reaction of the vinyllithium moiety by the aryllithium to afford dilithiated indoline derivatives **340**. Since an allylic rearrangement would involve the loss of aromaticity in the aromatic ring, elimination of lithium hydride takes place affording 3-lithiomethylindole derivatives. Reaction of these intermediates with electrophiles gives rise to the 3-functionalized indole derivatives **339**. Moreover, the preparation of *N*-unsubstituted indoles is also possible by this methodology using secondary amine **338** (R = H) as starting material and five equivalents of *t*-BuLi. Higher temperatures than



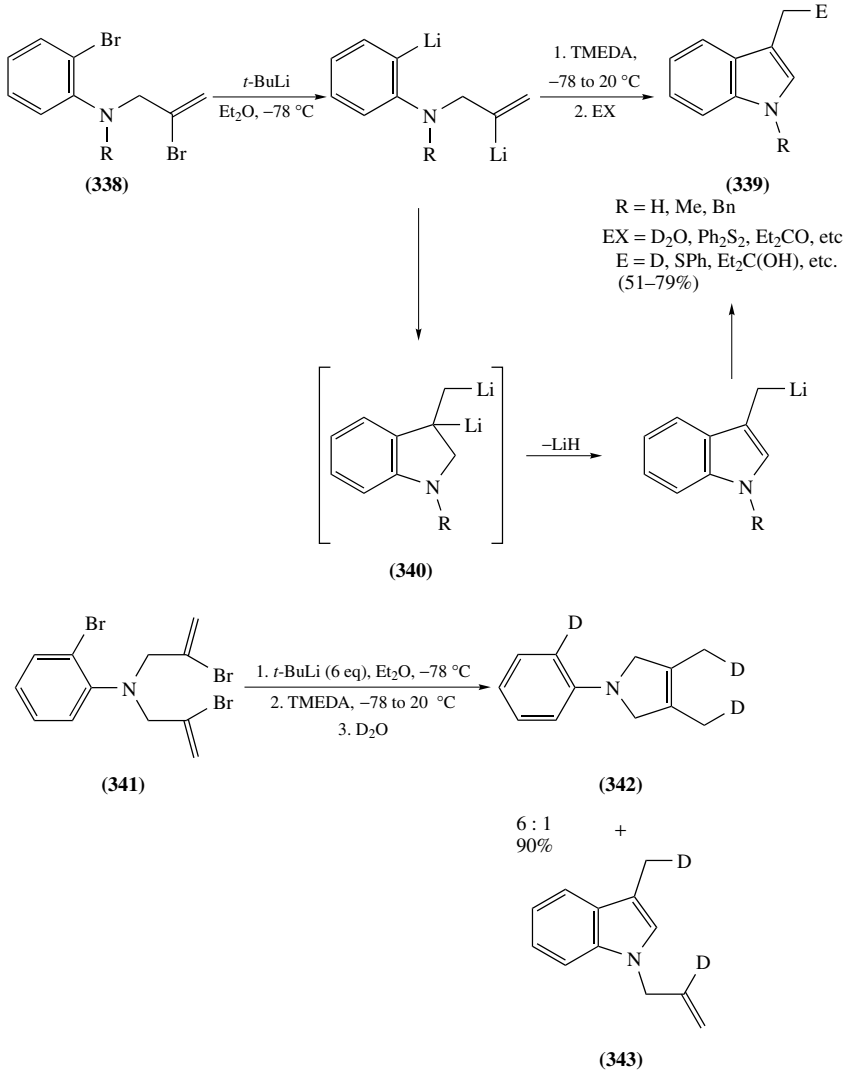
SCHEME 86



SCHEME 87

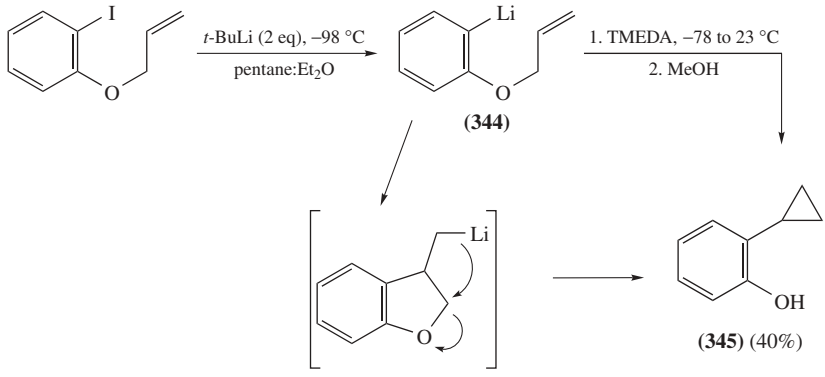
those used for tertiary amines **338** (R = Me, Bn) are also required to achieve an effective cyclization reaction[140, 141].

To check the different reactivity for the carbolithiation reaction of a lithiated double bond by vinyl- or aryllithiums, tertiary amine **341** was synthesized and treated with 6 equivalents of *t*-BuLi and TMEDA. Subsequent deuteriolysis led to a 6:1 mixture of the dihydropyrrole derivative **342** and the indole derivative **343** in very good overall yield, showing that intramolecular carbolithiation reaction of a lithiated double bond by a vinyllithium is faster than the corresponding carbolithiation reaction by an aryllithium (Scheme 88)[141].



SCHEME 88

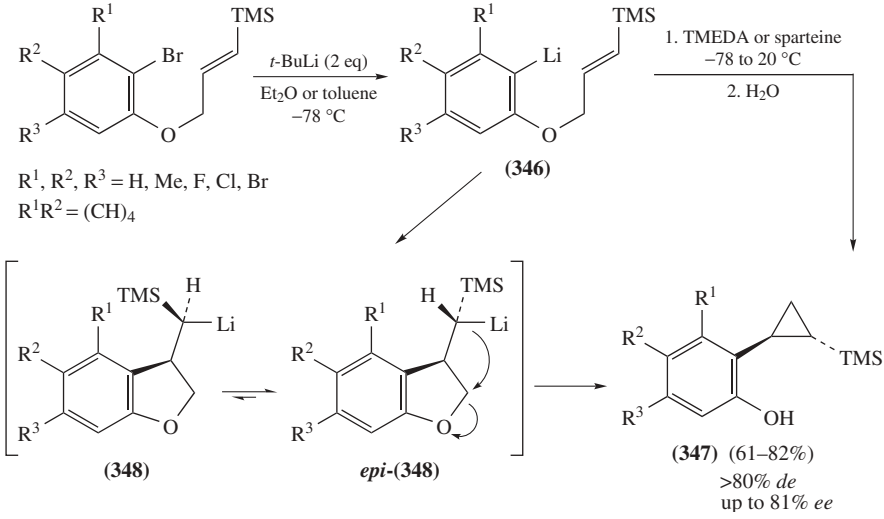
As we have discussed before, indolines are easily generated by a 5-*exo* carbolithiation reaction from *N*-allyl-2-lithioanilines. However, attempts to synthesize dihydrobenzofuran derivatives from the analogous oxygen-containing system led to different results. Consequently, initially, Bailey and Punzalan reported that allyl 2-lithiophenyl ether **344**, prepared by iodine–lithium exchange from allyl 2-iodophenyl ether, rearranges on warming in the presence of TMEDA to the lithium salt of 2-(cyclopropyl)phenol **345** (Scheme 89)[149]. The outcome of the reaction could be explained by a γ-elimination process in the intermediate (2,3-dihydrobenzofuranyl)methyllithium, generated by an initially 5-*exo* carbolithiation reaction. However, only 40% of **345** could be obtained due to a competitive S_N' cleavage of the allyl group in **344** by the excess of *t*-BuLi, as was demonstrated by the formation of 4,4-dimethyl-1-pentene and phenol.



SCHEME 89

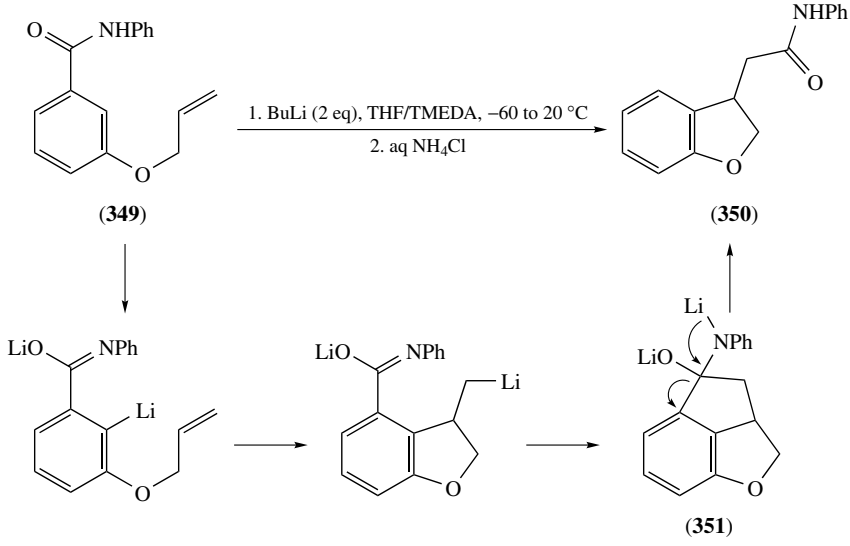
In this context we have recently reported that 2-lithioaryl 3-trimethylsilyl-2-propenyl ethers **346**, derived from the corresponding aryl bromides by bromine–lithium exchange, undergo similar tandem carbolithiation/γ-elimination reactions in diethyl ether/TMEDA affording *o*-cyclopropyl phenol or naphthol derivatives **347** in a diastereoselective manner. Moreover, the use of (−)-sparteine as a chiral ligand instead of TMEDA allows the synthesis of cyclopropane derivatives with up to 81% *ee* (Scheme 90)[150]. The major diastereoisomers are the corresponding *trans*-1-aryl-2-trimethylsilylcyclopropanes **347** and the stereochemical outcome is the same independently from the configuration (*Z* or *E*) of the allylic double bond. This fact can be understood taking into account that the organolithium intermediate **348**, derived from a *syn*-5-*exo* carbolithiation reaction of **346**, probably undergoes rapid epimerization to *epi*-**348** prior to the 1,3-elimination, that is assumed to occur with retention of configuration of the lithium-bearing carbon (Scheme 90). As expected, the best enantioselectivities were obtained when non-polar solvents like toluene or hexane were used instead of diethyl ether.

Although the synthesis of dihydrobenzofuran derivatives seems to be not possible by this anionic cyclization methodology, there are some particular examples in which these heterocycles are prepared by an intramolecular carbolithiation reaction. In this respect Baldwin and coworkers described in 1980 the preparation of **350** by rearrangement of **349** when it was treated with BuLi in THF/TMEDA (Scheme 91)[151]. The most likely explanation starts with an *ortho*-lithiation giving a dilithium intermediate, which undergoes an intramolecular 5-*exo* carbolithiation reaction affording a 3-lithiomethyldihydrobenzofuran



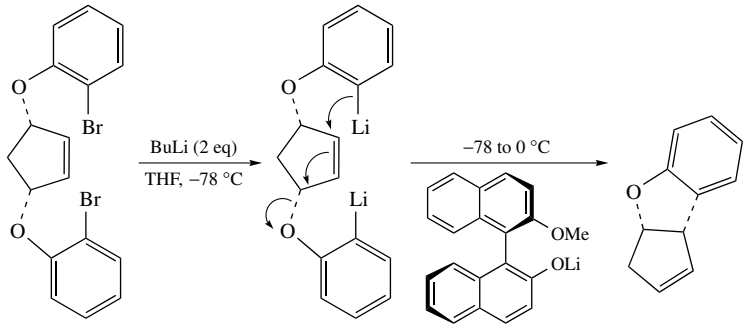
SCHEME 90

derivative. In this case, this intermediate does not eliminate to the phenolate, probably due to a favoured intramolecular attack onto the amide group leading to **351**, which subsequently undergoes Haller–Bauer-type cleavage giving rise to the final product **350** (Scheme 91).



SCHEME 91

On the other hand, Nishiyama and coworkers have reported an enantioselective synthesis of cyclopenta[*b*]benzofurans using chiral lithium alkoxides. In the absence of additives bis-phenyllithium species **352**, generated by addition of BuLi to the corresponding starting dibromide, undergoes a S_N2' intramolecular cyclization reaction, which could also be considered as an intramolecular 5-*exo* carbolithiation reaction followed by a β-elimination reaction, affording a racemic mixture of cyclopenta[*b*]benzofuran **353**[152]. Although the addition of (−)-sparteine gives no chiral induction, the presence of a stoichiometric amount of a chiral lithium naphthoxide like **354** produces **353** with high enantioselectivity (Scheme 92)[153].

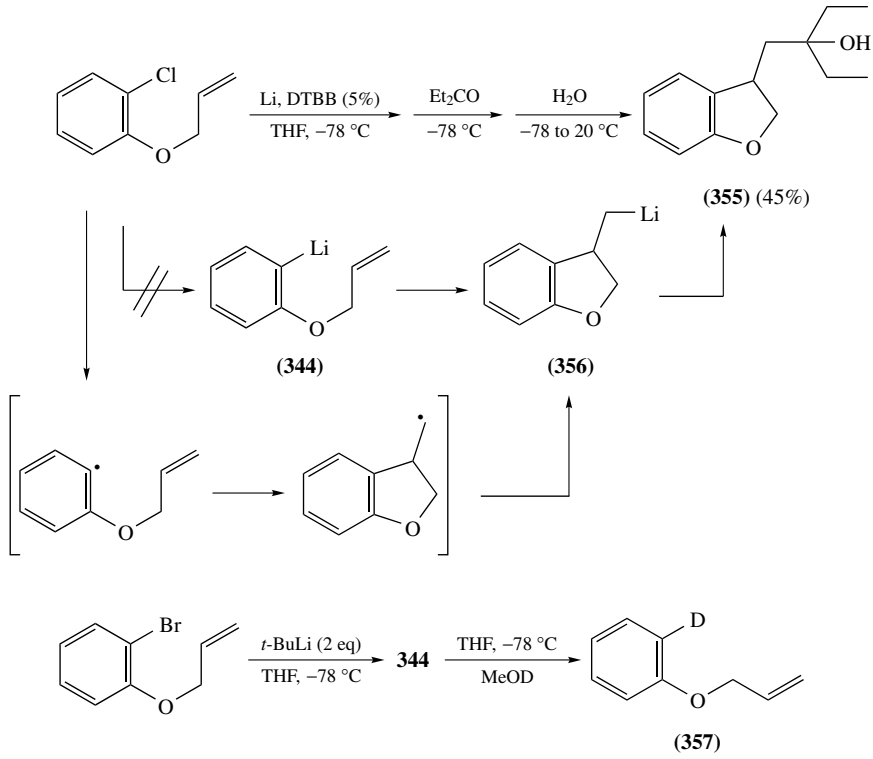


(352) **(354)** **(353)**
73%; 87% *ee*

SCHEME 92

As shown in Scheme 49, Yus and coworkers have studied some intramolecular carbolithation processes promoted by DTBB-catalysed chlorine–lithium exchange. When they extended this study to the lithiation of allyl 2-chlorophenyl ether they found that indeed at −78 °C in THF the only compound isolated, after reaction with 3-pentanone, was the alcohol **355** (Scheme 93)[87]. These authors state that organolithium intermediates **344** and **356** are probably involved in the process. However, our group has studied the reactivity of allyl *o*-lithioaryl ethers in THF and we know that these anions are stable in THF at −78 °C. So when anion **344**, generated by bromine–lithium exchange with *t*-BuLi, is treated with deuteriated methanol at −78 °C, compound **357** is obtained. On the other hand, upon warming from −78 to −30 °C, organolithium compounds similar to **344** mainly undergo a tandem anion translocation-Wittig rearrangement[154]. According to this, a radical mechanism rather than an anionic process probably operates in the reaction of allyl 2-chlorophenyl ether and lithium arene (Scheme 93).

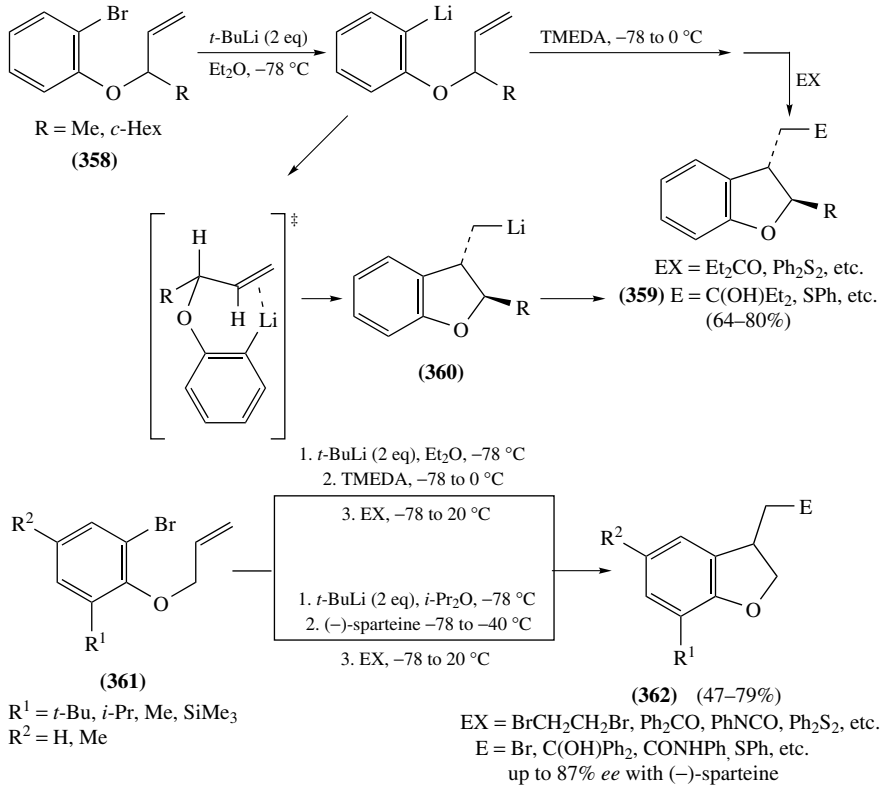
Looking for a suitable preparation of dihydrobenzofuran derivatives by carbolithiation reactions, we have recently described how allyl 2-bromophenyl ethers **358** with a substituent at the α-position afford, after treatment with *t*-BuLi, addition of TMEDA and further quenching with electrophiles, functionalized *trans*-2,3-dihydrobenzofuran derivatives **359** in a totally diastereoselective manner (Scheme 94)[155]. The key for the success of this reaction is the fact that intermediate organolithium **360** is not prone to undergo the 1,3-elimination process, probably due to the steric effect of the R substituent. The high diastereoselectivity of the ring closure could be explained by a transition state that accommodates the R group in a pseudoequatorial position. Moreover, simple allyl



SCHEME 93

ethers could also be useful substrates for the preparation of dihydrobenzofurans if a substituent is present at the 6-position of the aromatic ring. Hence, easily prepared ethers **361** give rise, after bromine–lithium exchange and TMEDA addition, to 3-functionalized 2,3-dihydrobenzofurans **362** in moderate to good yields (Scheme 94). At this moment the reason why the R^1 favours the carbolithiation reaction and avoids the γ-elimination reaction is not clear. Interestingly, if (−)-sparteine is used instead of TMEDA, the cyclization reaction takes place in an enantioselective way and enantio-enriched heterocycles **362** are obtained with 77–87% *ee*.

The first synthetically useful 6-*exo* carbolithiation reaction of unactivated alkenes has been described by Pedrosa and coworkers[156]. Aryllithiums prepared by lithium–bromine exchange in chiral 2-(*o*-bromophenyl)-substituted perhydro-1,3-benzoxazines like **363a** participate in 6-*exo* intramolecular carbolithiation reactions if the cyclized lithium derivative is moderately stable, as in the case of formation of 4-substituted tetrahydroisoquinolines precursors **364**. Moreover, the 6-*exo* carbolithiation reaction could also be possible if the lithium intermediate can evolve to a stable final compound by intramolecular ring opening of the *N*,*O*-acetalic system. This tandem process that takes place on **363b** constitutes a stereoselective synthesis of 7-substituted 2-azabenzonorbornane precursors **365** (Scheme 95).



SCHEME 94

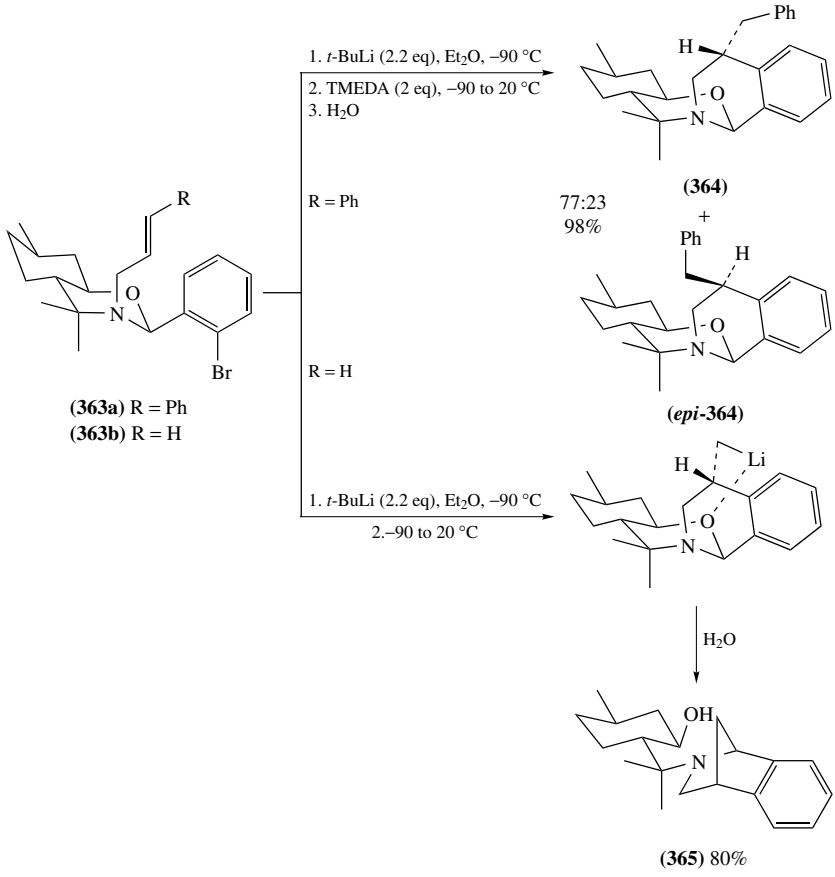
C. Cyclization Reaction of Acetylenic Allenyl Lithiums, Vinyllithiums and Aryllithiums

1. Acetylenic allenyllithiums

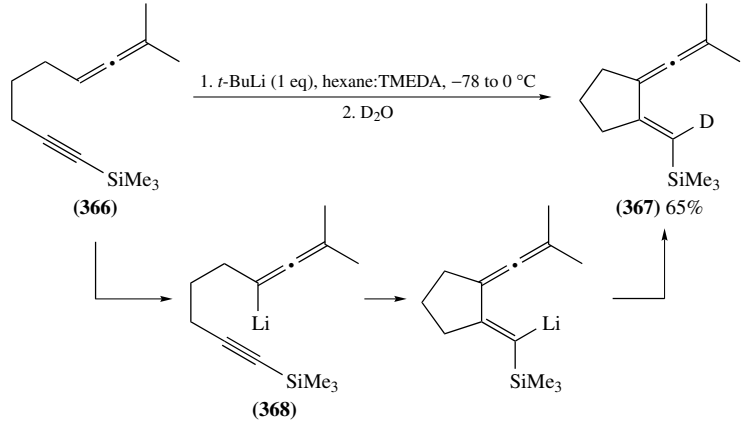
Negishi and coworkers have shown that trialkylsilylalkynes are able to trap intramolecularly alkyl-, vinyl-, allenyl- and aryllithiums[126]. For instance, allene **366** cyclizes to cyclopentane derivative **367** under treatment with *t*-BuLi and TMEDA. This is a remarkable example of a carbolithiation reaction initiated by a deprotonation that affords allenyllithium **368** which cyclizes onto the alkyne (Scheme 96).

2. Acetylenic vinyllithiums

On the other hand, the cyclization reaction of a vinyllithium onto an acetylenic unit provides an efficient route to five- and six-membered bis-exocyclic 1,3-dienes, which react stereoselectively with a wide range of dienophiles[157]. The 5-*exo* carbolithiation reaction of vinyllithiums **369**, derived from the corresponding vinyl bromides, is *syn*-stereospecific giving, after hydrolysis, the *E*-isomer of five-membered outer-ring dienes **370** and tolerates aryl-, silyl- or alkyl-substituents at the distal acetylenic carbon (Scheme 97). However, the alkyl-substituted alkynes are far more resistant to rearrangement than the aryl- or silyl-substrates and the addition of TMEDA and longer reaction times are needed for the latter

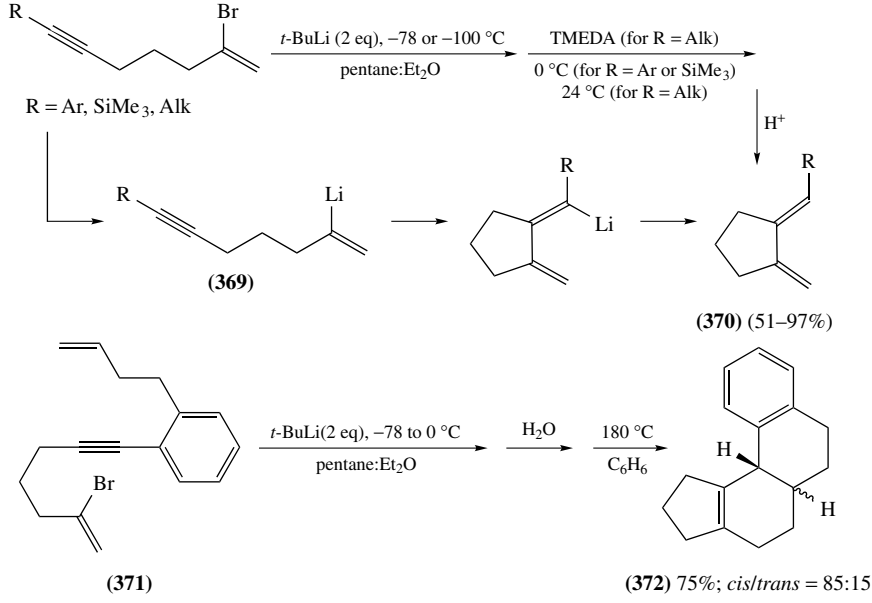


SCHEME 95



SCHEME 96

substrates. The preparation of polycyclic products can be accomplished without isolation of intermediates, as shown in the synthesis of **372** from the acyclic vinyl bromide **371** (Scheme 97)[158]. 6-*Exo* cyclization reactions are also possible, but they are much slower than the corresponding 5-*exo* and appear to be confined to substrates bearing an anion-stabilizing aryl- or silyl-substituent on the terminal acetylenic carbon. Whereas the first give rise to geometrically pure products, the 6-*exo* closure of the silyl-substituted system gives a mixture of diastereoisomers.

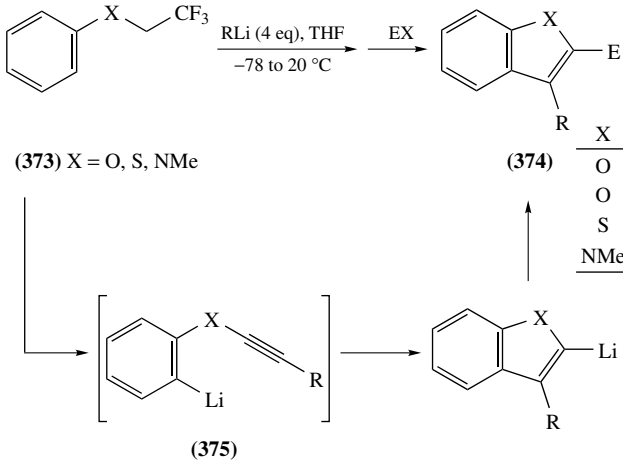


SCHEME 97

3. Acetylenic aryllithiums

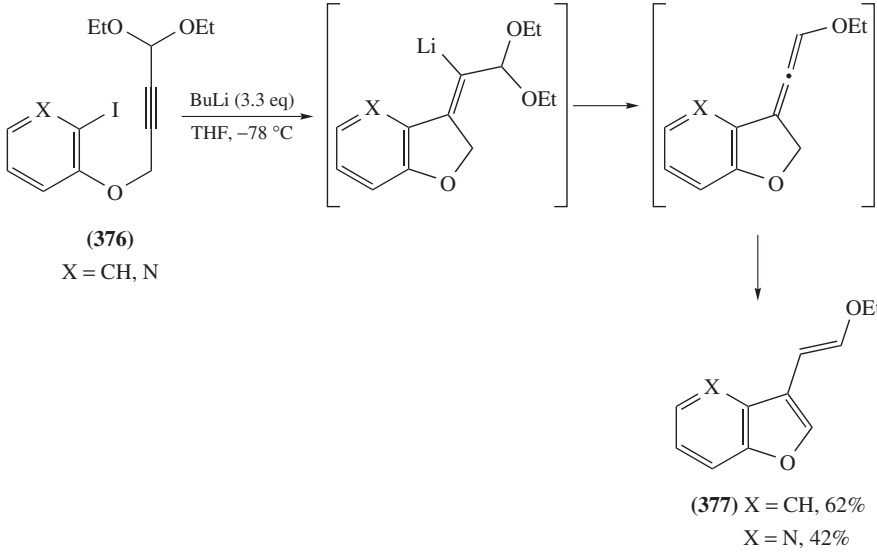
In contrast to the 5-*endo-trig* anionic cyclization reactions, rarely observed, there are several examples in which 5-*endo-dig* processes are involved. Hence 2,3-disubstituted benzofurans, benzothiophenes and indoles **374** have been synthesized starting from trifluoroethyl ethers, thioethers and anilines **373**, respectively, and alkyllithium compounds. A 5-*endo-dig* carbolithiation reaction on **375**, generated by two successive eliminations, one substitution and one *ortho*-lithiation reactions, is proposed to account for the formation of the corresponding 2-lithiated heterocycles. Further reaction of these intermediates with electrophiles affords compounds **374** (Scheme 98)[159]. In the case of thioether **373** (X = S) a bromine substituent must be present at the *ortho* position.

More recently, Maddaluno and Le Strat have described a new access to 3-vinylbenzofurans and 3-vinylfuropyridines **377** from acetylenic precursors **376**. Halogen–lithium exchange triggers an irreversible 5-*exo-dig* addition on the triple bond, followed by a lithium ethoxide elimination. A final isomerization of the exocyclic allene provides a useful 1,3-dienic system (Scheme 99)[160]. These authors also reported that the corresponding indoles could be obtained in a similar way, but a previous isomerization of the acetylenic moiety with *t*-BuOK is necessary to effect the cyclization reaction.



X	R	E	Yield (%)
O	Bu	H	40
O	*s*-Bu	H	40
S	Bu	I	40
NMe	Bu	CH_2OCH_3	50

SCHEME 98

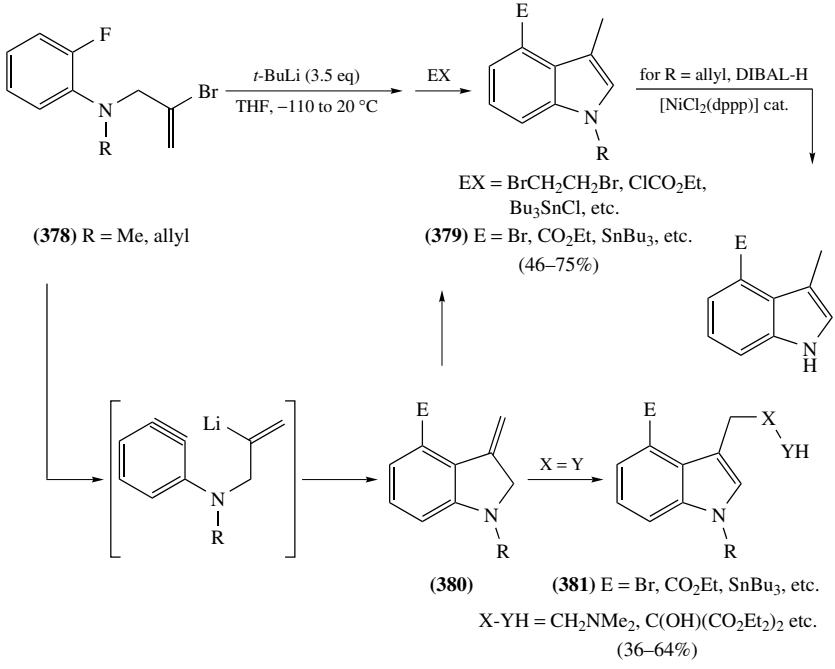


SCHEME 99

4. Benzyne-tethered vinyllithiums and aryllithiums

Again, benzyne derivatives could be considered as reactive alkynes and we have studied the anionic cyclization reactions of functionalized vinyl- and aryllithiums to these intermediates. We have developed a useful methodology that gives rise to a wide range of regioselectively functionalized heterocycles[161]. For instance, 4-functionalized indoles **379** have been prepared from simple *N*-2-bromoallyl-2-fluoroanilines **378**. Treatment of these

amines with *t*-BuLi initiates a cascade reaction that probably involves loss of lithium fluoride from the *ortho*-lithiated species. Then, intramolecular carbolithiation reaction of the benzyne intermediate and further addition of electrophiles allows the functionalization of the 4-position, hence the formation of 4-functionalized-3-methyleneindolines **380**. Subsequent aromatization on the workup gives rise to indoles **379**. Interestingly, the corresponding *N*-unsubstituted indoles could be obtained by an efficient removal of the allyl protecting group. Moreover, the 3-methyleneindolines **380** could undergo Alder-ene reaction with activated enophiles like Eschenmosher's salt, DEAD or diethyl ketomalonate, affording 3,4-difunctionalized indoles **381** in moderate to good overall yields (Scheme 100). This methodology allows the synthesis of interesting tryptamine analogues from readily available products in a 'one-pot' procedure.

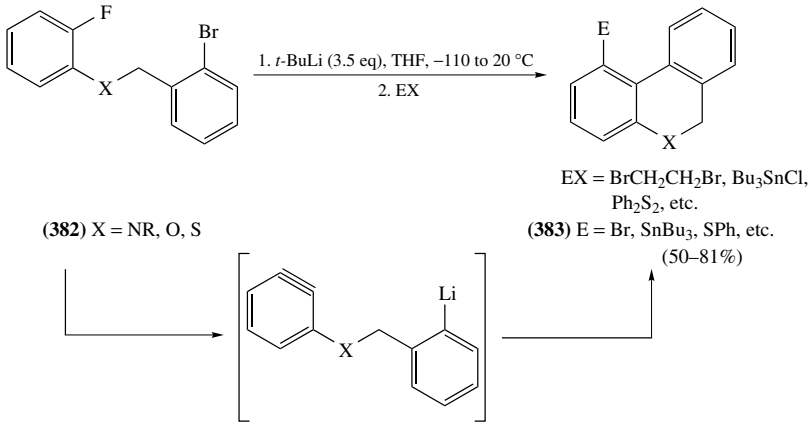


SCHEME 100

In this context aryllithiums are also able to carbolithiate a benzyne moiety, and so we have also described the preparation of several phenantridine, dibenzopyran and dibenzothiopyran derivatives **383**. In these cases γ-functionalized organolithiums, derived from bromides **382**, afford the corresponding and regiospecifically functionalized six-membered benzofused N-, O- or S-heterocycles through a 6-*exo* cyclization reaction onto a benzyne intermediate (Scheme 101)[161b].

V. CONCLUSIONS

The intramolecular addition of organolithiums to non-activated carbon–carbon double or triple bonds has now become an efficient way of constructing carbocyclic and heterocyclic systems. Although mainly confined to the formation of five-membered rings, the high regio- and stereoselectivity of these reactions and the possible functionalization of the



SCHEME 101

cyclization products make these processes a valuable complement to the related radical cyclization reactions. Moreover, enantioselective carbolithiation reactions may be carried out starting from an enantiomerically enriched secondary lithium derivative or by the use of a chiral ligand that may confer enantiofacial selectivity in cyclization reactions of achiral olefinic organolithiums.

VI. ACKNOWLEDGEMENTS

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CHAPTER 5

Structure and dynamics of chiral lithium amides

GÖRAN HILMERSSON and JOHAN GRANANDER

Department of Chemistry, Göteborg University, Kemivägen 10, SE-412 96, Göteborg, Sweden
Fax: +46 31 772 3840; e-mail: hilmers@chem.gu.se

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I. INTRODUCTION

Synthetic organic chemists often use the simple notation RLi in place of organolithium reagents in various reaction schemes, but it is well understood that this is an oversimplified picture. Organolithium compounds are aggregated to various extents and have a high propensity for forming mixed complexes with other organometallic compounds in solution, including reaction intermediates and products. This high tendency for aggregation is due to the inherent strong dipole moments within the compounds. Organolithium compounds are also known to coordinate strongly to various Lewis bases, such as ethers and amines. The structural diversity has been found to affect dynamics as well as reactivity of the organolithium compounds.

Lithium amides generally exhibit the same kind of characteristics, in terms of aggregation, solvation and dynamics, as organolithium compounds. The N−Li bond has properties similar to the C−Li bond, both are mainly ionic and have similar bond lengths. In the literature there is only a limited number of reports on the structures of chiral lithium amides; although much of the structure and dynamics are similar to the corresponding achiral lithium amides, there are also noticeable differences. Achiral lithium amides, e.g. lithium diisopropylamide (LDA) and lithium hexamethyldisilazide (LiHMDS), have been studied in great detail by Collum and coworkers using NMR spectroscopy[1–5]. Due to their extensive work the aggregation and solvation of the most common lithium amides are now well understood. However, the introduction of chirality into the lithium amides increases the number of possible structures, particularly when there are chelating groups present.

In this chapter the focus is on a few structures that serve to highlight the key factors controlling the structures of chiral lithium amides in general. For a complete review on structures of lithium amides there are a number of excellent articles[5–10]. The structures of the chiral lithium amides discussed herein have been determined either by X-ray analysis or by multinuclear NMR spectroscopy of isotopically labelled compounds. The basics of lithium amide structures and in particular the structures and dynamics of chiral lithium amides will be presented.

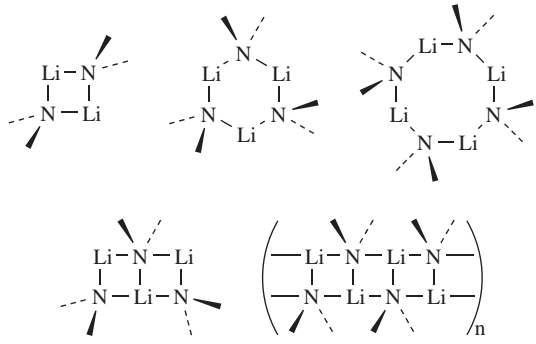
II. BASIC STRUCTURES OF LITHIUM AMIDES — AGGREGATES AND NMR STUDIES

Since much of the knowledge about chiral lithium amides has been obtained from research on achiral amides, this section will give a short overview of the field of lithium amides. Furthermore, without the development of NMR techniques in the last two decades the structural knowledge of organolithium compounds would still be in its infancy.

A. Structures and Aggregation

Lithium amides are dipolar compounds which form aggregates with the general formula $(RR'NLi)_n$. The degree of aggregation ranges from monomers to higher oligomers and even polymers depending on the steric requirements of the substituents on the nitrogen, the solvent, added ligands or complexing agents and temperature. Lithium amides generally form dimers in ethereal solution and larger aggregates of ladder type in non-coordinating

solvents. In Scheme 1 some of the most frequently found types of aggregates of lithium amide compounds are depicted.



SCHEME 1. Common structural motifs of lithium amides

Lithium amides often consist of $(N\text{-}Li)_n$ rings as basic building blocks. The high propensity for this ring formation is a result of the near-tetrahedral geometries around the nitrogen centers; the substituent groups of the nitrogens project above and below the $(N\text{-}Li)_n$ ring plane and therefore prevent stacking. The most common structures of lithium amides in non-polar hydrocarbon solvents are the ladder structures, which are formed by association of cyclic dimers in a lateral fashion. Unsolvated planar lithium amide rings $(N\text{-}Li)_n$, with $n = 2$, 3 and 4, have been isolated in the solid state. Large bulky substituent groups at the nitrogen centers favor larger rings, allowing the lithium amides to form cyclic trimers and tetramers. While lithium is often tetracoordinated and the ligands adopt tetrahedral geometry[8,11], exceptions are not uncommon. Di- and tricoordinated lithium centers have been observed in crystals of lithium amides[6,12]. Thus, the coordination number of the lithium ions seems to be governed mainly by the steric requirements of the ligands, i.e. the anion and the coordinating solvent molecules.

In coordinating solvents, e.g. diethyl ether (Et_2O) or tetrahydrofuran (THF), or in the presence of strongly coordinating ligands, e.g. hexamethylphosphoramide (HMPA), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) or *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA), both tri- and tetracoordinated lithium centers are common, depending on the steric requirements of the anion and the ligands. Solvents or added ligands with high affinity for lithium and strong Lewis basicity generally favor smaller aggregates. The aggregation number also reflects the steric requirements of the alkyl substituents at the nitrogen centers. Larger aggregates tend to be favored with more sterically demanding ligands.

The size of the aggregates is also dependent on the temperature. Due to entropy, smaller aggregates are favored at lower temperature in coordinating solvents, but in the absence of coordinating solvents larger aggregates dominate.

B. NMR Spectroscopy of Organolithium Compounds

Brown and coworkers[13–16] reported pioneering lithium NMR spectroscopic work on organolithium reagents in the late 1960s and early 1970s. These studies were performed with the most abundant lithium isotope, i.e. the ^{7}Li nuclei. However, the introduction of

the ^{6}Li NMR spectroscopy and later ^{6}Li-enriched reagents by Fraenkel and coworkers[17,18] and Seebach and coworkers[19,20] has made determination of the detailed structures of simple organolithium reagents in solution possible. Since the quadrupole moment of ^{6}Li is much smaller than that of the natural isotope ^{7}Li, it gives significantly sharper NMR signals, especially at low temperatures. Dynamic NMR studies of ^{6}Li-enriched alkyllithium reagents undergoing inter- and intra-aggregate exchange were extensively carried out in the 1980s. Simultaneously, there was a rapid development of new NMR techniques for structural investigations of organolithium compounds, most notably the ^{6}Li,^{1}H HOESY experiment introduced by Bauer and coworkers[21]. The use of ^{15}N labelled compounds has also been an important tool to elucidate the solution structures of chiral lithium amides. The NMR analysis of organolithium complexes in solution is often complicated by the presence of several aggregates. The ^{6}Li,^{6}Li COSY and ^{6}Li,^{6}Li EXSY experiments have been crucial in the assignment of the ^{6}Li signals arising from the same complex, since the lithiums can be scalarly coupled or undergo fast intramolecular exchange. There have been several review articles devoted to NMR spectroscopy of organolithium compounds[22–25].

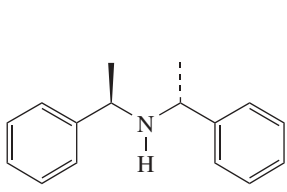
III. CHIRAL LITHIUM AMIDES — STRUCTURES

The interest in chiral lithium amides and their structures was sparked in the beginning of the 1990s when they proved useful in asymmetric synthesis. Over the years several chiral lithium amides have been structurally characterized. In this section the chiral lithium amides are discussed separately, depending on their structural basis. The chiral lithium amides with chelating groups constitute a central class of chiral amides widely used in various enantioselective reactions.

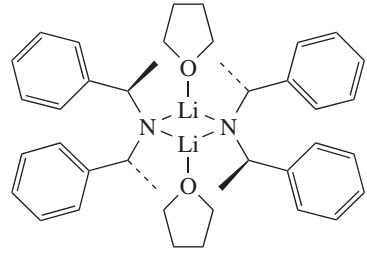
A. Dibenzyllithium Amides

Chiral lithium dibenzylamide derivatives have successfully been used in asymmetric deprotonation reactions and were among the first structures to be characterized.

The chiral lithium amide derived from (*R*,*R*′)-bis(1-phenylethyl)amine (**1**) was crystallized from a THF–hexane solution and characterized by X-ray crystallography as a bis THF-solvated dimer[26], (Li-**1**)$_2$•2THF. The two lithiums in the dimer are tricoordinated, as a result of the steric requirements of the large substituents on the nitrogen which prevent further solvation by THF. The same disolvated dimer was found to dominate in THF solution although a small amount of monomer was also observed[27].

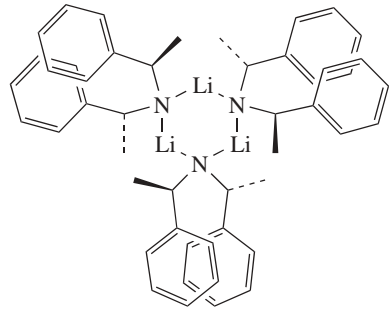


(1)



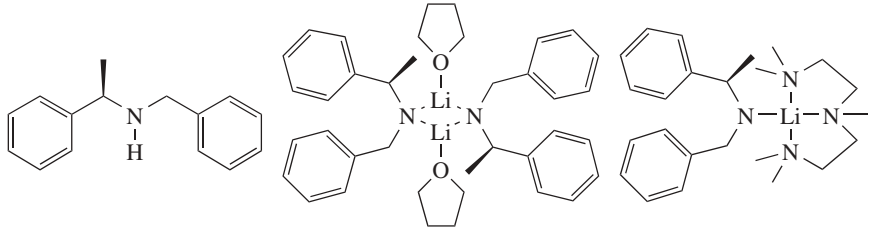
(Li-**1**)$_2$•2THF

Later, the same amide was crystallized as a cyclic trimer, (Li-**1**)$_3$, from the non-coordinating solvent hexane[28] showing that the nitrogen substituents are too bulky to allow lateral association into ladders.



(Li-**1**)$_3$

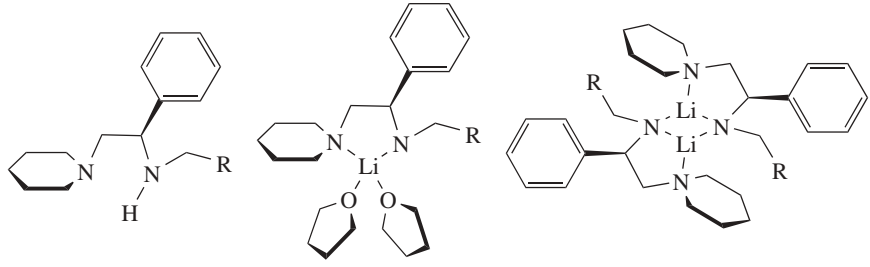
The lithium amide analogue with only one chiral center derived from (1-phenylethyl) benzyl amine (**2**) has been found to crystallize as a disolvated dimer from a THF solution, (Li-**2**)$_2$•2THF. With PMDTA added, the lithium amide crystallized as a monomer solvated by one triamine molecule, Li-**2**•PMDTA, showing the coordinating strength of PMDTA[29].



(**2**) (Li-**2**)$_2$•2THF Li-2•PMDTA

B. Chiral Lithium Amides with Chelating Amino Groups

Koga and coworkers[30–32] have studied the lithium amides of several chiral 1-phenyl-2-(1-piperidino)ethylamines with various substituents on the secondary nitrogen (**3**). NMR studies of the ^{15}N and ^{6}Li labelled lithium amides showed that they exist as monomers in THF, Li-**3**•2THF, and dimethoxyethane solvents, respectively. In Et_2O and in toluene solution, symmetrically coordinated dimers, (Li-**3**)$_2$, were observed. Addition of HMPA to either of the solutions resulted in monomers.

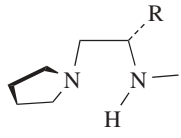


(**3**) Li-**3**•2THF (Li-**3**)$_2$

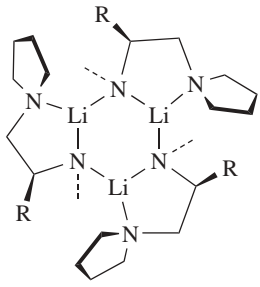
R = *t*-Bu or CF_3

The lithium amides were crystallized from THF and a toluene:Et_2O mixture and the structures were determined by X-ray diffraction. The amides crystallized as monomers solvated by two THF molecules and as symmetrically coordinated dimers, respectively, in agreement with the NMR observations.

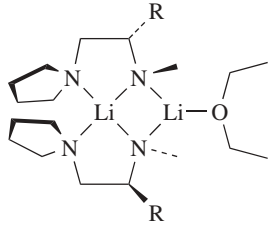
Arvidsson and Davidsson[33] have studied the lithium amides of chiral diamines, similar to those reported by Koga and coworkers, derived from phenylglycine and valine (**4**). In toluene, the lithium amides were observed to readily form cyclic trimers, (Li-**4**)$_3$, with all lithiums internally chelated. In Et_2O, these amides form unsymmetrically solvated dimers with one lithium solvated by both chelating nitrogens and the other by a solvent molecule, (Li-**4**)$_2$•Et_2O. However, monomers were not observed upon addition of THF but instead the ^{6}Li NMR spectrum displayed a single resonance peak from a symmetrically chelated dimer, (Li-**4**)$_2$•2THF.



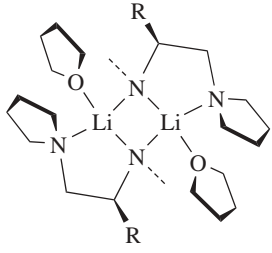
(4)



(Li-**4**)$_3$



(Li-**4**)$_2$•Et_2O



(Li-**4**)$_2$•2THF

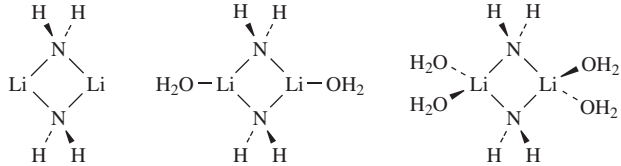
R = *i*-Pr or Ph

The difference in aggregation between these structurally similar amides, dimers versus trimers in toluene and monomers versus dimers in THF, is surprising. It is likely due to the different steric requirements of the substituents on the nitrogen, the smaller methyl group in Davidsson's study compared to the larger neopentyl or 2,2,2-trifluoroethyl group in Koga's study.

The structures in solution of these amides were established based on the observed scalar ^{6}Li,^{15}N NMR coupling constants. ^{6}Li is a spin 1 nucleus and ^{15}N is a spin $\frac{1}{2}$ nucleus. Thus, the multiplicity, N, of the ^{15}N signal is determined by $N = 2n + 1$ and the multiplicity of the ^{6}Li signal is correspondingly determined by $N = n + 1$, where n is the number of attached spin-coupled nuclei[17,19,34]. For a monomer of a doubly (^{6}Li,^{15}N) labelled lithium amide, the ^{6}Li signal would become a doublet and the ^{15}N signal a triplet. The

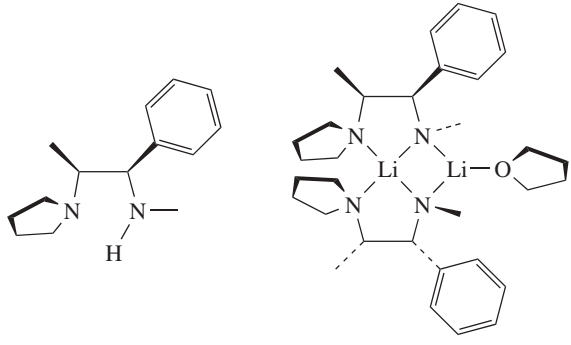
dimer, (Li-**4**)$_2$•2THF, was identified by a triplet signal in ^{6}Li NMR and a quintet signal in ^{15}N NMR. However, since cyclic trimers and tetramers also give rise to the similar splitting pattern, these complexes could only be unambiguously differentiated using the zero quantum coherence NMR experiment in two dimensions reported by Gilchrist and Collum[35].

In addition, Koizumi, Morihashi and Kikuchi[36] have suggested, based on computational studies on $LiNH_2$, that the size of the ^{6}Li,^{15}N coupling constant reflects the solvation number at lithium. A value of 4.9 Hz was calculated for the ^{6}Li,^{15}N coupling constant in unsolvated dimers of $LiNH_2$. Addition of a water molecule to each lithium, which then becomes planar tricoordinated, results in a lowering of the calculated coupling constant to 4.3 Hz. Addition of a second water molecule to each lithium, now becoming tetracoordinated, results in a further lowering of the calculated coupling constant to 3.5 Hz (Scheme 2). The magnitude of the observed ^{6}Li,^{15}N coupling constant has been employed elegantly by the Davidsson group in the assignment of the specific ^{6}Li resonances of chiral lithium amides.



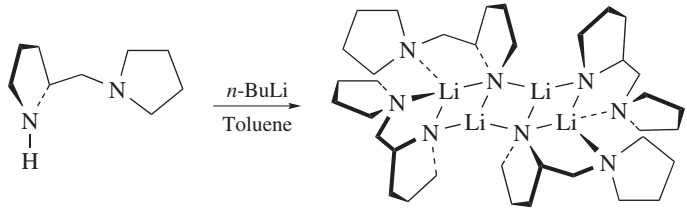
SCHEME 2. The magnitude of the calculated $J(^6\text{Li},^{15}\text{N})$ coupling constant reflects the coordination number of lithium

Ahlberg, Davidsson and coworkers[37] have studied a lithium amide of a chiral diamine prepared from norephedrine, i.e. (1*R*,2*S*)-*N*-methyl-1-phenyl-2-pyrrolidinylpropane amine (**5**), by NMR. It was found that this amide exists as unsymmetrically solvated dimers in THF, in which one of the lithiums is chelated by two pyrrolidine nitrogens, (Li-**5**)$_2$•THF, in contrast to similar chiral lithium amide dimers which have been found to be symmetrically solvated by THF. The only difference between this amide and the previously described example, Li-**4**, is the extra methyl group, but this small structural change is enough to change the solution structure in THF from a symmetrically solvated dimer to an unsymmetrically solvated dimer.



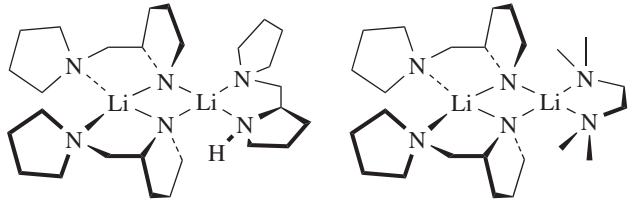
(5) (Li-**5**)$_2$•THF

The lithium derivative of the chiral chelating diamine (*S*)-2-(1-pyrrolidinylmethyl)-pyrrolidine (**6**) has been used extensively in stereoselective synthesis, i.e. in the deprotonation of ketones and rearrangement of epoxides to homoallylic alcohols. The lithium amide has been crystallized from toluene solution, and X-ray analysis revealed that it forms a ladder-type tetramer with the two pyrrolidine nitrogens solvating the two lithiums at the end of the ladder[38], (Li-**6**)$_4$.



(6) (Li-**6**)$_4$

In the presence of the corresponding pyrrolidine diamine, the chiral lithium pyrrolidide amide yields dimeric chelates composed of a lithium pyrrolidide amide dimer solvated by a pyrrolidine diamine, (Li-**6**)$_2$•**6**, as shown by NMR spectroscopy[39]. The lithium amide gives two ^{6}Li NMR signals in a 1:1 ratio. The addition of TMEDA to Li-**6** results in a similar complex where TMEDA coordinates to the lithium pyrrolidide amide dimer, (Li-**6**)$_2$•TMEDA.

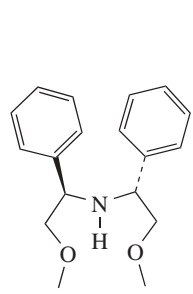


(Li-**6**)$_2$·**6** (Li-**6**)$_2$·TMEDA

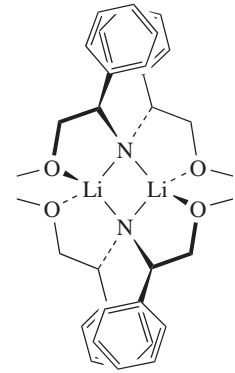
C. Chiral Lithium Amides with Chelating Ether Groups

Stoddart and coworkers[40] have synthesized a chiral lithium amide with C_2-symmetry and two chelating methoxy groups from the amine (*R,R*)-di(α-methoxymethylbenzyl)amine (**7**). This lithium amide was crystallized from a hexane solution and X-ray analysis revealed a dimeric structure where both lithiums are tetracoordinated, (Li-**7**)$_2$.

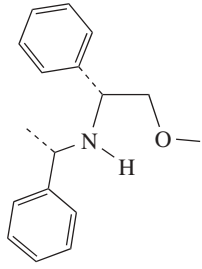
Eleveld and Hogeveen[41] prepared in 1984 a chiral lithium amide with a chelating methoxy group from (2-methoxy-(*R*)-1-phenylethyl)-((*S*)-1-phenylethyl) amine (**8**), for asymmetric alkylation reactions. Extensive NMR studies of this lithium amide in the mid-1990s showed that the lithium amide is an unsymmetrically solvated dimer in Et_2O solution, (Li-**8**)$_2$•Et_2O, with one lithium chelated by the two methoxy groups and the other lithium solvated by one molecule of Et_2O[42–44]. Later, the same lithium amide was crystallized from a hexane-THF (40:1) solution[45,46]. The crystal structure was found to be similar to the Et_2O solvated structure determined by NMR spectroscopy but instead solvated by THF, i.e. (Li-**8**)$_2$•THF.



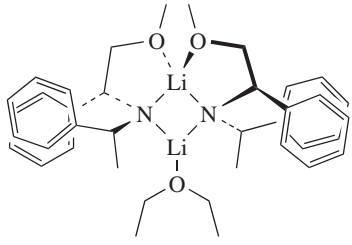
(7)



(Li-**7**)$_2$



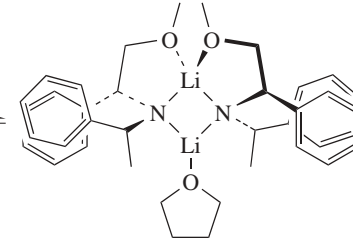
(8)



(Li-**8**)$_2$•Et$_2$O

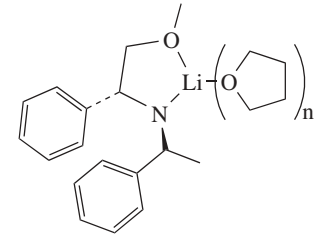
THF

Et$_2$O



(Li-**8**)$_2$•THF

THF THF



Li-**8**•nTHF

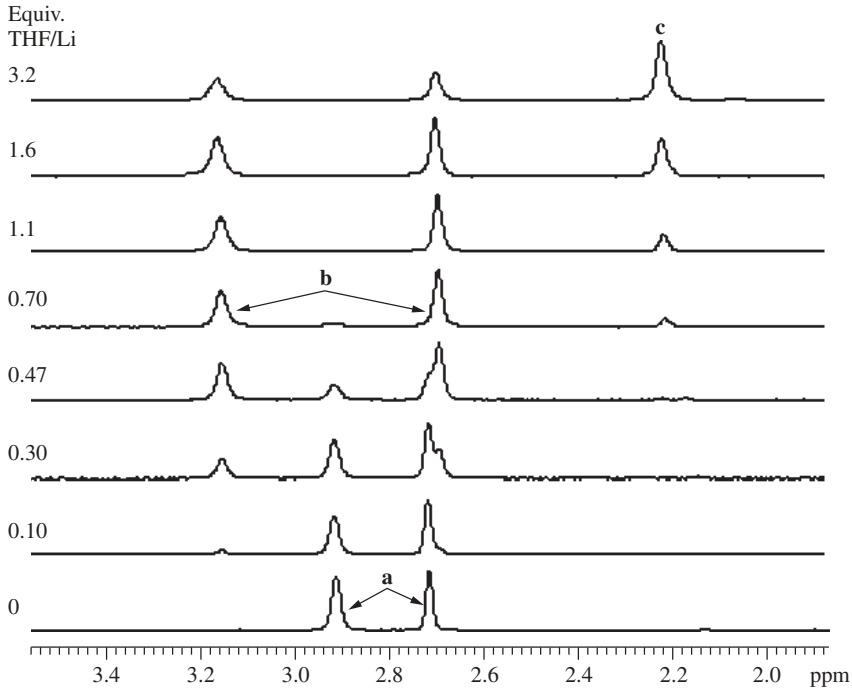


FIGURE 1. ^{6}Li spectra of Li-**8** in Et_2O at $-80\,^{\circ}C$ with increasing amounts of THF added. **a** = (Li-**8**)$_2$•Et_2O, **b** = (Li-**8**)$_2$•THF, **c** = Li-**8**•*n*THF

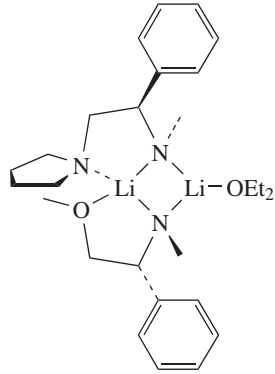
NMR studies have shown that, upon addition of one equivalent of THF to a Et_2O solution of the lithium amide, the Et_2O ligand is replaced by THF in the dimer. Further addition of THF or TMEDA at low temperature was reported to yield monomers solvated by THF, Li-**8**•*n*THF, where $n = 1$ or 2 (Figure 1).

Johansson and Davidsson[47] have reported on the NMR studies of a mixture of two different chelating lithium amides, one with an ether chelate, derived from (*R*)-1-methylamino-2-methoxy-1-phenylethane (**9**), and one with an amine chelate (Li-**4**). It was found that the Et_2O solution contained different dimers, both homo and hetero dimers. Based on NMR data it was concluded that a mixture of the two hetero dimers, both symmetrically ((Li-**4**/Li-**9**)•2Et_2O) and unsymmetrically ((Li-**4**/Li-**9**)•Et_2O) solvated, dominated in solution.

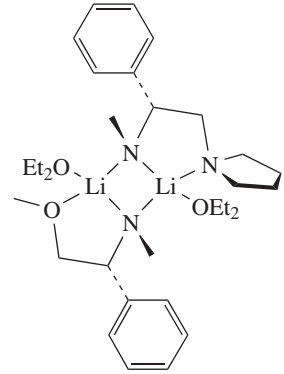
Our group has studied a large number of chiral lithium amides with this structural motif, i.e. chiral lithium amides of amino ethers derived from the α-amino acids alanine, valine, phenylalanine and phenylglycine (**10**). By employing the corresponding ^{15}N labelled amino acids, it has been possible to obtain doubly (^{15}N,^{6}Li) labelled chiral lithium amides. All of these amides have been shown to form unsymmetrically solvated dimers in Et_2O, (Li-**10**)$_2$•Et_2O, and symmetrically solvated dimers in THF[48–50], (Li-**10**)$_2$•2THF.

D. Chiral Lithium Amides with Chelating Thioether Groups

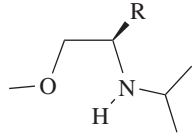
Chiral lithium amides with chelating sulfur atoms (Li-**11**) have also been prepared and studied[51]. The sulfur atom is less electronegative and has a larger radius than oxygen



(Li-**4**/Li-**9**)•Et_2O



(Li-**4**/Li-**9**)•$2Et_2O$



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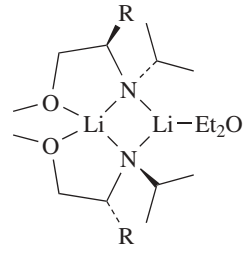
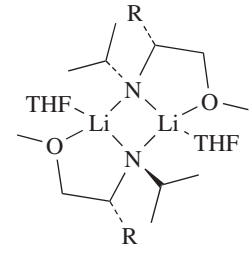


(Li-**10**)$_2$•Et_2O



(Li-**10**)$_2$•2THF

R = CH_3, *i*-Pr, Ph, CH_2Ph

and the coordination to lithium should be much weaker according to the HSAB principle. DFT calculations supported this hypothesis and indicated that the Li-S chelate would be much less stable than the corresponding Li-O chelate but still strong enough to favor internal chelation rather than external solvation by an ethereal solvent such as Et_2O or THF (Figures 2 and 3).

Multinuclear NMR studies confirmed these results and the chiral lithium amido sulfides were found to form unsymmetrically solvated dimers in Et_2O, (Li-**11**)$_2$•Et_2O, while upon addition of the more strongly coordinating solvent THF symmetrically solvated dimers, (Li-**11**)$_2$•2THF, dominate. This is in complete analogy with the complexes formed by chiral lithium amides with a chelating oxygen atom.

In summary, chelating chiral lithium amides exist in either of four major structural motifs or mixtures of them (Scheme 3). Non-coordinating solvents generally favor cyclic trimers, **A**. Ladder tetramers are favored for pyrrolidide amides in the absence of coordinating solvents.

In coordinating solvents like Et_2O the amides form dimers, with an unsymmetrical internal coordination, **B**. However, symmetrically solvated dimers, **C**, have also been observed. It appears that the size of the substituents on the nitrogen is crucial in controlling which of these dimers will dominate. The symmetrical structure **C** is less common and requires both a strongly coordinating solvent such as THF and a small substituent on the nitrogen such as methyl or isopropyl, as in structure **B**. Monomers **D** have been observed with large substituents on the nitrogen and a strongly coordinating solvent or ligand.

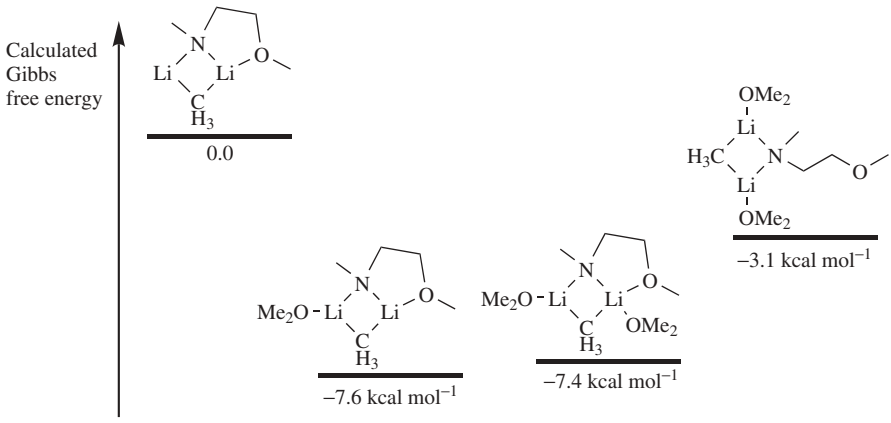


FIGURE 2. Calculated Gibbs free-energy values of unsolvated and solvated mixed complexes between a chiral lithium amido ether and methyllithium

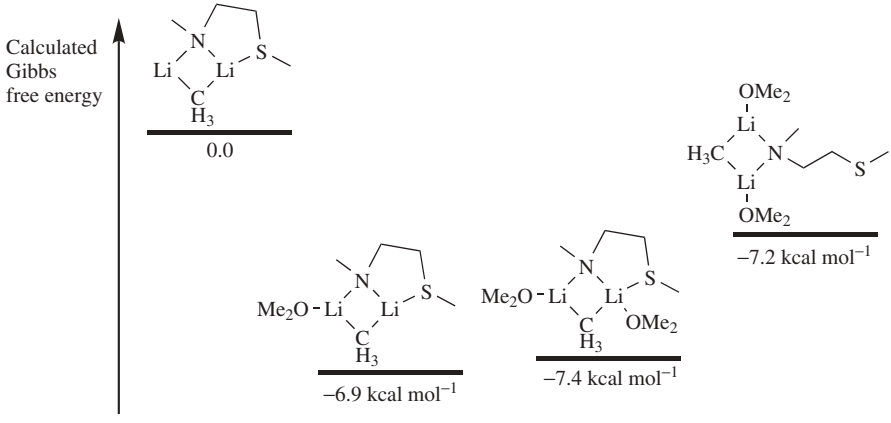
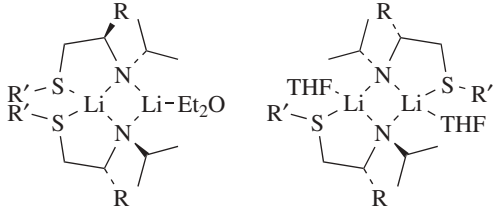


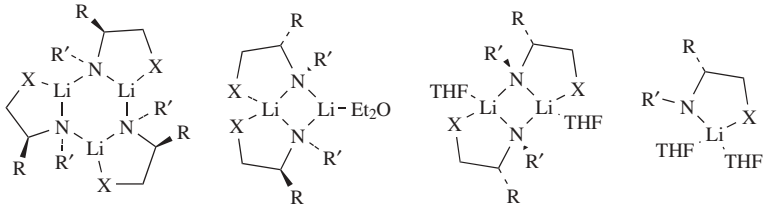
FIGURE 3. Calculated Gibbs free-energy values of unsolvated and solvated mixed complexes between a chiral lithium amido sulfide and methyllithium



(Li-**11**)$_2$•Et$_2$O (Li-**11**)$_2$•2THF

R = *i*-Pr, Ph, CH_2Ph

R′ = Et, Ph



(A) (B) (C) (D)

SCHEME 3. The most common structural motifs of chiral lithium amide chelates

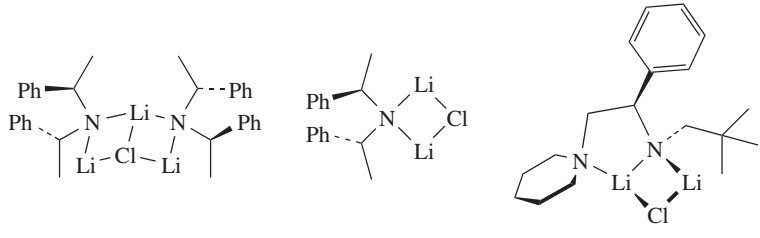
HMPA is a strongly coordinating additive that often generates monomers. It should also be noted that the amide nitrogen of chiral lithium amides is stereogenic and consequently can exist in two stereoconfigurations, but generally only one of these appears to dominate[52].

IV. MIXED AGGREGATES

The high propensity of organolithium compounds to form mixed complexes with other organolithium species in solution has been utilized successfully in synthesis using chiral lithium amides. Either the chiral lithium amides have been added to organolithium reagents in an effort to achieve asymmetry in addition reactions, or various additives have been introduced to alter the reactivity or selectivity of the chiral lithium amides themselves, e.g. in deprotonation reactions.

A. Mixed Complexes between Chiral Lithium Amides and Lithium Halides

Lithium halides have often been used as additives in LDA mediated ketone enolizations to alter the reactivity and/or selectivity of the reactions. In the early 1990s Collum and coworkers, using multinuclear NMR techniques, showed that both LiCl and LiBr form mixed complexes with LDA and lithium 2,2,6,6-tetramethylpiperidide in THF[53,54] and such a complex was crystallized from toluene by Mair and coworkers[55]. A few years later Koga and coworkers[56,57] studied the solution structures of mixed aggregates between chiral lithium amides and lithium halides. When LiCl was added to a solution of Li-**1** in THF, a ladder-like trimer, consisting of two lithium amides and one LiCl, (Li-**1**)$_2$/LiCl, was initially formed. As the concentration of LiCl was increased, the trimer disappeared in favor of a dimer between a lithium amide and LiCl, Li-**1**/LiCl. Addition of LiBr to the lithium amide was found to result in an equilibrium between homoaggregated lithium amide, free LiBr and a mixed dimer between LiBr and the lithium amide. Added LiI yielded no mixed complex at all[56]. Li-**3**, R = *t*-Bu, was later also shown to yield mixed dimeric aggregates with LiCl in THF[57], Li-**3**/LiCl.

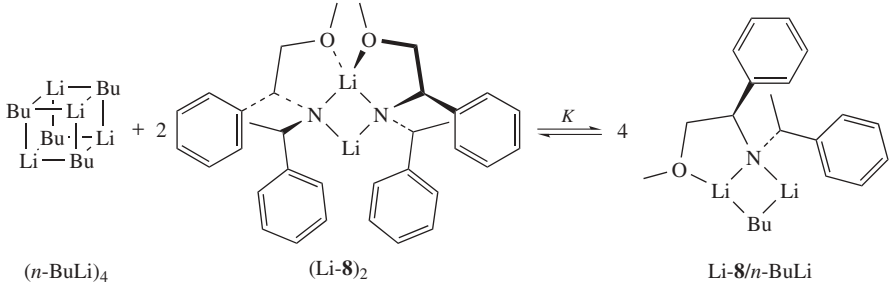


(Li-**1**)$_2$/LiCl Li-**1**/LiCl Li-**3**/LiCl

B. Mixed Complexes between Alkyllithiums and Chiral Lithium Amides with Chelating Ether Groups

Chiral lithium amides with internal coordinating groups have been reported to induce asymmetry in various alkylation reactions. One of the first successful amides in this respect was the chiral lithium amide reported by Eleveld and Hogeveen, Li-**8**[41]. The structure of this amide complexed with *n*-BuLi has been studied in detail using multinuclear NMR spectroscopy[42]. It was found that in Et_2O and THF solution at −80 °C a mixed 1:1 complex, Li-**8**/*n*-BuLi, is in a rapid equilibrium with homoaggregated amide dimers and tetramers of *n*-BuLi (Scheme 4 and Figure 4). A number of analogous amides with oxygen and nitrogen chelation have been prepared and they all form similar mixed complexes with *n*-BuLi[48]. The apparent equilibrium constants were found to vary between 4 and 800 M. Interestingly, it appears that there is almost no correlation between the equilibrium constant and the enantiomeric excess obtained in the asymmetric addition reaction.

NMR studies of the chiral lithium amide Li-**10** showed that in the absence of coordinating solvents, e.g. in hexane or toluene, mixed trimers (Li-**10**)$_2$/*n*-BuLi dominate, both



SCHEME 4. The equilibrium between free *n*-BuLi, Li-**8**, and the mixed complex, Li-**8**/*n*-BuLi

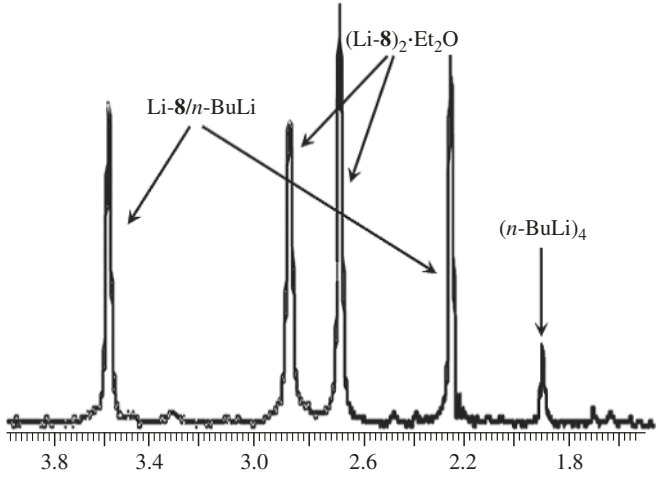
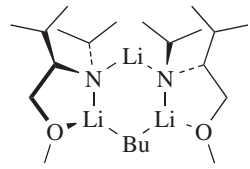


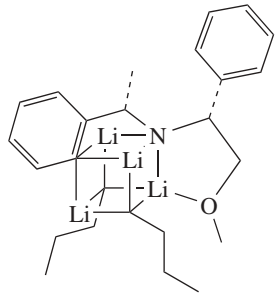
FIGURE 4. The ^{6}Li NMR spectra of a solution of Li-**8** and *n*-BuLi in Et_2O at −90 °C

in the solid state and solution[49,58]. Addition of Et_2O to the toluene solution results in mixed dimers along with the homoaggregates.



(Li-**10**)$_2$/*n*-BuLi

The mixed complex, Li-**8**/*n*-BuLi, has also been found to undergo an intramolecular *ortho*-lithiation at room temperature. The resulting dilithio-product, Li_2-**8**, is suggested to be aggregated as a dimer in Et_2O solution[59,60]. Addition of an excess of *n*-BuLi reveals a new mixed complex between the dilithiated amide and two *n*-BuLi molecules, Li_2-**8**/(*n*-BuLi)$_2$. In the ^{6}Li NMR spectrum there are four ^{6}Li signals and the ^{1}H NMR displays four α-proton signals from the non-equivalent protons of the two butyl anions.



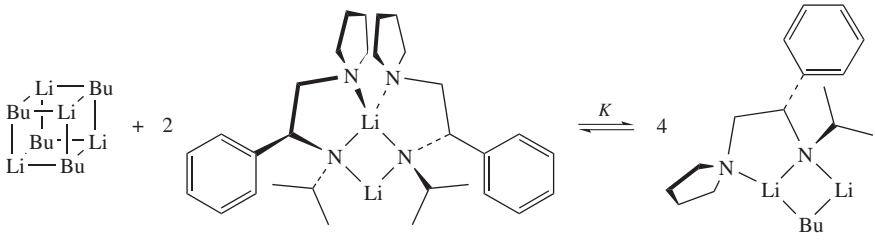
Li_2-**8**/(*n*-BuLi)$_2$

C. Mixed Complexes between Alkyllithiums and Chiral Lithium Amides with Chelating Amine Groups

With the lithium amide of the diamine (*S*)-1-isopropylamino-1-phenyl-2-pyrrolidinyl-ethane (**12**), an analogue of the ether amide shown previously, almost no mixed complexes were formed with *n*-BuLi (Li-**12**/*n*-BuLi), i.e. the equilibrium was almost completely shifted toward the homoaggregates. The apparent equilibrium constant, K, of Scheme 5 was determined to be 0.14 M.

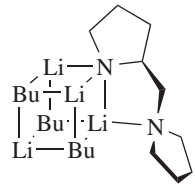
The chiral lithium amides can also be part of cubic tetrameric structures as shown by the mixed complex, Li-**6**/(*n*-BuLi)$_3$, consisting of the chiral lithium amide Li-**6** and three molecules of *n*-BuLi[61].

Maddaluno and coworkers[62,63] have reported the formation of mixed dimers between alkyllithiums and chiral 3-aminopyrrolidines with a chelating nitrogen atom (**13**). Interestingly, they showed that if the chiral lithium amide carried a second stereogenic center, on the lateral amino group, the mixed dimers with methyllithium, Li-**13**/CH_3Li, adopted different structures depending on the chirality of the lateral amino group. The complexes form norbornyl-like dimers with the methyllithium coordinated on either the '*endo*' or '*exo*' face of the structures in THF.

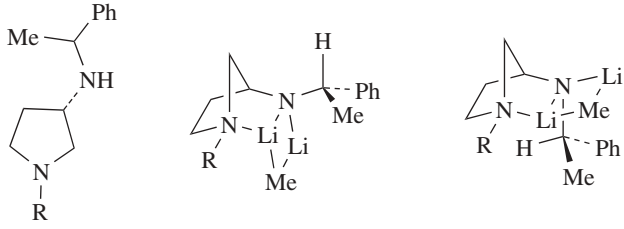


$(n\text{-BuLi})_4$ $(\text{Li-}\mathbf{12})_2$ (Li-**12**/*n*-BuLi)

SCHEME 5. The equilibrium between free *n*-BuLi, Li-**12** and the mixed complex Li-**12**/*n*-BuLi



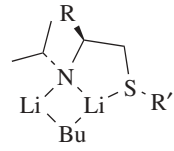
Li-**6**/$(n\text{-BuLi})_3$



(13) *endo*-(Li-**13**/CH_3Li) *exo*-(Li-**13**/CH_3Li)
R = CH_3, 2-NaphthylCH$_2$

D. Mixed Complexes between Alkyllithiums and Chiral Lithium Amides with Chelating Thioether Groups

Chiral lithium amido sulfides form the same type of mixed dimers with *n*-BuLi as the lithium amido ether analogues in both Et_2O and THF[51], i.e. Li-**11**/*n*-BuLi. Figure 5 shows the ^{6}Li,^{1}H HOESY spectrum of Li-**11**/*n*-BuLi. Each crosspeak in the HOESY spectrum is due to short (<5 Å) Li–H distances. The two lithiums within the mixed complex clearly show distinctly different proximities to the protons. Interestingly, the mixed dimers between a chiral lithium sulfido amide and an alkyllithium induce a substantially higher stereoselectivity in nucleophilic addition reactions than the corresponding ether analogues. The longer bond length between lithium and sulfur atoms of *ca* 2.3 Å for Li-S versus *ca* 2.0 Å for Li-O changes the geometry of the complex and forces the isopropyl group to be closer to the lithium, which coordinates to the substrate. This slightly altered geometry could be the reason for the reported enhancement of the stereoselectivity in asymmetric alkylation reactions.



Li-**11**/*n*-BuLi
R = *i*-Pr, Ph, CH_2Ph
R′ = Et, Ph

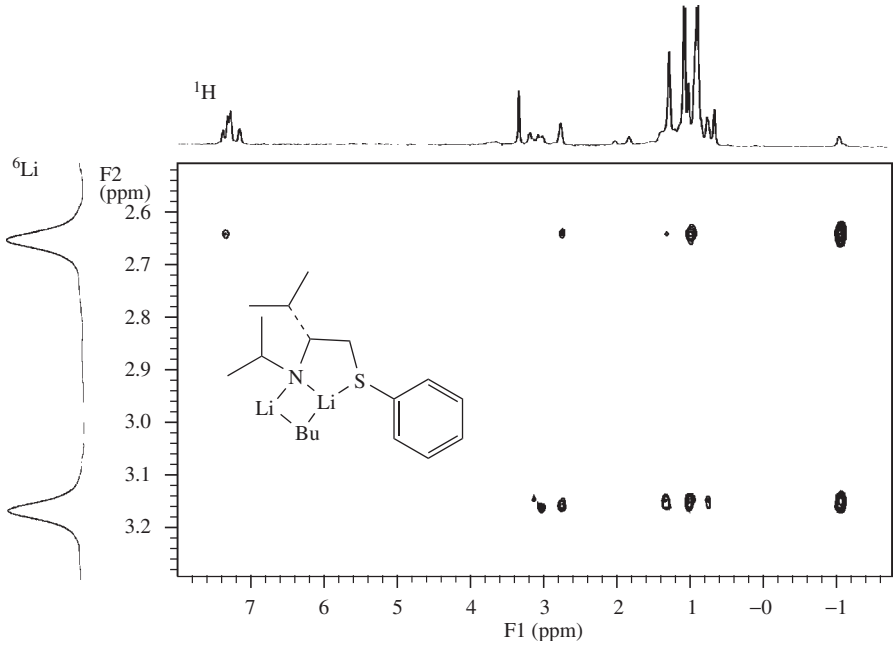


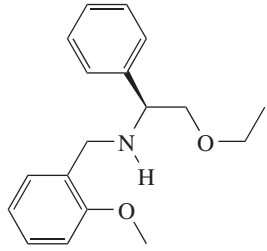
FIGURE 5. $^6Li,^1H$ HOESY spectrum of the mixed complex between Li-**11**/*n*-BuLi in Et_2O:THF 5:1 solution at −87 °C

Although these mixed complexes with chiral lithium amido sulfides appear promising structures for asymmetric addition reactions in general, it should be noted that they are only stable at low temperatures (<50 °C). At higher temperatures they readily decompose, most likely due to deprotonation of the acidic α-protons next to the sulfur.

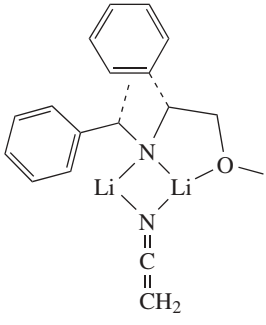
E. Mixed Complexes between Lithioacetonitrile and Chiral Lithium Amides with Ether Groups

Mixtures of lithioacetonitrile and chiral lithium amides with both one and two internally coordinating methoxy groups, Li-**8**, Li-**10** and Li-**14** respectively, have recently been subject to detailed NMR studies in our laboratory[64,65]. Mixed dimers are favored

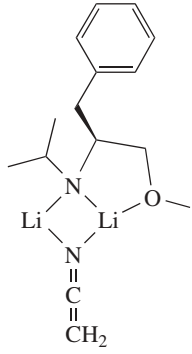
in ethereal solutions like Et_2O and THF. It has been discussed in the literature whether lithioacetonitrile is *N*- or *C*-lithiated. Based on NMR studies of ^{6}Li, ^{13}C and ^{15}N labelled compounds, it has been concluded that THF solvent favors mixed dimers with the acetonitrile anion being *N*-lithiated. The mixed dimer structures give rise to characteristic ^{13}C NMR chemical shifts for the α-carbon of the acetonitrile anion at -2.2 ± 0.2 ppm and $^{13}C-^{1}H$ spin coupling constants of 161 ± 1 Hz. Similar ketenimine structures, but with lithiophenylacetonitrile, have been reported to exist both in the solid state and in solution[66,67].



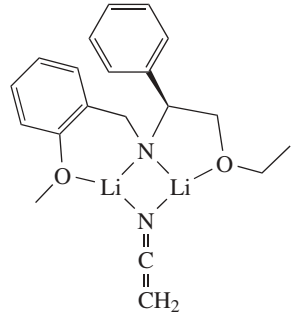
(14)



Li-**8**/$LiCH_2CN$



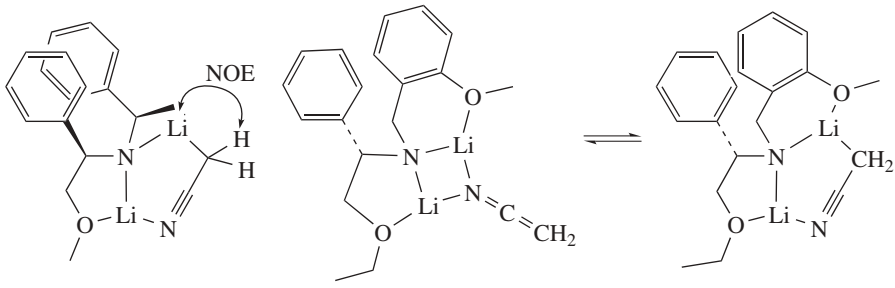
Li-**10**/$LiCH_2CN$



Li-**14**/$LiCH_2CN$

With Et_2O as solvent, the mixed complexes of lithioacetonitrile and chiral lithium amides exhibit a higher degree of structural diversity; this includes several dimeric complexes with substantial *C*-lithiation. The acetonitrile anion is found to bridge between the two lithiums within the dimer of lithioacetonitrile and chiral lithium amide to form a central six-membered Li-N-C-C-Li-N ring. Based on observed ^{13}C,^{6}Li and ^{6}Li,^{15}N couplings, it has been suggested that Li-**14**/$LiCH_2CN$ exists as a rapidly interconverting mixture of *C*- and *N*-lithiated complexes (Figure 6).

An eight membered ring consisting of two chiral lithium amides and one lithioacetonitrile, (Li-**10**)$_2$/$LiCH_2CN$, has also been observed by NMR. Based on the observed ^{13}C,^{6}Li and ^{15}N,^{6}Li, couplings, it was found that these mixed aggregates undergo fast degenerate exchange on the NMR time scale between ketenimine and bridged structures. The presence



Li-**8**/LiCH$_2$CN Li-**14**/LiCH$_2$CN

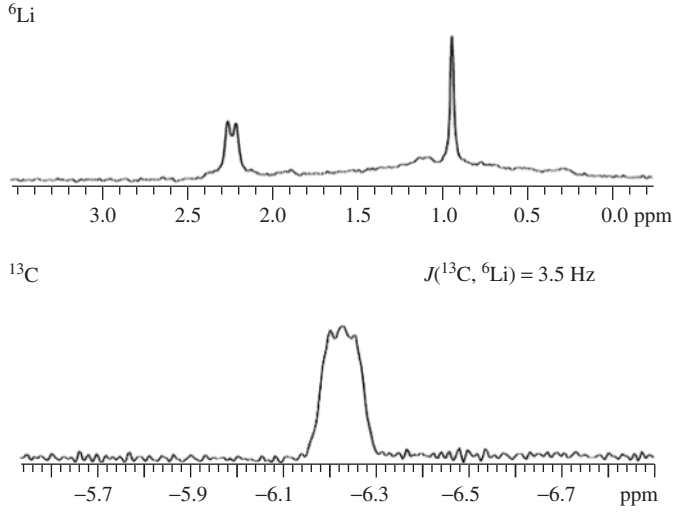


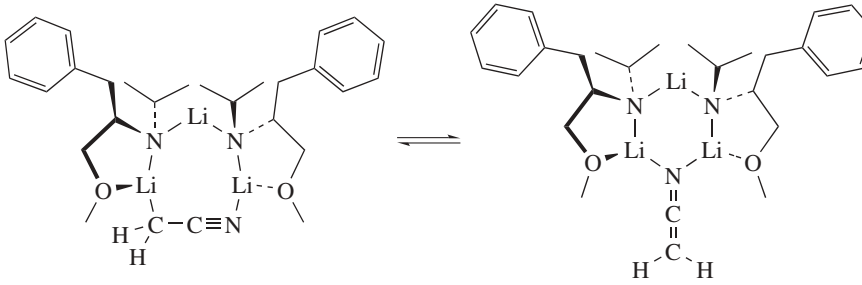
FIGURE 6. The ^{6}Li and ^{13}C NMR spectra of Li-**14**/LiCH$_2$^{13}CN in Et$_2$O at $-100\,^\circ$C showing the ^{6}Li,^{13}C coupling constant of 3.5 Hz

of a bridging acetonitrile anion is indicated by the large upfield α-carbon ^{13}C NMR shift at -6.8 ± 0.7 ppm and a smaller ^{13}C$-^1$H spin coupling constant of 150 ± 2 Hz.

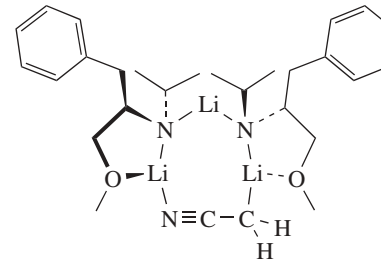
These mixed structures have been employed in asymmetric nucleophilic addition reactions. The asymmetric addition of acetonitrile anion to benzaldehyde gives access to synthetically important chiral hydroxy nitriles.

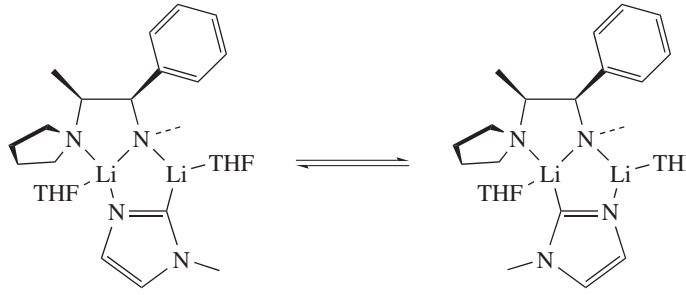
F. Mixed Complexes between Chiral Lithium Amides containing Amines and Lithiated Heterocycles

The groups of Ahlberg and Davidsson have reported the formation of mixed complexes between Li-**5** and lithiomethylimidazole (LiMIM), Li-**5**/LiMIM, used in catalytic asymmetric rearrangement of cyclohexene oxide[68].



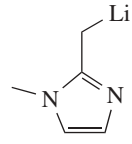
(Li-**10**)$_2$/LiCH$_2$CN



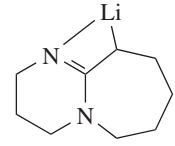


Li-**5**/LiMIM

Ahlberg and coworkers have also reported the presence of similar mixed complexes between chiral lithium amides and other lithiated bases such as lithiated 1,2-dimethyl imidazole (LiDMIM) and lithiated DBU (LiDBU)[69].



LiDMIM



LiDBU

V. DYNAMICS OF ORGANOLITHIUM COMPOUNDS

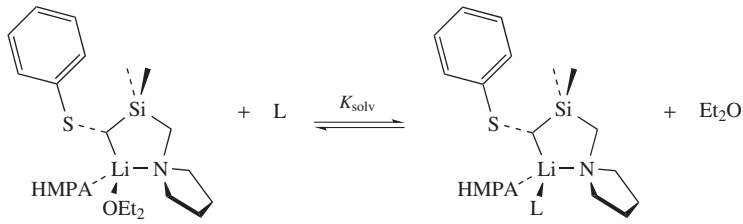
Organolithium compounds are known to be dynamic species and detailed NMR studies are generally conducted at low temperatures where the dynamics are slow on the NMR time scale. With the developments in NMR spectroscopy using ^{6}Li-labelled compounds it is now possible to study the various dynamic processes such as solvation, and various degenerate inter- and intra-aggregate exchange processes[23,59,61]. In this section some examples of solvation of lithium cations and exchanges between coordinated and free ligands, amide–amine and lithium–lithium, are discussed.

A. Solvation of Organolithium Compounds

Generally, the reactivity of organolithium compounds or reagents is much higher in ethers than in hydrocarbons. This difference in reactivity increases with increasing Lewis basicity of the solvent. It has been suggested to be the result of deaggregation of the organolithium aggregates and sometimes due to an increased stabilization of the transition state in the reactions.

The complexation of ligands to the lithium cation of organolithium reagents can be strong enough to allow the direct observation of non-coordinated and coordinated ligands by NMR spectroscopy[3,4,43,44,70–74]. The solvating strength of a specific ligand is determined by the strength of the ion–dipole interaction between the lithium and the solvating ligand. Steric requirements of the anion and the other ligands determine the coordination number.

Reich and Kulicke[73] have used the equilibrium shown in Scheme 6 to determine the relative lithium solvation strengths for a number of solvents (L). The relative values of K_{solv} were determined based on the integrals for the respective ^{31}P NMR resonances of the coordinating HMPA and are given in Table 1. Their findings indicate that THF is significantly better than Et_2O at solvating lithium cations but, in comparison with HMPA, both Et_2O–Li and THF–Li associations are rather weak.



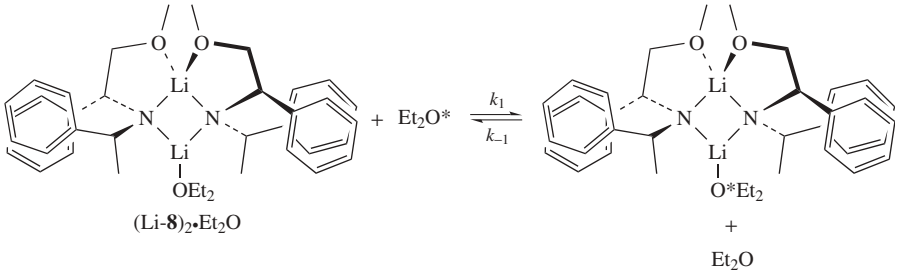
SCHEME 6. The solvation equilibrium studied by Reich

B. Ligand Exchange

Studies of lithium ion solvation of organolithium compounds are important for a thorough understanding of the behavior of these complex reagents. The chiral lithium amide

TABLE 1. Relative lithium solvation strengths (K_{solv}) for different solvents determined for the equilibrium in Scheme 6

Et_2O	THF	Oxetane	Pyridine	HMPA
1	7	16	100	2000



SCHEME 7. Degenerate Et_2O ligand exchange of (Li-**8**)$_2$•Et_2O. The Et_2O* represents an ether molecule from the solvent

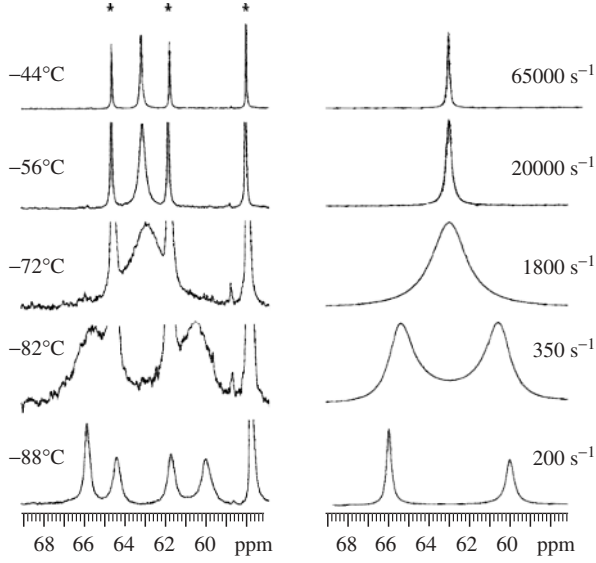


FIGURE 7. The experimentally observed (left) and calculated (right) ^{13}C NMR signals of the α-carbons of Et_2O coordinated to (Li-**8**)$_2$ and free in solution at different temperatures. In the spectra there are also three signals from the lithium amide, Li-**8**, marked with *

Li-**8** exhibits ligand exchange in ^1H, ^6Li and ^{13}C NMR at low temperature (Scheme 7). Separate resonances for free and coordinated ethers can thus be observed (Figure 7). The activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, of this exchange were determined by full line-shape analysis of the temperature-dependent NMR spectra[75]. The exchange rate is concentration-independent with positive entropy of activation, indicating an S_N1 or a dissociative mechanism for the ethereal ligand exchange.

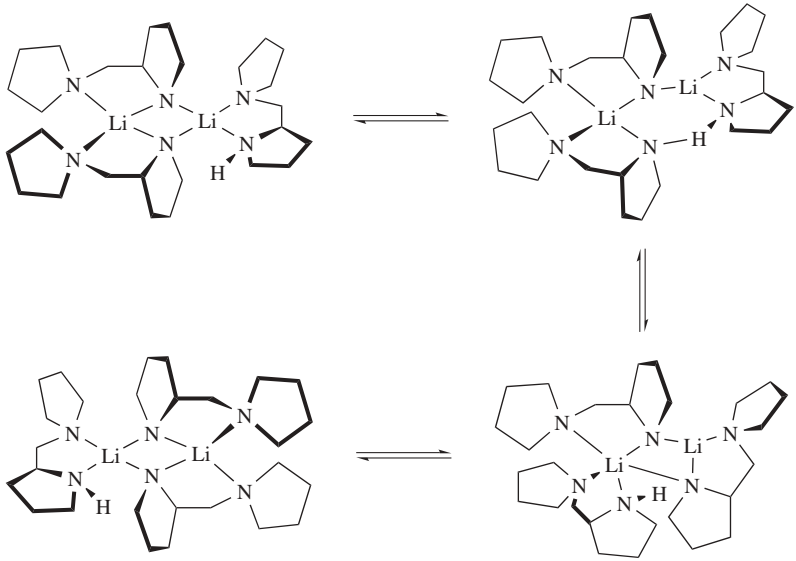
For Et_2O, the activation parameters were $\Delta H^{\ddagger} = 11.0$ kcal mol^{-1} and $\Delta S^{\ddagger} = 12.0$ cal mol^{-1} K^{-1}. The THF ligand exchange proceeds with a similar activation enthalpy of $\Delta H^{\ddagger} = 11.2$ kcal mol^{-1}, but the entropy is close to zero, i.e. $\Delta S^{\ddagger} = 1.6$ cal mol^{-1} K^{-1}.

The enthalpic contributions to the ethereal ligand exchange processes are similar for Et_2O and THF, but the entropy associated with the dissociation of THF from

its coordinated form to the transition state, $[(\text{Li-}\mathbf{8})_2\text{—THF}]^{\ddagger}$, is significantly smaller compared to the entropy of activation observed with Et_2O. The coordination of Et_2O results in substantial loss of vibrational and internal rotational entropy when the flexible Et_2O molecule becomes locked-up in a single conformer. In the case of THF, a much smaller loss of entropy is expected since THF is a five-membered cyclic compound with mainly ring puckering vibrations. Upon going from the coordinating initial state to the transition state, some of this entropy will be released.

C. Amide–Amine Exchange

From temperature-dependent NMR studies it has been shown that uncomplexed diamine **6** exhibits ligand exchange with complexed **6** in $(\text{Li-}\mathbf{6})_2\bullet\mathbf{6}$ by a dissociative mechanism with $\Delta G^{\ddagger}_{228} = 7.8\ \text{kcal mol}^{-1}$. The $(\text{Li-}\mathbf{6})_2\bullet\mathbf{6}$ chelate undergoes a fast intra-aggregate diamine–amide interconversion via degenerate proton transfer between diamine and amide with $\Delta G^{\ddagger}_{268} = 10.9\ \text{kcal mol}^{-1}$ (Scheme 8)[39].

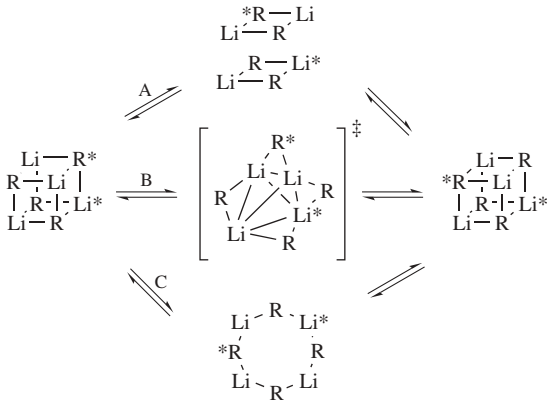


SCHEME 8. The amine–amide exchange process of $(\text{Li-}\mathbf{6})_2\bullet\mathbf{6}$

Thus the chiral diamine **6** appears to catalyze intra-aggregate lithium–lithium exchange when coordinated in the complex $(\text{Li-}\mathbf{6})_2\bullet\mathbf{6}$.

D. Intramolecular Lithium Exchange

Many reactions involving organolithium species are very fast with low barriers of activation. Hence it is likely that the Li–Li exchange or ligand exchange can be slower than the actual rate of bond formation or breakage. The nature of the lithium exchange has been investigated and different mechanistic pathways have been suggested to account for the exchange process. For alkyllithium reagents the proposed pathways are dissociation into dimers followed by association (A)[76], concerted face-to-edge to edge-to-face



SCHEME 9. Different pathways for the inversion and the fluxional carbon–lithium bond exchange processes of alkyllithiums

rotation (B)[77], and dissociation into an eight-membered ring followed by association (C)[78] (Scheme 9).

Haeffner and Brinck[79] have studied the inversion of CH_3Li by quantum chemical methods (DFT and the B3LYP level including a polarizable continuum model) and, based on their findings, concluded that the process proceeds via an eight-membered ring.

The lithium–lithium exchange has been studied for the unsymmetrically solvated dimer of Li-**8** in Et_2O. The two ^6Li resonances from (Li-**8**)$_2$•Et_2O are observed to average at temperatures above $-20\,^\circ C$, showing that the two lithiums undergo exchange (Figure 8). Coalescence is observed at $-23\,^\circ C$, corresponding to a $\Delta G^{\ddagger}_{250}$ of 12.7 ± 1 kcal mol^{-1}. In toluene/Et_2O, the coalescence temperature is independent of the Et_2O concentration at 1–13 M[43]. It has also been concluded that it is an intra-aggregate process, since the rate of the exchange is concentration-independent between 0.03–0.8 M. The thermodynamic parameters ($\Delta H^{\ddagger} = 12.0 \pm 0.5$ kcal mol^{-1} and $\Delta S^{\ddagger} = -2.4 \pm 2.4$ cal mol^{-1} K^{-1}) for the exchange process have been determined from the temperature dependence of the line shape of the ^6Li NMR signals. The small entropy of activation indicates a lithium exchange within the aggregate without association or dissociation of solvent molecules in the rate-limiting transition state.

The rate constant for the exchange of lithiums within the trimer (Li-**10**)$_2$/*n*-BuLi is reported to be 0.8 s^{-1} at $-33\,^\circ C$, corresponding to an exchange barrier $\Delta G^{\ddagger}_{240}$ of 14.7 kcal mol^{-1}. The rate of lithium–lithium exchange is suggested to be faster within mixed complexes of the chiral lithium amides with *n*-BuLi than within the homoaggregates[49].

The complex Li-**6**/(*n*-BuLi)$_3$ contains four non-equivalent lithiums and three non-equivalent butyl anions. Fluxional lithium and carbanion exchanges have been directly observed using exchange spectroscopy[61] (Figure 9). The rate constants for the degenerate intra-aggregate exchanges were determined from ^6Li,^6Li and ^{13}C,^{13}C EXSY experiments; the intra-aggregate exchange is faster than the inter-aggregate exchange. The activation energy for the fluxional exchange is $\Delta G^{\ddagger}_{192} = 11$ to 12 kcal mol^{-1}, the measured rate constants being between 0.1 and 3 s^{-1} at $-81\,^\circ C$. The degeneracy of the process is a consequence of different two-site lithium exchanges and two-site carbanion exchanges. These

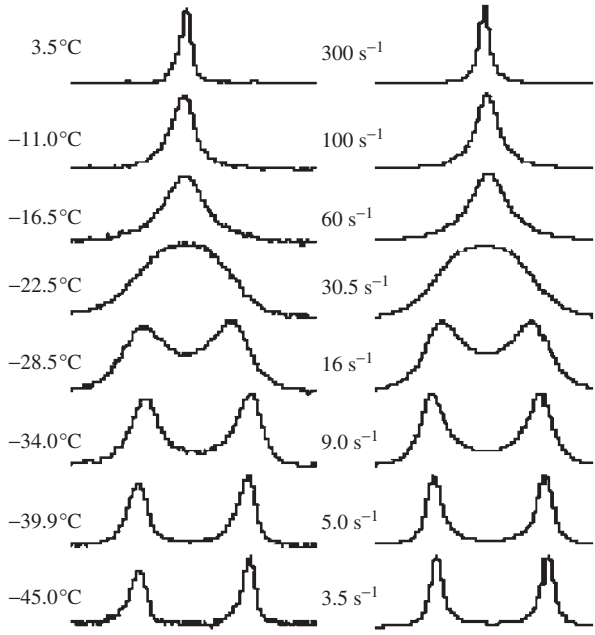
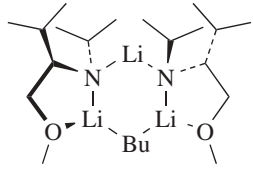


FIGURE 8. ^{6}Li NMR spectra of (Li-**8**)$_2$•Et_2O at different temperatures (left) and calculated line shapes (right) with rate constants

exchanges are suggested to proceed via mechanisms involving reversible reaction of the tetramer to associated dimers in which the dimeric parts may rotate. These mechanisms also explain the previously observed inversion of configuration at carbanionic centers bonded to lithium.



(Li-**10**)$_2$/*n*-BuLi

The processes for the exchange of lithiums in Li-**6**/(*n*-BuLi)$_3$ are likely similar to those responsible for the exchange of lithiums in *n*-BuLi tetramers. The intra-aggregate lithium exchange does not involve dissociation into free dimers (Scheme 10).

The rate constant for the lithium–lithium exchange within the mixed complexes of chiral lithium amides and lithioacetonitrile also differ, depending on the structure. The *C*-lithiated structures are significantly less fluxional than the *N*-lithiated mixed dimers. The activation energy, $\Delta G^{\ddagger}$, has been determined for two *C*-lithiated nitrile complexes in Et_2O

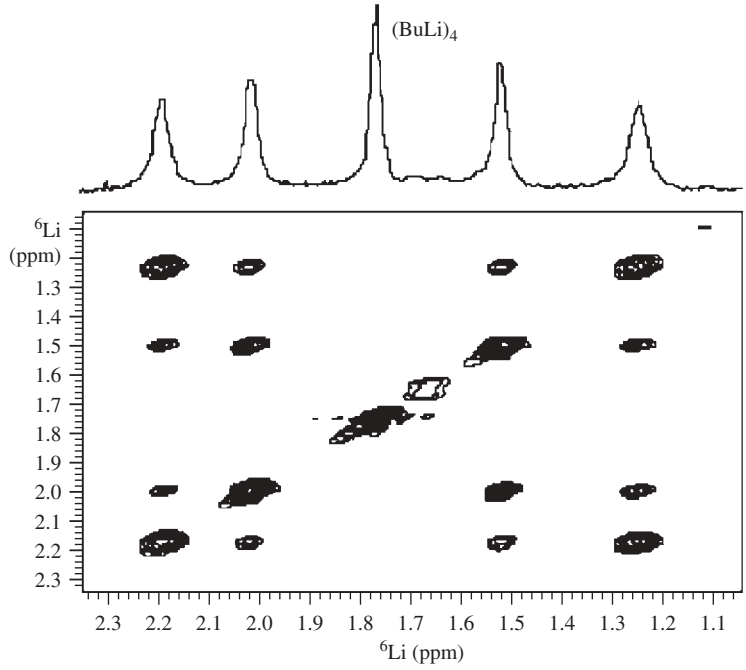
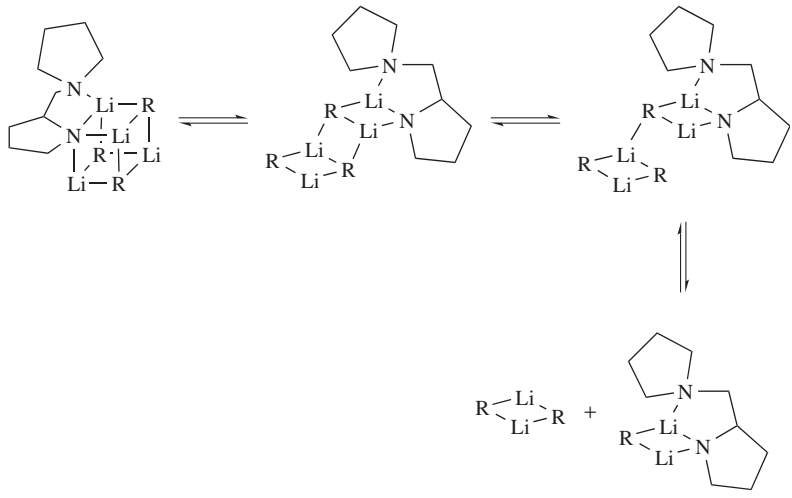


FIGURE 9. ^{6}Li,^{6}Li EXSY spectrum of Li-**6**/(n-BuLi)$_3$ at −81 °C



SCHEME 10. Exchange process for Li-**6**/(n-BuLi)$_3$, R = n-butyl

solution to be 12.6 kcal mol^{-1} (Li-**14**/$LiCH_2CN$) and 13.8 kcal mol^{-1} (Li-**10**/$LiCH_2CN$), respectively. In THF solutions, the activation energies for the lithium exchange of the corresponding *N*-lithiated nitrile complexes are 11.9 kcal mol^{-1} (Li-**14**/$LiCH_2CN$) and 10.9 kcal mol^{-1} (Li-**10**/$LiCH_2CN$), respectively. The difference in fluxionality of the two classes of structures does not necessarily reflect a difference in structure. It could also be the result of the higher coordinating ability of THF compared to Et_2O.

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CHAPTER 6

Chiral lithium amides in asymmetric synthesis

DANIEL PETTERSEN, MOHAMED AMEDJKOUH and PER AHLBERG

Department of Chemistry, Göteborg University, SE-41296 Göteborg, Sweden
Fax: +46 31 772 2908; e-mail: Per.Ahlberg@chem.gu.se

I. INTRODUCTION

The present review covers chiral lithium amides in asymmetric synthesis and related mechanistic investigations. The extensive work on use of achiral lithium amides in synthesis

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is not included. Focus is on recent progress in stereoselective deprotonations since prior work in the field already has been exhaustively reviewed[1–4].

The development of chiral lithium amides for asymmetric synthesis has mainly been by trial and error, i.e. chiral lithium amides have been synthesized and their performance in asymmetric synthesis has been investigated. The progress made by this approach is reviewed below.

More recently, along with an increased understanding of the mechanisms for stereoselective deprotonations more rational approaches, e.g. using computational chemistry, have been used. Easily accessible and inexpensive homochiral lithium amides have been designed having broad applicability. Products in high yields and enantiomeric excess have been obtained. These achievements are also reviewed below.

Like in other fields of asymmetric synthesis, catalysis is in focus. Catalysts for stereoselective synthesis utilizing chiral lithium amides are being developed to make such synthesis more useful in the laboratory as well as in industry. The progress made is also reviewed in detail below.

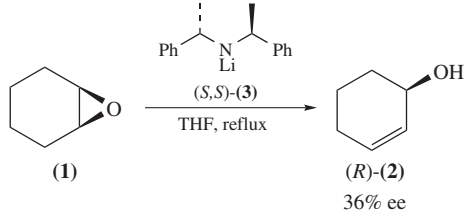
So far, chiral lithium amides for asymmetric deprotonation have found use only with a few types of substrates. The following sections deal with deprotonation of epoxides to yield chiral allylic alcohols in high enantiomeric excess, deprotonation of ketones, deprotonation of tricarbonylchromium arene complexes and miscellaneous stereoselective deprotonations. These sections are followed by sections in which various chiral lithium amides used in stereoselective deprotonations have been collected and various epoxides that have been stereoselectively deprotonated. The review ends with a summary of useful synthetic methods for chiral lithium amide precursors.

II. CHIRAL LITHIUM AMIDES IN ASYMMETRIC SYNTHESIS

A. Rearrangement of Epoxides to Allylic Alcohols

1. Stoichiometric processes

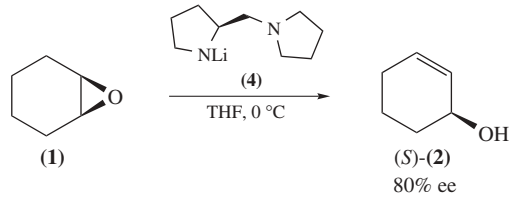
Lithium amide deprotonation of epoxides is a convenient method for the preparation of allylic alcohols. Since the first deprotonation of an epoxide by a lithium amide performed by Cope and coworkers in 1958[5], this area has received much attention. The first asymmetric deprotonation was demonstrated by Whitesell and Felman in 1980[6]. They enantioselectively rearranged *meso*-epoxides to allylic alcohols; for example, cyclohexene oxide **1** was reacted with chiral bases, e.g. (*S*,*S*)-**3**, in refluxing THF to yield optically active (*R*)-2-cyclohexenol ((*R*)-**2**) in 36% ee (Scheme 1).



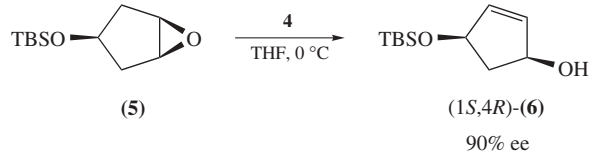
SCHEME 1

A few years later, Asami introduced the proline-derived chiral lithium amide **4** which proved to be more successful, producing (*S*)-2-cyclohexenol ((*S*)-**2**) with 80% ee (Scheme 2) [7].

This chiral base has been applied to deprotonate other cyclic *meso*-epoxides yielding allylic alcohols in high enantiomeric excess. Interestingly, the *meso*-cyclopentene oxide **5**



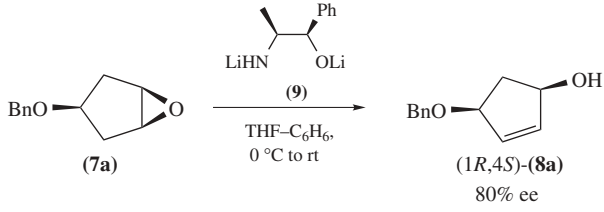
SCHEME 2



SCHEME 3

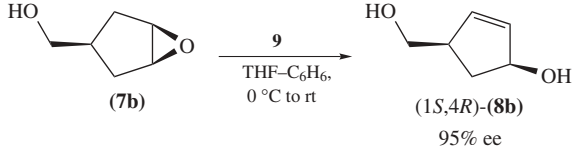
was rearranged into the corresponding allylic alcohol (1*S*,4*R*)-**6** in 90% ee (Scheme 3)[8]. This product has been used as a precursor in the synthesis of prostaglandins.

Based on Schlosser and coworkers' results[9] regarding the deprotonation of epoxides, Milne and Murphy rearranged the epoxide **7** by employing the norephedrine-derived dilithiated chiral base **9** to produce (1*R*,4*S*)-**8** in 80% ee (Scheme 4)[10,11]. Also, the enantiomer of this base is readily accessible, allowing a straightforward access to both enantiomers of the product alcohol.



SCHEME 4

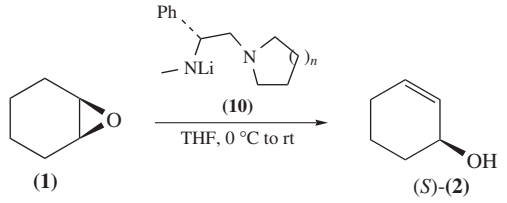
Hodgson and coworkers used lithium amide **9** to rearrange the cyclopentene oxide **10** into the allylic alcohol (1*S*,4*R*)-**11** with 95% ee (Scheme 5)[12,13]. The sense of asymmetric induction found in this case was opposite to that observed by Murphy. Interestingly, no allylic alcohol could be obtained with protected epoxide (TBS or benzyl) in the presence of **9**.



SCHEME 5

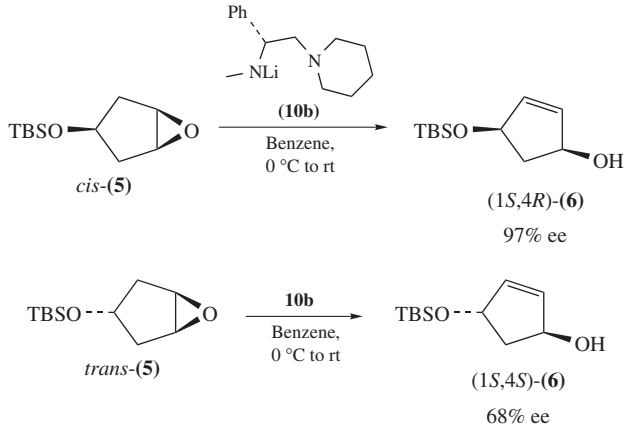
Inspired by Koga and coworkers' successful results[14] with chiral bases in deprotonation of ketones (see Section II.B), Singh and coworkers have rearranged cyclohexene oxide

using **10** to obtain (*S*)-2-cyclohexenol in up to 80% ee (Scheme 6)[15,16]. Thus, the ee values were similar to those obtained with Asami's chiral base (**4**)[17], but both enantiomers of the bases **10a** and **10b** are easily accessible.



SCHEME 6

The application of the chiral base **10b** has been extended to the rearrangement of epoxides *cis*- and *trans*-**5** to give allylic alcohols in 97% and 68% ee, respectively (Scheme 7).

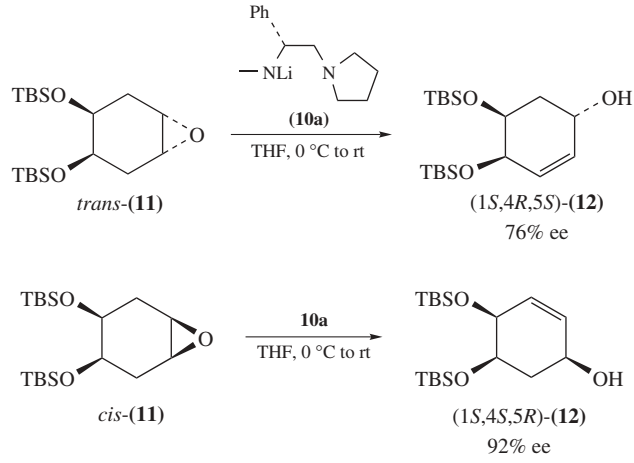


SCHEME 7

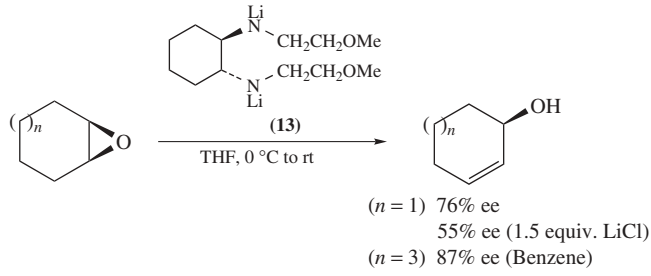
Similarly, O'Brien and Poumellec have converted the substituted cyclohexene oxide *trans*-**11** into allylic alcohol (1*S*,4*R*,5*S*)-**12** in 76% ee[18]. *Cis*-**11** afforded the corresponding allylic alcohol in 92% ee, with the same chiral base (Scheme 8).

Alexakis and coworkers introduced the dilithiated chiral base **13** prepared from C_2 symmetric *trans*-diaminocyclohexane (Scheme 9)[19]. Amide **13** rearranged cyclohexene oxide (**1**) to allylic alcohol (*R*)-**2** in 76% ee. Deprotonation in presence of 1.5 equiv. of LiCl in THF lowered the ee to 55%. When **13** was used to rearrange cyclooctene oxide in benzene, the allylic alcohol was obtained with an increased ee (87%).

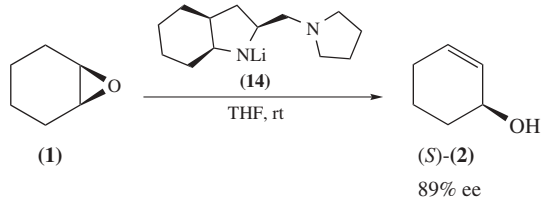
The search for new chiral bases yielding even higher enantioselectivities has resulted in a number of more complex diamines as amide precursors. For example, Asami and coworkers designed the chiral base **14**, which in the rearrangement of cyclohexene oxide **1** gave (*S*)-cyclohexen-2-ol ((*S*)-**2**) in 89% ee (Scheme 10)[20]. This result was a significant



SCHEME 8



SCHEME 9

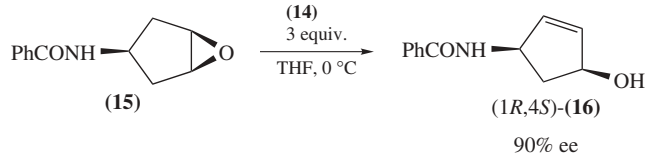


SCHEME 10

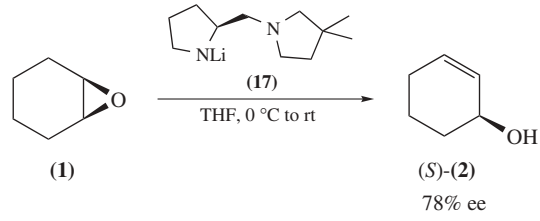
improvement, although the new chiral base is, at present, only accessible in one of the enantiomeric forms.

Chiral base **14** was also used to convert the substituted *cis*-cyclopentene oxide **15** to the corresponding cyclopentenol derivative (1*R*,4*S*)-**16** in up to 90% ee using 3 equiv. of chiral base (Scheme 11). The rearrangement in presence of 3.3 equiv. of DBU gave the product in 83% ee.

Another proline-derived chiral base, namely **17**, has been reported by Davidsson and coworkers[21]. It rearranges cyclohexene oxide **1** into (*S*)-**2** in 78% ee (Scheme 12).

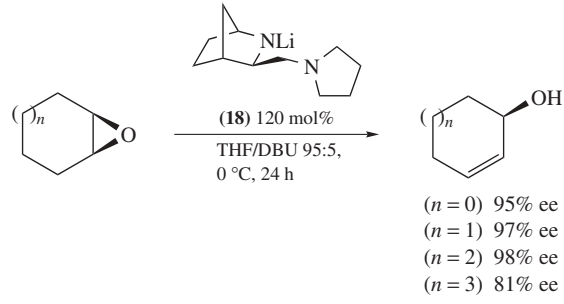


SCHEME 11



SCHEME 12

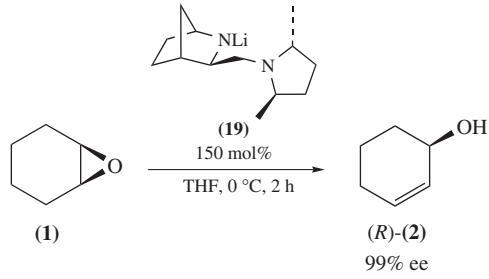
Using the methodology previously developed by Stella and coworkers[22] and by Waldmann and Braun[23] to synthesize 2-substituted aza-norbornanes (see Section II.C), Andersson and coworkers prepared chiral lithium amide **18**[24,25]. This chiral base has been reported to rearrange several epoxides in up to 98% ee in the absence or presence of high concentrations of DBU (Scheme 13).



SCHEME 13

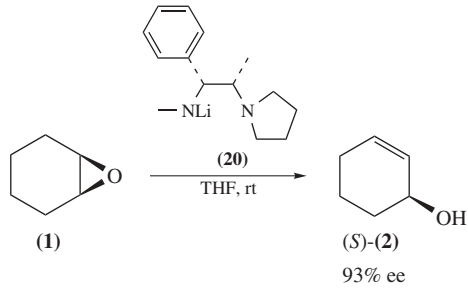
Incorporation of the (2*R*,5*R*)-dimethylpyrrolidinyl substituent gave the chiral lithium amide **19**[26]. This chiral base was found to give improved enantioselectivities; e.g. cyclohexene oxide could be deprotonated to give the allylic alcohol in 99% ee (Scheme 14). For a more detailed use of chiral bases **18** and **19**, see Section II.E.1.

Computational chemistry has been employed to calculate energy differences between diastereomeric activated complexes in the stereoselective deprotonations of cyclohexene oxide by monomeric, homo- and heterodimeric lithium amides (see Section II.A.2). Computational chemistry has also been used as a tool for design of highly stereoselective amides. Such a design approach has resulted in the homochiral base **20** and its enantiomer. These are readily available from both enantiomers of norephedrine, by inexpensive routes



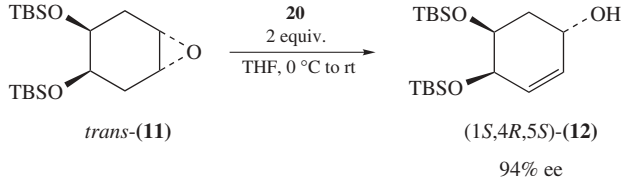
SCHEME 14

that have been developed independently by O'Brien and coworkers[27, 28] and by Ahlberg and coworkers[29]. Chiral lithium amide **20** rearranged *meso*-cyclohexene oxide **1** into (*S*)-*2* in 93% ee[29] (Scheme 15).



SCHEME 15

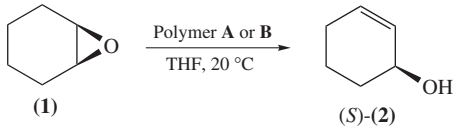
Base **20** has also been applied in the deprotonation of functionalized epoxides. Thus (1*S*,4*R*,5*S*)-**12** could be obtained in 94% ee using 2 equiv. of **20** (Scheme 16)[27].



SCHEME 16

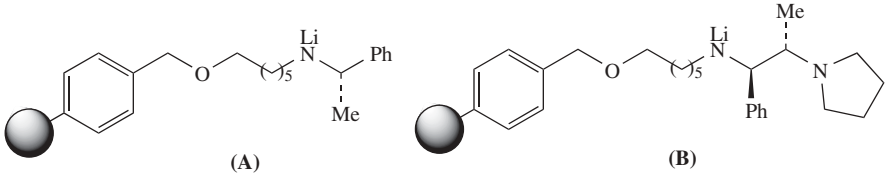
Davidsson, Johansson and Abrahamsson reported the use of polymer-supported chiral lithium amides in the deprotonation of cyclohexene oxide[30]. Interestingly, polymer base **A** provided allylic alcohol **2** in 67% yield and 91% ee of the (*S*)-enantiomer, after 12 h, which was a higher enantioselectivity than the non-polymer corresponding lithium amide which gave only 47% yield and 19% of the (*S*)-enantiomer (Scheme 17). In contrast, polymer **B** was found to show low efficiency: 12% yield and 70% ee of the (*S*)-enantiomer

after 72 h. Both the reactivity and enantioselectivity are lower than those of the non-polymer bound chiral lithium amide **20**.



(1) (*S*)-(**2**)

(A) 91% ee (67% yield)
(B) 70% ee (12% yield)



(A) **(B)**

SCHEME 17

2. Mechanistic investigations

Lithium amides are strong dipoles, since the bond between the nitrogen anion and the lithium cation is mainly ionic. Therefore, they are rarely present as monomers in solution. Rather, they tend to aggregate to yield dimers or larger aggregates. This is true even in ethereal solvents like THF or DEE, which show coordination to lithium. Multinuclear NMR spectroscopy[31–35] together with kinetics[29,36,37] and computational chemistry[38,39] have been used in studies of the initial state structures and transition states involved.

Attention has been given to the chiral lithium amide **4** developed by Asami[7]. ^{6}Li-NMR studies by Ahlberg and coworkers[40] and by Anders and coworkers[41] indicate that more than one type of aggregate are present in THF in dynamic equilibrium. In diethyl ether (DEE), compound **4** is found to be insoluble but dissolves upon addition of the precursor diamine of **4**. NMR investigations have shown that a diamine solvated dimer is formed (Figure 1).

Lithium amide **4** has been crystallized from toluene and X-ray crystallography has shown that the crystals are made up of tetramers of ladder type[35].

Thus, the determined composition of lithium amide **4** in the initial state in presence of excess of the corresponding diamine has been used in the kinetics to determine the composition of the activated complexes in cyclohexene oxide deprotonation. It appears

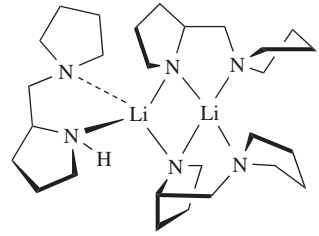


FIGURE 1

that an activated complex is built from one lithium amide monomer and one epoxide molecule[42]. Based on this result, a detailed computational study of possible activated complexes involved in the cyclohexene oxide deprotonations has been carried out[43]. Geometry optimizations of both specifically solvated and unsolvated activated complexes at various levels of theory ranging from PM3 to mPW1K/6-31+G(d) have been carried out. In Figure 2 the optimized structures of the activated complexes with the latter theory are shown.

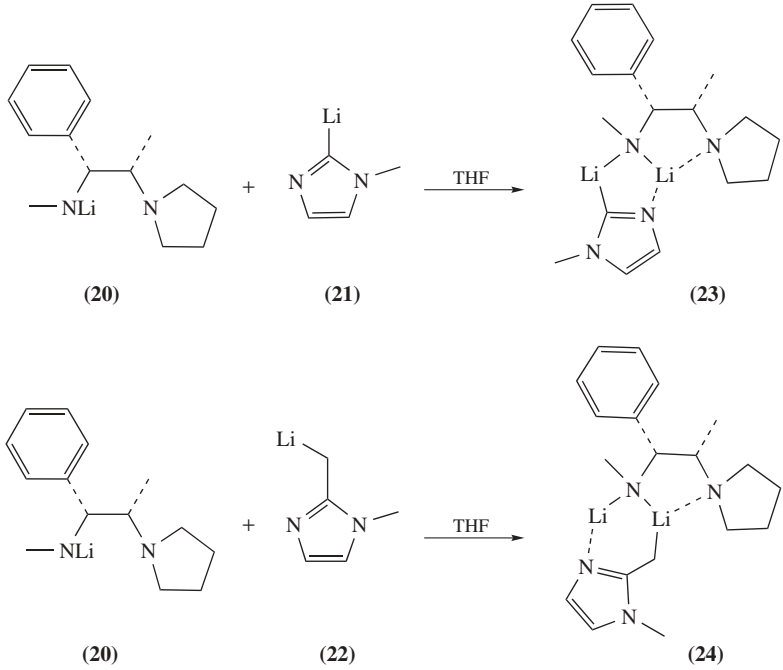
Ahlberg and coworkers also investigated the lithium amide **20** and their results showed that a dimer is present in THF solution, as shown by multinuclear NMR spectroscopy (Figure 3) [44].

A kinetic investigation using **20** in the deprotonation of cyclohexene oxide revealed that the composition of the activated complexes was different from that assumed in the theoretical model. The reaction orders showed that an activated complex is built from one molecule of chiral lithium amide dimer and one molecule of epoxide **1**. Such activated complexes have been computationally modeled by the use of PM3 and optimized structures are displayed in Figure 4[44].

In the search for new catalytic systems (see Section II.E.2) Ahlberg and coworkers found that lithiated 1-methylimidazole (**21**) and 1,2-dimethylimidazole (**22**) form mixed heterodimers (**23** and **24**) with chiral lithium amide **20** (Scheme 18)[45,46].

In Figure 5, structures of the heterodimers **23** and **24** computationally optimized at the B3LYP/6-311+G(d,p) or at the PM3-level of theory, respectively, are displayed.

Kinetic investigation of the deprotonation of **1** using **23** has been carried out and the reaction orders show that a stereoselecting activated complex is built from one heterodimer



SCHEME 18

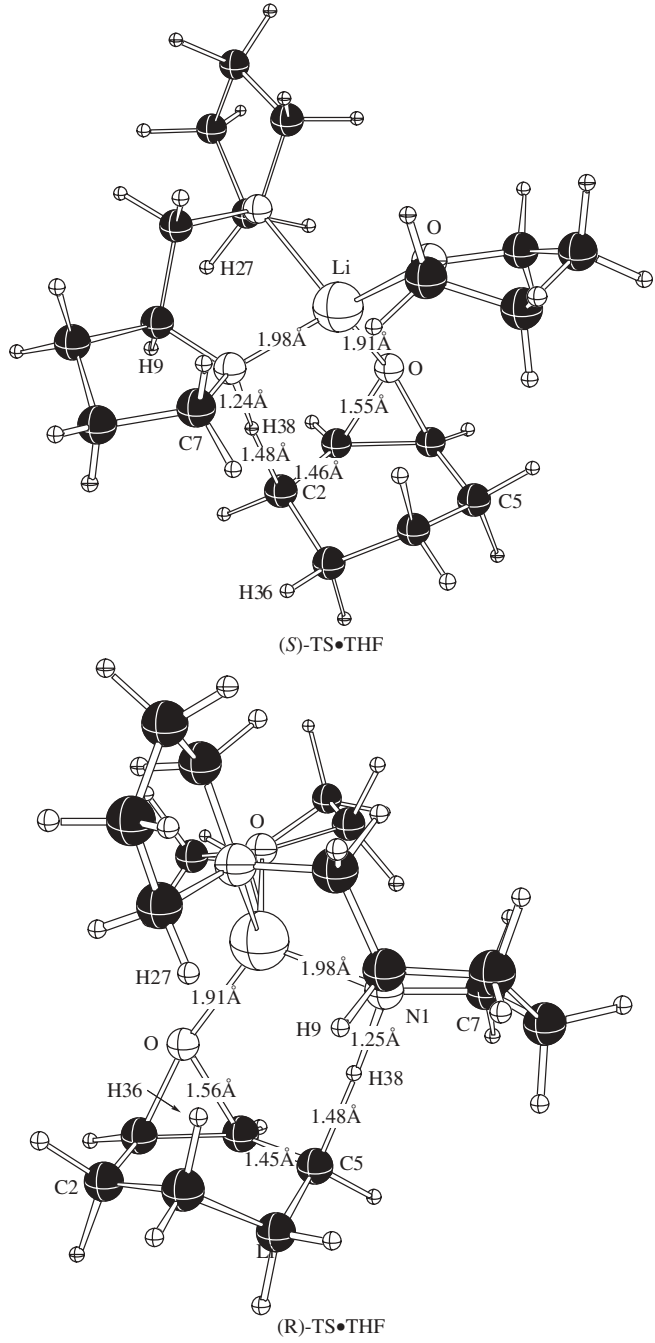


FIGURE 2. mPW1K/6-31+G(d) optimized THF-solvated diastereoisomeric TSs for deprotonation of **1** with lithium amide **4**

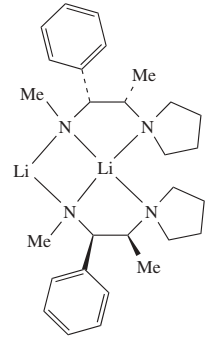


FIGURE 3

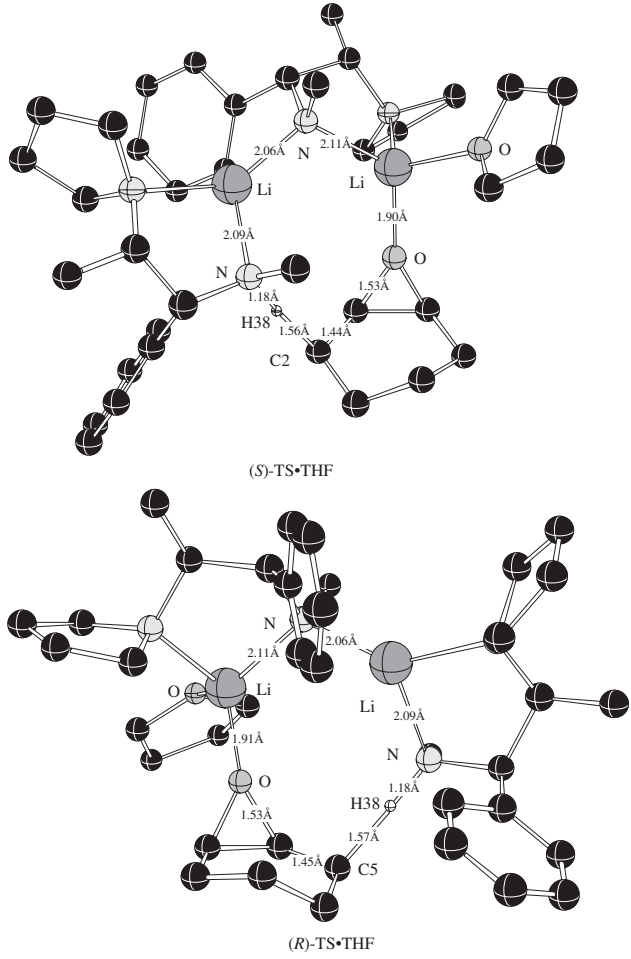


FIGURE 4. PM3-optimized THF-solvated diastereoisomeric TSs for deprotonation of **1** with chiral lithium amide **20**. Most hydrogen atoms are omitted for clarity

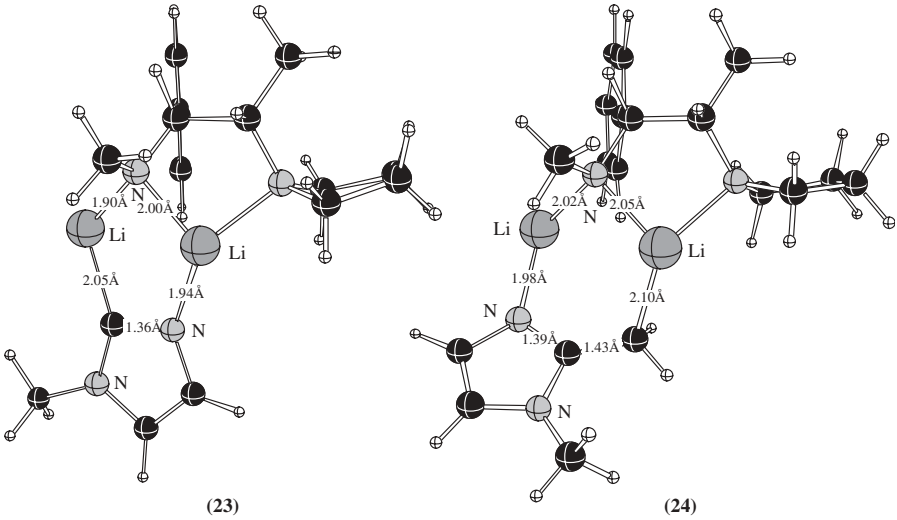
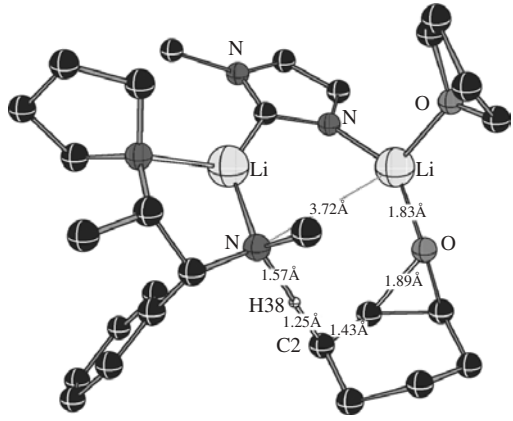


FIGURE 5. B3LYP/6-311+G(d,p) optimized heterodimer **23** and PM3 optimized heterodimer **24**

molecule and one epoxide molecule[37]. Geometry optimized structures of the stereoselecting activated complexes at the B3LYP/6-31G(d) level of theory are shown in Figure 6.

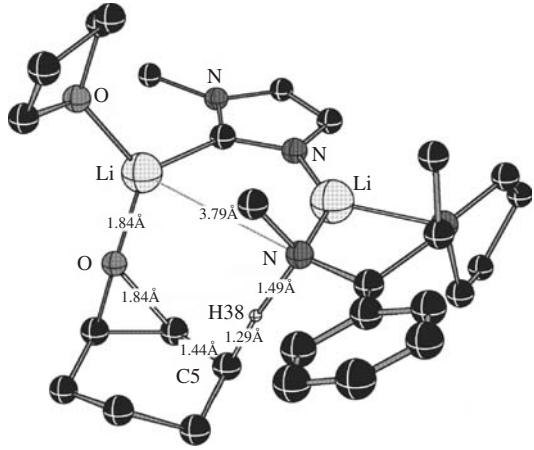
B. Deprotonation of Ketones

The exploration of chiral lithium amide bases to desymmetrize conformationally locked cyclic ketones began with Koga and coworkers'[14] work and has been followed by



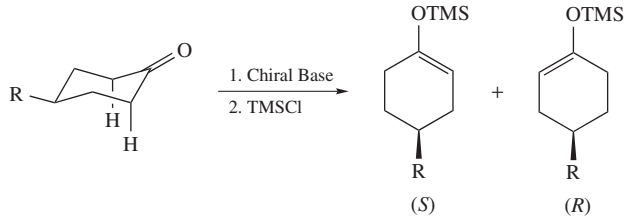
(*S*)-TS•THF

FIGURE 6. B3LYP/6-31G(d) optimized THF-solvated TSs for deprotonation of **2** with **23**. Most hydrogen atoms are omitted for clarity



(*R*)-TS•THF

FIGURE 6. (*continued*)



SCHEME 19

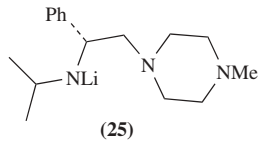
contributions by Simpkins and coworkers[47]. With such ketones, chiral lithium amides preferentially abstract one of the two prochiral axial protons (Scheme 19).

Using Corey and Gross's internal quench method[48] with TMSCl, silylenol ethers have been generated upon deprotonation of 4-substituted cyclohexanone with chiral lithium amides as shown in Scheme 20. It has been noted that the internal quench condition is crucial for achieving high level of enantioselectivity.

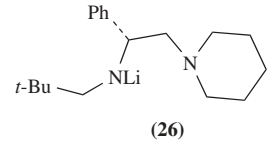
Investigation of the enantioselective deprotonation of 4-substituted cyclohexanones showed the importance of the internal quench condition and the role of lithium chloride which is generated during the course of the reaction. Bunn and Simpkins have reported a significant increase in enantioselectivity for reactions carried out under external quench conditions in the presence of LiCl[49]. Koga obtained similar results with even higher ee. Thus, silylenol ethers were isolated in 88% ee using up to 3 equivalents of LiCl (Scheme 21)[47,50–52].

This finding has been exploited using other ketones and chiral bases. Thus deprotonation of the bicyclic ketone **30** by chiral base **3** in THF yielded the silylenol ether **31** in 84% ee under external quench conditions with added LiCl (Scheme 22)[49]. In absence of LiCl the ee was lowered to 33%. Internal quench conditions gave an ee of 82%.

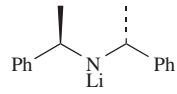
External quench protocols in the presence of LiCl have been extended to reactions with other electrophiles. Thus, both Simpkins and coworkers[49,52] and Majewski and coworkers[53–55] have investigated the aldol reaction of tropinone **32** with benzaldehyde



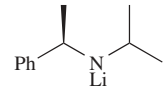
(25)



(26)



(*R*,*R*)-(**3**)

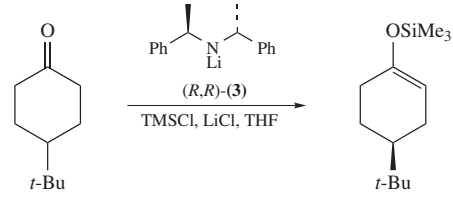


(27)

(28) (*S*)-(**29**)

Chiral lithium amide	Yield (%)	ee (%)
25	87	77
26	82	82
(R,R)-**3**	73	69

SCHEME 20

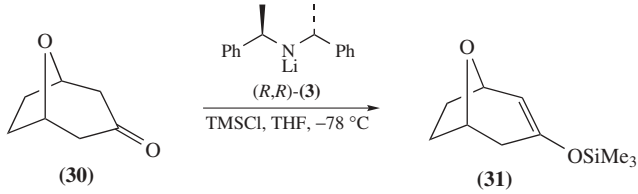


(28) (*S*)-(**29**)

Equiv. LiCl	Quench method	ee (%)
—	internal	90
—	external	44
0.5	internal	87
1.0	external	88
3.0	external	88

SCHEME 21

to give only aldol product **33** (Table 1). In the absence of LiCl the aldol product was obtained only up to 35% ee, but in the presence of LiCl higher ee values up to 88% were observed. Majewski has reported an ee of 95% if the chiral amide and LiCl is generated by deprotonation of the chiral amine hydrochloride using 2 equivalents of *n*-BuLi.

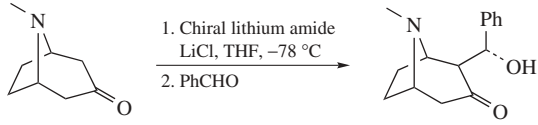


(30) (31)

Equiv. LiCl	Quench method	ee (%)
—	internal	82
—	external	33
1.5	external	84

SCHEME 22

TABLE 1. Deprotonation of tropinone **32**



(32) (33)

	Simpkins		Majewski	
	LiCl (equiv.)	ee (%)	LiCl (equiv.)	ee (%)
27	—	24	—	22
	0.5	66	0.5	71
(*R*,*R*)-**3**	—	24	—	35
	0.5	78	0.5	85

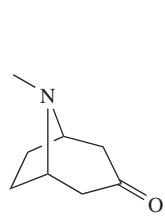
Deprotonation of other bicyclic ketones in the presence of LiCl has shown similar results (Scheme 23). Interestingly, deprotonation of tropinone (**32**) by **27** and using benzyl chloroformate as the electrophile resulted in ring opening to yield the enone **34** (Scheme 23a)[55,56]. The ee increased from 45% up to 62% upon addition of LiCl. The effect of LiCl on the enantioselectivity is also displayed in the reactions of **35** and **37** to give **36** and **38**, respectively, in Schemes 23b and 23c[53,54,57].

In some cases, any effect of added LiCl was not noticeable in aldol reactions under external quench conditions. Majewski and coworkers have observed that aldol reaction of tropinone **32** and benzaldehyde using the chiral lithium base **26** in the presence as well as in the absence of added LiCl gave the aldol product with the same 90% ee (Scheme 24)[53,56].

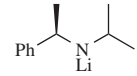
Koga and coworkers have investigated the steric effect of the 4-substituent in the deprotonation of cyclic ketones. Small substituents (e.g. R = Me) gave silylenol ether in 46% ee using (*R*)-**25** as chiral base and the ee increased up to 78% with larger aryl substituents (R = Ph, *i*-Pr, *t*-Bu)[50].

Deprotonation of 4-substituted cyclohexanones using Koga's chiral base **39** gave silylenol ethers with 93–94% ee (Scheme 25)[58,59]. Variation of the aromatic ring in such chiral bases did not display any noticeable improvement in enantioselectivity[60,61]. However, some drawbacks have to be noted as optimal enantioselectivity requires HMPA as co-solvent.

(a)

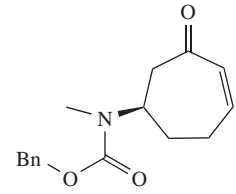


(32)



(27)

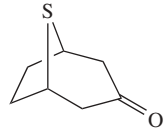
1. LiCl, THF, −78 °C
2. $PhCH_2OCOCl$



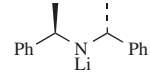
(34)

Equiv. LiCl	ee (%)
—	45
0.1	50
0.5	62

(b)

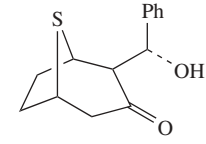


(35)



(*R*,*R*)-(**3**)

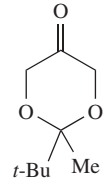
1. LiCl, THF, −78 °C
2. PhCHO



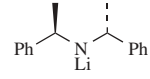
(36)

Equiv. LiCl	ee (%)
—	16
0.1	73
0.6	86
1.0	76

(c)

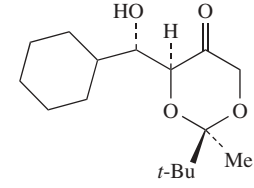


(37)



(*R*,*R*)-(**3**)

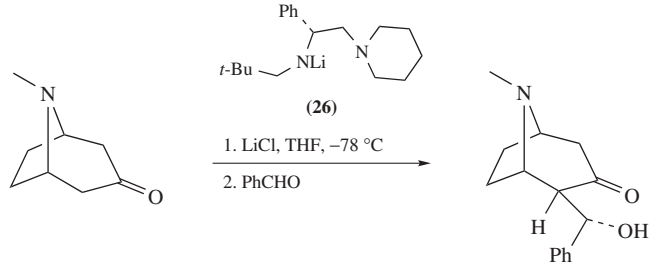
1. LiCl, THF, −78 °C
2. $c\text{-}C_6H_{11}CHO$



(38)

Equiv. LiCl	ee (%)
—	18
1.0	54
2.0	60

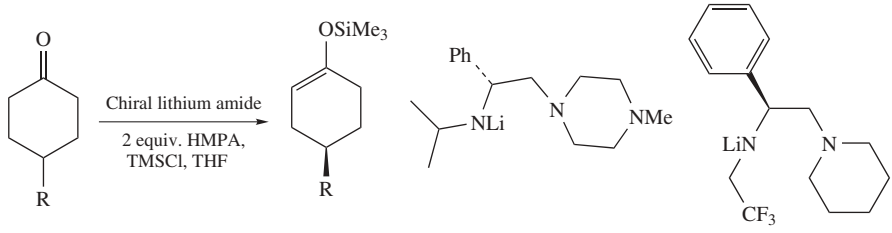
SCHEME 23



(32) (35)

Equiv. LiCl	ee (%)
—	90
0.5	90
1.0	90

SCHEME 24



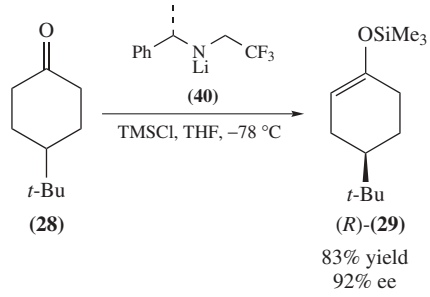
(25) (*R*)-(**39**)

R	(*R*)-**25** at −78 °C ee (%)	(*R*)-**39** at −100 °C ee (%)
t-Bu	77	93
Me	46	94

SCHEME 25

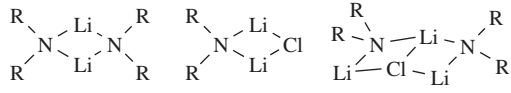
Aoki and Koga also reported a structurally simpler trifluoromethyl-containing and readily accessible chiral base. Deprotonation of **28** with **40** did not require HMPA to yield the silylenol ether (*R*)-**29** in high ee (92%) (Scheme 26)[62].

How lithium halides affect the aggregation state of lithium amides in THF has also been investigated. For example, lithium diphenylamide has been shown to exist as a homodimer in solution at low concentration in THF but as a mixed dimer in the presence of lithium bromide[63]. Koga and coworkers have used a combination of X-ray diffraction and ^{6}Li and ^{15}N NMR spectra to show that the chiral lithium amide **26** (see Scheme 20) is a homodimer in which both lithium atoms are tricoordinated[64]. (*R*,*R*)-**3** has also been crystallized and characterized by X-ray diffraction as a bis-THF-solvated homodimer[65]. Based on these results and by comparing the different reaction conditions, Koga suggested that the higher enantioselectivity in the internal quench method could be due to the LiCl produced along with the formation of silylenol ether. Thus it is proposed that LiCl in the



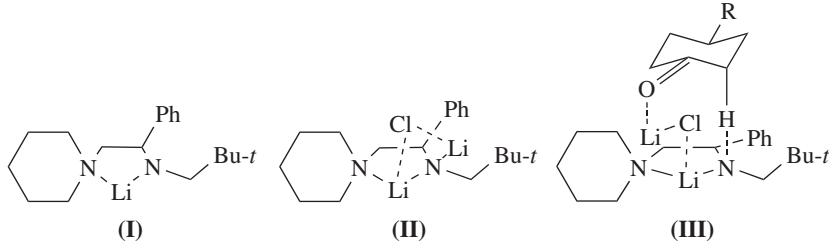
SCHEME 26

presence of chiral lithium base results in the formation of a more enantioselective mixed dimer as the major aggregate[51]. Indeed ^{6}Li and ^{15}N NMR studies of (*S*,*S*)-**3** in THF-d_8 solution revealed formation of the homodimer **A** as the major aggregate in the absence of lithium salt (Scheme 27). In the presence of LiCl, two new mixed aggregates appeared, a heterodimer **B** and a mixed trimer **C**. The mixed dimer **B** predominated in solution in the presence of up to 3 equiv. of LiCl. It was concluded that heterodimer **B** is the reactive species responsible for the higher enantioselectivity in deprotonation of ketones.

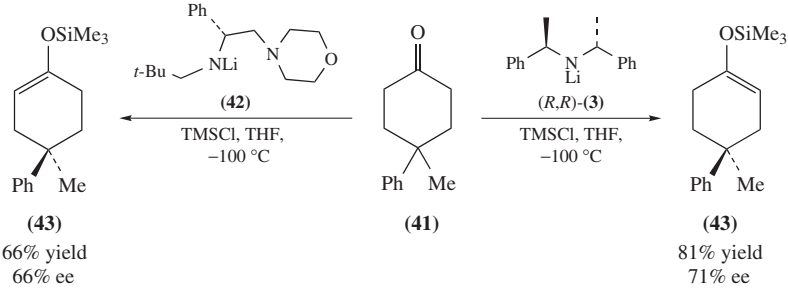


SCHEME 27

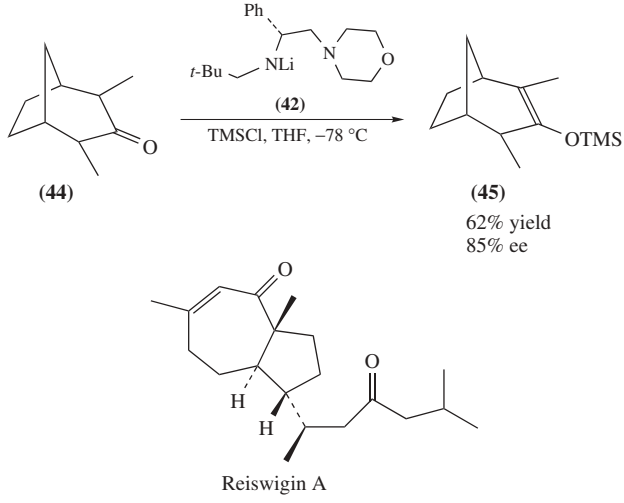
A similar phenomenon was observed in the deprotonation using the bidentate chiral lithium amide (*R*)-**29**, which was found to exist almost exclusively as monomer **I** in solution in THF-d_8 in the absence of LiCl[60,61]. Addition of up to 3 equiv. LiCl resulted in a new set of signals presumably stemming from the mixed dimer **II**. Since the heterodimer **II** was considered to be the reactive species under both external and internal quench conditions, Koga concluded that the eight-membered cyclic transition state model **III** was a better rational for the high enantioselectivity in reaction involving chiral bidentate lithium amides, rather than Ireland's previously proposed six-membered transition state model.



4,4-Disubstituted cyclohexanone such as **41** has also been shown to be deprotonated stereoselectively using (*R*,*R*)-**3** or **42** but with slightly lower enantioselectivity of the obtained silylenol ether **43** (Scheme 28)[66].



SCHEME 28



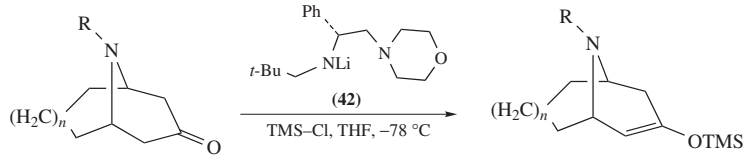
SCHEME 29

In the synthesis of Reiswigin A, MaGee and coworkers used **42** to deprotonate the bicyclic ketone **44** to generate silylenol ether **45** in 85% ee in the absence of HMPA (Scheme 29)[67].

Similarly, chiral bases have found use in the preparation of building blocks for synthesis of alkaloids. A range of *N*-protected azabicyclic ketones was deprotonated to yield corresponding silylenol ethers (Scheme 30)[68–70]. The highest ee (93%) was obtained using **42** under internal quench conditions. These chiral ethers found use as key intermediates in the preparation of naturally occurring alkaloids.

Tetrahydroisoquinoline-based diamines, such as **46**, have been reported by Aggarwal and coworkers. Its use in the deprotonation of 4-*t*-butyl cyclohexanone **28** gave low enantioselectivity, but in the presence of HMPA an ee of 81% of (*S*)-**29** was obtained. In this case, external quench conditions gave the highest enantioselectivity (Table 2)[70].

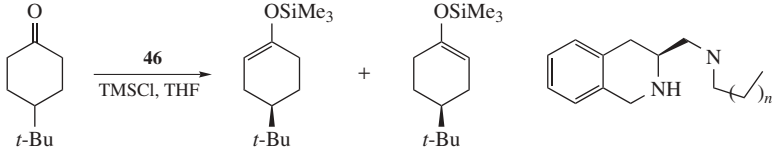
Knochel and coworkers have reported the use of lithiated *N*,*N*-dialkylureas (such as **47**), which have proved to be useful for enantioselective deprotonation and alkylation of ketones. Enantioselectivities up to 88% were achieved across a range of 4-substituted cyclohexanones in the absence of HMPA. On addition of HMPA, both yield and enantioselectivity were lowered (Scheme 31)[71,72].



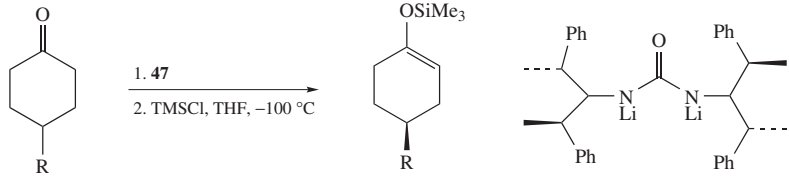
n	R	ee (%)
0	CO_2Bn	90
1	CO_2Me	93
2	CO_2Bn	90

SCHEME 30

TABLE 2. Deprotonation of **28** under internal and external quench conditions



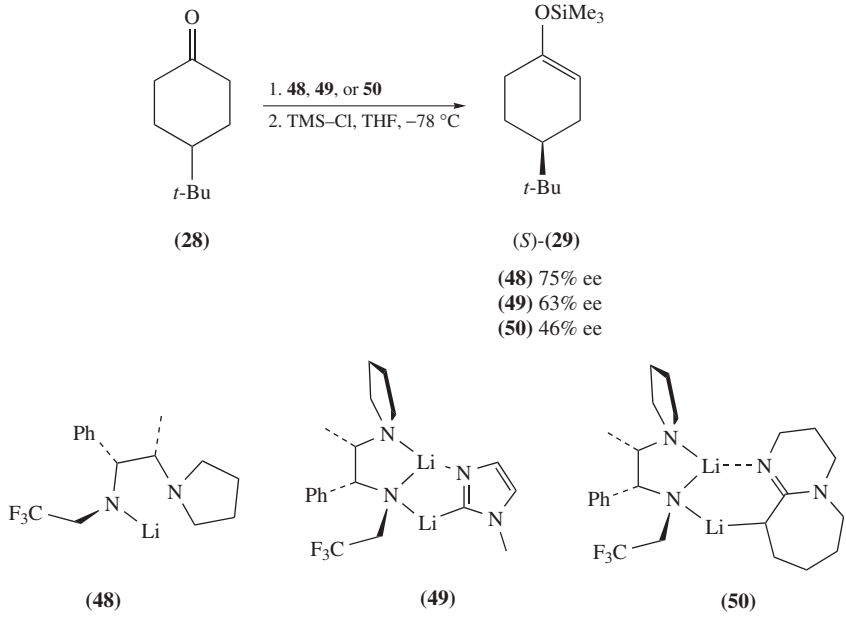
Quench Method	*n*	Temp (°C)	Yield (%)	ee (%) (*R*/*S*)
Internal	1	−78	52	0
External	1	−78	82	54 (*S*)
Internal	2	−100	38	12 (*S*)
External	2	−100	89	81 (*S*)



R	Yield (%)	ee (%)
t-Bu	85	87
Me	87	84
i-Pr	84	87
Ph	88	83
OTBS	85	88

SCHEME 31

More recently, Amedjkouh has described the use of **48** in deprotonation of **28**. Silylenol ethers could be obtained with 85% and 75% ee under internal quench and external quench conditions, respectively (Scheme 32). Mixed dimers **49** and **50** (see Section II.E.2) proved to be effective under external quench conditions and provided silylenol ether in up to 63% ee[73].



SCHEME 32

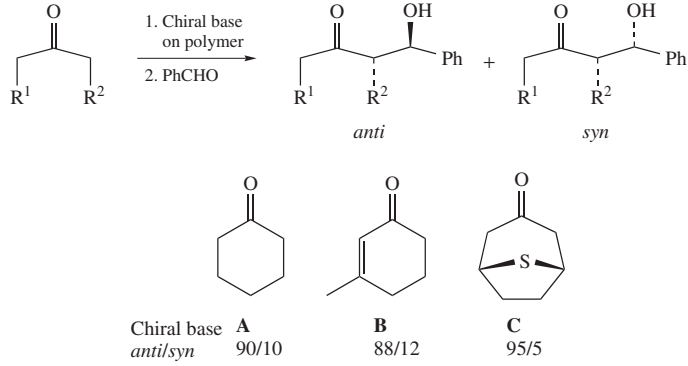
Majewski and coworkers developed polymer-supported chiral lithium amides and applied them to the aldol reaction (Scheme 33)[74]. The amide precursor amines were prepared either from the insoluble Merrifield resins or from copolymerized styrene and 4-chloromethylstyrene yielding soluble polymer (SP).

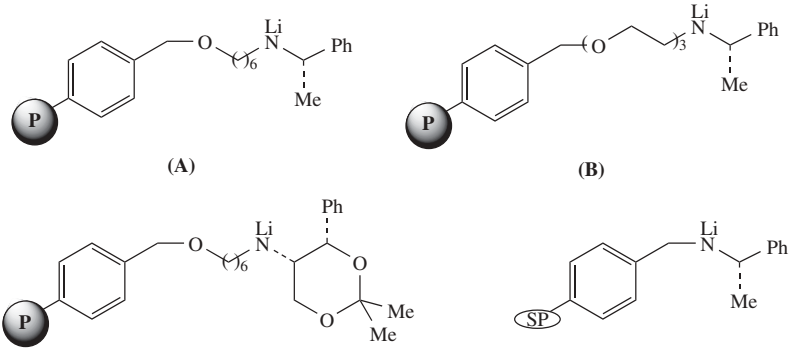
A study of the aldol reaction of cyclic ketones using polymer-supported lithium amides showed high *syn*/*anti* diastereoselectivity. Thus deprotonation of tropinone **32** followed by trapping of the enolate with benzaldehyde gave *syn*-aldol adduct with enantioselectivities up to 75% when reactions were promoted by chiral lithium amides on the soluble polymers **D** and **E** (Scheme 34). Interestingly, the enantioselectivities obtained were similar to those obtained using the chiral lithium amide not bonded to polymer. In contrast, chiral lithium amides on insoluble solid polymer support gave low yields and enantioselectivities (59% ee) in the ring-opening reaction of tropinone.

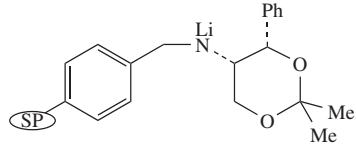
8-Thiabicyclo[3.2.1]octan-3-one (**51**) has also been enantioselectively deprotonated by **52** to provide the sulfur analog **53** of chalcostrobamines in 87% ee upon reaction of the enolate with a cinnamoyl cyanide as electrophile (Scheme 35)[75]. Quenching the enolate with senecioyl cyanide followed by a subsequent cyclization gave the sulfur analog **54** of a tropane alkaloid in 92% ee.

Simpkins and coworkers reported the use of chiral bases in the enantioselective generation of bridgehead enolates (Scheme 36)[76]. Initial studies revealed that external quench protocols were ineffective in trapping the carbanion. Addition of a mixture containing chiral base (*R*,*R*)-**3** and LiCl to a solution of ketone **55** and TMSCl at $-105\,^{\circ}C$ gave mono (−)-α-silylated ketone **56** in 76% yield and >96% ee.

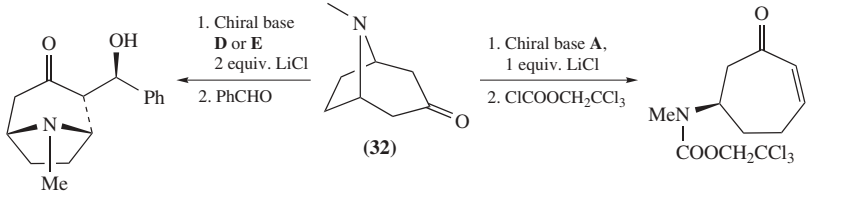
The corresponding saturated ketone gave, under similar conditions, (−)-α-silylated ketone in 53% yield and >92% ee. A drawback of this reaction is the incompatibility of *in situ* quench conditions with most electrophiles.



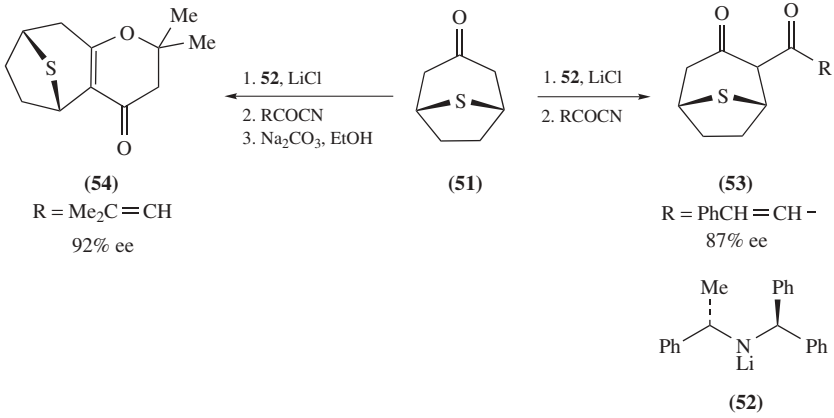




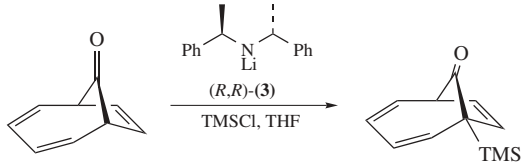
SCHEME 33



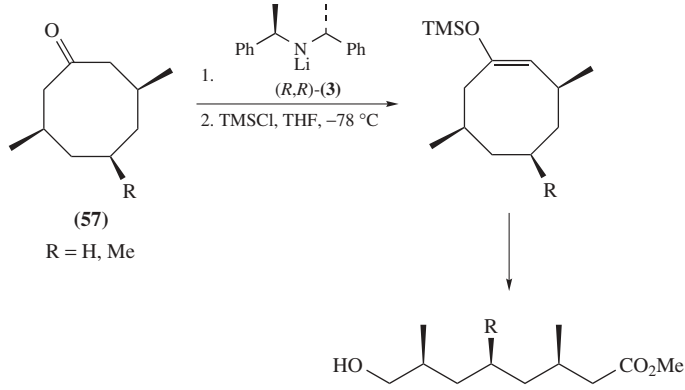
SCHEME 34



SCHEME 35



SCHEME 36



SCHEME 37

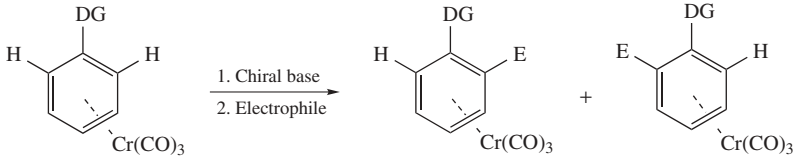
The methyl ester of 3,7-dimethyl-8-hydroxyoctanoic acid have been prepared in good yields and with ee >98% by deprotonation of the starting trimethyl cyclooctanone **57**, R = Me using (*R*,*R*)-**3** and LiCl at −78 °C (Scheme 37)[77]. This reaction is a key step in a versatile synthesis of optically active isoprenoid, which is present as a sub-unit in vitamins, plant metabolites, antibiotics and other naturally occurring compounds.

C. Deprotonation of Tricarbonylchromium Arene Complexes

The first enantioselective functionalization of tricarbonylchromium arene complexes using chiral bases, to generate planar chiral chromium complexes, was reported by Simpkins and coworkers in 1994 and involved a directed *ortho*-lithiation and subsequent quench with an electrophile[78]. Both aromatic and benzylic functionalization of tricarbonylchromium arene complexes has been achieved.

1. Aromatic functionalization

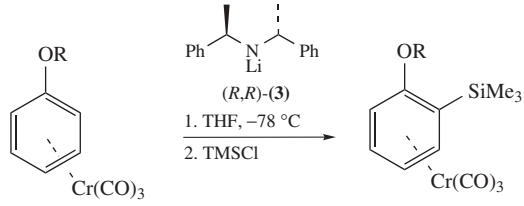
Aromatic functionalization has been developed by Simpkins and coworkers[78–80], Kündig and Quattropani[81], Schmalz and Schellhaas[82] and Uemura and coworkers[83]. Uemura used in his early work an alkyl lithium/chiral ligand mixed reagent, but such reagents are outside the scope of this review. In general, the most common bases used are (*R*,*R*)-**3** and Kündig's amide **58**. They have been used to stereoselectively deprotonate mono-substituted arene complexes containing directing groups (DG) to produce a variety of *ortho*-substituted complexes (Scheme 38).



DG = OR, MOM, CON(Pr-*i*)$_2$, 1,3-dioxolane
P(O)Ph$_2$, N(Me)COBu-*t*, F, Cl

SCHEME 38

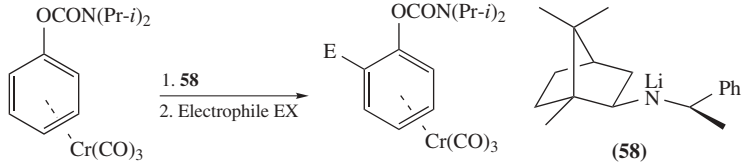
Simpkins and coworkers found increasing enantioselectivity with increasing size of alkoxy *ortho*-directing group. A 90% ee was achieved with R = *i*-Pr (Scheme 39)[78, 80], but no reaction occurred with the arene complex with R = *t*-Bu.



R	Yield (%)	ee (%)
Me	83	84
Et	82	81
i-Pr	65	90

SCHEME 39

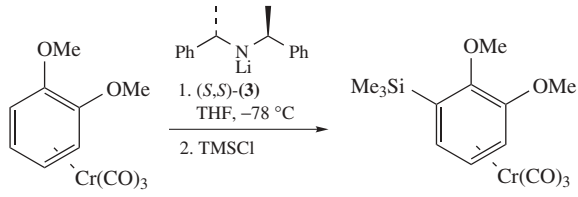
Kündig and Quattropani investigated the effect on the stereoselectivity of electrophiles in metallation of the carbamate-containing arene complexes. Modest stereoselectivities were obtained as seen in Scheme 40[81].



(58)

E	X	Yield (%)	ee (%)
Me	I	93	64
TMS	Cl	86	67
MeO_2C	Cl	71	73

SCHEME 40



(59)

97% ee
92% yield

SCHEME 41

Using (*S*,*S*)-**3** as lithium base, Schmalz and Schellhaas were able to desymmetrize the disubstituted veratrole-$Cr(CO)_3$ complex **59** to afford the monosilylated product with excellent yield and selectivity (Scheme 41)[82].

Arene complex bearing the carbamate directing group has been employed to initiate an *ortho*-Fries rearrangement, which was induced by warming the lithiated intermediate of **60** to −20 °C (Scheme 42)[84]. The formed Li-phenolate **61** was reacted directly with the electrophile. The rearranged complex **62** was isolated, in 42% yield and 54% ee. The authors suggested that racemization may result before the 1,3-carbamoyl transposition when keeping the anion solution for 12 h at −20 °C (Scheme 42).

Recent developments by Simpkins and by Kündig include the preparation of new arene complexes such as **63**[84] and **64**[85], which could be isolated in enantiomerically pure form after a single crystallization (Scheme 43).

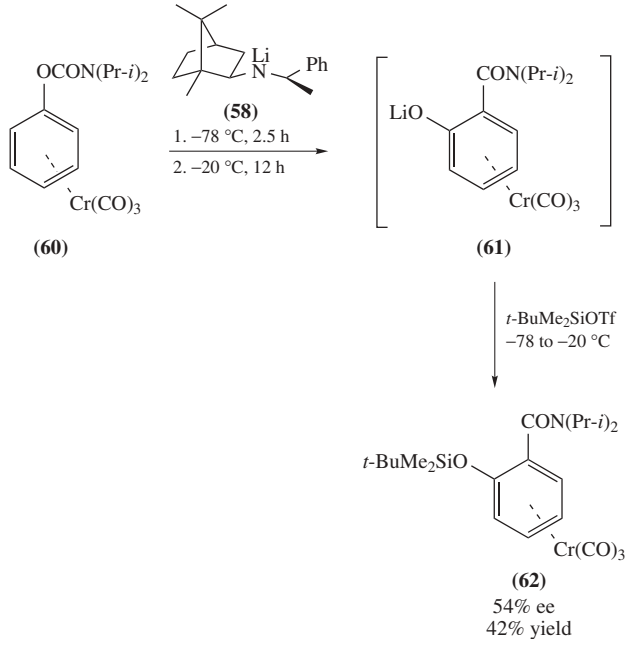
Kündig and coworkers have reported on the application of an azepine-derived lithium base **65** in the asymmetric desymmetrization of the carbamate arene complex **60** (Scheme 44)[86].

Compared to (*R*,*R*)-**3** which gave 39% ee, **65** was found to be more stereoselective and gave the silylated complex in 62% ee.

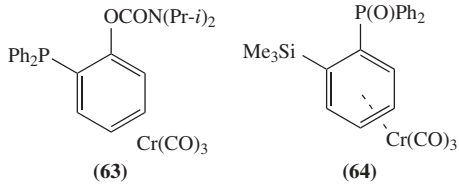
Deprotonation of benzaldimine arene complexes using (*R*,*R*)-**3** gave enantioselectivities up to 92%[87]. A series of lithium bases derived from constrained cyclic amines did not show significant increase in asymmetric induction (Scheme 45).

2. Benzylic functionalization

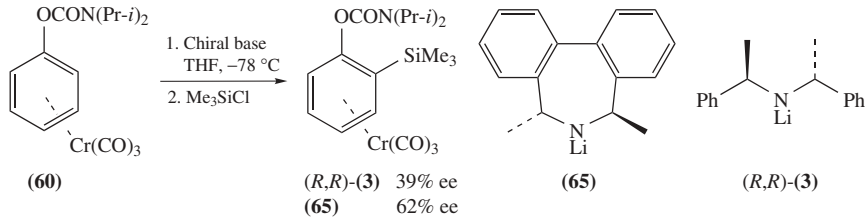
Gibson and coworkers have examined the possibility of using chiral base methodology to enantioselectively lithiate the benzylic position of arene complexes (Scheme 46). (*R*,*R*)-**3** has been used in combination with LiCl and followed by quenching with



SCHEME 42



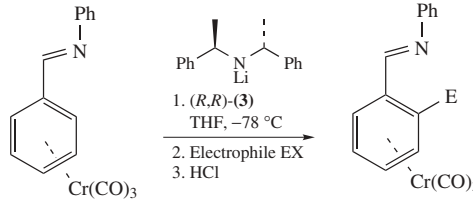
SCHEME 43



SCHEME 44

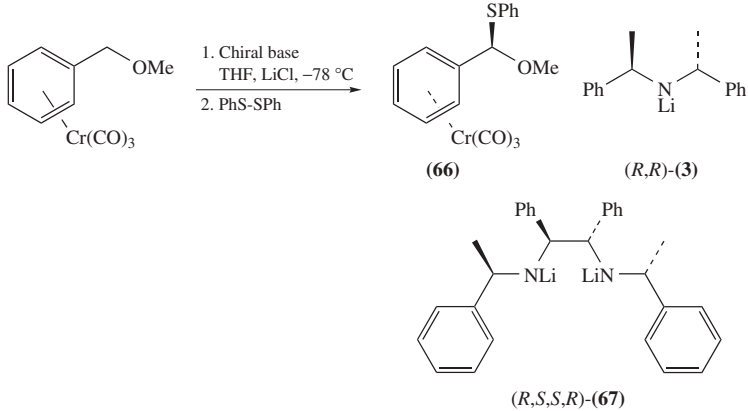
diphenyl disulfide to provide α-phenylsulfenyl complex **66** in 52% yield but only 22% ee (Scheme 46)[88]. Reaction with the chiral base (*R*,*S*,*S*,*R*)-**67** produced (−)-α-phenylsulfenyl complex **66** in 97% ee and in 86% yield.

Variation of ether alkyl group, arene complex or electrophile resulted in similar high enantioselectivity (Scheme 47).



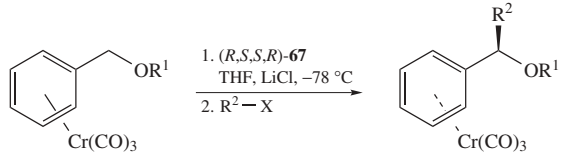
E	X	yield %	ee %
TMS	Cl	67	92
MeO_2C	Cl	68	90
Me_3Sn	Cl	65	89

SCHEME 45



Base	yield (%)	ee (%)
(*R*,*R*)-**3**	52	22 (+)
(*R*,*S*,*S*,*R*)-**67**	86	97 (–)

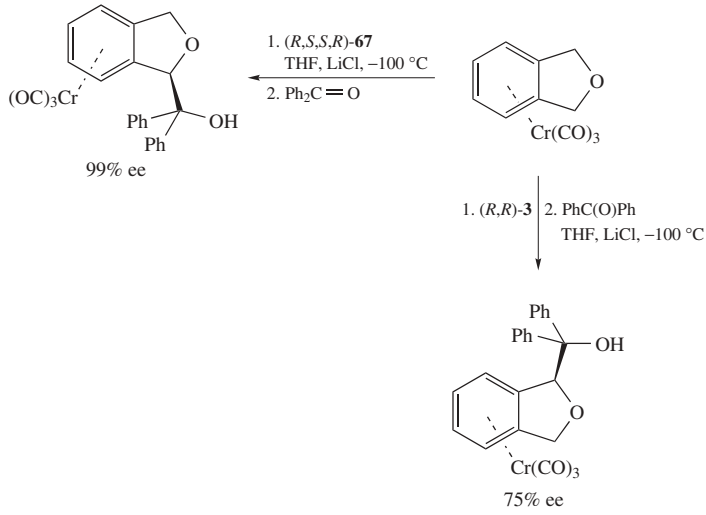
SCHEME 46



R^1	R^2	yield (%)	ee (%)
Me	Me	96	97
Bn	SPh	95	99
Bn	Me	89	99

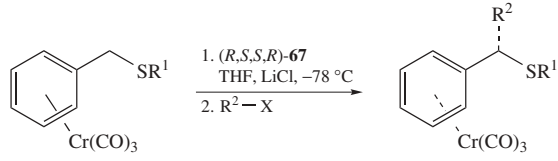
SCHEME 47

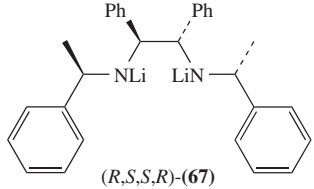
Similar improvements have been reported by Ewin and Simpkins for the asymmetric deprotonation of cyclic ether complexes and subsequent quenching with benzophenone (Scheme 48)[80, 89]. Interestingly, switching from the monoamide (*R*,*R*)-**3** to the bisamide (*R*,*S*,*S*,*R*)-**67** resulted in increased ee from 75% to 99% and, as with acyclic ether complexes, the absolute configurations of the products were different.



SCHEME 48

The reactivity of a series of thioethers has also been examined. It was found that the enantioselectivity is a function of the thioether alkyl group. The highest ee values were obtained with methyl and benzyl groups. Interestingly, X-ray analysis revealed that the stereochemistry of the reaction was the opposite of that obtained with analogous ether complexes (Scheme 49)[90].





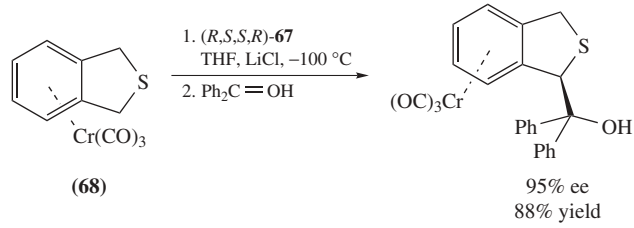
(*R*,*S*,*S*,*R*)-(**67**)

R^1	R^2	yield (%)	ee (%)
Me	Bn	91	88
Me	$C_{11}H_9$[a]	93	88
Me	TMS	62	89
Bn	Me	84	91
Bn	$C_{11}H_9$[a]	83	91
Et	TMS	72	82

[a] 1-naphthylmethyl-.

SCHEME 49

Attempts to deprotonate cyclic thioether complexes such as **68** with monoamide (*R*,*R*)-**3** and subsequent quench resulted in ee values of only *ca* 5%[89]. However, bisamide (*R*,*S*,*S*,*R*)-**67** gave the product in 88% yield and 95% ee (Scheme 50)[91]. The stereochemistry of the product was similar to that observed with acyclic systems.

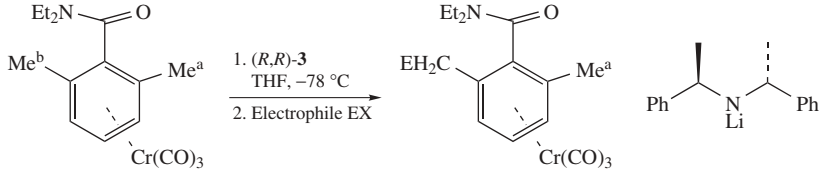


(68)

95% ee
88% yield

SCHEME 50

Direct synthesis of atropisomeric benzamides and anilides from prochiral precursors has been reported using chiral-amide-mediated deprotonation of 2,6-dimethyl-substituted benzamide and anilide chromium complexes. A screening of amides revealed that (*R*,*R*)-**3** was the most selective in the deprotonation of the benzylic methyl groups (Scheme 51)[92–94].



(1*pR*,*aR*)

E = Me, Bn, Allyl
up to 86% ee

(*R*,*R*)-(**3**)

SCHEME 51

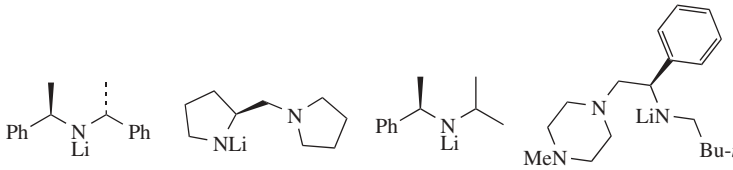
With *N*-pivaloyl 2,6-dimethylaniline chromium complex **69**, the chiral lithium amide **70** derived from 1-phenyl-2(4′-methylpiperazinyl)ethylamine turned out to be the base of choice for the asymmetric lithiation at the benzylic methyls (Table 3). With almost all electrophiles, chromium complexes bearing different substituents on the nitrogen atom could be obtained in up to 99% ee[92,93]. In contrast, the chiral bases (*R*,*R*)-**3**, (*R*)-**27** and (*S*)-**4** resulted in modest asymmetric induction ranging from 44% to 78% ee.

In the case of *N*-benzoylaniline complex **71**, the chiral lithium amide asymmetric induction was found to be dependent upon the substituent group on the *N*-acyl part of the chromium complex. Thus for EX = BnCl, (*R*)-**27** resulted in higher enantioselectivity than (*R*,*R*)-**3** (Scheme 52)[92]. This was attributed to an equilibrium between the *trans*- and *cis*-rotamers of the amide.

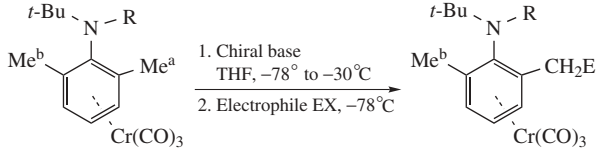
Corresponding *N*-*ortho*-methylbenzoylaniline resulted predominantly in *trans*-rotamer. In this case (*R*,*R*)-**3** gave an enantioselectivity of 94% ee, and as high as 99% ee when MeI was used as an electrophile.

Interestingly, (*R*,*R*)-**3**, (*R*)-**27** and (*S*)-**4** gave (*R*)-axially chiral anilide chromium complex, involving lithiation at Me^a and subsequent quenching with electrophile, whereas the opposite result is observed with *N*,*N*-diethyl-2,6-dimethylbenzamide chromium complex. This difference in stereochemical outcome was attributed to the positioning of the carbonyl

TABLE 3. Deprotonation of **69** by various chiral lithium amides

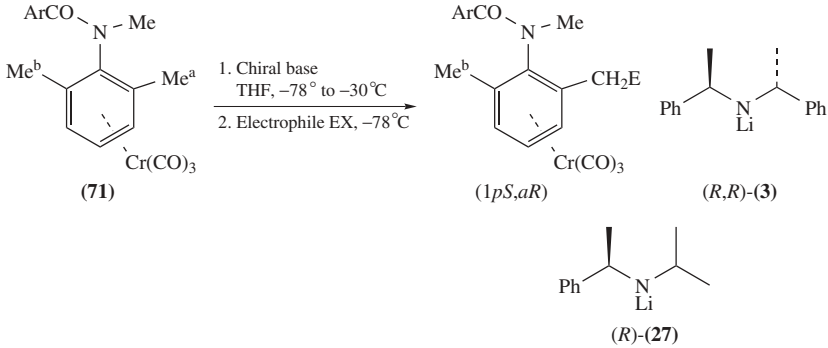


(*R*,*R*)-(**3**) (**4**) (*R*)-(**27**) (**70**)



(**69**) (1*pS*,*aR*)

R	Chiral base	E	X	Yield (%)	ee (%)
Me	(*R*,*R*)-**3**	Me	I	50	44
Me	(*R*)-**27**	Me	I	51	72
Me	(*S*)-**4**	Me	I	44	78
Me	(*R*)-**70**	Me	I	90	95
Me	(*R*)-**70**	$PhCH_2$	Br	90	97
Me	(*R*)-**70**	Allyl	Br	81	92
Et	(*R*)-**70**	Me	I	83	98
Et	(*R*)-**70**	$PhCH_2$	Br	71	99
CH_2OMe	(*R*)-**70**	Me	I	73	96
CH_2OMe	(*R*)-**70**	$PhCH_2$	Br	78	94



(**71**) (1*pS*,*aR*) (*R*,*R*)-(**3**)

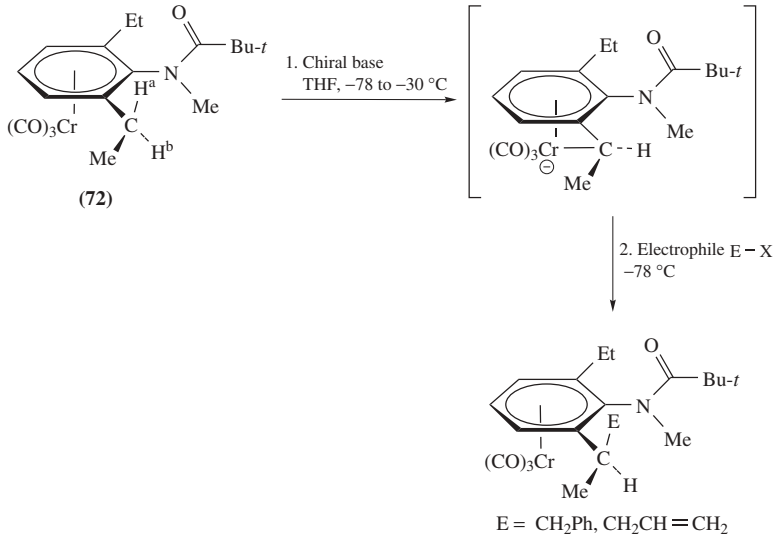
(*R*)-(**27**)

Chiral base	Ar	yield (%)	ee (%)
(*R*,*R*)-**3**	C_6H_5	26	35
(*R*)-**27**	C_6H_5	63	67
(*R*,*R*)-**3**	2-MeC_6H_4	58	94
(*R*)-**27**	2-MeC_6H_4	62	81

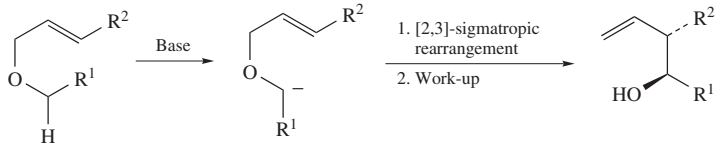
SCHEME 52

group with respect to $Cr(CO)_3$. In the anilide chromium complex the amido carbonyl oxygen is oriented *trans* to the *N*-methyl group and forced *anti* to the tricarbonylchromium fragment, above the arene plane.

In the same work Koide and Uemura further investigated the enantiotopic lithiation of 2,6-diethylaniline chromium complex **72** (Scheme 53)[92]. Interestingly, the lithium amide was shown to be able to discriminate not only between the two ethyl groups, but also between the prochiral hydrogens on the preferred methylene. The authors suggest that the chiral lithium amide would selectively abstract a proton H^a in the sterically favored conformation from the *exo* side to generate a configurationally stable carbanion. Thus an additional stereocenter was created at the favored benzylic position, but only a single diastereoisomer was isolated when allyl bromide and benzyl bromide were used as electrophiles.



SCHEME 53



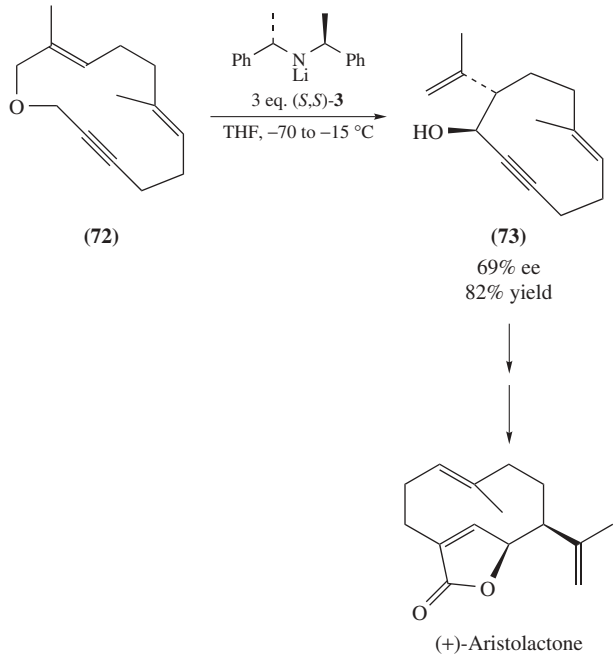
SCHEME 54

D. Miscellaneous Stereoselective Deprotonations

1. Deprotonation α to oxygen

The original Wittig rearrangement[95] is a rearrangement of α-alkoxycarbanion to alkoxide upon deprotonation of an ether and involves migration of an alkyl group from oxygen to carbon (Scheme 54). The vinylogous variant gives [2,3]-sigmatropic rearrangement of allylic ether or propargylic α-oxycarbanion affording homoallylic alcohols or allenic alcohols. This is generally known as [2,3]-Wittig rearrangement.

Chiral lithium bases have been used for enantioselective deprotonation to yield configurationally stable α-oxy carbanions. This holds potential for asymmetric [2,3]-Wittig rearrangement in stereoselective synthesis. Thus, treatment of propargylic ether **72** with (*S*,*S*)-**3** in THF at $-70\,^{\circ}C$ to $-15\,^{\circ}C$ afforded propargylic alcohol **73** in 82% yield and in 69% ee of the shown enantiomer[96, 97]. This product was successfully employed as a precursor of (+)-Aristolactone (Scheme 55).



(72) **(73)**

69% ee
82% yield

(+)-Aristolactone

SCHEME 55

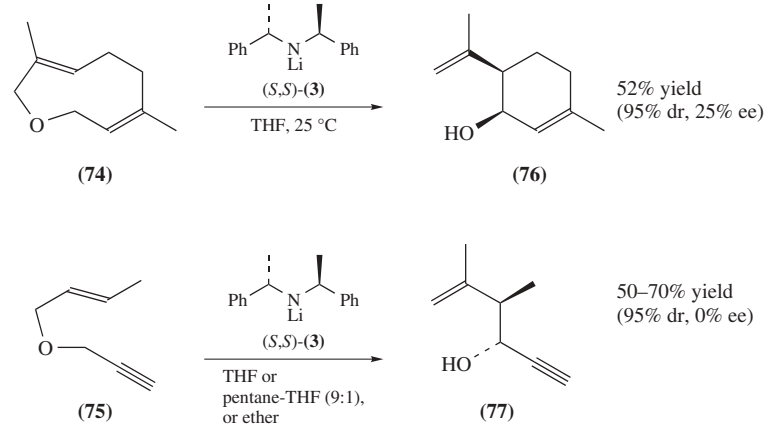
Deprotonation of ethers **74** and **75** using (*S*,*S*)-**3** was found to give alcohols **76** and **77**, respectively (Scheme 56)[97].

Possible transition states for [2,3]-Wittig ring contractions have been proposed by Marshall and Lebreton[97].

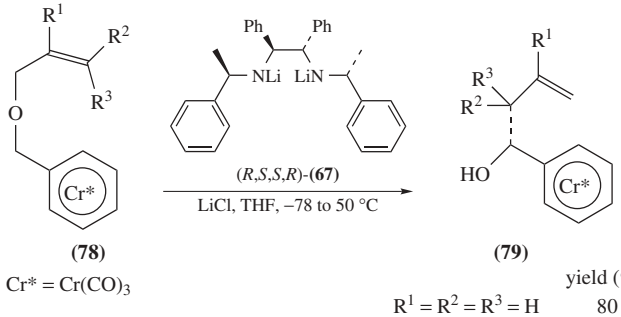
Chiral lithium amides were found useful in performing stereoselective rearrangement of tricarbonylchromium(0) complexes of allyl benzyl ethers. Reaction with (*R*,*S*,*S*,*R*)-**67** in the presence of LiCl in THF at $-78\,^{\circ}C$ of allyl benzyl ether complex **78** resulted in rearrangement into a homoallylic benzyl alkoxy complex (**79**) (Scheme 57)[98]. The product was obtained in good yield (80%) and high optical purity (96% ee). A series of rearrangements, carried out in order to examine the effect of substituents, gave products with 84–96% ee and yields ranging from 24% to 82%.

α-Lithiation of epoxides to generate oxiranyl anions has been extensively studied, but with only few examples with lithium amides as bases. *Exo*-norbornane oxide rearranges to enantiomerically enriched nortricyclanol in 49% ee (70% yield), upon reaction with (*S*,*S*)-**3** in diethyl ether (Scheme 58)[99, 100]. This reaction is assumed to proceed via α-lithiated epoxide followed by C–H insertion.

Anionic migration of an alkylsilyl group from carbon to oxygen to afford silyl ether α-oxycarbanion is known as a Brook rearrangement, and the reverse reaction is called

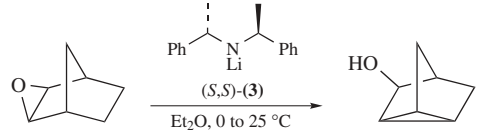


SCHEME 56



	yield (%)	ee (%)
$R^1 = R^2 = R^3 = H$	80	(96)
$R^1 = H, R^2 = R^3 = Me$	82	(84)
$R^1 = R^2 = H, R^3 = Me$	24	(90) 50% *syn*
$R^1 = Me, R^2 = R^3 = H$	33	(91)
$R^1 = R^3 = H, R^2 = Me$	82	(96) 95% *syn*

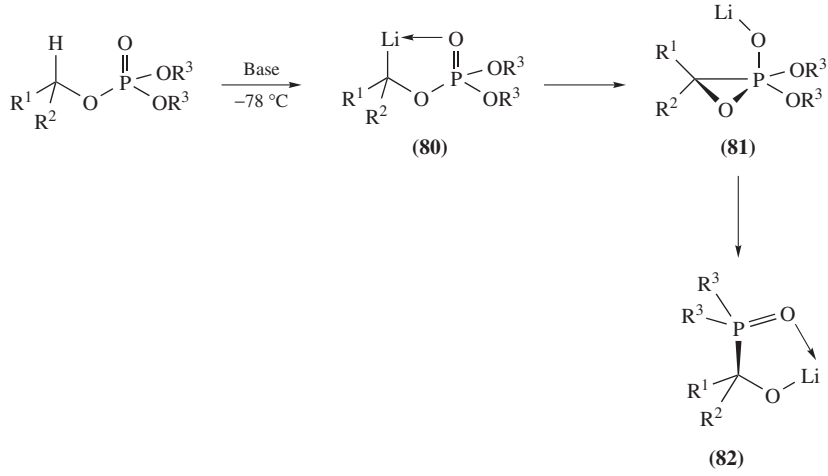
SCHEME 57



SCHEME 58

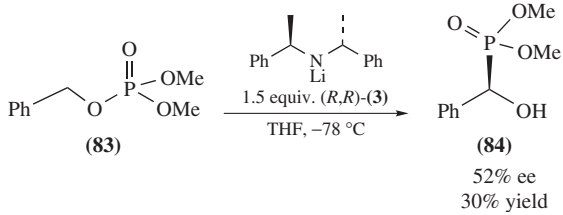
retro-Brook rearrangement. The processes are believed to proceed intermolecularly via pentacoordinated silicon-containing intermediates. Recently, a similar rearrangement has been reported by Hammerschmidt and coworkers describing the rearrangement of phosphate into phosphonate. The lithium carbanion intermediate **80** formed by deprotonation of

the substrate is a short-lived species with lithium suggested to be part of a five-membered ring, prior to rearrangement to lithiated hydroxyphosphonate **82** via a pentacoordinated phosphorus-containing intermediate (**81**) (Scheme 59)[101–103]. This rearrangement proceeds with retention of configuration at the α-carbon.



SCHEME 59

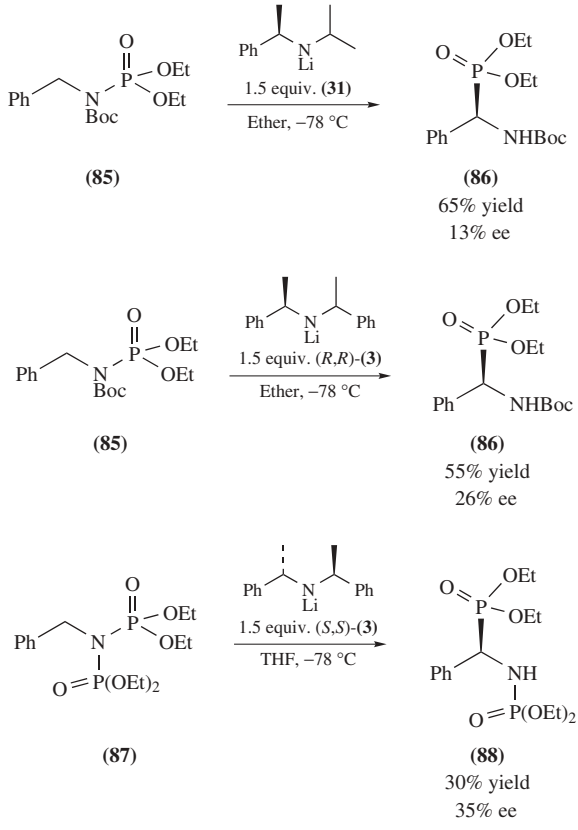
Employing the chiral lithium amide (*R*,*R*)-**3** as a base in THF at −78 °C gave the hydroxy phosphonate **84** in 30% yield and 52% ee upon deprotonation of phosphate **83** (Scheme 60)[102,103]. The use of BuLi as base with (−)-sparteine as chiral ligand in ether at −78 °C resulted in a lower optical activity (8% ee) and 65% yield[102].



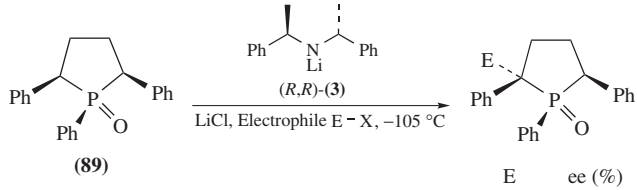
SCHEME 60

Phosphoramidates rearrange into α-aminophosphonates using chiral lithium amide bases; e.g. **31** afforded aminophosphonate **86** from phosphoramidate **85** in 13% ee and 65% yield (Scheme 61)[104]. A slightly higher optical purity of 26% (55% yield) was obtained with chiral (*R*,*R*)-**3** as base. The application of (−)-sparteine and BuLi gave 13% ee and a yield of 30%. A higher level of enantioselectivity was reached when a bisphosphonate (**87**) was reacted with (*R*,*R*)-**3** in THF. Although the yield was only 30%, aminophosphonate **88** was obtained in 35% ee (Scheme 61).

Similarly, phospholane **89** could be deprotonated by chiral lithium amides in the presence of LiCl, followed by quenching with various electrophiles (Scheme 62)[105]. The enantioselectivity was found to range from 82% up to 92% ee, and in each case only one



SCHEME 61



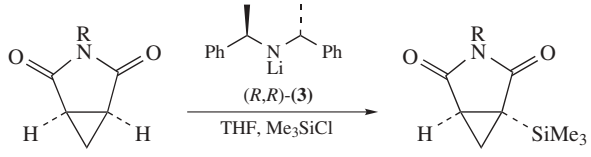
E	ee (%)
Me	84
Allyl	87
Et	90
PhCHO	92

SCHEME 62

diastereoisomer was obtained with the all-*syn* arrangement of ring phenyl substituents maintained. The reaction with benzaldehyde resulted in a 7:1 mixture of diastereoisomers and with 92% ee for the major diastereoisomer. Interestingly, several of these compounds could readily be enriched to >98% ee by recrystallization.

2. Deprotonation β to oxygen

The desymmetrization of several ring-fused imides has been reported by Simpkins and coworkers. Thus enantioselective deprotonation of cyclopropyl imide **90** with the chiral base (*R*,*R*)-**3**, followed by electrophilic quenching with TMSCl under *in situ* conditions, gave mono-silylated adducts with high ee, up to 95% (Scheme 63)[106].

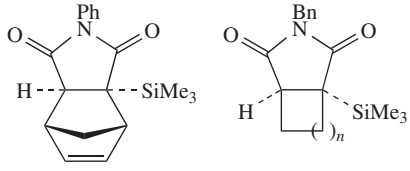


(90)

R	Yield (%)	ee (%)
Ph	80	95
Bn	67	91
OBn	66	89

SCHEME 63

This reaction could be extended to other imide systems giving various silylated compounds such as **91** and **92** with enantioselective excess up to 98% (Scheme 64).



(91)

98% ee

(92)

n = 1; 93% ee

n = 2; 91% ee

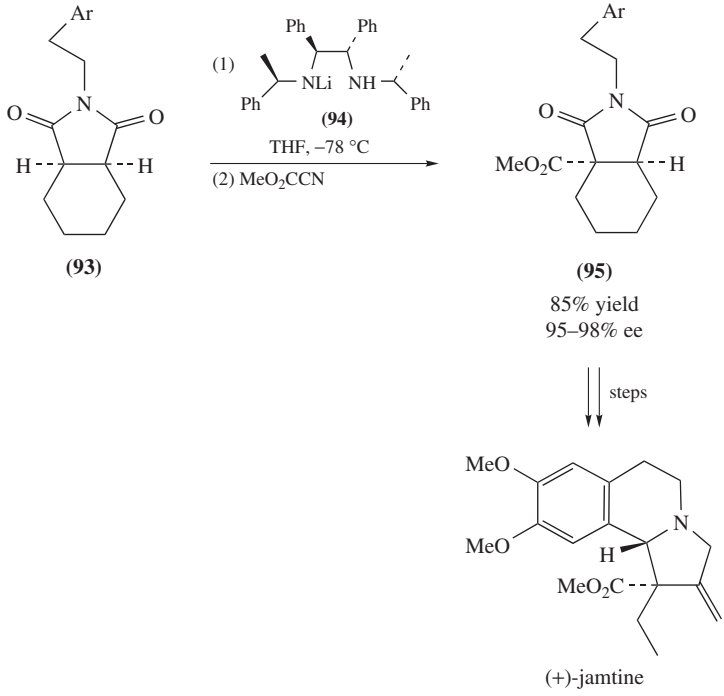
SCHEME 64

Chiral base was applied in the synthesis of the alkaloid (+)-jamtine (Scheme 65). The key step consisted in deprotonation of the cyclohexane fused imide **93** with the monolithiated chiral diamine **94**, which allowed highly enantioselective carboxymethylation on quenching with Mander's reagent to give compound **95** in up to 98% ee[107, 108].

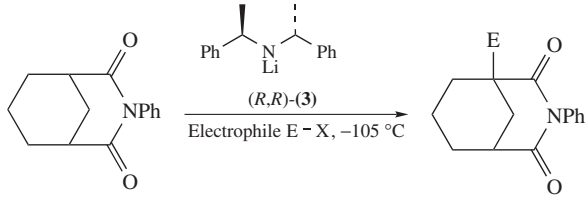
A major problem with these reactions is the bis-lithiation of the imides which results in modest yields. However, high enantioselectivity up to 98% ee is kept with a large variety of electrophiles as outlined in Scheme 66[109].

Expanding the range of application of chiral lithium amides led to desymmetrization of various glutarimides. Thus the use of **67** enabled the formation of **96** in up to 97% ee and as single diastereoisomer with a *trans* arrangement of the newly installed substituents (Scheme 67)[107].

The use of chiral lithium amides in the preparation of biologically potent piperidines from highly enriched glutarimides is illustrated in the synthesis of the antidepressant drug substance (−)-paroxetine (Figure 7)[107].



SCHEME 65

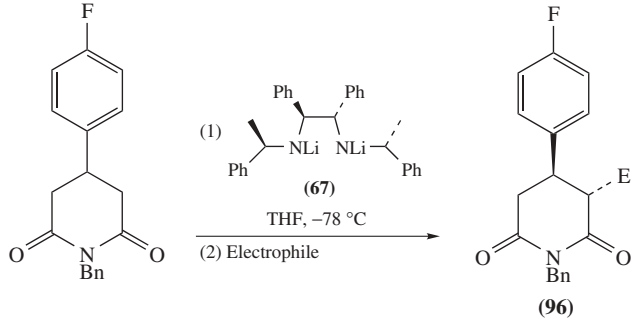


E	Yield (%)	ee (%)
Me	57	97
Prenyl	50	98
Pivaloyl	56	98
TMS	74	98

SCHEME 66

E. Catalytic Stereoselective Deprotonations

The driving force for the development of catalysts for stereoselective deprotonations is similar to that of other asymmetric catalysts. It is desirable to have access to highly reactive and stereoselective deprotonation catalysts of general applicability. However, the experimental situation for deprotonations differs from that for many other catalyzed



E	Yield (%)	ee (%)
Me	65	97
Benzyl	61	97
$MeOC_2CN$	71	97

SCHEME 67

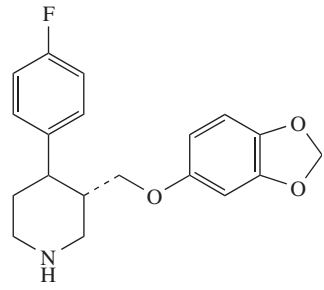


FIGURE 7

reactions in that the lithium amide base is consumed in the deprotonation. Most of the reactions reviewed above therefore made use of stoichiometric or larger amounts of the base to complete the deprotonation of the substrate. Thus, catalytic systems are needed in which the chiral lithium amide is regenerated in the reaction mixture by a bulk base that does not react with the substrate.

Since most chiral lithium amides are expensive to produce, an effective, readily available and cost-efficient catalytic system using a catalytic amount of chiral lithium amide is currently a significant challenge. The chiral lithium amide should also be available in both enantiomeric forms. Asami and coworkers reported in 1994[110] the first catalytic enantioselective deprotonation using chiral lithium amides.

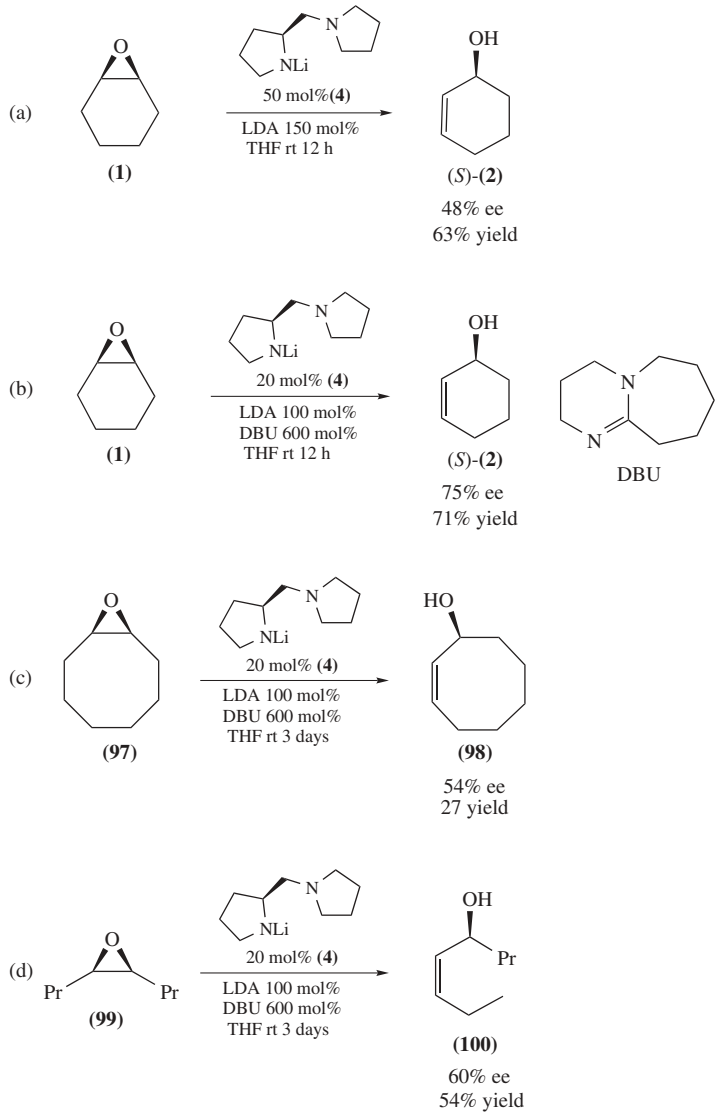
Below, the progress for each type of substrate is reviewed separately.

1. Catalyzed epoxide rearrangement

Asami and coworkers discovered that the chiral lithium amide **4** was more reactive toward epoxides than lithium diethylamide ($LiNEt_2$) or lithium diisopropylamide (LDA) are[110]. He reasoned that an achiral lithium amide could be used to regenerate the chiral

lithium amide from the product chiral diamine formed in the substrate deprotonation. In this way it should be possible to use the chiral lithium amide in catalytic amounts.

Upon deprotonation of cyclohexene oxide (**1**) using 50 mol% of the chiral base **4** and 150 mol% of LDA, the (*S*)-allylic alcohol (*S*)-**2** was formed in 48% ee (63% yield) (Scheme 68a). This lower enantioselectivity compared with the stoichiometric deprotonation (80% ee, see Scheme 2) was probably due to non-enantioselective deprotonation of the epoxide by LDA yielding racemic product.



SCHEME 68

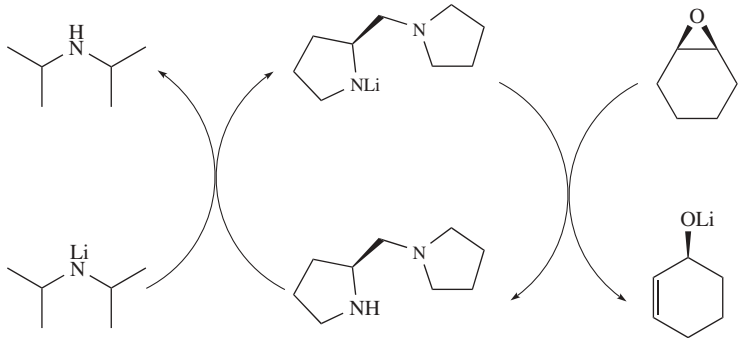
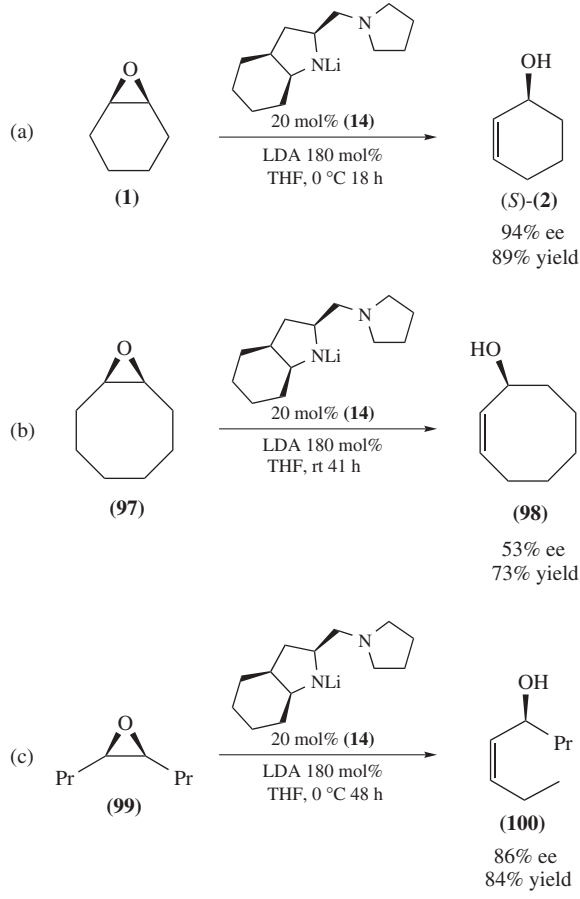


FIGURE 8



SCHEME 69

The addition of additives such as DBU was found to increase the enantioselectivity. In the presence of DBU (600 mol%), deprotonation of cyclohexene oxide using **4** (20 mol%) and LDA (100 mol%) resulted in product yield of 71% and 75% ee of (*S*)-**2** (Scheme 68b), which is a slightly lower ee than that obtained under stoichiometric conditions (80% ee, see Scheme 2). Asami and coworkers summarized the results with the catalytic cycle shown in Figure 8[110].

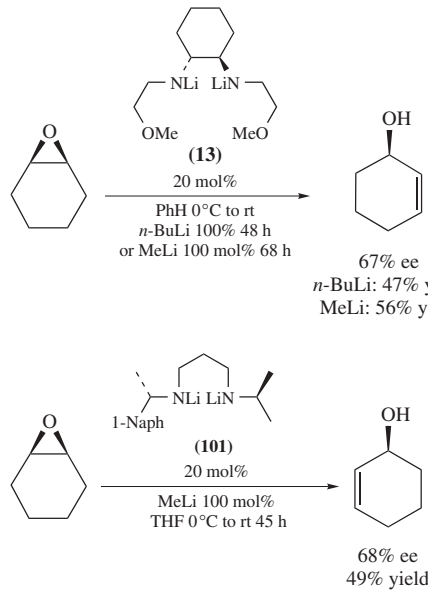
The finding that the use of LDA as bulk base results in non-enantioselective deprotonation indicated that bulk bases which are much less reactive toward the epoxide substrate compared with the chiral lithium amide are needed. But they should be strong enough to regenerate the chiral amide from the amine formed in the epoxide rearrangement.

Asami and coworkers also investigated the deprotonation of cyclooctene oxide **97**, which is known to undergo both α-deprotonation to yield transannular products and β-deprotonation to yield allylic alcohols **98** upon reaction with lithium amides. Using his catalytic system Asami and coworkers obtained the allylic alcohol in 27% yield and 54% ee of (*S*)-**98** (Scheme 68c). (*Z*)-4-Octene oxide **99** was deprotonated yielding the allylic alcohol **100** in 54% yield and 60% ee of the (*S*)-enantiomer (Scheme 68d)[110].

Asami and coworkers synthesized and applied the chiral lithium amide **14**, which appeared to be more reactive than **4**. It was successfully used in catalytic enantioselective deprotonation of both cyclic and acyclic epoxides (Scheme 69). Interestingly, the addition of DBU lowered the enantioselectivity!

Thus, the allylic alcohol (*S*)-**2** could be obtained in high yield (89%) with 94% ee by using only 20 mol% chiral lithium base **14** (Scheme 69a). Reduction of the amount of chiral base to 5 mol% lowered the ee to 85%. Interestingly, epoxides such as **99**, which previously had rearranged with low enantioselectivity, were deprotonated with high enantioselectivity under such catalytic conditions (Scheme 69c).

Alexakis and coworkers have developed several homochiral bis-lithium amides such as **13** and **101** (Scheme 70)[19,111]. Interestingly, efficient recycling of the chiral lithium



SCHEME 70

amide was obtained with *n*-BuLi or MeLi in benzene and THF, respectively. The use of LDA as bulk base dramatically decreased the enantiomeric excess of the allylic alcohol. The reactivity of these carbon bases toward cyclohexene oxide itself was not reported.

Andersson and coworkers presented chiral lithium amides (**18** and **19**) based on the homochiral aza-norbornane moiety[24–26]. These ligands were available in both enantiomeric forms via the asymmetric Diels–Alder reactions developed by Stella and coworkers[22] and by Waldmann and Braun[23] (see Section III.C). The catalytic ability of **18** was found to be most effective using the conditions developed by Asami. Using 5–15 mol% of **18** in the presence of LDA (150 mol%) and DBU (500 mol%) in THF resulted in highly enantioselective epoxide rearrangement of several epoxides (Scheme 71).

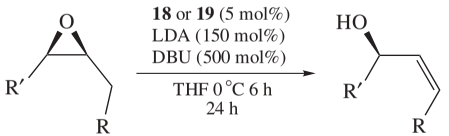
Replacing the pyrrolidine moiety in **18** by more bulky enantiopure (2*R*,5*R*)-dimethylpyrrolidine resulted in a chiral lithium amide (**19**), which to date is the most selective and general ligand for catalytic enantioselective deprotonation of several substrates yielding allylic alcohols with ee values up to 99% (Scheme 71). Also, cyclopentene oxide and substituted derivatives thereof could be deprotonated under catalytic conditions with ee values up to 96%. However, these high enantioselectivities obtained under catalytic conditions could only be accomplished in the presence of high concentrations of DBU for chiral bases **18** and **19**. Results by Ahlberg and coworkers on the intricate role of DBU[112] is described below (Section II.E.3). High stereoselectivities were obtained in the absence of DBU in the presence of stoichiometric amounts of the chiral base **19** as reviewed above (Section II.A.1). However, these chiral lithium amides are expensive and not easily accessible.

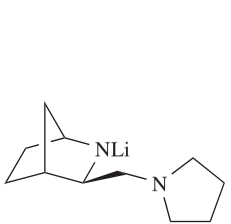
2. Development of bulk bases and their function

In order to further develop the field of enantioselective catalytic deprotonation, it was necessary to develop bulk bases that show low reactivity toward the epoxide but have the ability to regenerate the chiral catalyst. Thus, the bulk bases should show low kinetic basicity toward the substrate, but be thermodynamically and kinetically basic enough to be able to regenerate the chiral lithium amide from the amine produced in the rearrangement.

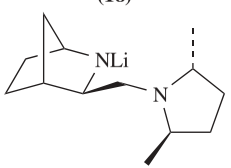
Ahlberg and coworkers have found that lithiated 1-methylimidazole (**21**) and lithiated 1,2-dimethylimidazole (**22**) work as such bulk bases in the presence of catalytic amounts of a readily accessible homochiral lithium amide **20** (both enantiomers are readily available) (see Section III.C)[45,46]. These new bulk bases are easily accessible by deprotonation of 1-methylimidazole and 1,2-dimethylimidazole by, e.g., *n*-BuLi (Scheme 72). Using chiral lithium amide **20** (20 mol%) and bulk base **21** or **22** (200 mol%) in the deprotonation of cyclohexene oxide **1** gave (*S*)-**2** with the same enantiomeric excess (93%) as under stoichiometric conditions (Scheme 15). Apparently, any background reactions of the bulk bases are insignificant. Interestingly, no addition of DBU was needed to obtain the high enantioselectivities under these catalytic conditions.

Ahlberg and coworkers noted that in some cases the enantioselectivity was increased when running the deprotonations with equimolar amounts of the novel bulk bases and the chiral lithium amide[113]. This finding initiated a detailed mechanistic investigation using isotopically labeled compounds and multinuclear NMR spectroscopy and kinetics, to elucidate the nature of the reagents and transition states in the deprotonations. They discovered that mixed dimers **23** and **24** are formed in solution from monomers of chiral lithium amide **20** and bulk base **21** and **22**, respectively (Scheme 73).

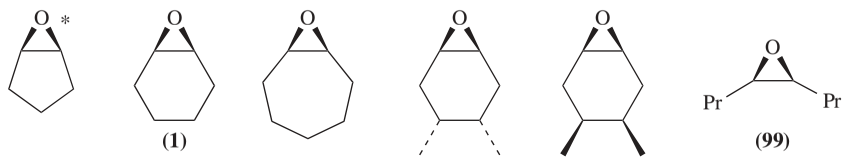




(18)



(19)

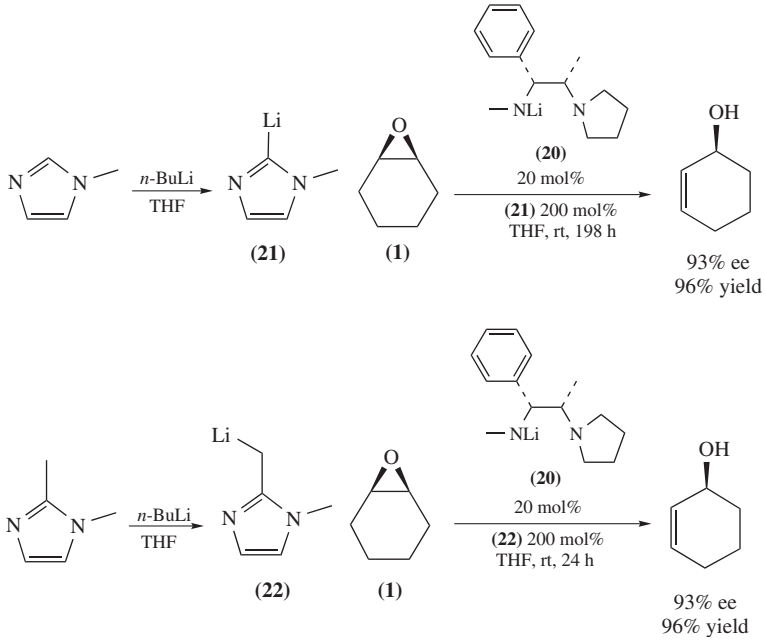


(1) **(99)**

49% ee 67% yield	96% ee 91% yield	96% ee 89% yield	94% ee 95% yield	97% ee 95% yield	66% ee 82% yield
96% ee 81% yield	99% ee 95% yield	>99% ee 93% yield	98% ee 94% yield	99% ee 85% yield	91% ee 80% yield

* 15 mol% catalyst run at rt

SCHEME 71



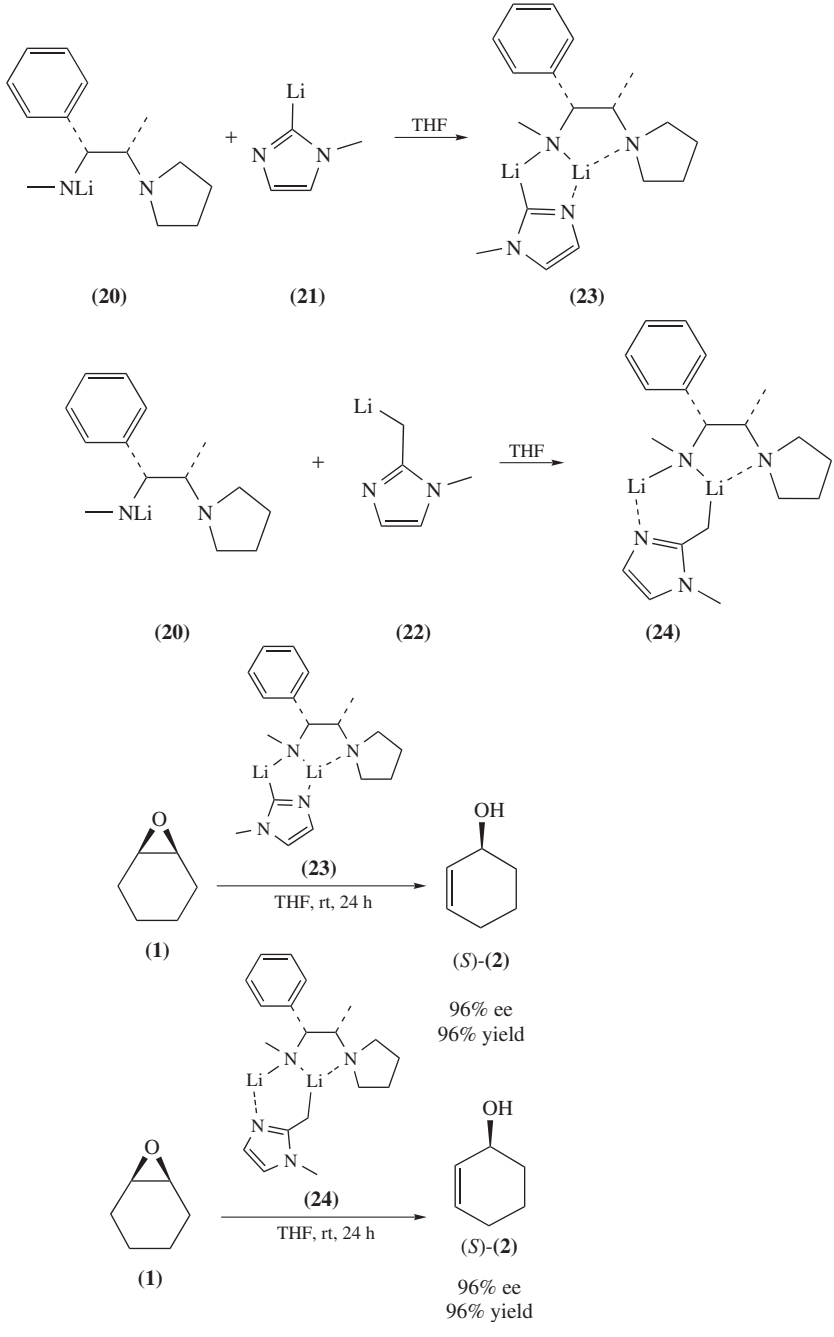
SCHEME 72

This finding together with kinetic results showed that the activated complexes were built from such mixed dimers and an epoxide molecule[37]. The catalytic cycle proposed is shown in Figure 9.

3. The role of DBU in the deprotonations

In several reports it has been shown that the use of DBU alters the reactivity and enantioselectivity in both catalytic and stoichiometric deprotonations[25, 110]. The commonly used bulk bases LDA and $LiNEt_2$ almost exclusively require high concentrations of DBU to yield high enantioselectivities under catalytic conditions. This intriguing DBU effect has been puzzling and has been suggested to be due to deaggregation of the chiral lithium amide by DBU. Ahlberg and coworkers envisioned, in light of their findings concerning mixed dimers[45, 46] involving lithium amide **20** and **21** and **22**, that DBU under the conditions used may be lithiated by LDA. Yoneda and coworkers had previously reported lithiation of DBU by *n*-BuLi[114, 115]. Indeed, they showed by NMR spectroscopy that DBU is lithiated by LDA to give **102** (Scheme 74)[112]. But LDA appears not to be strong enough for complete deprotonation. The equilibrium set-up is shown in Scheme 74. Similar to **21** and **22**, lithiated DBU (**102**) was found to act as a bulk base which was much less reactive toward the epoxide substrate than the chiral lithium amide.

Thus LDA is not needed for efficient recycling, which was demonstrated by deprotonation of cyclohexene oxide using **4** in catalytic amounts together with **102** as bulk base generated from DBU and *n*-BuLi, (*S*)-**2** is formed in 79% ee (Scheme 74) (80% ee under stoichiometric conditions, Scheme 2). In contrast, when **4** was used in catalytic amounts


NLi
N
Li
N
N
THF
Li
N
N
Li
Li
N
N
(20)
(21)
(23)
NLi
N
Li
N
N
THF
Li
Li
N
N
N
(20)
(22)
(24)
O
(1)
(23)
THF, rt, 24 h
OH
(S)-(2)
96% ee
96% yield
O
(1)
(24)
THF, rt, 24 h
OH
(S)-(2)
96% ee
96% yield

SCHEME 73

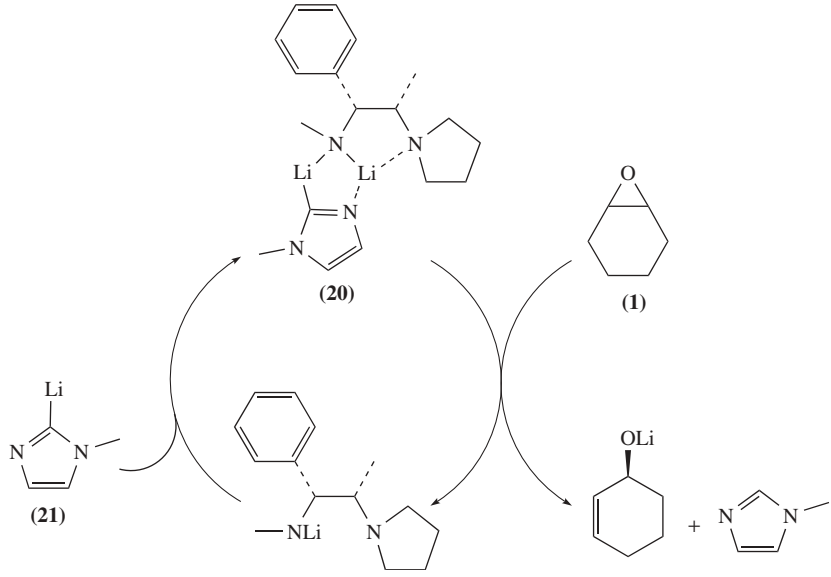
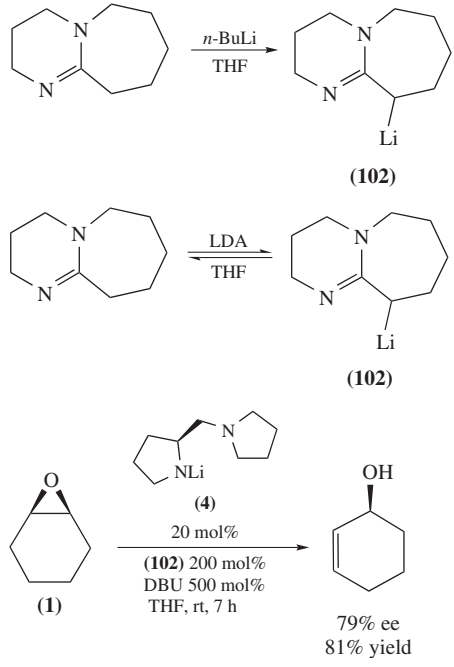


FIGURE 9



SCHEME 74

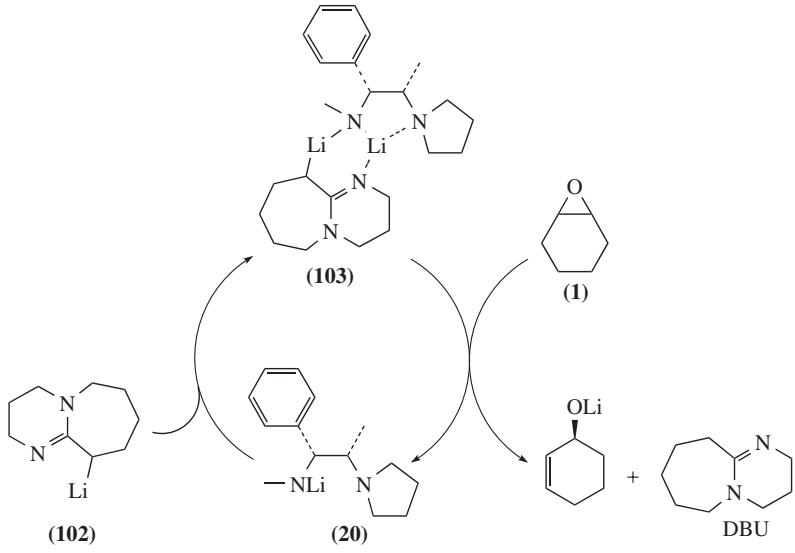


FIGURE 10

in the presence of excess LDA and DBU, the ee decreased to 74% ee. Several authors have shown that much higher concentrations of DBU than the bulk base concentration are needed for optimal enantioselectivity[24, 110]. This indicates an even more complex role of DBU than just acting as a bulk base precursor.

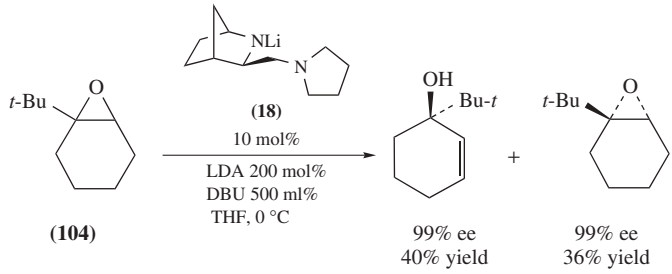
In an investigation by Ahlberg and coworkers using multinuclear NMR, they have shown that the deprotonating reagent in the solution is a mixed dimer **103** which is composed of one monomer of the lithium amide and one monomer of lithiated DBU[112]. Apparently, lithiated DBU (**102**) behaves like **21** and **22** and therefore the catalytic cycle shown in Figure 10 was proposed.

In the light of these results it is interesting to analyze some previously reported findings. For instance, Bertilsson and Andersson have also used other simple alkyl lithium amides than LDA or *n*-BuLi as bulk bases[116]. In the absence of DBU the ee values varied in the range of 7–56%. In contrast, the ee values obtained were all in the range of 93–96% when DBU was present, despite reactivity differences of the achiral bases toward cyclohexene oxide. Presumably, the addition of DBU changed the bulk base to lithiated DBU and possibly **102** is forming a mixed dimer with the chiral lithium amide[112].

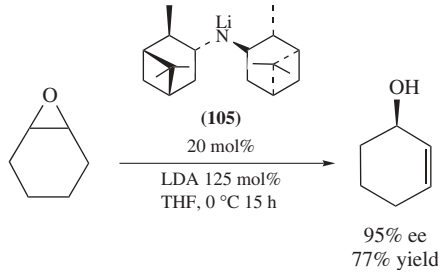
The chiral lithium amide **18** has also been used for catalytic kinetic resolution of epoxides[117]. Epoxide **104** was subjected for kinetic resolutions under the conditions shown in Scheme 75, which resulted in roughly enantiopure epoxide and allylic alcohol.

Malhotra introduced monodentate amines derived from α-pinene as chiral lithium amide precursors[118]. Using 20 mol% of the base **105** with excess LDA resulted in 95% ee of the corresponding (*R*)-allylic alcohol (Scheme 76).

Since Asami[7] presented his seminal ligand (**4**) in 1984 based on a diamine, most of the ligands developed and used as chiral lithium amides have been based on bidentate ligands. Malhotra's results clearly show that monodentate bases can also be used for highly selective deprotonations.

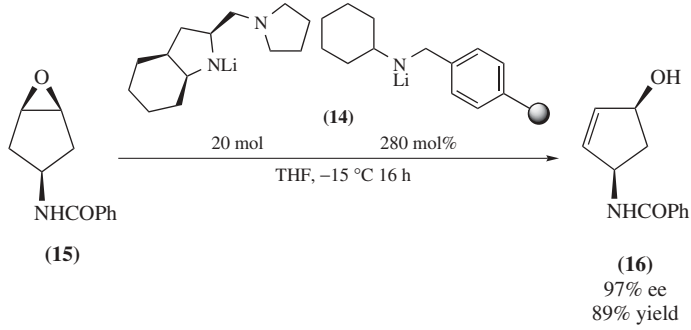


SCHEME 75



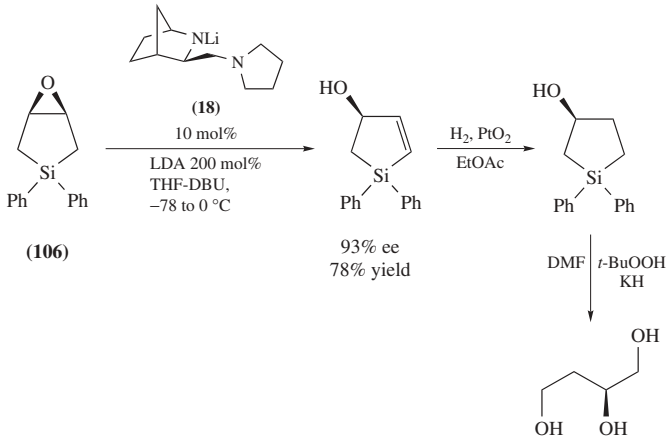
SCHEME 76

Asymmetric catalytic deprotonation using solid phase has been performed using bulk base attached to solid phase. Seki and Asami reasoned that using polymer-bound bulk base would diminish the non-enantioselective background reaction since cross-linked polymer-bound reagents may be less reactive than the corresponding monomeric reagents[119]. For example, the epoxide **15** was deprotonated by **14** yielding the allylic alcohol **16** with high ee and yield using bulk base on solid support (Scheme 77).



SCHEME 77

Liu and Kozmin used the asymmetric deprotonation of hetero-epoxides such as **106** as key step in the synthesis of chiral polyols[120]. The deprotonation was carried out using the chiral lithium amide pool published in the literature and both stoichiometric and catalytic deprotonations gave satisfactory results (Scheme 78).

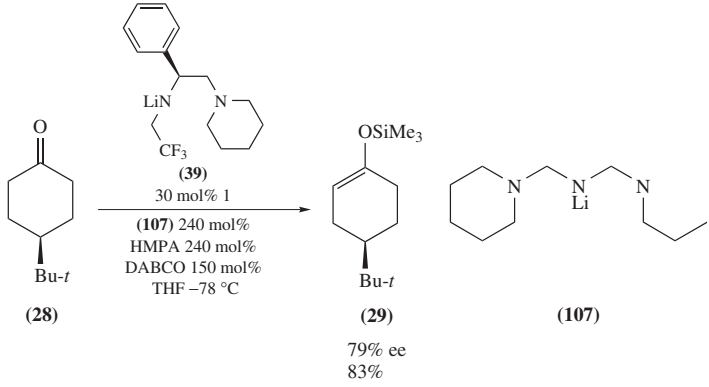


SCHEME 78

4. Catalyzed ketone rearrangement

Catalytic enantioselective deprotonation of ketones has been much less explored than deprotonation of epoxides. Koga and coworkers have reported a catalytic system[121] which has a similar basis to that developed by Asami for deprotonation of epoxides. However, LDA used by Asami and coworkers as bulk base[122] cannot be used for regeneration of the chiral base since most ketones bearing hydrogen at α-position are not compatible with LDA. Koga and coworkers found that the tridentate lithium amide **107** is less reactive in ketone deprotonation. They also found that the chiral bidentate amines are exclusively deprotonated by the tridentate lithium amide, thus making a catalytic cycle possible. However, for optimal enantioselectivity, both DABCO and HMPA had to be used as additives.

Deprotonation of 4-*t*-butyl cyclohexanone **28** with chiral lithium amide **39** (30 mol%) and bulk base **107** (240 mol%) in the presence of HMPA (240 mol%) and DABCO (150 mol%), under external quench conditions, resulted in 79% ee of the silyl enol ether **29** (Scheme 79)[121]. This stereoselectivity is only slightly lower than that of the stoichiometric reaction (81% ee).



SCHEME 79

III. COMMON CHIRAL LITHIUM AMIDES AND SUBSTRATES

A. Chiral Lithium Amides Employed in Epoxide Rearrangement

In this section, structures of the chiral lithium amides employed in enantioselective deprotonation of epoxides are shown. These compounds have emerged mainly from the trial and error approach. Interestingly, they are all derivatives of compounds from the chiral pool or prepared by using chiral auxiliaries also available from the chiral pool. Four main groups of compounds have been used to obtain chiral lithium amides: (i) α-methylbenzyl amine (Figures 11, 18, 21, 23), (ii) amino acids, mainly proline and phenyl glycine (Figures 12, 13, 15, 17, 19, 20), (iii) ephedrines (Figures 14, 19), (iv) α-pinene (Figure 22). Figures 11, 14, 17 and 19 contain, besides the compounds of the main groups, respectively, also a few non-related chiral lithium amides described in the cited publications. Moreover, most chiral lithium amides are derivatives of ethylenediamines and often a cyclic amine is used as coordinating group (pyrrolidine, piperidine, morpholine). In Figure 16 compounds based on *trans*-1,2-cyclohexanediamine are shown. An efficient monodentate amide has also been reported (Figure 22). Examples of C_2 symmetric chiral lithium amides are few. Below, different types of chiral lithium amide bases are displayed chronologically. The references given are to the publications in which the bases have been used for the first time for deprotonation of epoxides.

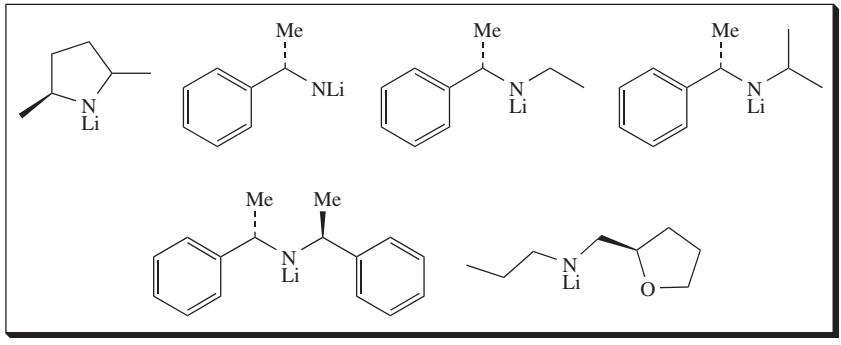


FIGURE 11[6, 123]

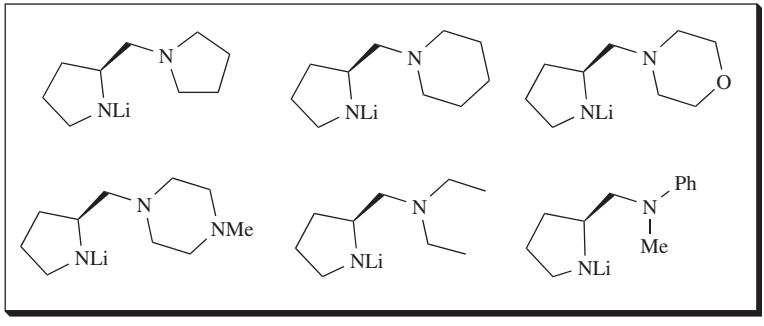


FIGURE 12[7]

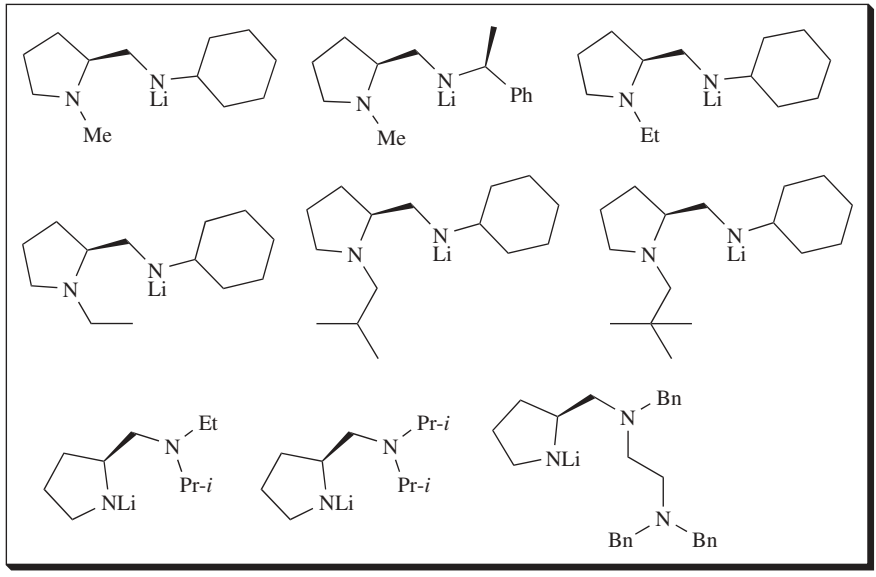


FIGURE 13[124]

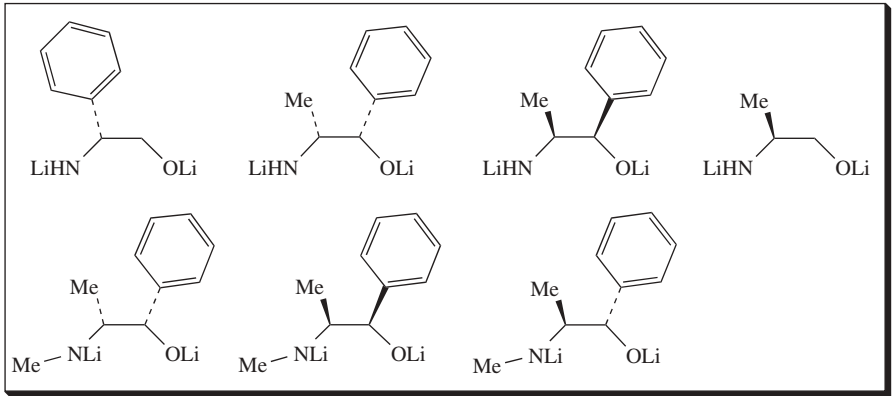


FIGURE 14[10, 125]

B. Epoxides Deprotonated Stereoselectively

Below, the different types of epoxides that have so far been substrates for asymmetric deprotonation are displayed. References are also given.

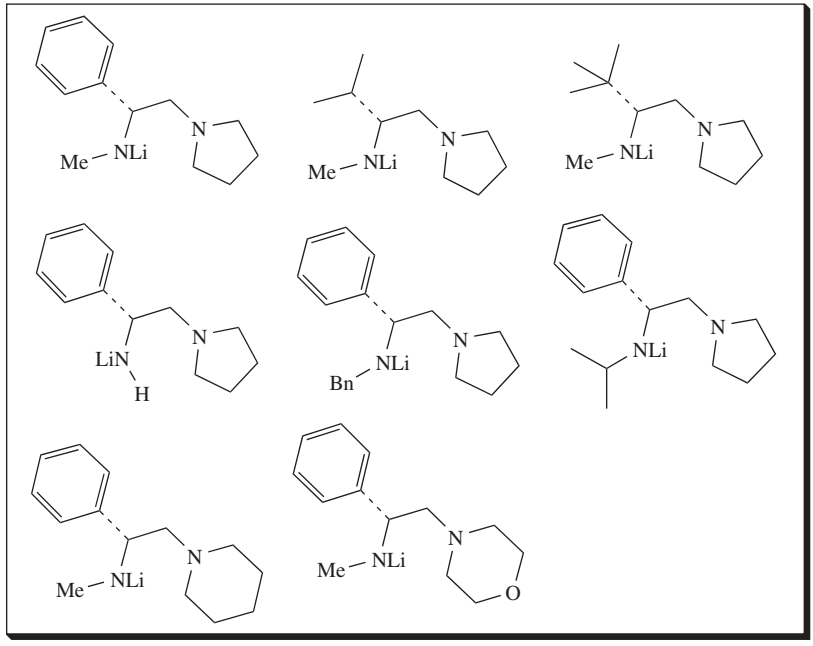


FIGURE 15[15]

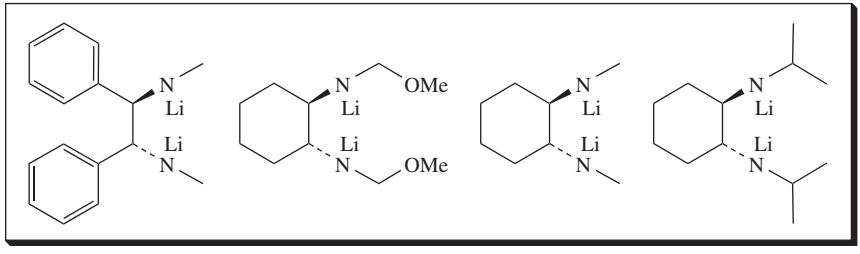


FIGURE 16[19]

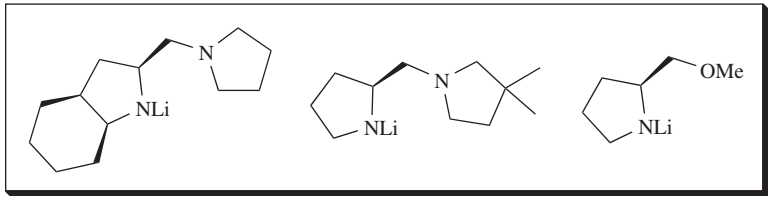


FIGURE 17[20, 21, 120]

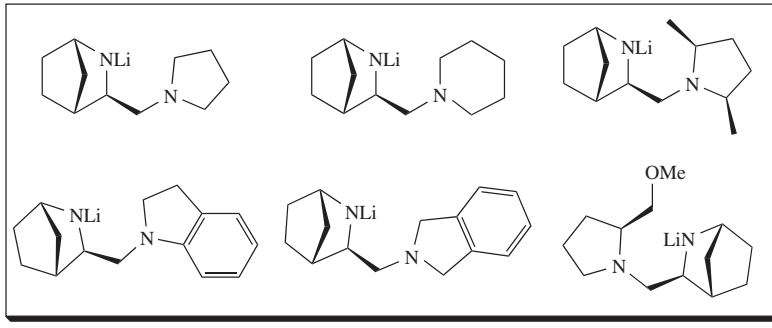


FIGURE 18[24, 25]

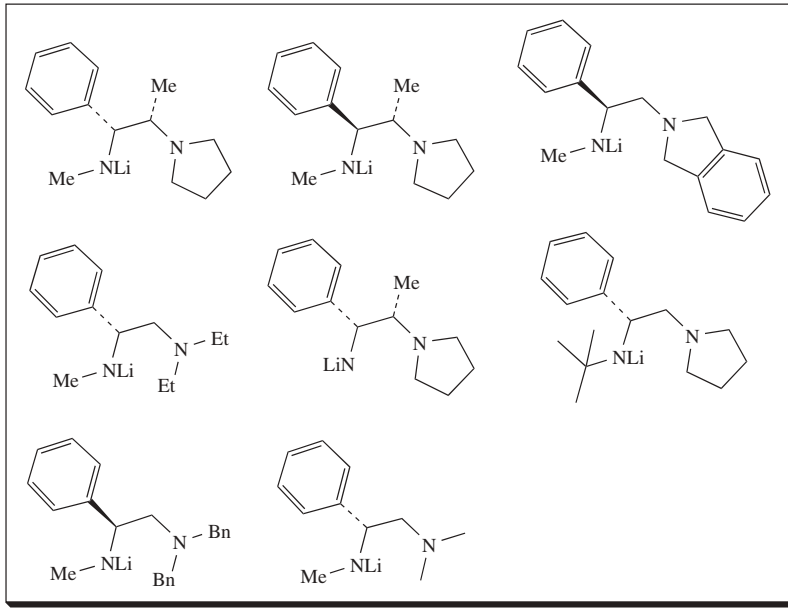


FIGURE 19[28, 29]

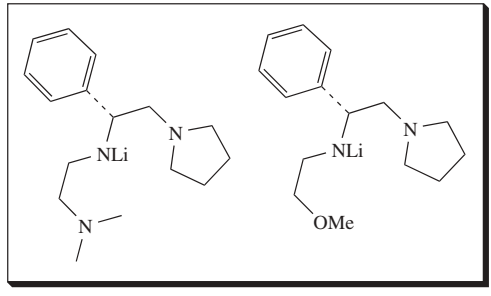
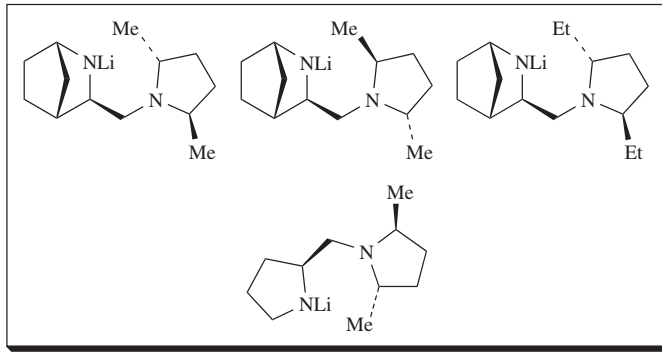


FIGURE 20[126]



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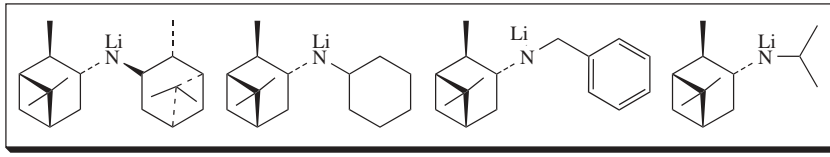


FIGURE 22[118]

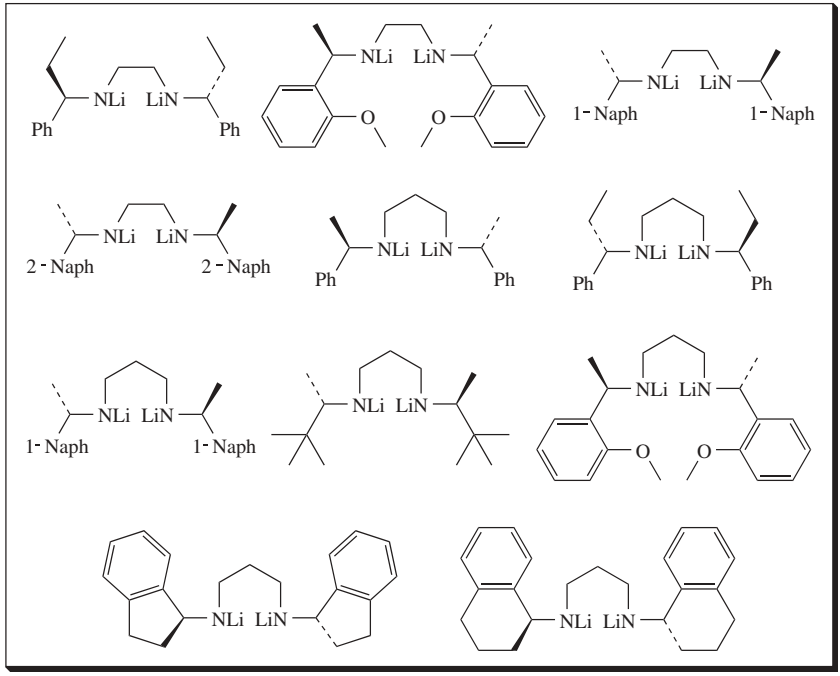
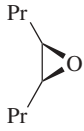
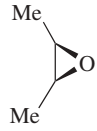


FIGURE 23[111]



20, 24, 26, 110, 127



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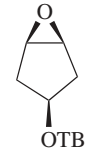
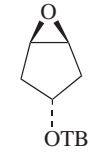
24–26, 127



15, 17, 24, 25, 125, 128, 129



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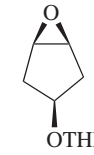

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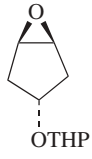

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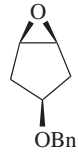

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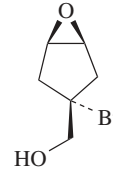

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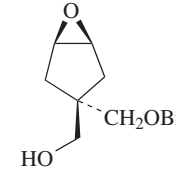

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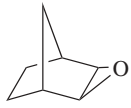

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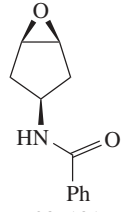

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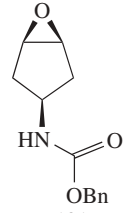

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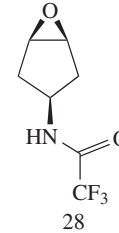

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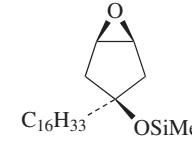
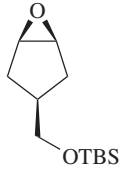


131, 132



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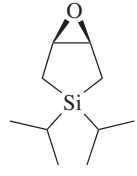

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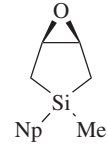

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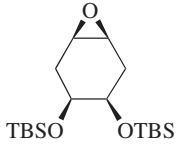
6, 7, 15, 19, 20, 110, 111, 124, 21, 24–26, 29, 37, 45, 46, 112, 113, 118, 126



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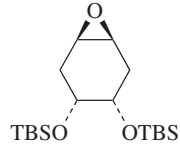
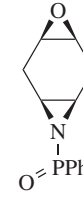
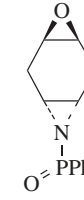


18, 24, 28

133



134, 135



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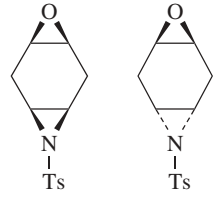

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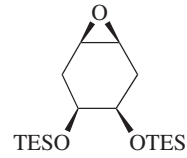

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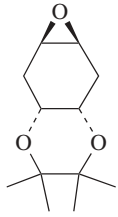
24, 26, 136

24, 26



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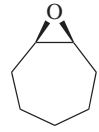

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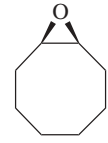
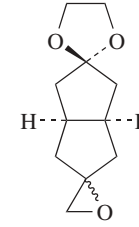


19, 24, 26, 110, 127



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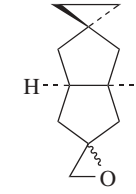

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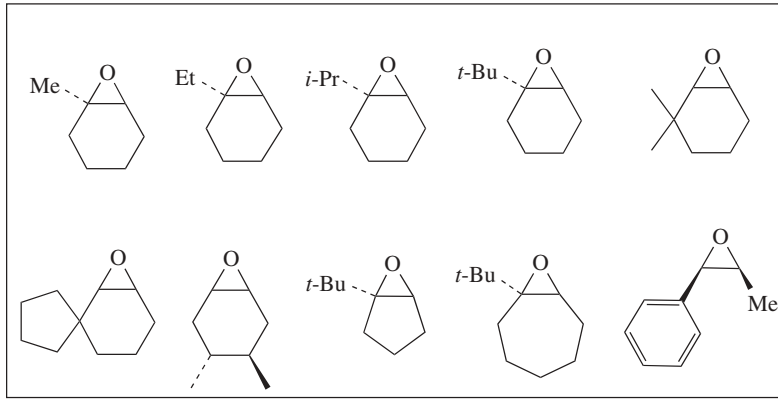
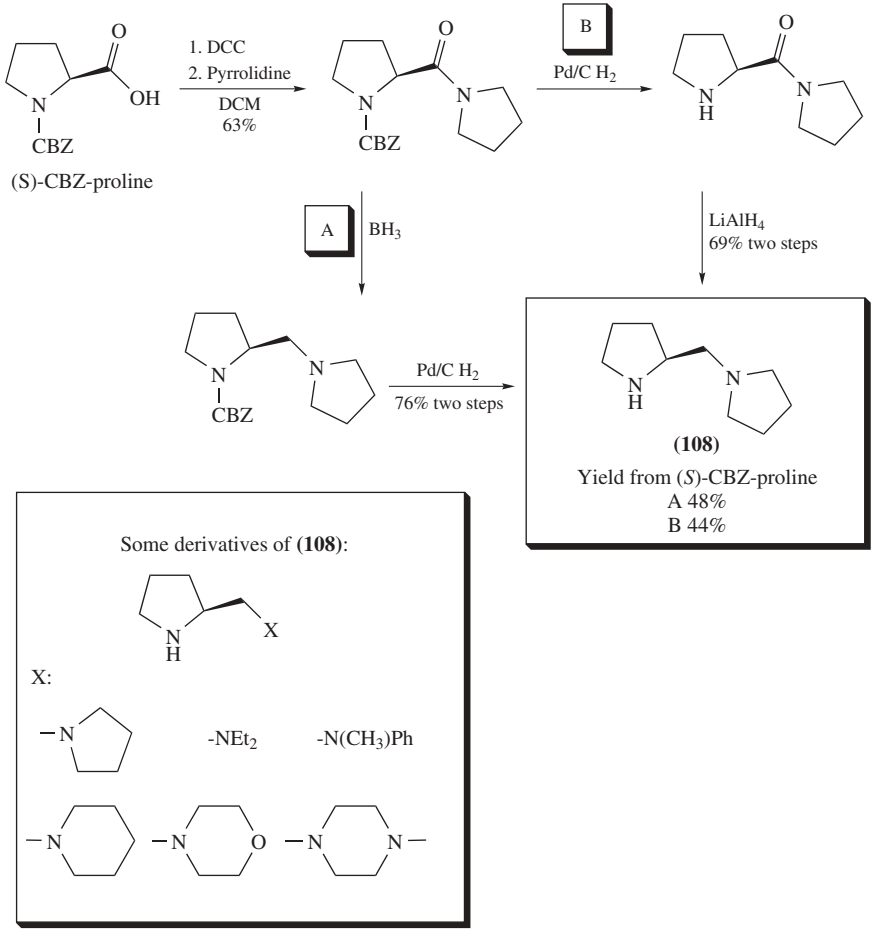


117

C. Synthesis of Chiral Lithium Amide Precursors

Although the number of chiral lithium amides used for asymmetric deprotonations are numerous, as indicated above, there is only a small number of ligands that have found frequent use. In this section, syntheses of some amine precursors of these chiral lithium amides are summarized.

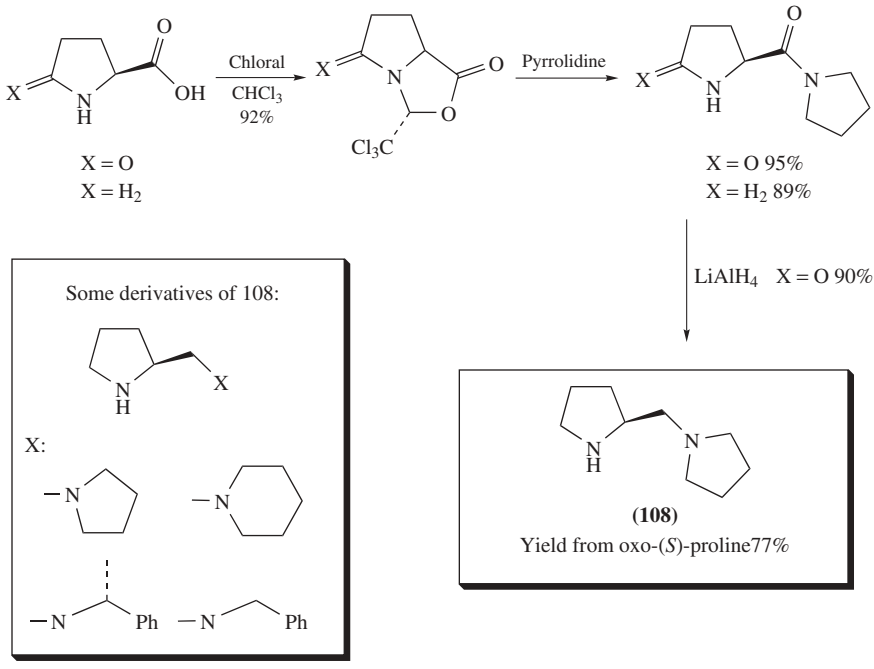
The diamine precursor **108** to the chiral lithium amide **4** introduced by Asami is accessible by different routes starting from (*S*)-proline. In Asami's own synthesis, (*S*)-CBZ-proline was activated by DCC and then coupled by an amine such as pyrrolidine (Scheme 80). The reduction of the formed amide could then be carried out with $LiAlH_4$ or BH_3, with the latter giving a cleaner reaction. After deprotection, the diamine was obtained by distillation in 44–48% yield from (*S*)-CBZ-proline.



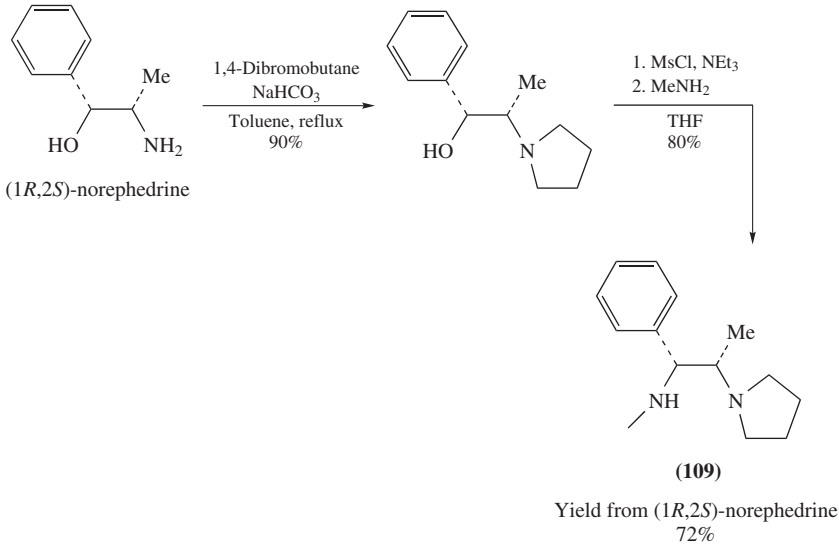
SCHEME 80[127]

More recently, Amedjkouh and Ahlberg[138] have described another route to **108** and derivatives (Scheme 81). Condensation of proline or pyroglutamic acid with chloral rendered crystalline bicyclic oxazolidinones as a single enantiomer. Reaction with pyrrolidine followed by reduction of the amide gave diamine **108** in 77% yield. Both enantiomers of pyroglutamic acid are commercially available at moderate cost. Thus this route represents a practical protocol for both enantiomers of **4**.

Ahlberg and coworkers developed computationally the norephedrine-derived chiral lithium amide **20** for stereoselective deprotonation[29]. O'Brien and coworkers[28] and Ahlberg and coworkers[29] have independently developed the synthesis of the precursor **109** (Scheme 82). Enantiopure norephedrine, commercially available in both enantiomeric forms, was reacted with 1,4-dibromobutane to introduce a pyrrolidine moiety. Mesylation led to the formation of an aziridinium ion by an intramolecular nucleophilic substitution. Ring opening of the aziridinium ring with methyl amine occurred at the benzylic position, yielding the product diamine **109** in a total yield of 72%.



SCHEME 81[138]



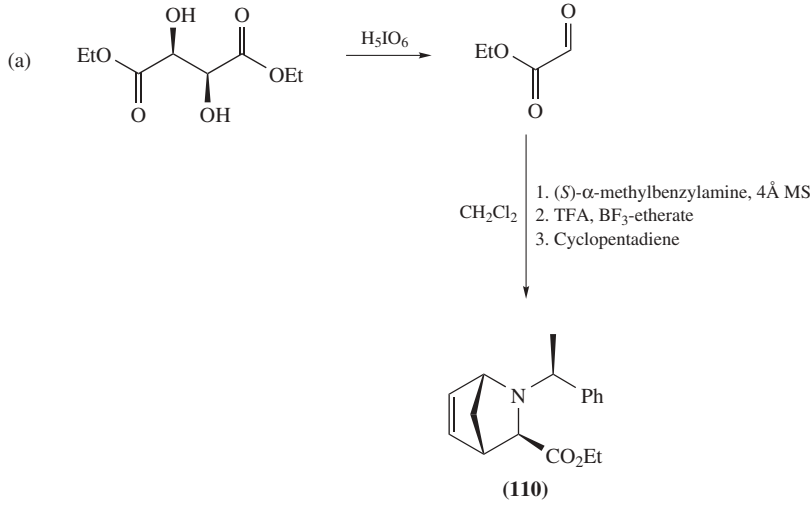
SCHEME 82[29]

Stella and coworkers[22] and Waldmann and Braun[23] have developed synthetic routes to substituted aza-norbornanes from glyoxals[139] by an aza-Diels–Alder route as shown in Scheme 83a. Andersson used this methodology to synthesize the chiral diamine **111**[25] (Scheme 83b). By a one-pot synthesis the aza-norbornane **110** could be obtained from the diethyl tartrate. Removal of the chiral auxiliary and hydrolysis of the ester was followed by EDC coupling and reduction to give the chiral diamine **111** in a reported 77% yield from **110**. Andersson also used the route in Scheme 83c to obtain diamine **111**, thus using the tartaric amide in the aza-Diels–Alder reaction to give the substituted aza-norbornane **112**. Hydrogenolysis of the auxiliary, hydrogenation of the double bond and reduction of the amide furnished the desired diamine **111** in 40% yield from the tartaric amide.

Monoamine **113**, the precursor of chiral lithium amide **3** which is frequently used, was first synthesized by Overberger and coworkers[140] and was later applied by, e.g., Marshall and Lebreton[96] and Simpkins[49] (Scheme 84). In Overberger's two-step synthesis, (*R*)-α-methylbenzylamine is condensed with acetophenone to lead to the benzylidine derivative, which could be hydrogenated in the presence of Pd/C. Interestingly, the chiral center present in the imine directed the hydrogenation to yield a 85:15 mixture of diastereomers. Distillation and fractional crystallization of the HCl salt gave the C_2-symmetric amine **113** in over 95% ee.

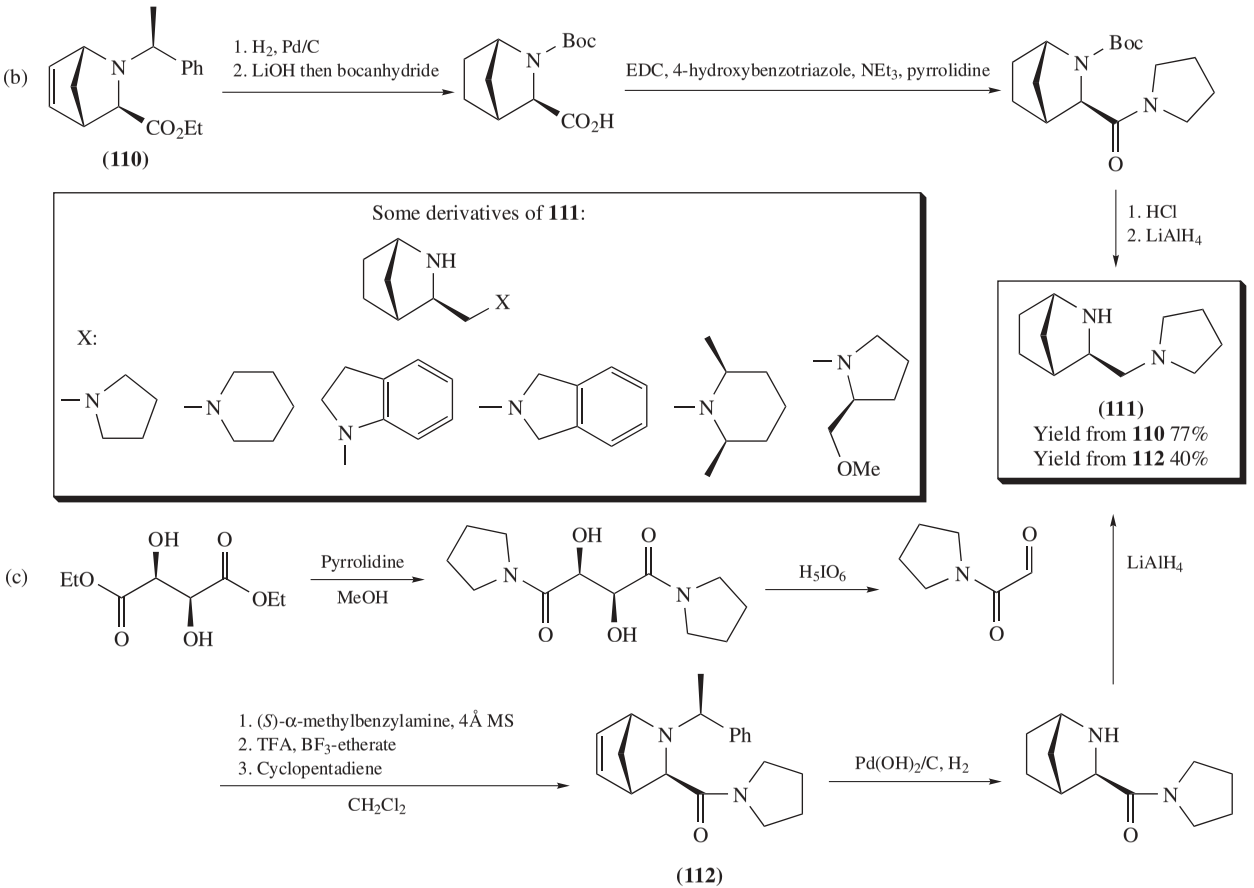
Simpkins has developed the diamine **114** obtained by alkylation via the chiral bisimine derived from glyoxal and (*R*)-α-methylbenzylamine (Scheme 85) by the method reported by Neumann and coworkers[141].

Several of Koga's chiral lithium amides precursors, such as **115**, were prepared from commercially available CBZ-(*R*)-phenylglycine, which was converted to the corresponding amides with coupling of piperidine using diethylphosphorocyanidate (DEPC) as coupling agent (Scheme 86). After removal of the protecting group and lithium aluminum hydride reduction, the diamine product was acylated using trifluoroacetic anhydride. After borane reduction, the desired diamine **115** was obtained in a total of 43% yield from CBZ-(*R*)-phenylglycine.

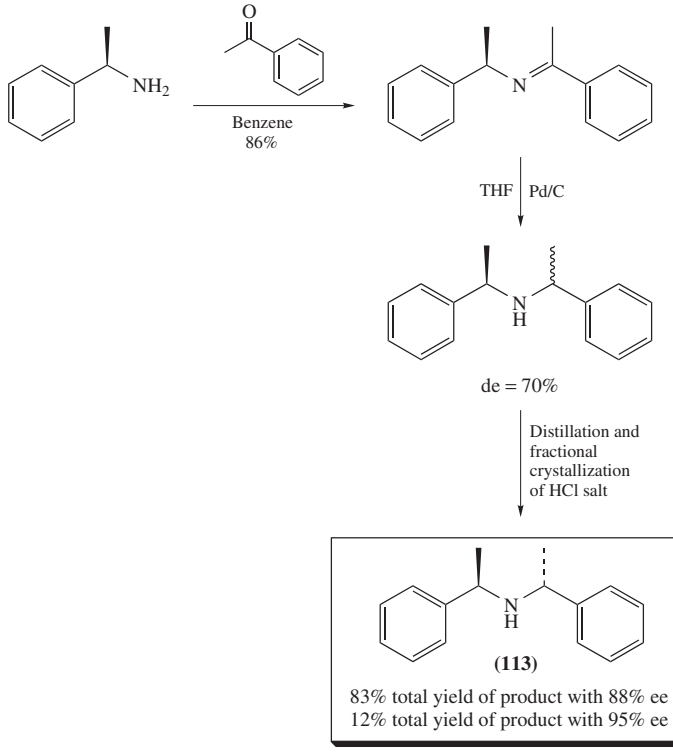


(110)

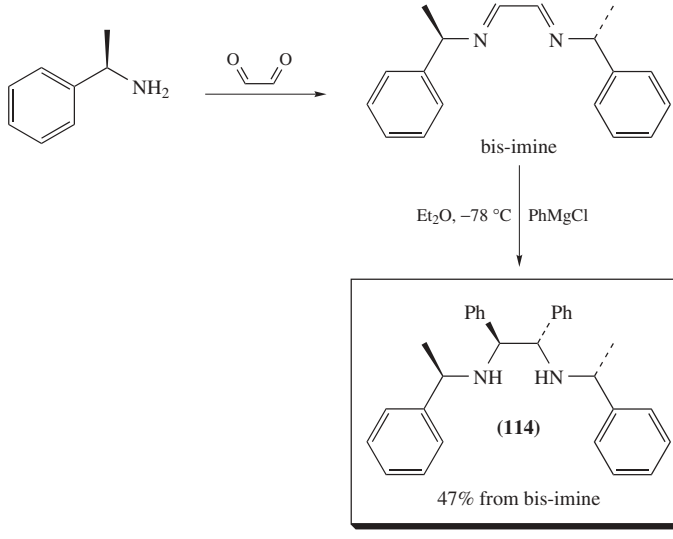
SCHEME 83[25]



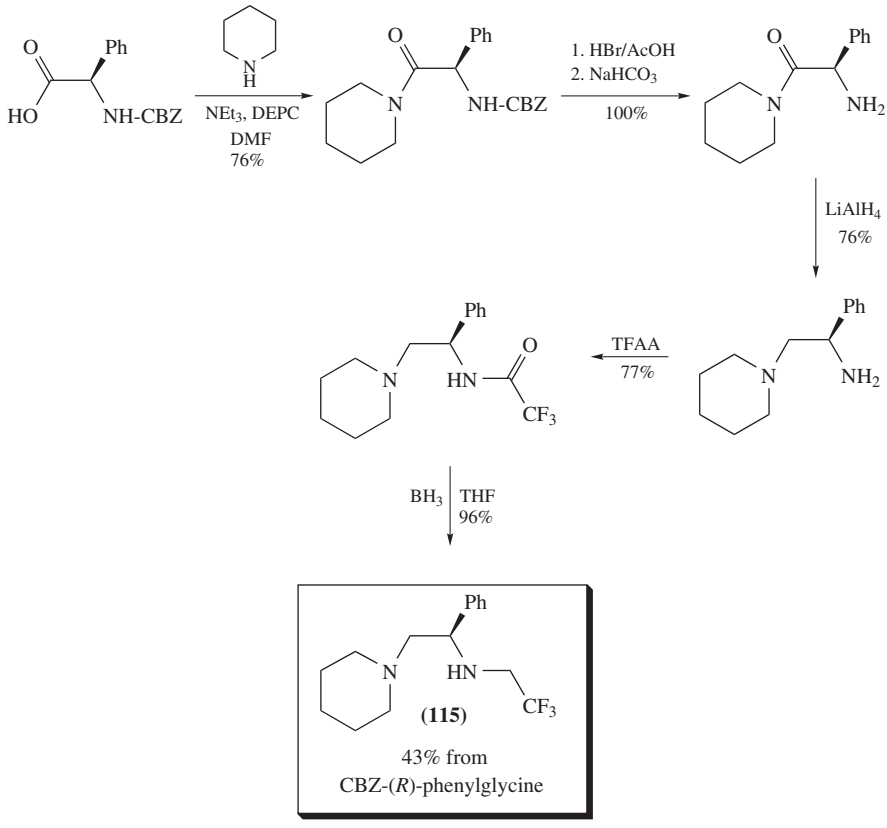
SCHEME 83. (*continued*)



SCHEME 84[140]



SCHEME 85[142]



SCHEME 86[143]

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CHAPTER 7

The lithium metal reduction of π-conjugated hydrocarbons and fullerenes

IVAN APRAHAMIAN and MORDECAI RABINOVITZ

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem, 91904, Israel
Fax: +972 2652 7547; e-mail: mordecai@vms.huji.ac.il

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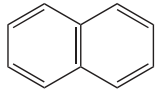
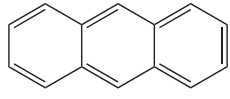
I. INTRODUCTION

Studies on metal reduction of polycyclic hydrocarbons[1] were reported as early as 1867 by Berthelot[2], where he described the fusion of metallic potassium with naphthalene (**1**). Studies in solution of electron transfer from sodium and potassium to polycyclic hydrocarbons started as early as 1913 by Schlenk and coworkers[3], who reported that when anthracene (**2**) reacted with the alkali metal in ether, 1:1 and 2:1 metal:anthracene adducts were obtained. Not understanding what the 1:1 adduct really was, it was termed 'radical' and later on it was suggested by Hückel and Bretschneider that the 'radical' is a singly charged species[4]. For many years the reduction of polycycles with lithium was neglected, but with time it became the metal of choice for such reductions[1,5].



(1)

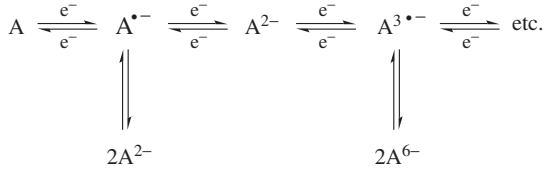


(2)

This chapter will deal only with even-number electron transfers to polycycles. Proton, carbon and lithium NMR spectroscopies are the main methods used for gaining a better understanding of the polycycle–lithium complex in solution. Special attention will be given to modes of electron delocalization, aromaticity, antiaromaticity as well as aggregation, bond formation and bond cleavage processes of diamagnetic electron transfer products. Disproportionation of radical-anions to dianions and their photophysical[6] properties are thoroughly discussed in the monograph of Szwarc[1a]. Electrochemical reductions will not be discussed, as they are reported in the literature[7]. The NMR studies are carried

out in ethereal solvents, mainly deuteriated tetrahydrofuran (THF-d_8). Upon reaction with the metal, the spectrum of the neutral hydrocarbon first disappears, due to one-electron transfer from the metal. This step can be studied by ESR spectroscopy[1a, 6]. Later on the diamagnetic spectrum is observed as the electron transfer process continues on.

Electron transfer processes of conjugated polycyclic hydrocarbons can be achieved by the following sequence:



The charged system can be quenched by electrophiles. This will not be discussed here unless quenching aids the study of the diamagnetic reduction product.

A. Ion Solvation Equilibria of Lithium Cations

The reduction process of polycycles by lithium metal converts the neutral atoms to anions. The electron transfer is best achieved in ethereal solvents. This enables the stabilization of the lithium cation by coordination to the oxygen atoms of the solvent. The hydrocarbon anion and the cation are linked together by electrostatic forces in which the solvent molecules are also involved, therefore the ion–solvation equilibrium should be considered[8]. The limiting cases in this equilibrium are free ions and contact ion-pairs (CIP), and in between there are several forms of solvent separated ion-pairs (SSIP)[9]. In reality, anionic species of aromatic hydrocarbons in ethereal solvents exist between CIP and SSIP. Four major factors influence the ion–solvation equilibrium of lithium-reduced π-conjugated hydrocarbons, as observed by ^{1}H and ^{7}Li NMR spectroscopies[8, 10].

(a) *Charge delocalization of the anion*. Local charge density may form contact ion-pairs. In the case of polycyclic systems solvent separated ion-pairs are preferred.

(b) *Size of the cation*. Hard lithium cations prefer to form SSIP unless the lithium cation resides inside a molecular cage or in between layers of anions.

(c) *Ethereal solvents* having a high dielectric constant prefer the formation of SSIP.

(d) *Temperature*. Generally speaking, CIP are preferred from entropy arguments (less ordered than SSIP). Higher temperatures will encourage the formation of CIP.

The following observation emphasizes the influence of the temperature on ion–solvation equilibrium. The reduction product of **1** with lithium metal in methyltetrahydrofuran is temperature-dependent[11]. At −120 °C only the radical anion (**1**$^{\bullet-}$) could be observed by ESR, while at higher temperatures the paramagnetism disappears and the dianion (**1**$^{2-}$) is detected. This reaction must be endothermic; it therefore seems that disproportionation is driven by entropy and not by energy, due to ion-pair–solvation equilibrium. It is noteworthy that **1**$^{2-}$ cannot be observed by NMR spectroscopy due to its special electronic structure[12].

^{7}Li NMR spectra show several peaks as a result of several different CIP modes arising from coordination to different sites of the anion, and (temperature-dependent) exchange between CIP and SSIP. Solvent separated lithium cation ion-pairs appear at *ca* +2 ppm relative to the NMR standard (LiBr in THF, 0.0 ppm)[13]. In the CIP solvation state the line shows a sharp deviation from the standard. Proximity to the anion shows lines at *ca*

−2.0 ppm[14]. The high-field shift due to a high concentration of charge shows bands at *ca* −8.0 ppm and in some aggregates the ^{7}Li lines appear even at higher field (*vide infra*).

The effect of the magnetic anisotropy of the anion on the cation becomes important when the cation is located above the center of the anionic skeleton[15]. In such cases high-field shift of the lithium cation is expected[16]. Antiaromaticity shows the opposite effect[12]. Reactions with complexing agents like TMEDA enabled crystallization of the lithium-reduced dianion salts. The anions of **1** and **2**, as well as other polycycles, were studied by X-ray crystallography, which gave additional information about ion-pairing. However, these studies cannot always be directly related to studies in solution[17].

B. NMR Spectroscopy — The Tool of Choice for the Study of Polycyclic Anions

The stability of anionic systems is governed by several factors: (a) carbon hybridization; (b) effective overall π-conjugation; (c) inductive effects; (d) aromatic stabilization and (e) environmental factors, e.g., ion–solvation equilibrium.

The ^{1}H, ^{13}C and ^{7}Li study of polycyclic anions includes 1D and 2D methods that enable an unequivocal structure elucidation of the molecules. Through-bond and through-space interactions as well as correlation spectroscopy allow the study of various aspects of lithium-reduced polycyclic hydrocarbons described in the following sections.

The carbon and proton chemical shifts tell us about the charge delocalization[8,18], conformation of the system under study, the mode of conjugation[19] and the magnetic anisotropy of the system.

It is possible to use the carbon chemical shifts to get information about the charge density at each carbon atom. The linkage between chemical shift and charge density was studied both experimentally and theoretically[8,20,21]. A linear dependency between charge density and NMR chemical shifts was suggested by Fraenkel and coworkers[21]. An empirical relationship (equation 1) has been formulated,

$$\Delta\delta = K\,\Delta q_{\pi} \tag{1}$$

where $\Delta\delta$ is the chemical shift difference relative to the neutral polycycle, Δq_{π} is the charge density difference, K is a constant ($K_{\mathrm{H}} = 10.7$ ppm e^{-1}; $K_{\mathrm{C}} = 160$ ppm e^{-1})[22]. In reality K depends on the class of the systems under study, being $70 < K < 200$[23]. A generalized equation was suggested by Karplus and others[24] that takes into account the paramagnetic term (σ_{para}) of the basic Ramsey equation[25] that links the three components of the shielding of a nucleus (equation 2).

$$\sigma_{\mathrm{total}} = \sigma_{\mathrm{dia}} + \sigma_{\mathrm{para}} + \sigma' \tag{2}$$

The effect of environmental factors is included in σ', and σ_{dia} represents the diamagnetic effects. The Karplus equation relates the paramagnetic term to the carbon type, polarity of bonds and average excitation energy (ΔE) of the anion. When ΔE is small, the paramagnetic term becomes significant[26]. An improved relationship between the total carbon shift difference and the number of negative charges on the anion was reported by Eliasson, Edlund and Müllen giving greater weight to anion anisotropy[23]. This equation better evaluates the degree of charging and the mode of charge delocalization.

II. DIFFERENT MEANS FOR GAINING STABILITY

A. Charge Segregation

Magnetic properties of polycyclic anions serve as a probe for the mode of delocalization of the added electrons. These anions gain stability either by minimizing paratropicity or by

gaining diatropicity[1]. Paratropicity can be minimized by modifying the system's geometry or by partitioning the extra charge. On the other hand, diatropicity can be satisfied by the reorganization of the path taken by the π-electrons. The latter can be achieved by obeying the Randić conjugated $(4n + 2)\pi$ circuits model[27] or by delocalization of the electrons along the molecular periphery.

The reduction of dibenzo[*a*,*c*]tetracene (**3**) with lithium metal yields a radical anion ($\mathbf{3}^{\bullet-}$) followed by a dianion ($\mathbf{3}^{2-}$)[28]. NMR and ESR studies indicate that $\mathbf{3}^{\bullet-}$ and $\mathbf{3}^{2-}$ behave as if they were composed of two separate substructures, thus indicating segregation within the pertinent antibonding orbital. The ^{1}H NMR spectrum of $\mathbf{3}^{2-}$ consists of high-field signals (2.7–4.7 ppm) that belong to the linear 'anthracene' moiety and low-field signals (6.6–7.6 ppm) that belong to the angular 'phenanthrene' moiety (Figure 1). The ^{13}C NMR chemical shifts, which are very sensitive to the charge density, show that most of the charge is indeed located in the linear 'anthracene' part of the molecule, while the 'phenanthrene' is almost neutral. ESR studies on $\mathbf{3}^{\bullet-}$ also showed that the spin density mainly resides on the linear part of the molecule[28b].

The reduction of dibenzo[*b*,*g*]crysene (**4**), an isomer of **3**, with lithium metal gave similar results[29]. According to the ^{1}H and ^{13}C NMR spectra the dianion, $\mathbf{4}^{2-}$, shows the

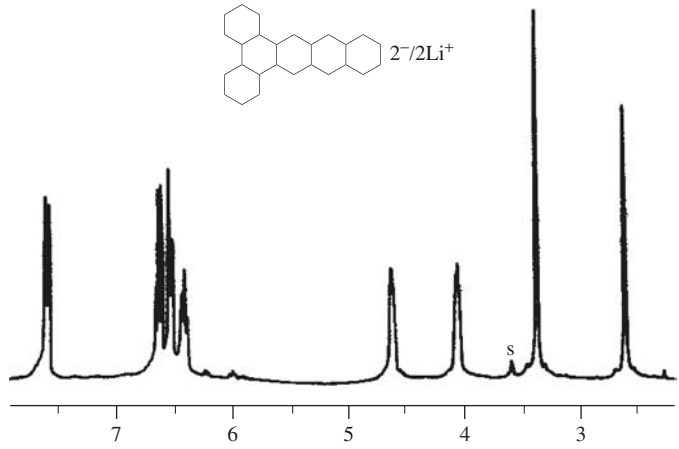
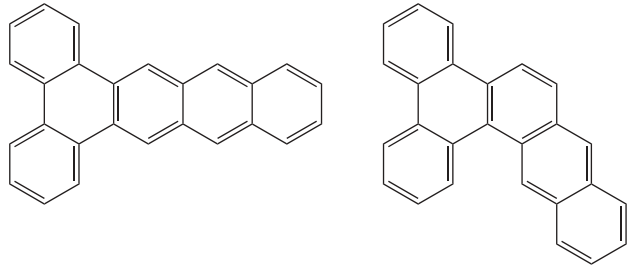


FIGURE 1. The ^{1}H NMR spectrum of $\mathbf{3}^{2-}$. Reprinted with permission of the American Chemical Society, from Reference 28a



(3) **(4)**

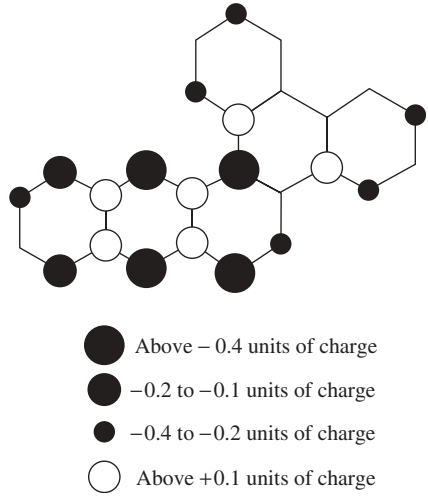


FIGURE 2. Charge distribution over the carbon skeleton of $\mathbf{4}^{2-}$. Reproduced by permission of The Royal Society of Chemistry from Ref. 29

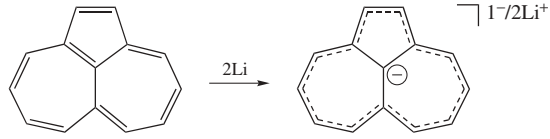
same tendency of charge segregation as in $\mathbf{3}^{2-}$. Again, it has been demonstrated that the charge distribution is not homogeneous and that most of the charge is located on the linear part of the molecule (Figure 2).

This unusual charge distribution in these $4n\pi$-conjugated dianions can be interpreted in terms of minimization of paratropicity (antiaromaticity) and seems to be a general property of such anions. By forcing the charge into the 'anthracene' moiety, the phenanthrene moiety remains almost neutral and aromatic and thus the total paratropicity is reduced and destabilization due to antiaromaticity is minimized.

B. Redistribution of Electrons

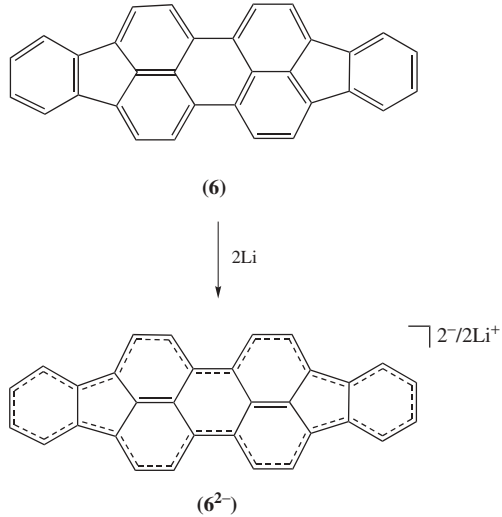
Since antiaromaticity is unfavorable, the charged system may find routes leading to greater thermodynamic stability by converting to aromatic forms. These routes can either be electronic reorganization of the system, or bond rearrangement or both. In electronic reorganization, the path of the π-conjugation is changed as a consequence of the reduction process to achieve aromaticity, and not just to minimize antiaromaticity. The aceheptylene (**5**) is a good example of this. Whereas the neutral compound hardly shows an aromatic character, the dianion ($\mathbf{5}^{2-}$), which is produced by lithium metal reduction, is an aromatic species[30]. This can be explained by the localization of one of the electrons on the central carbon and the delocalization of the other on the periphery (Figure 3). This charge distribution affords a peripheral 14π-electron system that exhibits aromatic character.

On the other hand, diindeno[*cd*:*lm*]perylene (**6**) 'uses' a different type of reconfiguration to attain aromaticity[31]. In this system, two different types of π-delocalization patterns are applied in order to account for its aromaticity. The neutral molecule appears to comply with the Randić conjugated circuits model[27], as it is a diatropic system despite having 28π-electrons in the periphery. The lithium reduction of the compound yields a two-electron reduction product ($\mathbf{6}^{2-}$), which is also diatropic (Figure 4). In this case it is assumed that a nodal plane is present through the central carbon atoms. This leaves behind a peripheral



(5) **(5^{2-})**

FIGURE 3. Reduction of **5** to $\mathbf{5}^{2-}$



(6)

(6^{2-})

FIGURE 4. Reduction of **6** to $\mathbf{6}^{2-}$

$(4n + 2)\pi$-system of 26-electrons on the perimeter that accounts for the diatropicity of the dianions.

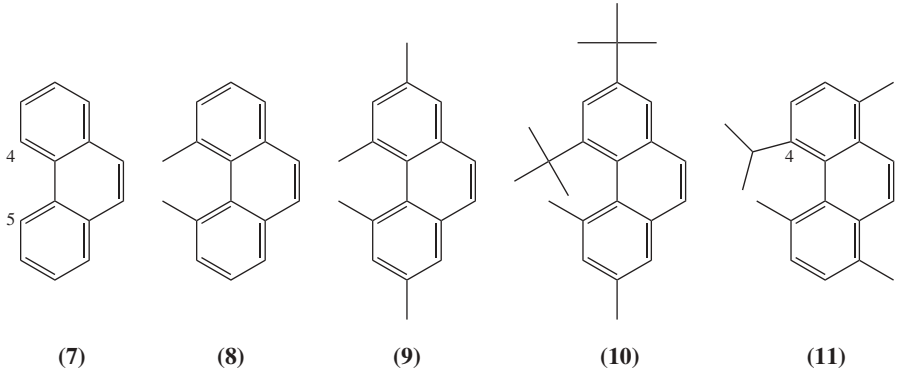
C. Structural Deformation

1. Reduction of phenanthrene and its derivatives

Paratropicity of lithiated polycycles can be minimized also by geometrical deformation within the molecular skeleton. In such cases minimizing antiaromaticity is not achieved by splitting the molecule into two fully conjugated subsystems, but rather by the out-of-plane deformations of the molecular skeleton. This minimizes the entire π-conjugation by reducing the π-orbital overlap[1]. Such a phenomenon is observed while reducing small helicenes[32]. These molecules adopt a helical configuration in the neutral state with C_2 symmetry[33] as a result of severe steric interactions between the terminal benzene rings.

Phenanthrene (**7**), the smallest member of the helicene series, is planar in its neutral state and shows aromatic character. Reducing the compound with lithium affords a highly paratropic dianion[34] ($\mathbf{7}^{2-}$) that, according to calculations, is not planar[35]. It is possible to twist the sp^2 framework of phenanthrene by its alkylation at the 4- and 5-positions[36], i.e. in 4,5-dimethylphenanthrene (**8**), 2,4,5,7-tetramethylphenanthrene (**9**) and 2,4-di-*tert*-butyl-5,7-dimethylphenanthrene (**10**). When these systems are reduced with lithium metal, three

important effects are noticed as a function of twist[35a, 37]. Firstly, the more the phenanthrene is twisted the less the spectrum is shifted to high field (Figure 5). Secondly, the bulkier the alkyl group, i.e. the greater the twist, the narrower the linewidth becomes in the ^{1}H NMR spectrum. Thirdly, the temperatures at which a resolved ^{1}H NMR spectrum can be observed get higher. These effects imply that the paratropicity of the systems is decreasing and this can be attributed to the increase in deviation from planarity that is imposed by the bulky substituents. The deviation from planarity reduces the π-orbital overlap in the $4n\pi$-systems, thus making the dianions more stable[37].



(7) **(8)** **(9)** **(10)** **(11)**

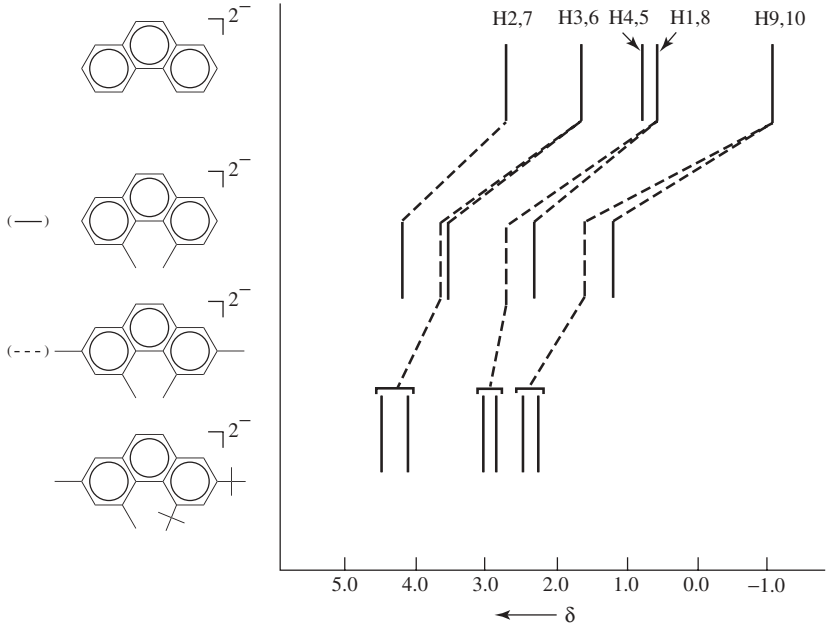
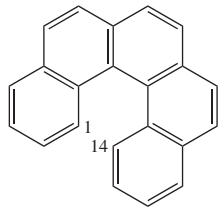


FIGURE 5. The effect of twist on the ^{1}H NMR of the dianions of phenanthrene and its twisted derivatives. Reproduced by permission of Wiley-VCH Verlag GmbH from Reference 37

In addition to probing the effect of nonplanarity on the antiaromatic character of these phenanthrene-based systems, it is also possible to analyze the effect of charge on their racemization barrier. This can be achieved by studying systems like 4-isopropyl-1,5,8-trimethylphenanthrene (**11**)[38]. The diastereotopic isopropyl marker at the bay region position **C4** yields a free-energy barrier ($\Delta G^{\ddagger}$) of 22.2 kcal mol^{-1} for the racemization process of the neutral compound and 15.4 kcal mol^{-1} for the racemization of the dianion (**11**$^{2-}$). Although the barrier of racemization decreases as a result of reduction, the system still maintains its helicity.

2. Higher homologues of phenanthrene — helicenes

Higher homologues of **7**, such as pentahelicene **12** and benzo[*a*]pentahelicene **13**, are reduced by lithium metal to stable dianions (**12**$^{2-}$, **13**$^{2-}$), which upon further electron transfer afford the cyclization products **14** and **15**, respectively (*vide infra*)[39]. Alkyl substitution at positions **C1** and **C14** of **12** or further arene annelation at the terminal positions of the pentahelicene prevent such cyclizations and allow the isolation of the reduced states. The inability of helicenes **12, 13**, 1,12-dimethylbenzo[*c*]phenanthrene (**16**), 1,3-di-*tert*-butyl-benzo[*c*]phenanthrene (**17**), 2,15-dimethylhexahelicene (**18**) and heptahelicene (**19**) to bear a large excess of charge is evident from their reduction only to dianions (**16**$^{2-}$–**19**$^{2-}$)[40]. Due to the helicity of the system and the close proximity of the terminal benzene rings, charge distribution is incapable of depositing electron density at the far ends of the molecule. As a consequence, coulombic repulsions between the charged layers result in the relocation of charge at the central rings of the helicene units that, in turn, prevent the storage of further imposed charge. This explanation is borne out by the localization patterns observed in the ^{1}H NMR spectra of **16**$^{2-}$, **18**$^{2-}$ and **19**$^{2-}$ as compared with their neutral analogues.



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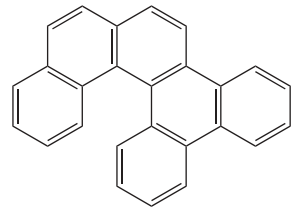

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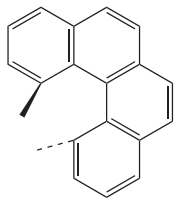

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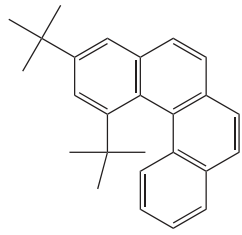

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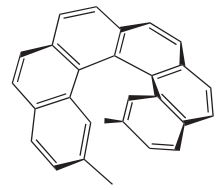

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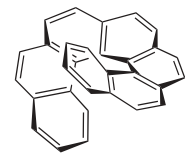


(19)

III. CHEMICAL REACTIONS OF LITHIUM SALTS

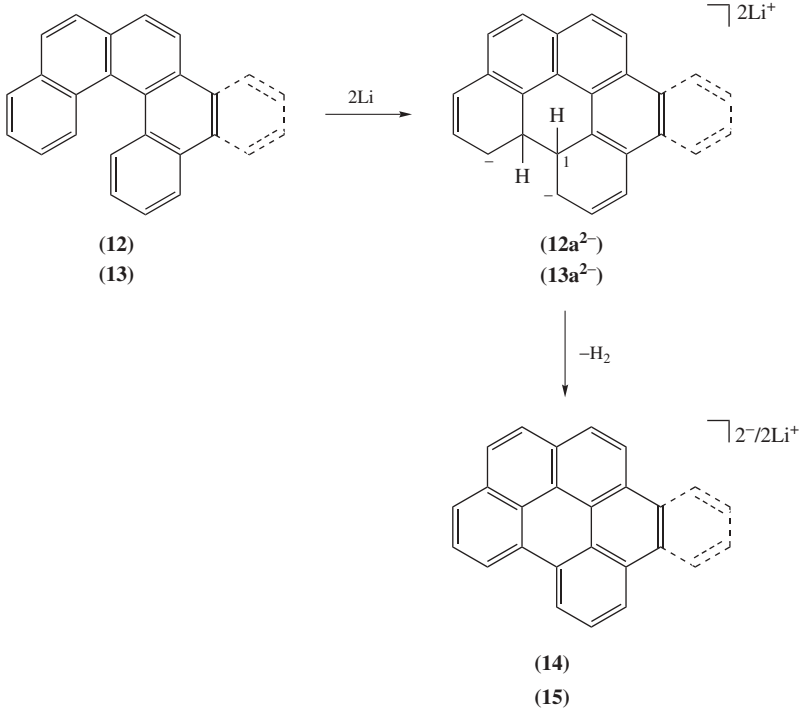
The reduction of polycycles can in some cases afford reactions that can be subsequently utilized in the preparation of other complex and novel polycyclic systems. Such reactions

were encountered in various systems, for example the unexpected processes observed in the reduction of pyrenophanes and the ring closures of pentahelicenes and cross-conjugated enediyne.

A. Ring Closure in Pentahelicene

In the first step of the ring closure, **12** and **13** yield the appropriate dianionic dihydro intermediates, namely **12a**$^{2-}$ and **13a**$^{2-}$ which, upon further reduction, undergo dehydrogenation to afford the dianions **14** and **15** (Figure 6)[39]. The dihydro compounds were identified using the ^{13}C satellites of hydrogen atom **H1** that resides on the newly formed σ-bond. For example, the signal of this hydrogen in **12a**$^{2-}$ appears as a singlet at 4.37 ppm and shows no coupling with its vicinal proton due to their mutual stereochemistry (same applies for **13a**$^{2-}$). However, the ^{13}C satellites ($^{1}J_{C,H} = 123$ Hz) of this singlet appear as doublets ($^{3}J_{H,{*}H} = 11$ Hz). The scalar coupling between protons **H1** and its symmetrical equivalent (***H1**) proves the formation of a new covalent bond between the carbons they reside on. In addition, the value of the $^{3}J_{H,{*}H}$ coupling constant indicates that the protons are in *anti* configuration. This line of reasoning has been shown to be of great importance and will be used to explain other instances where new σ-bonds are used.

After a few days of exposure of **12a**$^{2-}$ and **13a**$^{2-}$ to the alkali metal (the process can be accelerated by raising the temperature to room temperature), a new spectrum evolves



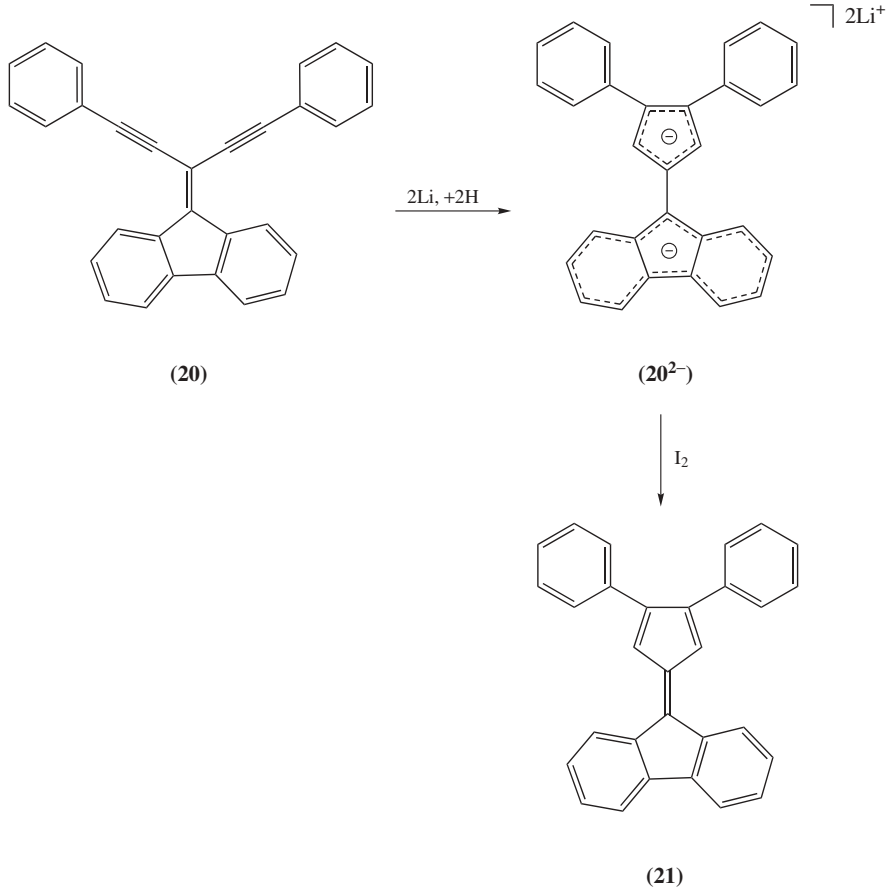
(12)
(13)
(12a^{2-})
(13a^{2-})
(14)
(15)

FIGURE 6. The reduction-induced ring closure in **12** and **13** (**13, 13a**$^{2-}$ and **15** are the systems with the extra ring)

that can be assigned to **14** and **15**, respectively. It can be argued that the second process is more time-consuming because the compounds are being transformed from stable diatropic species, $\mathbf{12a}^{2-}$ and $\mathbf{13a}^{2-}$, to paratropic ones, **14** and **15** (Figure 6)[39].

B. Cycloaromatization Initiated by Reduction

Linear-conjugated (*Z*)-enediynes undergo the famous Bergman cycloaromatization to yield a reactive benzene biradical[41]. The fulvene 9-(3-phenyl-1-phenylethynylprop-2-ynylidene)-9*H*-fluorene (**20**)[42] is an example of molecules with a cross-conjugated enediynes, also referred to as Y-enediynes[43]. Unlike linear enediynes, **20** cannot undergo the Bergman cycloaromatization as it is made of a methylenediyne moiety (two triple bonds conjugated through one sp^2-hybridized carbon atom) with only five π-electrons, which is insufficient for aromatization. However, it has been shown that under reductive conditions **20** undergoes cyclization and generates a product with a Hückel number of π-electrons ($\mathbf{20}^{2-}$, Figure 7)[44].



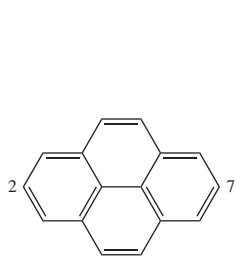
(20) **(20^{2-})** **(21)**

FIGURE 7. The reduction of **20** with lithium

Quenching the anionic solution of $\mathbf{20}^{2-}$ with iodine yields neutral 3′,4′-diphenyldibenzo-[*a*,*c*]pentafulvalene (**21**) in 32% yield (Figure 7). Hence, this reaction offers a new approach for the synthesis of fulvalenes.

C. The Effect of Strain on the Reduction of Bent Hydrocarbons

The effect of curvature on the aromatic character of polyaromatic hydrocarbons (PAHs) can be studied by comparing planar PAHs and their curved analogues. In order to address this issue a variety of [*n*](2,7)pyrenophanes ($n = 7–10$) in which the pyrene (**22**) moiety is strongly distorted from planarity have been synthesized and studied[45]. The degree of distortion from planarity and therefore the strain in these systems is controlled by the length and type of the tether that connects the two remote ends (positions 2 and 7) of **22**.



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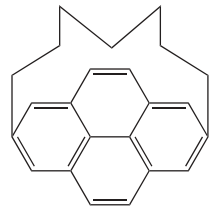

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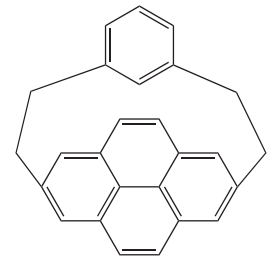

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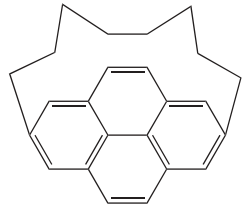

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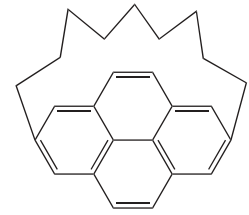

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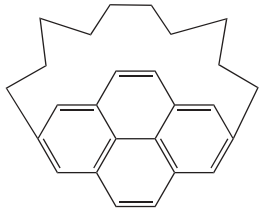

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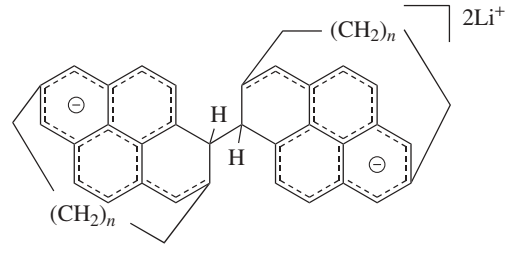


(24a^{2-}), $n = 5$
(26a^{2-}), $n = 6$
(27a^{2-}), $n = 7$
(28a^{2-}), $n = 8$

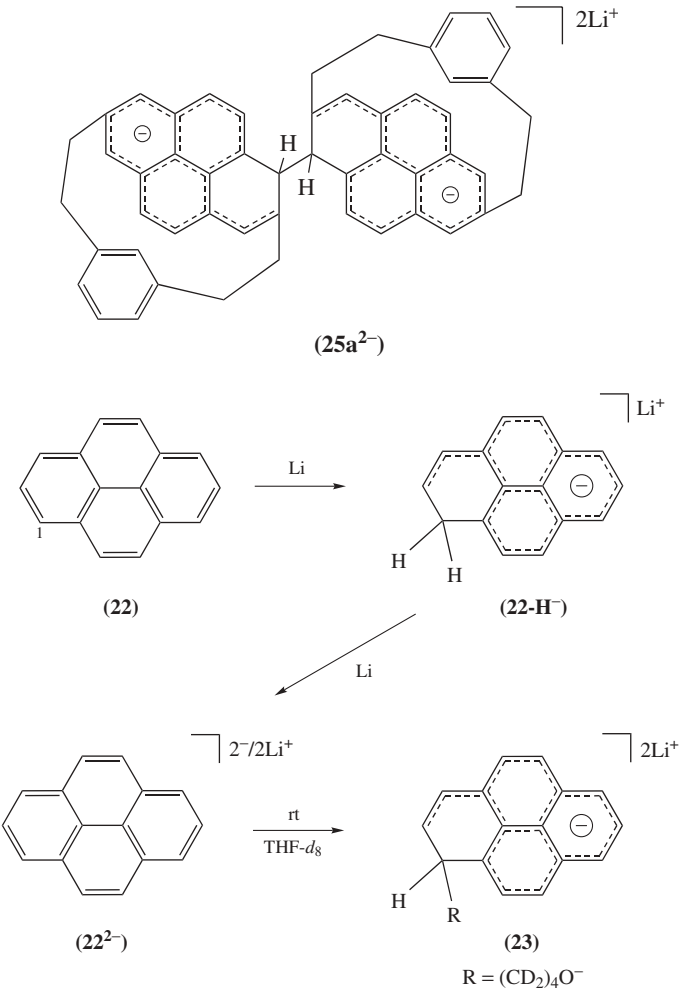


FIGURE 8. The reduction of **22** with lithium metal

Three successive diamagnetic species can be detected when **22** is reduced with lithium metal in THF-d_8 (Figure 8): a protonated pyrene monoanion (**22-H**$^-$), a dianion (**22**$^{2-}$) and finally a monoanion that incorporates the atoms of a former solvent molecule (solvent cleavage) (**23**)[46]. It has been shown that the reduction of the strained pyrene systems [7](2,7)pyrenophane (**24**), [2]metacyclo[2](2,7)pyrenophane (**25**), [8](2,7)pyrenophane (**26**), [9](2,7)pyrenophane (**27**) and [10](2,7)pyrenophane (**28**) with lithium metal can afford totally different results than those encountered in the reduction of the planar parent pyrene system[47]. The reduction of these systems shows that the strain in the pyrene moiety profoundly affects its reactivity.

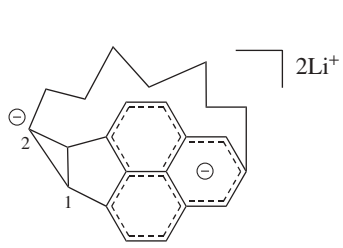
The first step of reduction, which is common to all the compounds, is a reductive dimerization process via electron coupling. The dimers formed in this process (**24a**$^{2-}$–**28a**$^{2-}$)

contain an aromatic phenalenyl anion subunit[48], which contributes to their stability. The formation of the new σ-bond connecting the dimers was shown using the aforementioned NMR method of measuring the scalar coupling between two seemingly identical protons (from the ^{13}C satellites) that reside on newly formed sp^3-hybridized carbons. The $^3J_{H,^*H}$ coupling constants for the dimers showed that they adopt an *anti* conformation about the new σ-bond, but unfortunately, a full assignment of the relative stereochemistry of the dimers was not possible.

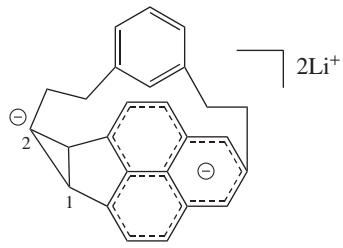
To explain why dimerization occurs, one should refer to the radical anion of **22** (**22**$^{\bullet-}$). It has been shown for **22**$^{\bullet-}$ that position **C1** (and its symmetrical counterparts) has the highest spin density for the odd electron in the monoanion radical[49]. This explains the high reactivity of this site and the likelihood of it undergoing radical coupling. Why is it then that **22** itself does not dimerize but is rather protonated? It is argued that such a dimerization might also happen in **22** but low solubility prevents its identification.

Whereas in the first reduction process the length of the tether has no influence on the nature of the reduction product, in the second reduction step, the product depends on the length of the tether, i.e. strain.

When the dimers **24a**$^{2-}$ and **25a**$^{2-}$ are further reduced, the 'intermolecular' σ-bond connecting the dimers is cleaved, to afford monomers **24b**$^{2-}$ and **25b**$^{2-}$. The new compounds, **24b**$^{2-}$ and **25b**$^{2-}$, exhibit again a scalar coupling between two seemingly identical protons, **H1** (from the ^{13}C satellites), but this time the one-bond CH-coupling was unusually high ($^1J_{C1,H1} = 163.2$ and 162.3 Hz for **24b**$^{2-}$ and **25b**$^{2-}$, respectively). In addition, carbon atom **C2** showed a dramatic high-field shift (29.2 and 30.1 ppm for **24b**$^{2-}$ and **25b**$^{2-}$, respectively). The $^1J_{C,H}$ values are consistent with a strained sp^3-hybridized carbon, as is the case in a cyclopropane ring, and thus it was concluded that **24b**$^{2-}$ and **25b**$^{2-}$ have a new *intramolecular* σ-bond that transforms one of the benzene rings into a 'cyclopropano-cyclopentano' (bicyclo[3.1.0]) ring system. In this scenario, the high-field shift of carbon atom **C2** results from the localization of charge on it. It was also shown that the phenalenyl anion stays intact.



(**24b**$^{2-}$)



(**25b**$^{2-}$)

Further reduction has no effect on dimer **26a**$^{2-}$, which remains intact even after long periods of contact with the reducing metal. However, **27a**$^{2-}$ and **28a**$^{2-}$ can be reduced further, but this time the reduction takes a totally different path than in **24a**$^{2-}$ and **25a**$^{2-}$. The new reduction products **27b**$^{2-}$ and **28b**$^{2-}$, respectively, are dianionic paratropic species, like **22b**$^{2-}$ (Figure 9). The paratropicity of these anions was based on the high-field shift of the pyrene protons ($\delta = 1.4–2.6$ ppm) and the chemical shifts of the tether hydrogens. These hydrogens function as probes for the anisotropy effect prevailing in the system, which is most notable at hydrogen atoms **H14** and **H14′**. For example, in **27b**$^{2-}$ the latter resonates at $\delta = 2.58$ ppm and the former, which feels the paramagnetic currents more strongly, resonates at $\delta = 7.98$ ppm.

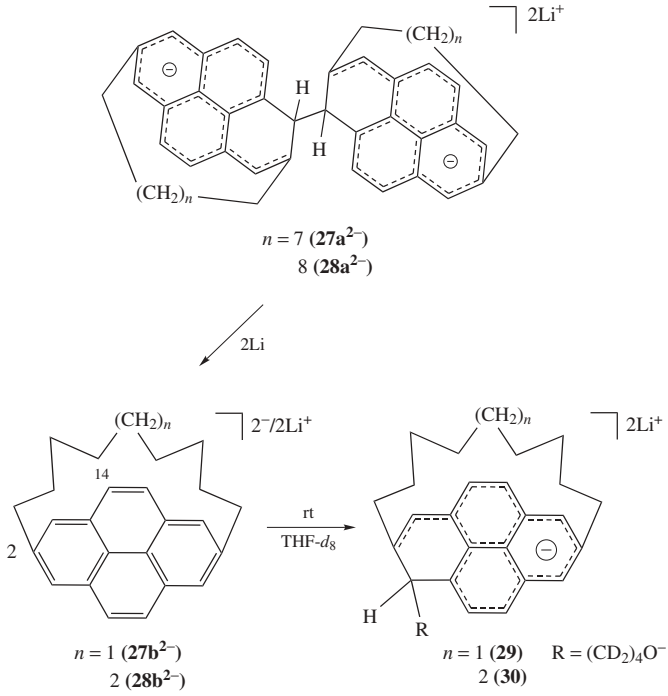


FIGURE 9. The first, second and third diamagnetic reduction products of **27** and **28**

When $\mathbf{27b}^{2-}$ and $\mathbf{28b}^{2-}$ are heated to room temperature they afford **29** and **30** (Figure 9). The new compounds are the result of solvent cleavage that yields a monoanionic pyrene moiety, in which the charge is concentrated on the phenalene subunit. Again this is reminiscent of the behavior of **22**.

It can be seen that compounds **27** and **28**, which have relatively long tethers, behave like **22**. Therefore, their two-electron reduction yields antiaromatic species, $\mathbf{27b}^{2-}$ and $\mathbf{28b}^{2-}$, which eventually cleave the solvent (giving **29** and **30** after reaction) as a means of gaining stability.

The surprising finding is that the strain in **24** and **25** brings about the formation of an intramolecular σ-bond as a means of avoiding an unfavorable strained dianionic antiaromatic state.

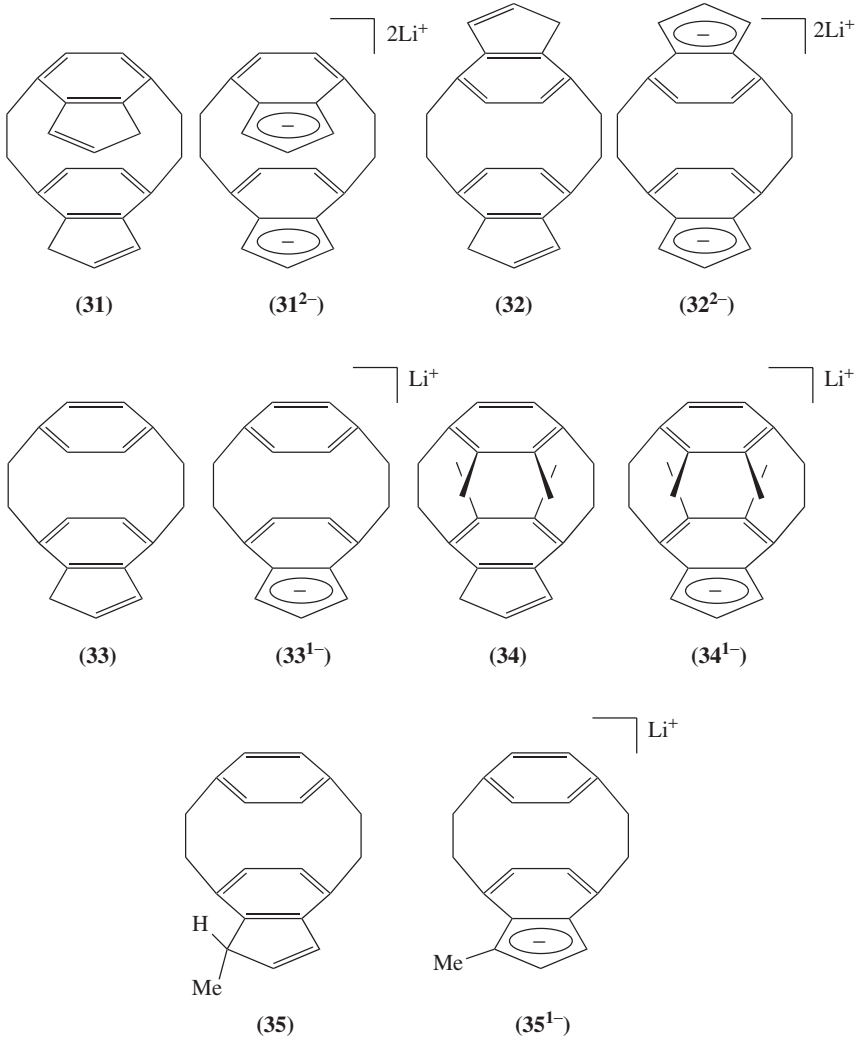
The threshold is a tether of eight carbon atoms where no two-electron reduction occurs. It seems that the strain in **26** is large enough that it does not get into an antiaromatic state. Moreover, it seems that the formation of an intramolecular σ-bond is not favored either, because insufficient stabilization is gained in this way.

IV. LITHIUM-REDUCED CYCLOPHANES

A. [2.2]Paracyclophanes — Through-space Interaction

[2.2]Paracyclophanes are aromatic hydrocarbons with unique steric and electronic properties. The two π-systems in such compounds interpenetrate, so that they behave as one π-system[50]. Paracyclophane anions are of interest in view of the proximity of the two anionic moieties and their mutual interaction.

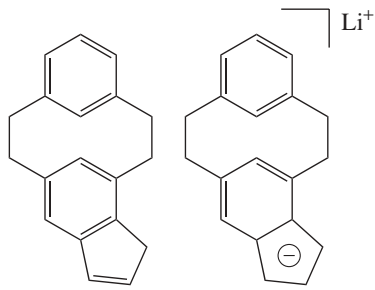
The through-space electronic interactions and anisotropy effects of the anions derived from the reduction a series of [2.2]indenophanes, namely *syn*- and *anti*-[2.2]indenophane (**31** and **32**, respectively)[51], [2.2]benzoindenocyclophane (**33**)[52], 4,5,17,18-tetramethyl[2.2] benzoindenocyclophane (**34**)[51a] and 12-methyl[2.2]benzoindenocyclophane (**35**)[51a] were deduced from ^{1}H and ^{13}C NMR spectroscopic data[53]. The comparison between the anions (**31**$^{2-}$, **32**$^{2-}$, **33**$^{1-}$, **34**$^{1-}$ and **35**$^{1-}$), their neutral counterparts and model compounds made it possible to differentiate between the anisotropy and charge effects and thus to estimate the net through-space interaction. Although the interaction between the two negatively charged moieties in **31**$^{2-}$ and **32**$^{2-}$ is larger than the effect in the monoanions **33**$^{1-}$, **34**$^{1-}$ and **35**$^{1-}$, the magnitude of the effect is still smaller than that of anisotropy, but nevertheless not negligible.



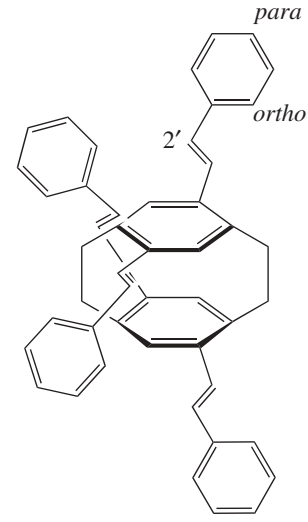
(31) **(31^{2-})** **(32)** **(32^{2-})**

(33) **(33^{1-})** **(34)** **(34^{1-})**

(35) **(35^{1-})**



(36) (36^{1-})



(37)

A different way of assessing the importance of through-space interaction is by studying systems like [2]metacyclo[2]indenophane **36**, where the spatial structure does not allow such an interaction. Indeed, the lithium salt of **36**$^{1-}$ only shows through-space anisotropy effects in its NMR chemical shifts[54].

More information about the interaction between different anionic layers comes from the reduction of 4,7,12,15-tetrastyryl[2.2]paracyclophane[55] (**37**), which was first synthesized and characterized by de Meijere, and coworkers. Careful reduction with lithium metal affords only one species, identified as the tetraanionic salt (**37**$^{4-}$), which gives a highly resolved NMR spectra[56]. The charge distribution, which is deduced from the ^{13}C NMR chemical shift, shows that the excess charge is localized over the entire molecule with the highest densities being on carbons **C2′** and at the *ortho* and *para* positions of the phenyl moieties. In addition, it was noticed that the charge density on the central ring is relatively low. This strange charge delocalization was attributed to a strong interaction in the 'cyclophane hub', which inherently shifts the added charge to the molecular periphery.

Another interesting aspect in the reduction of **37** is the fact that the intermediate dianion (**37**$^{2-}$) was not detected by NMR spectroscopy. This is somewhat peculiar because the cyclic voltammogram indicated the presence of four redox steps, which lead to the tetraanion. Moreover, the radical species (**37**$^{\bullet-}$) and **37**$^{2-}$ were observed in the UV-VIS spectrum. A simple explanation is given to this: in all stages before reaching **37**$^{4-}$ there exists a fast electron exchange between two states, radical and dianion, which prevents the observation of the NMR spectrum (Figure 10)[56].

B. Cyclooctatetraene-based Cyclophane

The nonplanar cyclooctatetraene (**38**, COT) and its planar aromatic dianion (**38**$^{2-}$) have been extensively studied because these systems represent a textbook example for the application of the Hückel $4n + 2$ rule[57]. Recently, Rabideau and coworkers were able to establish the first crystal structure of a dilithiated COT system by reducing dibenzo[*a*,*e*]cyclooctatetraene (**39**) in TMEDA to its dianion (**39**$^{2-}$)[58]. The X-ray of **39**$^{2-}$

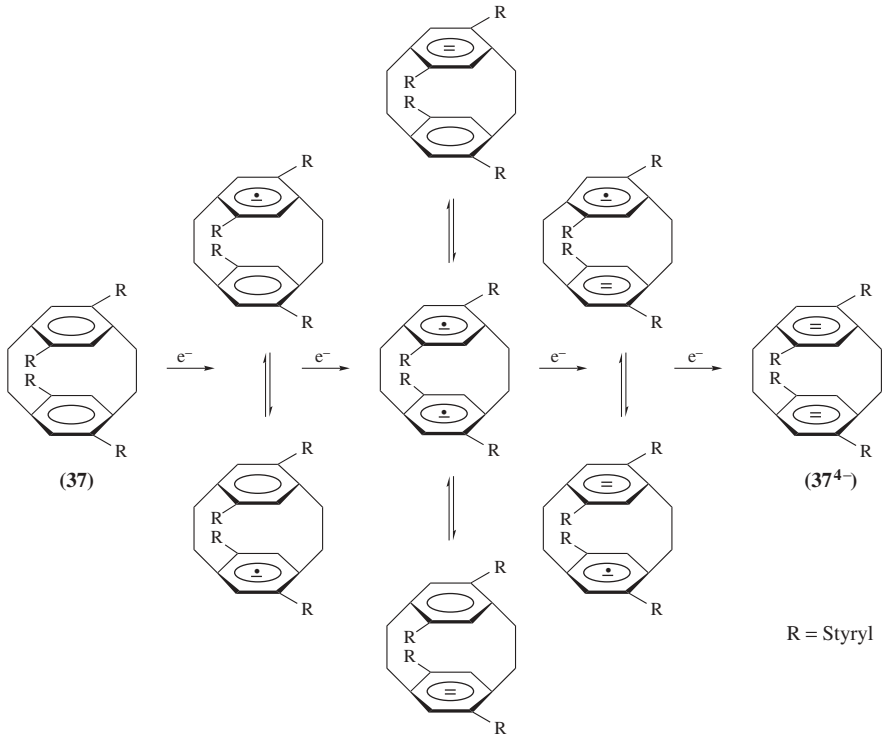
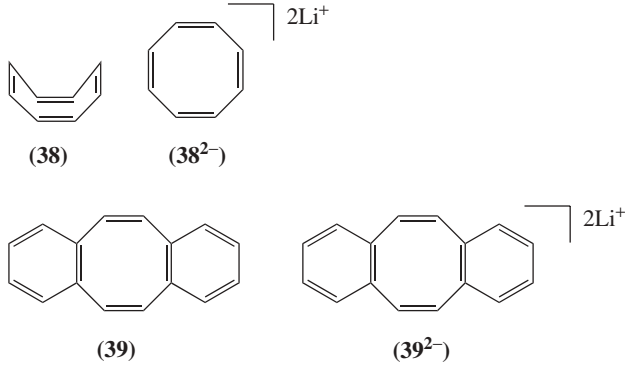


FIGURE 10. Proposed reduction pathway of **37** to $\mathbf{37}^{4-}$. Reproduced by permission of The Royal Society of Chemistry from Reference 56



showed that the two lithium cations, which are η^8 coordinated, are symmetrically arranged over and under the center of the eight-membered ring (Figure 11).

Müllen and coworkers synthesized and characterized 1,5,22,26-tetraoxa-[5,5]-(2,8)-dibenzo[*a*,*e*]cyclooctatetraenophane (**40**), which consists of two **39** units in face-to-face arrangement[59]. It was found that neutral **40** undergoes a dynamic process which causes

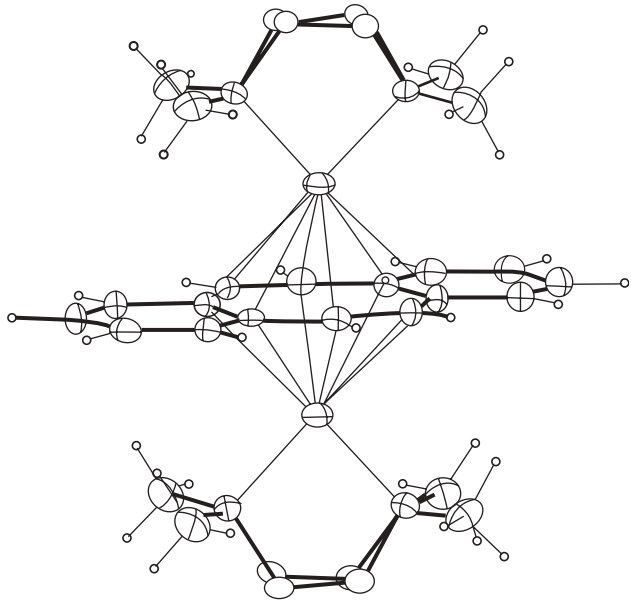


FIGURE 11. X-ray structure of $\mathbf{39}^{2-}$. Reprinted from Reference 58, Copyright (1996), with permission from Elsevier

a rapid interconversion of its *meso*- and *dl*-forms. **40** was also reduced in order to assess the effect that redox processes might have on the cavity size of this cage-type molecule.

The reduction of **40** with lithium metal affords a pair of diastereomeric tetraanions ($\mathbf{40}^{4-}$, Figure 12). In contrast to the neutral compound the internal rotation of the dibenzo-COT unit in $\mathbf{40}^{4-}$ is slowed at low temperatures, due to steric hindrance caused by the solvation shells of the ion-pairs. At ambient temperatures, dynamic behavior is observed and only broad and averaged signals can be seen. This is attributed to the rotational process observed in **40**. It should be noted that this dynamic behavior is not observed in the potassium salt of $\mathbf{40}^{4-}$ because this cation favors the formation of CIPs.

Molecular models suggest that a charge-induced flattening of the COT units in $\mathbf{40}^{4-}$ should significantly alter the size of the cyclophane cavity. Indeed, such an effect is observed in the ^{1}H NMR spectrum. The mutual shielding of the flattened, parallel-oriented subunits causes a substantial upfield shift of the proton signals[59].

Cyclovoltammetric reduction of **40** showed two well-separated waves, the spacing of which indicates that there is only a weak coulombic interaction between the doubly charged subunits of $\mathbf{40}^{4-}$.

C. Lithium Reduction of Annulenes — Extended Cyclophanes

Paracyclophanes, in which benzene units are linked at the 1,4-positions by ethylene bridges, show annulene characteristics upon reduction. The reduction of annulenes allows a straightforward alternating interconversion of $[4n]$- and $[4n + 2]\pi$-systems, and so can be used as a good model for theory and spectroscopy[1b].

[2.2.0.2.2.0]Paracyclophane-1,9,23,31-tetraene[60] (**41**) is a rigid annulene with a well-defined ring configuration. The neutral cyclophane, which formally has 32π-electrons $(4n)$

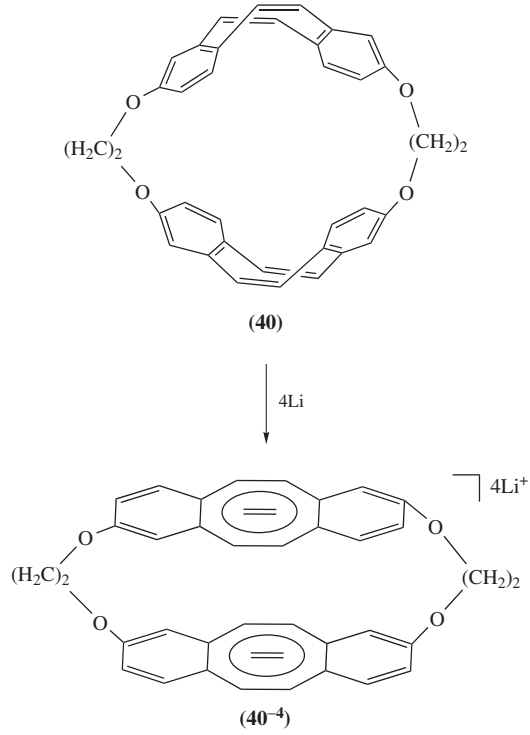
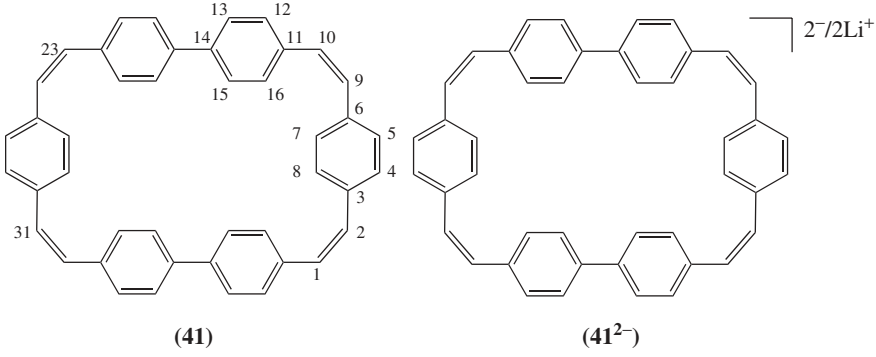
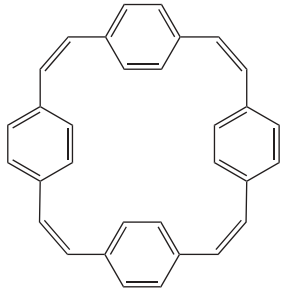


FIGURE 12. Reduction of **40** to $\mathbf{40}^{2-}$. Only one diastereomer is shown

around the periphery, can be regarded as a normal aromatic compound with no significant contribution from the large conjugated perimeter.

Careful reduction of **41** with lithium metal at low temperature (195 K) leads to a salt that shows a temperature-dependent ^{1}H NMR spectrum, assigned as the dianion ($\mathbf{41}^{2-}$)[61]. As a result of the strong diatropic ring current, the signals of the inner protons are shifted to high field, while an opposite effect is exerted on the peripheral protons (Table 1).





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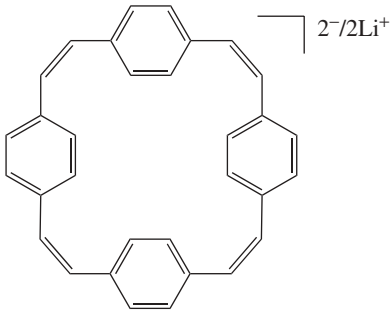
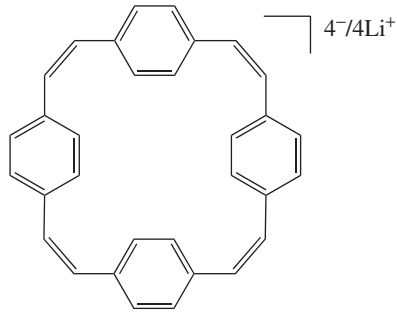


(42^{2-})



(42^{4-})

TABLE 1. ^{1}H NMR chemical shifts of **41** and its dianion $\mathbf{41}^{2-}$

	H-1	H-2	H-4	H-8	H-12	H-13	H-15	H-16
41	6.62	6.57	7.35	7.35	7.53	7.79	7.79	7.53
$\mathbf{41}^{2-}/2Li^{+}$	6.64	6.45	7.35	−2.89	7.87	7.95	−0.89	−3.40
$\mathbf{41}^{2-}/2K^{+}$	9.90	9.99	9.60	−5.89	9.99	10.53	−3.52	−5.50

Further contact of $\mathbf{41}^{2-}$ with the metal does not yield the expected tetraanion. The stable $\mathbf{41}^{2-}$ is the only species detectable in solution.

The reduction of **41** with potassium, however, proceeded differently[62]. The peripheral ring current effect of the potassium salt of $\mathbf{41}^{2-}$, as reflected in the change in proton chemical shifts, is dramatically enhanced relative to that of the lithium salt (Table 1). The small lithium cation is more effective in attracting the π-charge and thus in decreasing the ring current effect of the perimeter.

[2.2.2.2]Paracyclophane-1,9,17,25-tetraene (**42**)[62] can be reduced using lithium to yield a stable dianion ($\mathbf{42}^{2-}$) followed by a tetraanion ($\mathbf{42}^{4-}$)[63]. Both anions show pronounced anisotropy effects that are manifested by their ^{1}H NMR signals. The signals of the inner protons of the diatropic species, $\mathbf{42}^{2-}$, absorb at high field, whereas the peripheral ones are shifted to low field. $\mathbf{42}^{4-}$, which is paratropic, shows an opposite effect. In contrast to $\mathbf{41}^{2-}$, the lithium and potassium salts of $\mathbf{42}^{2-}$ exhibit very similar ^{1}H and ^{13}C NMR spectra. However, the potassium salt of $\mathbf{42}^{4-}$ is afforded only after a long contact with the metal[62]. The opposite behavior is found in compound **41**. While the reduction with

lithium stops at the dianion $\mathbf{41}^{2-}$, potassium reduces **41** to its tetraanion and even further. Such a situation, where small polycyclic compounds yield stable anions with lithium while larger systems prefer a heavier alkali metal like potassium, is a common phenomenon. The explanation is based mainly on the differences in ion pairing equilibria and the ability of the lithium cations to aggregate and to stabilize the anions.

V. REDUCTION OF POLYCYCLIC BOWLS — THE CASE OF CORANNULENE

A. Reduction of Corannulene

1. Corannulene tetraanion: Self-assembly and formation of a dimer

Corannulene (**43**), the smallest curved subunit of C_{60}, was first synthesized by Barth and Lawton in 1966[64]. However, this bowl-shaped hydrocarbon remained relatively inaccessible prior to the studies of the groups of Scott[65], Siegel[66] and Zimmermann[67].

The ^{1}H NMR spectrum of **43** consists of one line ($\delta = 7.93$ ppm), indicating a diamagnetic ring current about the perimeter. It was found that the reduction of **43** with lithium metal in THF-d_8 leads to a series of color changes: green, purple and finally brownish-red[68]. The ^{13}C NMR spectrum corresponding to the final stage shows three carbon absorptions ($\delta = 86.8$, 95.1 and 112.4 ppm) that are shifted to very high field compared with those of the neutral hydrocarbon ($\delta = 127.9$, 132.3 and 136.9 ppm). The total change in chemical shift ($\Sigma\Delta\delta = 722$ ppm, $K_c = 180$ ppm e^{-1}) as well as quench experiments provide convincing evidence for the presence of a tetraanionic species, $\mathbf{43}^{4-}$. The 'annulene-within-an-annulene' model, first suggested by Barth and Lawton for $\mathbf{43}^{4-}$[64], can account for the high stability of $\mathbf{43}^{4-}$ (Figure 13). According to this model, $\mathbf{43}^{4-}$ is made up of an aromatic cyclopentadienyl anion ($6e^-/5C$) surrounded by an aromatic ($18e^-/15C$) annulenyl trianion. MNDO calculations on the lithium salt of $\mathbf{43}^{4-}$ support this charge distribution[69]. However, molecular orbital calculations, carried out at both the semiempirical AM1 and *ab initio* levels, suggest that the tetraanion structure may be more complicated than the highly symmetrical 'anion-within-a-trianion' model[70].

The first evidence for the self-assembly of corannulene tetraanions into a supramolecular dimer, **44**, was provided by studies on derivatives of **43**[71]. Owing to their lower symmetry, dimers of monosubstituted corannulene tetraanions are expected to exhibit supramolecular stereochemistry, and thus exist in *meso* and/or as *dl* dimeric forms (Figure 14a, and b respectively). Reduction of *tert*-butylcorannulene (**45**) with excess lithium metal in THF-d_8 leads to two sets of alkyl groups in almost equal abundance, thus pointing to the presence of tightly bound dimers. Compelling evidence for dimerization comes from the successful detection of a 'mixed dimer' between $\mathbf{43}^{4-}$ and $\mathbf{45}^{4-}$. In addition, diffusion

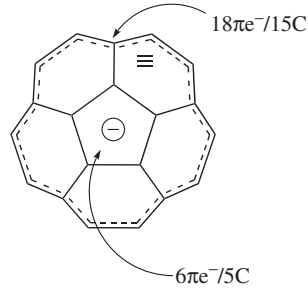


FIGURE 13. The 'annulene-within-an-annulene' model for $\mathbf{43}^{4-}$

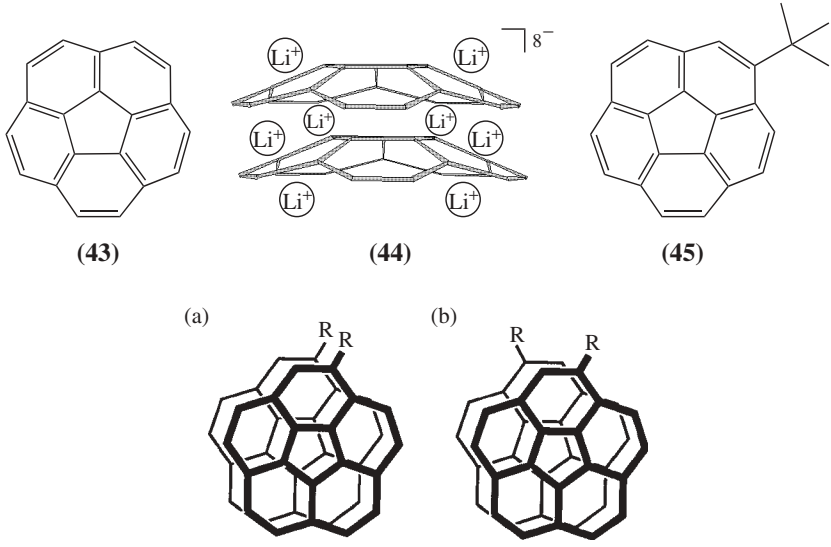


FIGURE 14. The *meso* (a) and *dl* (b) dimers of monosubstitute (d) corannulene tetraanions. Reproduced by permission of Science from Reference 71

measurements[72] show a significant decrease in the self-diffusion coefficient of **44**, thus supporting the presence of a dimer.

The ^{7}Li NMR spectrum of **44** recorded at a low temperature (210 K) features two signals of equal intensity at $\delta = -4.5$ and -11.7 ppm. These chemical shifts represent two different types of lithium cations: those sandwiched between the two-tetraanionic decks (CIP) and those on the outside[71].

Although the geometries of the corannulene moieties in these dimers could not be obtained from NMR experiments, semiempirical MNDO molecular orbital calculations clearly favor a 'stacked-bowl' geometry (convex face to concave face). The equivalence of the four external lithium cations is explained in terms of rapid intermolecular exchange. Moreover, the equivalence of the two corannulene units is accounted for by a rapid bowl-to-bowl inversion of both corannulene decks. The validity of this proposal was supported both theoretically[71] and experimentally[73].

2. Intermediate reduction steps of corannulene

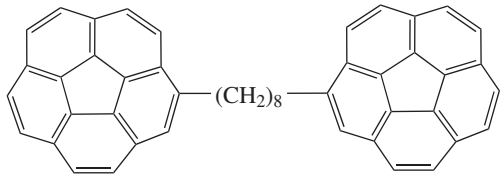
Due to its doubly degenerate, low-lying LUMOs, the corannulene dianion was thought to be paramagnetic. However, a Jahn–Teller distortion allows the detection of the ^{1}H and ^{13}C NMR spectra of the dianion[74]. The protons of the dianion of **43** show a broad absorption at a very high field ($\delta = -5.6$ ppm), which is typical of molecules with a paratropic ring current[75]. This can be explained by the 'annulene' model, where a cyclopentadienyl anion ($6e^{-}$/5C) is placed in the center of an antiaromatic ($16e^{-}$/15C) annulene perimeter.

The ^{13}C NMR spectrum of the dianion of **43** shows three carbon peaks ($\delta = 120$, 154 and 204 ppm) that are shifted to a lower field than those of the neutral compound. The extremely low field signal of the quaternary hub carbon ($\delta = 204$ ppm) can be explained by the strong deshielding effect of the outer antiaromatic ring current.

The radical anion and the triradical anion of **43** are both paramagnetic species and can be detected by EPR. The EPR spectrum of the radical anion of **43** shows an 11-line hyperfine pattern for the ten equivalent protons[76]. The trianion radical of **43** shows a highly resolved EPR spectrum where additional ^{7}Li (and ^{6}Li) couplings are evident[74, 76b].

B. 1,8-Dicorannulenyloctane: Intra- vs. Intermolecular Dimerization

1,8-dicorannulenyloctane (**46**)[77], which consists of two corannulene units connected by an octamethylene chain, is expected to provide a pre-organized sandwich in the reduced form. The reduction of such an organized system with lithium metal is expected to form either *intra-* or *inter*-molecular sandwiches. The reduction process of **46** with lithium (and other alkali metals) is similar to that of **43** and thus yields a paramagnetic tetraanion followed by the appearance of a diamagnetic octaanion[77].



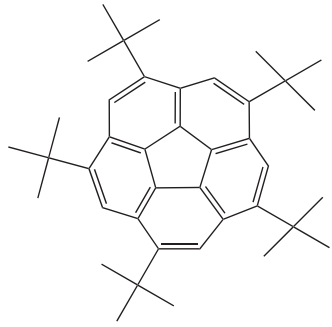
(46)

The question of *inter- vs. intra*-molecular dimerization in the octaanion of **46** was investigated by diffusion measurements[72] and by conducting competition studies, i.e. aggregation with free $\mathbf{43}^{4-}$. Both experiments pointed to the formation of *intra*-molecular dimers.

Despite its considerable curvature, **43** is surprisingly flexible and undergoes a rapid bowl-to-bowl inversion. The barrier for this inversion was determined by NMR methods to be $\Delta G^{\ddagger}_{230} = 10.2 \pm 0.2$ kcal mol^{-1} [73]. In **46**, each methylene unit of the octamethylene bridge can, in principle, serve as a diastereotopic probe for the bowl-to-bowl inversion process of the corannulene units. The barrier for the bowl-to-bowl inversion in **46** was found to be $\Delta G^{\ddagger}_{230} = 10.9 \pm 0.3$ kcal mol^{-1}. The bowl-to-bowl inversion barriers of the anions were also measured. The lines of the methylene groups of the lithium salt of $\mathbf{46}^{4-}$ only broaden at low temperatures and thus its inversion barrier was not determined. Nevertheless, such a determination was possible for the salts of other alkali metals ($\Delta G^{\ddagger}_{230} = 8.8 \pm 0.3$ kcal mol^{-1} and $\Delta G^{\ddagger}_{230} = 9.2 \pm 0.3$ kcal mol^{-1}, for $\mathbf{46}^{4-}$/4K^{+} and $\mathbf{46}^{4-}$/4Cs^{+} respectively). According to the study, the octaanion $\mathbf{46}^{8-}$ has a very low inversion barrier[77].

C. Reduction of Penta-*tert*-butylcorannulene — Effect of *peri* Derivatization

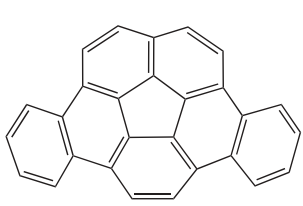
The reduction of 1,3,5,7,9-penta-*tert*-butylcorannulene (**47**) with lithium progresses in four steps, and affords a paratropic dianion and a diatropic tetraanion[78]. This is reminiscent of the reduction process of **43**. In the final stage of the reduction, however, three distinct tetraanionic species could be detected: two sandwich-type diastereomers, similar to **44**, and another species assigned to a tetraanionic monomer of **47**, that slowly disappears. This study showed that the *peri* derivatization of **43** with bulky alkyl groups has little effect on its dimerization.



(47)

D. Corannulene with Extended π-Systems — From Bowls to Balls

Dibenzo[*a*,*g*]corannulene (**48**)[79] and dibenzo[*a*,*g*]cyclopenta[*kl*]corannulene (**49**)[80] can be considered as corannulenes with added conjugation. The additional five-membered ring in **49** significantly increases its curvature relative to **43**[81]. In **48** and **49**, the LUMO is nondegenerate, but there is only a small energy gap between the LUMO and the NLUMO (0.22 eV and 0.62 eV, respectively). This allows the formation of highly reduced species[82]. Both **48** and **49** can be reduced by lithium metal to dianions (**48**$^{2-}$ and **49**$^{2-}$, respectively)[83]. The total changes in the carbon chemical shifts in **48**$^{2-}$ and **49**$^{2-}$ are $\Sigma\Delta\delta = +50$ ppm and $\Sigma\Delta\delta = -178$ ppm, respectively ($K_c = +25$ and -89 ppm e^{-1}, respectively). These values are markedly different from those obtained for **43**$^{2-}$ ($\Sigma\Delta\delta = +366$ ppm and $K_c = +183$ ppm e^{-1}). It seems that the strong paratropic effect that operates in **43**$^{2-}$ and leads to very low field shifts in its carbon spectrum is absent in **48**$^{2-}$ and **49**$^{2-}$. Such behavior is reasonable, since the magnitude of a paramagnetic ring current is known to be inversely related to the size of the HOMO–LUMO gap[12a,b], and the gap for these dianions increases in the order **43**$^{2-}$ < **48**$^{2-}$ < **49**$^{2-}$. The K_c values of **48**$^{2-}$ and **49**$^{2-}$ are characteristic of polycyclic systems. The external fused rings, especially the five-membered ring in **49**$^{2-}$, exert a strong charge-withdrawing effect, thus distorting the 'annulene behavior'. However, some annulenic effect is still present in the internal five-membered rings, especially in **48**$^{2-}$.



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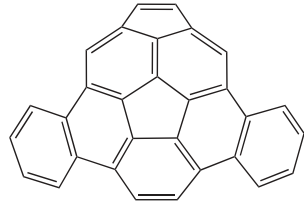
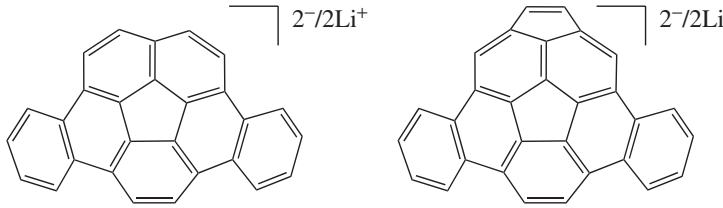


(49)

Further reduction of the dianions, **48**$^{2-}$ and **49**$^{2-}$, with lithium metal gave the corresponding trianion radicals, but in contrast to the reduction of **43**, the reduction could not be made to proceed further. This behavior can be explained by the tendency of **43**$^{4-}$ to dimerize, unlike the tetraanions of **48** and **49.** When the reduction is performed with potassium metal, both **48** and **49** yield tetraanions (**48**$^{4-}$/4K^{+}, **49**$^{4-}$/4K^{+}). The tetraanion **48**$^{4-}$/4K^{+}



(**48**$^{2-}$) (**49**$^{2-}$)

was found to be diatropic, though less than **43**$^{4-}$, whereas the tetraanion **49**$^{4-}$/4K^{+} was found to be weakly paratropic[83].

VI. OTHER SUPRAMOLECULAR DIMERS WITH LITHIUM

A. Dimers of Lithium Isodicyclopentadienide and Cyclopentadienide

The stereoselective reaction of lithium isodicyclopentadienide (**50**) with methyl iodide and trimethylchlorosilane shows an amazing dependency on temperature. Electrophilic attack at the *endo* face occurs at −78 °C in THF, whereas **50** is attacked from the *exo* face at room temperature (Figure 15)[84].

In order to rationalize these findings, Paquette, Schleyer and coworkers have investigated the structure of the reactive species, **50**, under conditions similar to those of the quench experiments[85]. NMR and calculations have revealed that a monomer–dimer equilibrium exists for **50** in THF at low temperatures. The monomer is a CIP, in which the lithium is located at the *exo* face (**51**) and resonates at $\delta = -7.6$ ppm, whereas the dimer consists of a lithium cation 'sandwiched' between the *exo* faces of two anion moieties (**52**). The signal for this sandwiched lithium is greatly shifted, appearing at $\delta = -12.8$ ppm. Such high-field lithium shifts (as previously discussed) have since become an important indicator for the presence of dimers and higher aggregates in solution. It was also shown that a rapid exchange exists between 'external' solvated lithium cations ([Li(THF)$_4$]$^{+}$) and the monomer-bound lithium and a slower exchange between the sandwiched and monomer-bound lithium. The results also indicate that the *exo* lithium isomers of the

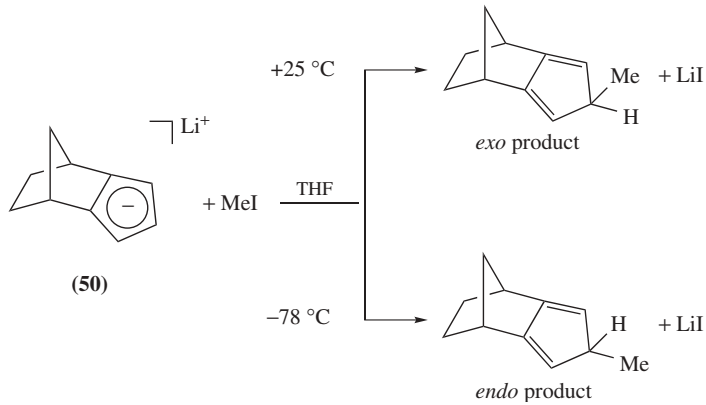
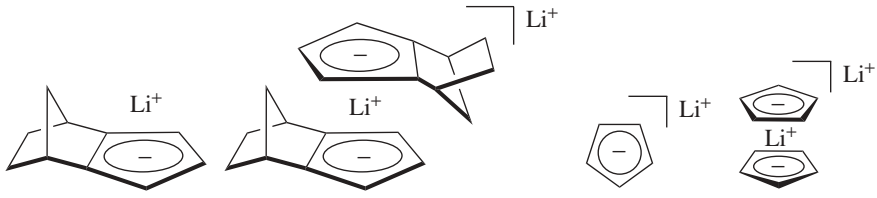


FIGURE 15. The temperature-dependent stereoselective quench reaction of **50**

monomer and dimer are more stable than their *endo* counterparts. This, in addition to the fact that the monomer–dimer equilibrium is shifted towards the monomer at high temperatures, can explain the stereoselectivity encountered in the quench reactions of **50**[85].

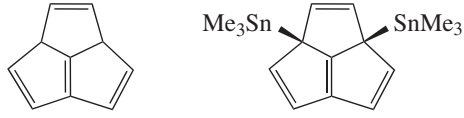


(51) **(52)** **(53)** **(54)**

The study of **50** also helped in understanding the behavior of lithium cyclopentadienide (**53**) in solution. The high-field shift of the lithium cations of **53** in THF ($\delta = -6.3$ and -13.1 ppm) make it clear that it also exists in a monomer–dimer equilibrium at low temperatures. However, the exchange process this time was found to be faster than in **50** and it was not possible to tell to which side the equilibrium is shifted at room temperature. MNDO calculations have shown that the sandwich dimer (**54**) deviates slightly from perfectly staggered (D_{5d}) and eclipsed (D_{5h}) structures. It was also shown that the cyclopentadiene rings rotate freely around the longitudinal axis in the dimer[85].

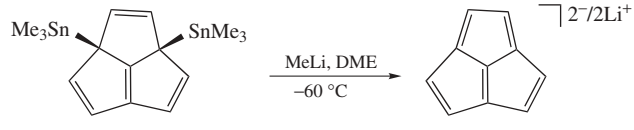
B. Solid State Dimer of Acepentalene Dianion

Acepentalene (**55**) and its dianion ($\mathbf{55}^{2-}$) have attracted much interest due to their unique tricyclic structure, curved molecular surface and interesting electronic properties[86]. Because of the large strain in **55** it has not been isolated at ambient temperatures. However, de Meijere and coworkers were able to prepare $\mathbf{55}^{2-}$ [86,87], which is less strained and has a closed-shell system, and therefore electronically more favorable than the neutral system.



(55) **(56)**

The dilithium acepentalenediide ($\mathbf{55}^{2-}$) [87b] can be obtained by transmetalation of 4,7-bis(trimethylstannyl)dihydroacepentalene (**56**) with methyllithium at low temperature (Figure 16). $\mathbf{55}^{2-}$ can readily be crystallized at low temperatures from dimethoxyethane (DME). The low-temperature crystal structure analysis revealed an interesting dimer-sandwich structure in which two lithium counterions 'glue' the convex surfaces of two bowl-shaped $C_{10}H_6$ dianions together (Figure 17). The structure of $\mathbf{55}^{2-}$ in the solid state is an example of a contact ion triplet with all the implications of ion-pairing phenomena[88]. This dimeric assembly of $\mathbf{55}^{2-}$ in the solid state is analogous to the dimer formed by corannulene tetraanion in solution (**44**)[71]. However, the solid state structure of $\mathbf{55}^{2-}$ was not verified in solution. According to the NMR spectroscopic data, the compound is C_3



(56) **(55^{2-})**

FIGURE 16. The preparation of dilithium acepentalenediide $\mathbf{55}^{2-}$

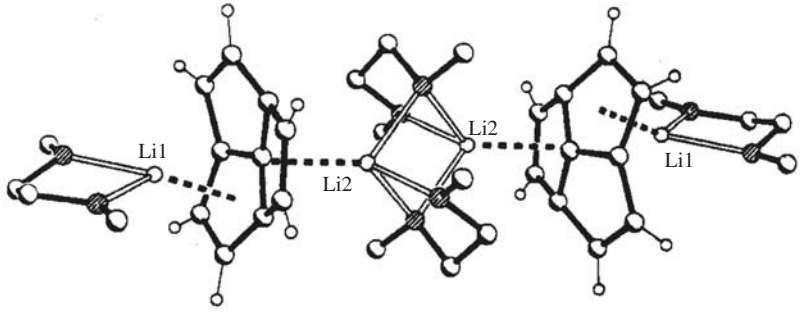
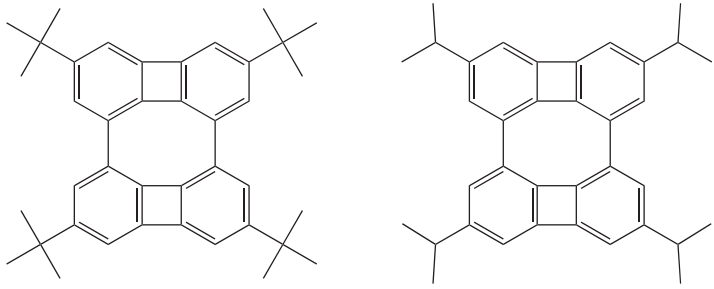


FIGURE 17. The X-ray structure of $\mathbf{55}^{2-}$. Reproduced by permission of Wiley-VCH Verlag GmbH from Reference 87b

symmetric in solution, as there must be a rapid exchange between the inside and the outside of the sandwich, even if it is dimeric[87b].

C. Dimer, Trimer and Tetramer of Cyclooctabisbiphenylene Tetraanion

Another interesting system that also undergoes aggregation upon reduction with lithium metal in solution is the highly symmetrical and almost planar tetra-*tert*-butyl derivative of cycloocta[1,2,3,4-*def*;5,6,7,8-*d′e′f′*]bisbiphenylene[89] (**57**, a substituted biphenylene-dimer, termed BPD). Preliminary studies have revealed that **57** can be reduced to a radical anion followed by a dianion. However, further reduction usually ended in precipitation[89]. Later on, it was found that performing the reduction at low temperatures enables the observation of three new species, appearing at high field and showing a multiplication of the NMR spectral absorption pattern. These species are all attributed to tetraanions of **57**[90].



(57) **(59)**

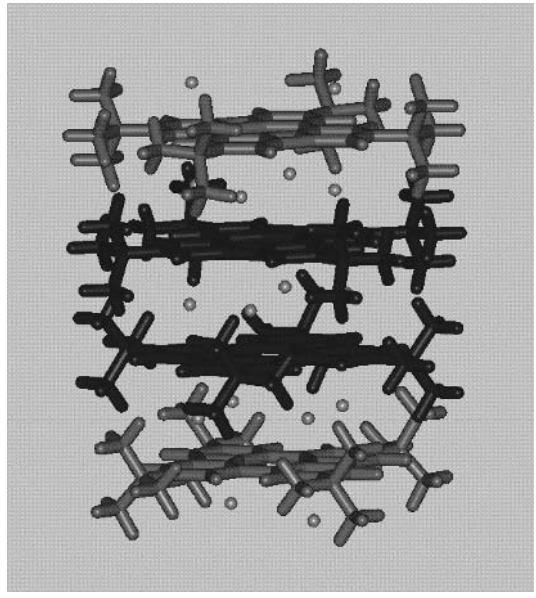


FIGURE 18. Computed structure of the helical tetramer, **58**. Reprinted with permission from the American Chemical Society, from Reference 90

Detailed analysis of the NMR spectra of the tetraanions reveals a fascinating structure of a helically stacked tetramer (**58**, Figure 18), which consists of four tetraanionic decks of **57** 'glued' together by twelve lithium cations. Moreover, analogous helically stacked trimer and dimer were also identified. Further support for the aggregation was achieved by using a 2,5,8,11-tetraisopropyl-BPD (**59**)[90], in which the pro-chiral methyl groups in the isopropyl substituents become diastereotopic in the tetraanionic stage due to the lowering of the local (molecular) symmetry in the aggregated structure. Self-diffusion NMR measurements[72] provide compelling evidence for the different sizes of aggregates.

Interproton distances were computed with semiempirical MNDO calculations (Figure 18) in order to elucidate the structure of **58**, and the results compared well with distances calculated from peak integration of the through-space correlation spectrum (ROESY). It was found that the interlayer distance is slightly over 4 Å, which leaves the appropriate spacing for lithium cations to intercalate between the layers. The phase angle between each two layers is approximately 45°, caused by the bulkiness of the *tert*-butyl groups, which lock **58** in a gear-meshed structure[90].

The aromatic nature of the tetraanionic layers of **58** was established by the shielding/deshielding effects found in the system. Ring currents cause enhanced shielding inside the tetramer core and thus some of the lithium cations are shifted to −14.5 ppm. In addition, the substituent groups of the two inner layers that extend to the sides of the tetramer structure are deshielded relative to analogous nuclei in the two outer layers.

Temperature-dependent ^{1}H NMR spectra showed that the octaanionic dimer of **57** undergoes a dynamic process, rationalized as a fast in-plane rotation motion of each layer against the other, which corresponds to an enantiomerization process. This dynamic motion is inhibited at low temperatures. In **58** and the trimer (dodecaanion of **57**) this enantiomerization process is severely hindered by the interlocked, gear-meshed structure[90].

VII. LITHIUM REDUCTION OF FULLERENES — REDUCED POLYCYCLIC BALLS

A. Reduction of C_{60} and C_{70} to their Hexaanions

For polycyclic π-systems, there is not always a correlation between aromatic character and the total number of π-electrons, as is the case for monocyclic annulenes[91]. In fullerenes, which are not only polycyclic but also three-dimensional, such a correlation is even less apparent. These carbon allotropes embody completely conjugated spheroidal π-systems, so the carbon skeletons are boundary-less, and large numbers of Kekulé structures can be drawn[92]. The aromaticity of fullerenes has been investigated theoretically and substantiated experimentally by using NMR studies[93].

Fullerenes have a characteristic pattern of low-lying unoccupied molecular orbitals and high electron affinity, which allow them to accommodate large numbers of electrons in their π-systems, as indicated by their electrochemistry[94]. Since reduction is not expected to modify their shape and symmetry, the effect of added electrons is expected to manifest itself mainly in the magnetic and electronic properties of the fullerenes, i.e. their aromaticity.

There is clear evidence for the electrochemical production of the C_{60} and C_{70} hexaanions (C_{60}^{6-} and C_{70}^{6-}) in the cyclic voltammetry data of Echegoyen and coworkers[95]. C_{60} and C_{70} have also been reduced to hexaanions in the solid state by exposing them to vapors of various alkali metals[96]. Olah and coworkers performed the first lithium reduction of a mixture of C_{60} and C_{70} in solution, with the aid of an ultrasonic bath[97]. The ^{13}C NMR spectrum at room temperature showed a single line at $\delta = 156.7$ ppm for C_{60}^{6-} and five resonances for C_{70}^{6-} ($\delta = 158.3$, 152.3, 149.6, 137.9 and 133.7 ppm). Despite the additional charge, both anions are deshielded. However, in contrast to the remarkable deshielding effect exhibited by C_{60}^{6-} ($\Delta\delta = 14$ ppm per carbon atom), only a slight deshielding is shown by C_{70}^{6-} ($\Delta\delta = 0.9$ ppm per carbon atom). The ^{7}Li NMR spectrum of a mixture of C_{60}^{6-} and C_{70}^{6-} at room temperature shows a broad signal at $\delta = 1.6$ ppm, indicating a solvent-separated ion-pair/contact ion-pair equilibrium[97].

In the meantime, it was found that addition of corannulene, which serves as an efficient electron shuttle between the lithium metal and the solid fullerenes, facilitates the reduction of the fullerenes to their hexaanions (Figure 19). This finding was very crucial for the continuing study of charged fullerenes[40b].

B. Lithium Reduction of Methanofullerenes

The aromatic character of fullerene anions can be better understood by monitoring the local ring currents of the 5-membered rings (5MRs) and 6-membered rings (6MRs) in

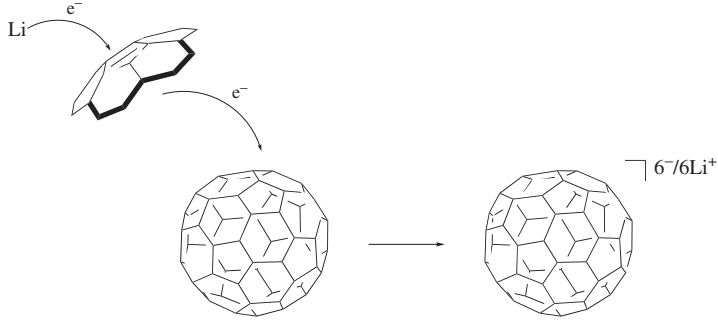
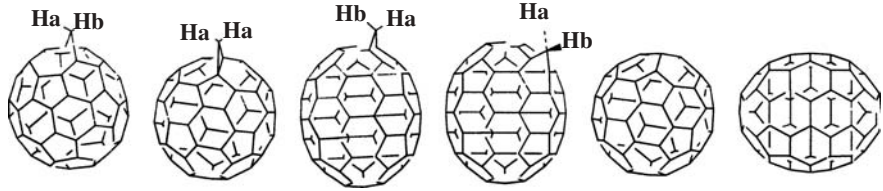


FIGURE 19. Corannulene as an electron shuttle in the reduction of fullerenes

the reduced fullerenes and comparing them with the neutral ones[98]. This is accomplished using carbon-bridged fullerenes[99] as sensors for local magnetic contributions.

Two isomers of $C_{61}H_2$ (**60** and **61**)[99] and two isomers of $C_{71}H_2$ (**62** and **63**)[99] were reduced and analyzed by NMR methods by Rabinovitz and coworkers, in order to account for the aromatic behavior of the hexaanions of the parent fullerenes, C_{60} and C_{70}[100]. In all these bridged fullerenes, the protons are located above the centers of the rings, either one above a 5-MR and the other above a 6-MR (depicted as [5,6]) (**60, 62** and **63**) or above two 6MRs ([6,6]) (**61**)[98,99]. The location of the protons enables them to act as sensors of the ring's magnetic character. Comparison between the ^{1}H NMR chemical shifts of the neutral systems and their hexaanions allows assessment of the changes in the local ring current of each ring.



(60) **(61)** **(62)** **(63)** C_{60} C_{70}

The ^{13}C NMR and the ^{7}Li NMR chemical shifts of all the anions appear in the same region as those of the corresponding 'parent fullerenes' (C_{60}^{6-} and C_{70}^{6-}), confirming that **61–63** are reduced to hexaanions (**60**$^{6-}$**–63**$^{6-}$) and that the effect on the π-system is minimal[100].

The ^{1}H NMR of **60**$^{6-}$ shows two doublets at 2.74 and 1.34 ppm. The ^{1}H NMR spectrum of **61**$^{6-}$ contains one singlet at $\delta = 2.33$ ppm, which is shielded by 1.6 ppm compared to the signal of the neutral compound[100a]. Based on the ^{1}H NMR spectrum of **61**$^{6-}$, in which both protons sit above 6-MRs, the two doublets of **60**$^{6-}$ at $\delta = 2.74$ and 1.34 ppm were assigned as **Ha** (above 6-MR) and **Hb** (above 5-MR), respectively. While there is almost no change in the chemical shift of **Ha** ($\Delta\delta = -0.13$ ppm), the signal of **Hb**, compared to the neutral state, shows a dramatic upfield shift ($\Delta\delta = -5.01$ ppm). This leads to the conclusion that the added electrons are located mainly in the 5-MRs, thus converting them from paratropic to diatropic rings, while the ring currents of the 6-MRs experience little change. These results agree well with calculations performed by Haddon and coworkers[98,101].

The isomers **62** and **63** were reduced to their respective hexaanions as a mixture and were distinguished according to their peak area ratio[100b]. The ^{1}H NMR spectrum of **62**$^{6-}$ contains two doublets at $\delta = 2.27$ ppm (**Ha**) and $\delta = -0.255$ ppm (**Hb**). The ^{1}H NMR spectrum of **63**$^{6-}$ contains two doublets, one at 2.34 ppm (**Ha**) and the other at 3.6 ppm (**Hb**).

The full assignment of the ^{1}H NMR chemical shifts, of the two isomers **62**$^{6-}$ and **63**$^{6-}$, was possible because the proton **Ha** of both isomers is located above the same 6-MR of the C_{70} framework. The substantial upfield shifts of both **Hb** peaks indicate increased diamagnetism of the 5-MRs in C_{70}^{6-}. While the chemical shifts of protons **Ha** are very similar in both **62**$^{6-}$ and **63**$^{6-}$, those of the **Hb** are quite different. In **62**$^{6-}$, where the bridge is positioned at the C_{70} pole, the chemical shift of **Hb** is shifted to much higher field than in **63**$^{6-}$. This indicates that the added charge is more concentrated on the polar 5-MRs and that the charge distribution is not homogeneous.

The study of the ^{1}H NMR chemical shifts of the reduced methanofullerenes (**60**$^{6-}$**–63**$^{6-}$) provides an understanding of the aromatic behavior of both C_{60}^{6-} and C_{70}^{6-}. The extra

electrons in both hexaanions are located mainly in the 5-MRs, rendering them diatropic (aromatic). The lower symmetry of C_{70}^{6-} causes an asymmetrical charge distribution, where the extra charge concentrates mostly in the 5-MRs, especially the polar ones. Hence, the difference in the aromatic character of the hexaanions of C_{60} and C_{70} stems from the difference in geometry and symmetry[100].

C. ^{13}C NMR Spectra of Fullerene Anions

More light can be shed on the effect of geometry and symmetry on fullerene anions by studying their ^{13}C NMR chemical shifts that are affected by both charge distribution and ring currents.

1. INADEQUATE experiment of C_{70}^{6-}

In order to conclusively determine the chemical shift of each carbon type in C_{70}^{6-}, a 2D INADEQUATE NMR experiment was performed on a carbon-13 enriched fullerene[102]. This experiment correlates between the ^{13}C NMR absorption of a carbon to that of its bonded neighbor.

Four interactions make the assignment of the carbon connectivity possible. The interaction between the peak that appears at 133.6 ppm and the peak at 158.3 ppm, both representing 10 carbons, leads to the following assignment: $\delta_{\mathbf{a}} = 133.6$, $\delta_{\mathbf{b}} = 158.3$, $\delta_{\mathbf{c}} = 152.3$, $\delta_{\mathbf{d}} = 138.1$, $\delta_{\mathbf{e}} = 149.8$ (Figure 20).

Comparison between the ^{13}C NMR chemical shifts of the neutral C_{70} and the hexaanion shows a large shift change for carbons **a** and **e**, which are located at the pole and the 'equator' of the fullerene, respectively. Carbons **a** have a strong upfield shift ($\Delta\delta = -17$ ppm), due to the concentration of the negative charge on the polar 5-MR. On the other hand, the **e**-type carbons have a strong low-field shift ($\Delta\delta = 19$ ppm), which originates from a decrease in the charge distribution on the carbons at the equator of the C_{70}^{6-} surface, as well as from global ring currents. Carbons **b, c** and **d** have smaller changes in their chemical shifts. These shifts most likely result from local effects in the magnetic ring currents of neighboring rings[102].

It is also possible to measure the carbon–carbon couplings from an INADEQUATE experiment. The most significant change in the magnitude of the coupling constants was

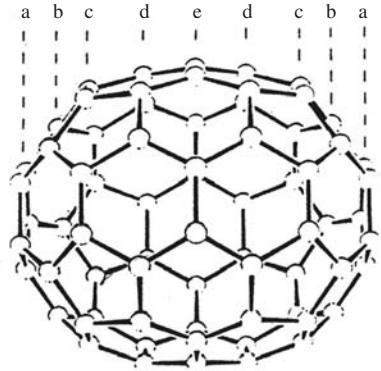


FIGURE 20. The different types of carbon in C_{70}. From, R. Taylor, J. P. Hare, A. K. Abdul-Sada and H. W. Kroto, *J. Chem. Soc., Chem. Commun.*, 1423 (1990)—Reproduced by permission of The Royal Society of Chemistry

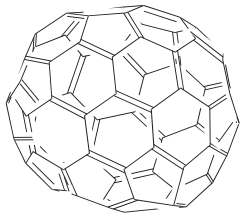
observed for $^{1}J_{a,b}$, which becomes smaller by 7 Hz in the hexaanion. This confirms that the location of the charge is at the poles, leading to an increase in the bond length between carbons **a** and **b**.

These results are in good agreement with the findings of the methanofullerene study[100] and calculations[101b]. Thus, it was concluded that the low aromatic character of C_{70}^{6-} results from an asymmetrical charge distribution in the hexaanion and reduced aromaticity of some of the 6-MRs.

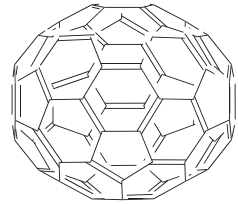
2. *^{13}C NMR spectra of the anions of higher fullerenes*

As mentioned previously, the ^{13}C NMR signals of both C_{60}^{6-} and C_{70}^{6-} are deshielded in comparison to the spectra of the neutral species, even though negative charge is added[97]. In order to broaden the picture and obtain a better understanding of the reduction effect, higher fullerenes with different sizes and symmetries have also been studied.

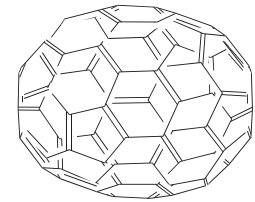
Higher fullerenes with different symmetries[103], $\mathbf{C_{76}}$-$\boldsymbol{D_2}$, $\mathbf{C_{78}}$ ($\boldsymbol{C_{2v}}$, $\boldsymbol{C_{2v'}}$ and $\boldsymbol{D_3}$) and $\mathbf{C_{84}}$ ($\boldsymbol{D_2}$ and $\boldsymbol{D_{2d}}$), were reduced with lithium metal to diamagnetic, multiply charged anions[104]. It was found that the overall ^{13}C NMR chemical shifts (i.e. the centers of gravity) of all of the anions are deshielded, compared to the neutral fullerenes. The shifts in the centers of gravity, compared to the neutral, were found to be $\Delta\delta = 6.8$, 8.5, 5.5 and 8.2 ppm for $\mathbf{C_{76}}$-$\boldsymbol{D_2}$, $\mathbf{C_{78}}$-$\boldsymbol{D_3}$, $\mathbf{C_{78}}$-$\boldsymbol{C_{2v}}$ and $\mathbf{C_{84}}$ ($\boldsymbol{D_2}$+$\boldsymbol{D_{2d}}$), respectively. These shifts are smaller than that of C_{60} ($\Delta\delta = 14$ ppm), but larger than that of C_{70} ($\Delta\delta = 0.9$ ppm)[97].



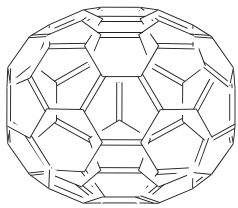
$\mathbf{C_{76}}$-$\boldsymbol{D_2}$



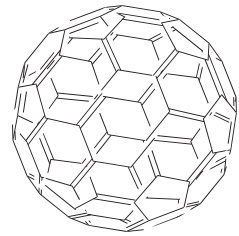
$\mathbf{C_{78}}$-$\boldsymbol{C_{2v}}$



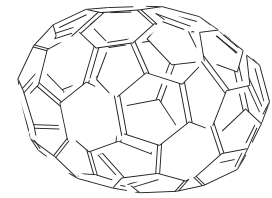
$\mathbf{C_{78}}$-$\boldsymbol{D_3}$



$\mathbf{C_{78}}$-$\boldsymbol{C_{2v}'}$



$\mathbf{C_{84}}$-$\boldsymbol{D_2}$



$\mathbf{C_{84}}$-$\boldsymbol{D_{2d}}$

The comparison between the experimental ^{13}C NMR shifts with those calculated by DFT as well as MO energy considerations made it possible to assign the higher fullerene anions as hexaanions. Therefore, as for C_{60} and C_{70}, the higher fullerenes can accept six electrons to their π-systems and form stable diamagnetic hexaanions[104]. In order to assess the aromaticity of these charged higher fullerenes, it is imperative to study the ^{3}He

NMR chemical shifts of the appropriate endohedral fullerenes (fullerenes that contain helium atoms)

D. ^{3}He NMR Spectra of Lithium-reduced Fullerenes — Anisotropy Inside the Cage

The internal cavities of fullerenes were found to be sufficiently large to encapsulate helium atom(s) and thus form stable helium compounds[105]. The ^{3}He atom can be used as an internal probe for the magnetic shielding environment inside the fullerene, thus allowing the study of the aromaticity of the fullerenes. The ^{3}He NMR chemical shifts of ^{3}He atoms encapsulated in C_{60} and C_{70} are found to be $\delta = -6.3$ and -28.8 ppm, respectively[106]. These results indicate a significant diamagnetic ring current in C_{60} and an even larger one in C_{70}.

Reduction of a mixture of ^{3}He@C_{60} and ^{3}He@C_{70} with lithium metal led to the ^{3}He NMR spectra of both endohedral fullerene hexaanions[107]. As predicted by calculations[108], the ^{3}He inside the C_{60}^{6-} was strongly shielded ($\delta = -48.7$ ppm) while that inside the C_{70}^{6-} was strongly deshielded ($\delta = +8.3$ ppm) relative to those in the neutral fullerenes (Figure 21). The shielding/deshielding effect is an indication of an increase/decrease, respectively, in the aromatic character of the fullerenes. In addition, this effect provides compelling evidence for the ability of electrons to move freely about the surfaces of such spheroidal π-systems.

As far as the lithium reduction products of higher fullerenes are concerned, their ^{3}He NMR chemical shifts lie between two extremes: the high-field shift of ^{3}He@C_{60}^{6-} and the low-field shift of ^{3}He@C_{70}^{6-}[109]. Therefore, an 'aromaticity scale' of the fullerene anions can be suggested: $C_{60}^{6-} > \mathbf{C_{78}}^{6-}(\boldsymbol{D_3}) > \mathbf{C_{84}}^{6-}$ (two isomers)$> \mathbf{C_{76}}^{6-} > \mathbf{C_{78}}^{6-}(\boldsymbol{C_{2v'}}) > \mathbf{C_{78}}^{6-}(\boldsymbol{C_{2v}}) > C_{70}^{6-}$ (Table 2).

Comparison between the ^{3}He NMR chemical shifts of the neutral fullerenes and their anions shows that the changes in the chemical shifts are different from one fullerene to

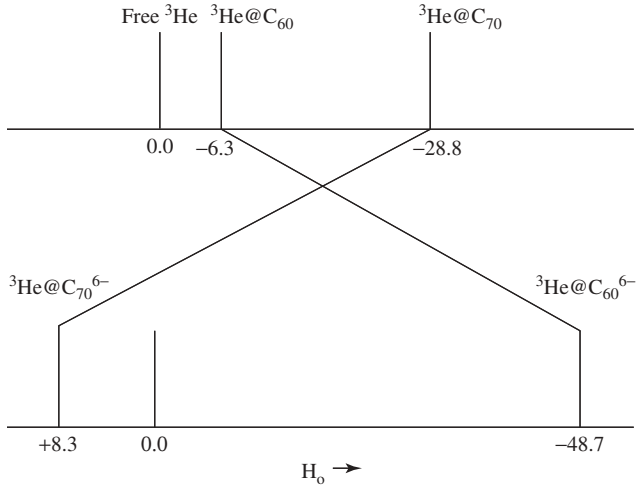


FIGURE 21. The ^{3}He NMR chemical shifts for C_{60}, C_{70} and their hexaanions. Reprinted with permission from Reference 107. Copyright 1998 American Chemical Society

TABLE 2. ^{3}He NMR chemical shifts of ^{3}He@C_n, ^{3}He@C_n^{6-} and their respective di-helium species (in parentheses) (Reproduced by permission of Wiley-VCH Verlag GmbH from Reference 109)

	Neutral	Anion	$\Delta\delta$ (δ^3He@C_n^{6-} − δ^3He@C_n)
^{3}He@C_{60}	−6.40	−49.27, (−49.17)	−42.87
^{3}He@C_{70}	−28.82, (−28.81)	+8.20, (+8.04)	+37.02
^{3}He@C_{76}	−18.75, (−18.61)	−20.62, (−20.55)	−1.87
^{3}He@C_{78}-C_{2v}	−16.91, (−16.79)	−10.02	+6.89
^{3}He@C_{78}-D_3	−11.94	−32.39, (−32.54)	−20.45
^{3}He@C_{78}-$C_{2v'}$	−17.60, (−17.45)	−13.50, (−13.61)	+4.1
^{3}He@C_{84}	−7.53, (−7.57)	−22.12, (−22.06)	*ca* − 12
Mixture of isomers	−8.40, (−8.43) −8.99 −9.64, (−9.68)	−22.80, (−22.76)	

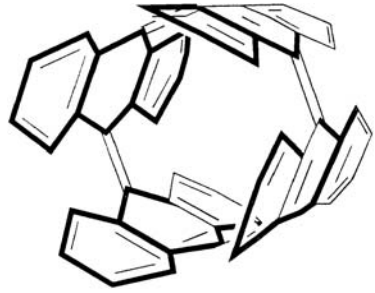
another. While the ^{3}He bands of $\mathbf{C_{78}}^{6-}$-$\boldsymbol{D_3}$, $\mathbf{C_{84}}^{6-}$ and $\mathbf{C_{76}}^{6-}$ are shifted to a higher field as a result of their reduction, those of the two isomers of $\mathbf{C_{78}}^{6-}$-$\boldsymbol{C_{2v}}$ are shifted to a lower field. These changes point to an increase or decrease, respectively, in the aromaticity of the fullerenes. These two opposite trends were observed in the reduction of C_{60} and C_{70}, but in a much more 'dramatic' manner. These results show that the magnetic properties of fullerenes and their anions are not simply related to the number of carbons or the number of electrons in the π-system. This is demonstrated by the three C_{78} isomers, which behave differently. The aromatic character of $\mathbf{C_{78}}$-$\boldsymbol{D_3}$ increases upon reduction, whereas that of the two $\boldsymbol{C_{2v}}$ isomers decreases[109].

The $^3He_2$@C_n^{6-} signal was also observed in most of the ^{3}He NMR spectra of the fullerenes[109], including $^3He_2$@C_{70}^{6-} and $^3He_2$@C_{60}^{6-} [110]. The di-helium signals are significantly smaller than those of the mono-helium, and appear in a slightly higher or lower field. A general trend is suggested, namely that the helium absorptions of $^3He_2$@C_n^{6-} are shifted to a lower field for the 'highly aromatic' fullerene anions (C_{60}^{6-}, $\mathbf{C_{84}}^{6-}$, $\mathbf{C_{76}}^{6-}$). On the other hand, when the mono-helium signal is shifted to a low field (C_{70}^{6-}, $\mathbf{C_{78}}^{6-}$-$\boldsymbol{C_{2v}}$), the di-helium shift absorbs at a higher field.

VIII. PICOTUBE — A SIMPLE MODEL OF NANOTUBES

The conjugated tubelike PAH 5,24:6,11:12,17:18,23-tetra[1,2]benzenotetrabenzo[*a*,*e*,*i*,*m*] cyclohexadecene (**64**), also known as 'picotube', has been synthesized by Herges and coworkers in gram quantities via dimerization metathesis of tetradihydrodianthracene[111]. The crystal structure of neutral **64**, which consists of four anthracene units, shows D_{4h} symmetry[112]. However, DFT calculations and low-temperature IR studies indicate that the D_{4h} structure is only a time-averaged structure of two D_{2d} rapidly interconverting isomers, obtained by twisting of the quinoid double bonds[113].

The ^{1}H and ^{13}C NMR spectra indicate that neutral **64** possesses D_{4h} symmetry in solution (NMR timescale)[111]. The reduction of **64** with lithium metal affords a stable tetraanionic species ($\mathbf{64}^{4-}$) that has lower symmetry than in the neutral state[114]. The reason behind the symmetry change is attributed to the encapsulation of two lithium cations inside the tube-shaped molecule. This finding has been corroborated using ^{7}Li NMR spectroscopy and DFT calculations. The calculations suggest the formation of doubly bridged ethylene units by the coordination of two endohedral Li cations to the double bonds that are already coordinated by Li cations from outside the tube (Figure 22). Such a structure explains the charge alternation found in the system and the conformational change accompanied by lithium reduction[114].



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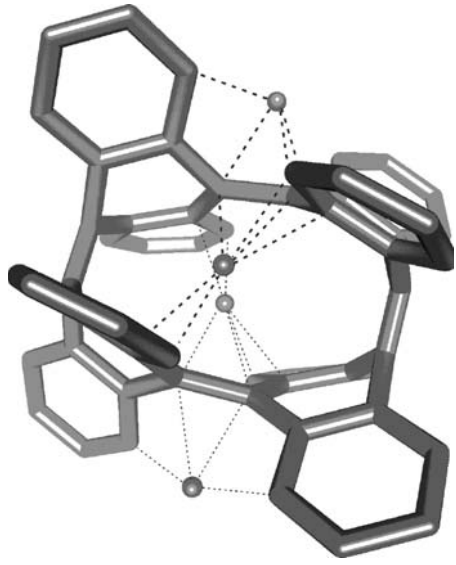


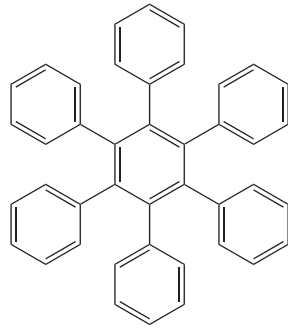
FIGURE 22. The calculated structure of $\mathbf{64}^{4-}$. Reproduced by permission of Wiley-VCH Verlag GmbH from Reference 114

IX. PER-ARYLATED BENZENES — TOWARDS EXTENDED POLYCYCLES

A. Reduction of Hexaphenylbenzene and Hexa(4-*n*-dodecylbiphenyl)benzene

Benzene, the basic subunit of π-conjugated systems, can only be reduced to a radical anion[115]. When the benzene ring contains stabilizing substituents, like trimethylsilyl, it is possible to further reduce it to a dianion[116]. Phenyl groups can also stabilize the dianion of benzene by extending its π-system. The reduction of numerous phenyl-substituted benzenes has shown that this is indeed the case[117].

Due to the high symmetry of hexaphenylbenzene (**65**)[118], it was expected that its reduction by alkali metals would form a paramagnetic triplet state anion. However, the initial findings on the reduction of **65** using lithium metal pointed to the formation of three diamagnetic species[119]. The first two species were assigned as the dianion ($\mathbf{65}^{2-}$) and tetraanion ($\mathbf{65}^{4-}$) salts, whereas the third species was suggested to be a hexaanionic one ($\mathbf{65}^{6-}$).



(65)

The NMR spectra of $\mathbf{65}^{6-}$ showed that it has a lower symmetry than the parent neutral molecule, for it has two different patterns for the phenyl substituents (ABCDE and AA′BB′C). Phenyl-substituted benzenoid systems can undergo a dehydrogenative cyclization reaction when reduced[120]. The intermediate of such a reaction is consistent with the lower symmetry of $\mathbf{65}^{6-}$ and could be an alternative assignment to the third diamagnetic species.

The hexaanionic state of reduction of $\mathbf{65}^{6-}$ was established by finding a ROESY exchange crosspeak between the two types of *para* protons, which indicated that the ABCDE pattern in the NMR spectra corresponds to a phenyl group, and not to a fixed benzo substituent in a hypothetical intermediate[119]. Thus, it was ruled out that the third species is an intermediate of a cyclization reaction. Attempts were made in parallel to prove the high reduction state by quenching reactions with electrophiles. However, these attempts failed to yield a hexa derivative, probably due to a combination of the thermal instability of the hexaanion, re-aromatization and disproportionation reactions.

The charge distribution in $\mathbf{65}^{6-}$ resembles six covalently linked benzyl anions, in which each carbon of the central benzene ring is the benzylic position of the phenyl to which it is attached (Figure 23). As a result, the central benzene ring carries two charge units (the first example of a formal benzene dianion), and in order to avoid antiaromaticity it adopts a twist-boat conformation, as suggested by DFT (B3LYP/6-31G*) calculations. These

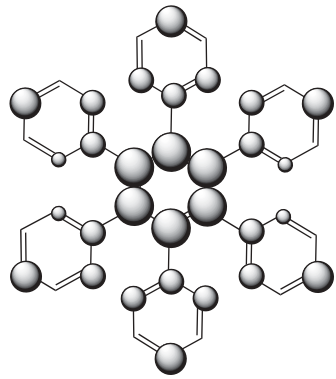


FIGURE 23. Charge distribution of $\mathbf{65}^{6-}$

calculations indicate that the D_2 twist-boat conformation is a minimum of the reduction species while the boat and chair structures were found to be transition states[119].

The stereodynamics of the twist-boat moiety is a pseudorotation process (Figure 24) that could only be observed in the NMR timescale in the hexaanion of an analogue system, i.e. hexa(4-*n*-dodecylbiphenyl)benzene (**66**)[121]—a more stable system due to the extension

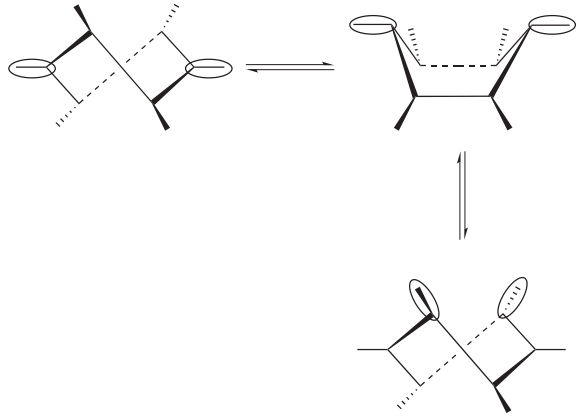
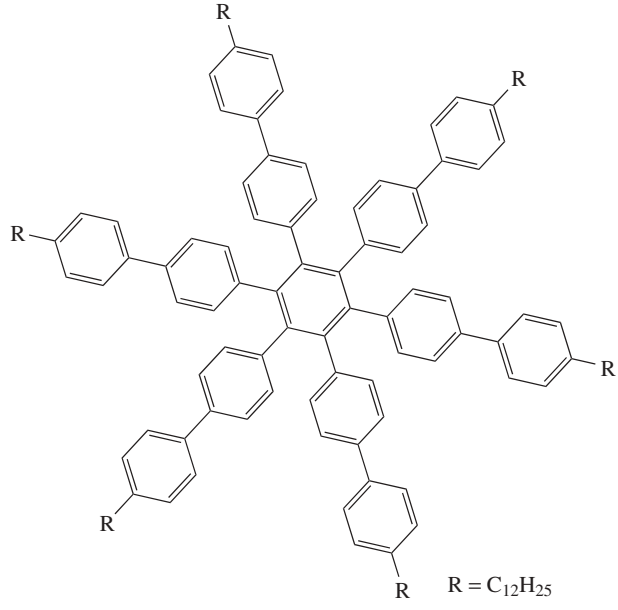


FIGURE 24. The pseudorotation process found in $\mathbf{65}^{6-}$ and $\mathbf{66}^{6-}$



(66)

of the π-system[122]. The hexaanion of **66** (**66**$^{6-}$) demonstrates yet another stereodynamic process: a slowing of phenylene rotation about the inner biphenyl bonds (which connect the inner phenylene rings to the central benzene ring), in contrast to the outer phenylene rings that maintain a fast rotation about the outer biphenyl bonds. The rate differences, beside the steric hindrance around the inner bonds, are a consequence of the increased conjugation in the hexaanion between the phenyl rings and the 'benzylic' positions at the central benzene ring. This stems from the charge distribution pattern, which showed that the charge is concentrated over the core of the molecule, i.e. the central benzene ring and the adjacent six phenylene rings connected to it (Figure 25). It also shows that the benzene ring accepts the greatest amount of charge, which accounts for adoption of the twist-boat conformation as in the case of **65**$^{6-}$. The charge distribution of the fragment that consists of a biphenylyl and the carbon of the central ring to which it connects resembles that of a biphenylmethyl anion, and **66**$^{6-}$ as a whole could therefore be considered as six covalently linked biphenylylmethylenyl anions[122].

The dynamic behavior in **66**$^{6-}$ could be followed by temperature-dependent ^{1}H NMR spectroscopy. A barrier of $\Delta G^{\ddagger}_{335} = 17.5 \pm 0.2$ kcal mol^{-1} was measured for the phenylene rotation, while the pseudorotation of the twist-boat benzene ring afforded a barrier of $\Delta G^{\ddagger}_{386} = 18.3 \pm 0.3$ kcal mol^{-1}. Advanced EXSY technique confirmed the validity of these findings and yielded the enthalpy and entropy of activation for the two processes.

The difficulties in chemical determination of the hexaanion reduction state of **65**$^{6-}$ were overcome in the extended system of **66**$^{6-}$. This was done by a redox experiment between the suspected hexaanion (**66**$^{6-}$) and the neutral parent compound (**66**) in the ratio of 2:1, which yielded the tetraanion (**66**$^{4-}$)[122].

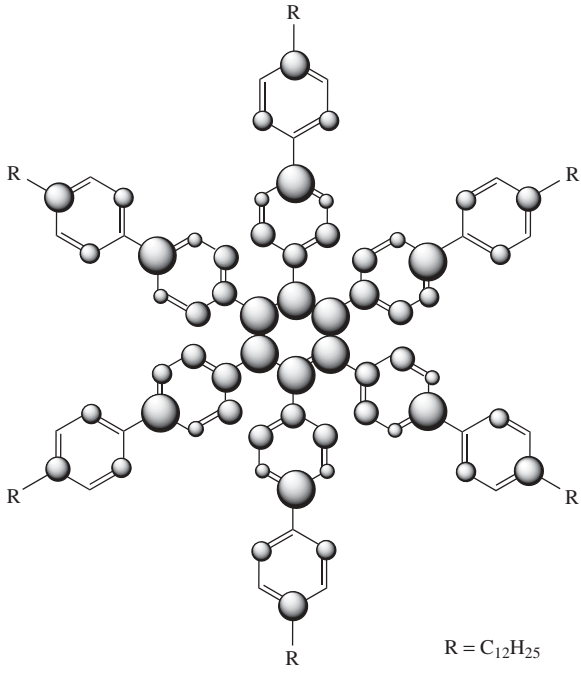
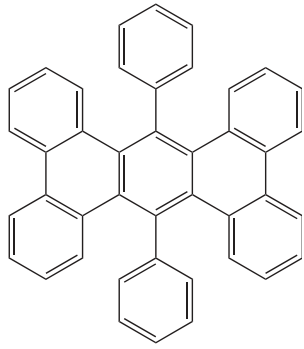


FIGURE 25. The charge distribution of **65**$^{6-}$

B. Reductive Cyclization of Hexaphenylbenzene Dianion

It was also found that the dianion $\mathbf{65}^{2-}$ undergoes partial regioselective dehydrogenative cyclization to yield $\mathbf{67}^{2-}$. The latter compound was oxidized and isolated as **67** in higher yields than previously published[122]. Bock and coworkers have reported the crystal structure of $\mathbf{67}^{2-}$, which has a highly distorted molecular skeleton (Figure 26)[123]. It was shown experimentally and by using quantum-chemical calculations that the lithium cation initiates the skeletal deformation, which eventually leads to the formation of the new C−C bonds.



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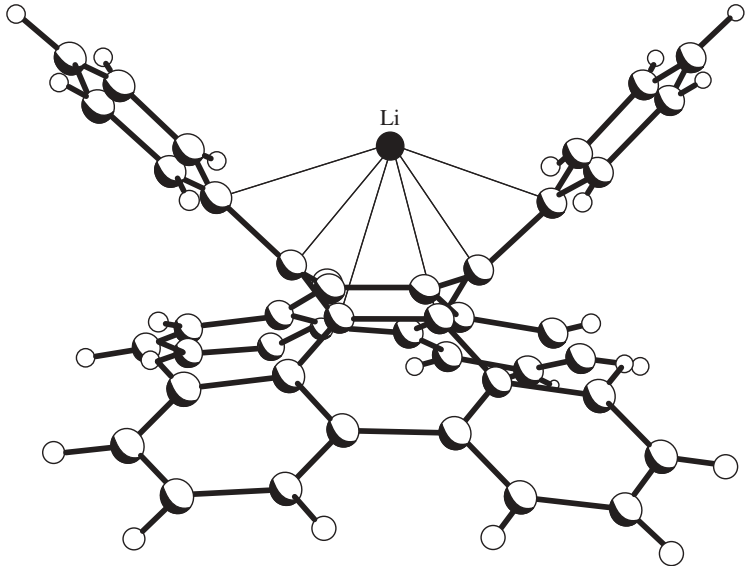


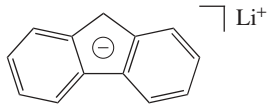
FIGURE 26. The X-ray structure of $\mathbf{67}^{2-}/2Li^{+}$. Reproduced by permission of Wiley-VCH Verlag GmbH from Reference 123

X. SOLID STATE NMR

Recently, solid state NMR has been applied in elucidating the structure of numerous lithium carbanions[124]. The solid state structures of such systems have so far been determined by X-ray crystallography, mostly in the presence of strong complexing agents[15c]. It was hoped that a comparison between solution and solid NMR data with information from X-ray crystallography would clarify whether the solid state structures of organolithiums are relevant models for the complexes in solution.

The X-ray and solution structures of lithium fluorenide (**68**) have been reported earlier[125, 126]. It was found that whereas the X-ray study suggested that the lithium is asymmetrically positioned above the fluorenyl unit, calculations and solution ^{13}C NMR showed a symmetrical structure. Thus, Johnels and Edlund used ^{13}C cross-polarization/magic angle spinning (CP/MAS) NMR in order to get further insight about the structure **68**.

It was found that the structure of **68** is dependent on the type of ligand used. In the bisquinuclidine complex (the same ligand as in X-ray study) it was found that the lithium cation is positioned asymmetrically above the fluorenyl framework, in accordance with the X-ray structure. The same is true for the diethyl complex. However, in the *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) complex the system was found to be symmetrical. It was argued that these results show that factors such as crystal packing may determine the actual crystal structure in such systems[124].



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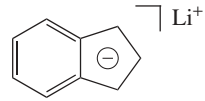

(69)

The symmetric geometry of the TMEDA complex of **68** was also confirmed by using the Rotational-Echo Double Resonance (REDOR) method, and the position of the lithium cation was determined with an error of about ± 0.2 Å[127]. However, the accuracy of the REDOR method could not be confirmed, because this complex has not been investigated by X-ray crystallography.

In order to get an indication about the accuracy of REDOR, the TMEDA complex of indenyllithium (**69**), a complex whose structure has been established by X-ray diffraction[17b], was studied[128]. It was found that the REDOR method systematically overestimates the Li−C distances by *ca* 0.2–0.15 Å (depending on the optimization method), and that the error becomes larger for longer distances. These studies have shown that the REDOR method is a valuable tool for the structural characterization of organolithium complexes and for correlating their solid state and solution structures.

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CHAPTER 8

Aspects of the synthesis, structure and reactivity of lithium enolates

JEAN-YVES VALNOT and JACQUES MADDALUNO

Laboratoire des Fonctions Azotées & Oxygénées Complexes de l'IRCOF, UMR 6014 CNRS, Université de Rouen, F-76821 Mont St Aignan Cedex, France
Fax: +33 23 552 2971; e-mails: jean-yves.valnot@univ-rouen.fr, jmaddalu@crihan.fr

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I. INTRODUCTION

Enolates, and in particular lithium enolates, are central intermediates in a wide range of reactions. These reactions encompass most of the basic organic chemistry programs since

they are key partners in the chemistry of carbanions, and their development has been continuous since the 1970s.

Therefore, writing a review on the synthesis, structure and reactivity of lithium enolates in 2005 is a formidable challenge and the result would probably require an entire (quite large!) volume of the collection. Obviously, many reviews have been written over time on the different aspects of this chemistry and some among the most important ones are cited throughout the chapter. Thus, the organization of this chapter required many choices. This was both difficult and arbitrary and is reflected in the organization of the whole chapter. Generally speaking, we have chosen to give first an overview about the different topics covered here, taken in most cases from previous compilations. We have then tried to update these fundamental concepts with data taken from more recent works, giving a complementary point of view to well-established results or proposing new models or theories. In particular, we have tried to place special emphasis on the problems related to asymmetric synthesis involving enolates.

The second section, immediately following this introduction, tries to provide an account on the theory and the methods known to give (stereocontrolled) access to the enolates. The third section gathers the most important descriptions available about lithium enolates in the gas or solid phase, as well as in solution. These data are classified according to the physicochemical techniques employed. The fourth section of this chapter, dedicated to the reactivity of lithium enolates, has been restricted to three of their main applications, namely the protonation, alkylation/acylation and aldolisation reactions.

For the sake of brevity, such important transformations as the conjugate addition of lithium enolates on activated olefins or the halogenation, amination, oxidation ... of enolates have not been considered here. Each of these reactions has been the object of considerable developments lately, in particular for their asymmetric versions, and giving even short accounts about the state of the art would have been extremely space-consuming.

To close this introduction, we wish to apologize to authors who may feel that their contribution has not been given the importance it deserves: the amount of literature to be covered in the field is far more than what we could embrace.

II. SYNTHESIS OF LITHIUM ENOLATES

Lithium enolates result formally from the deprotonation of a carbonyl compound bearing at least one α-proton by a lithiated base through a simple acid–base reaction, made possible by the relatively high acidity of protons in α of carbonyl groups. These reagents have been known for a very long time, although the originally protic conditions in which they were prepared implied their reversible formation. The pivotal role played by preformed lithium enolates since the 1970s explains why the development of their chemistry parallels the progress of synthesis. Their versatility and efficiency as nucleophiles is exceptional (particularly in aldolisation and alkylation), and these reagents are a unique asset for the C–C bond formation.

Actually, until the 1960s, sodium and potassium enolates were generally preferred because they are easily prepared with bases such as alcoholates. These bases lead to the corresponding enolates under thermodynamic equilibrium, the difference between the pK values of the ketone and of the conjugate alcohol affording a partial and reversible deprotonation. However, the case of ketones bearing two different deprotonation sites raises the issue of the regioselectivity, known to depend on the size of the cation, the temperature, the solvent as well as conformational effects. The stereocontrol of the enolate C=C double bond is another crucial problem, in particular because of the stereochemical implications. These phenomena explain that multiple side-reactions and low selectivities are commonplace, hampering the applications of enolates in synthesis for a while.

The situation changed dramatically in the early sixties when Stork and coworkers showed that lithium enolates can be reacted with electrophiles without equilibration, even when they are regiounstable[1,2]. This fundamental finding was confirmed soon after by House and Kramar[3] and then by Caine[4]. From there, considerable attention has been paid to the syntheses of these species, and in particular to the regio- and stereoselective routes. The use of strong and relatively non-nucleophilic bases such as lithium amides (and in particular LDA, LiHMDS or LiTMP) in an appropriate solvent (generally THF, in which the enolates are soluble and reactive) thus became a standard for the total and irreversible transformation of a carbonyl compound into its lithium enolate[5,6]. The early developments of the use of lithium amides as strong bases to generate enolates is covered in an important review by Heathcock[7]. Note, however, that solutions of LDA in hydrocarbon solutions such as hexane or toluene are suited to generate lithium enolates from ketone, *t*-butyl esters or carboxamides as isolable non-solvated white solids[8].

The position of the lithium cation in the enolates has been the object of much debate. It is now well established that the cations of the strongly electropositive metals of groups I, II and III stand closer to the oxygen than to the carbon atom while this metalotropy is more balanced with transition metal enolates. The structure of the lithium enolates in vacuum, in the solid state as well as in solution is discussed in detail in the next section of this chapter.

Trying to organize the information extracted from the enormous amount of data about lithium enolates accumulated over time constitutes a challenge which involves many arbitrary choices. Lithium enolates are so close to the heart of organic chemistry that their general properties and reactivity are evoked in all organic chemistry textbooks at almost every level. Thus, advanced courses provide compilations of basic information and some recent literature on this topic. For an extensive coverage of the historical and general background regarding lithium enolate synthesis, the reviews by d'Angelo[9], Caine[10] and Heathcock[7] are strongly recommended. Other good reviews are also available and should be consulted for the main applications of enolates, in particular for the aldolisation reaction[11,12].

Rather than arranging this presentation according to the structure of the original carbonyl substrates (ketones, aldehydes, esters, amides, thioesters ...), we prefer to focus on the major routes employed to generate enolates, with emphasis on the important results published in recent years. Four sections will thus describe: (i) direct deprotonation; (ii) access from enones and other particular α-substituted ketones; (iii) access from enol ethers and esters; and (iv) access by miscellaneous methods. This list of topics is similar to that employed in the reviews mentioned above, a characteristic which can be regarded as an advantage or a disadvantage. The problems arising from the regio- and stereoselectivities will be discussed separately in the relevant cases.

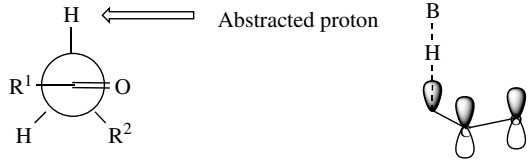
A. Synthesis of Enolates by Direct Hydrogen Abstraction

As mentioned above, the protons α to carbonyls are relatively acidic ($pK = 20-28$ in DMSO)[13] and can be directly abstracted by a large set of bases (mostly alcoholates, amides, aryl- and alkyllithiums). The relative acidities induced by the esters and ketone functions and the influence of their cyclic or acyclic character on this parameter have been determined in DMSO by Bordwell[14] and confirmed by Arnett and coworkers[13]. The measurements of the pK_a values and the calculation of the associated thermodynamic characteristics led the same authors to conclude that acyclic ketones are slightly more acidic than the corresponding esters, cyclic members of both series are more acidic than acyclic analogues, and alkyl substitution on the carbon bearing the acidic proton reduces acid strength while accumulating carbonyl groups increases the acidity[15]. The pK_a of

t-butyl phenylacetate in THF and the thermodynamic values associated to the equilibrium with its lithium enolate have also been determined[16].

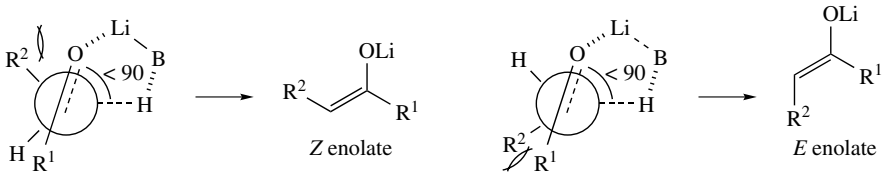
1. Mechanistic aspects

The incidence of the mechanistic course of the deprotonation on the geometry of the resulting enolate explains why many physicochemical studies have been devoted to this problem. The initial approaches attempted to predict the orientation of the leaving proton with respect to the carbonyl group. As early as 1956, Corey and Sneen proposed that stereoelectronic effects could account for several results showing that the proton abstracted by the base lies in a plane more or less perpendicular to the vicinal carbonyl group[17]. A 'CH-π overlap', that is a stabilizing proper orbital overlap of the C−H σ bond with the carbonyl π orbital (Scheme 1), would explain the stabilization of the transition structure[18,19].



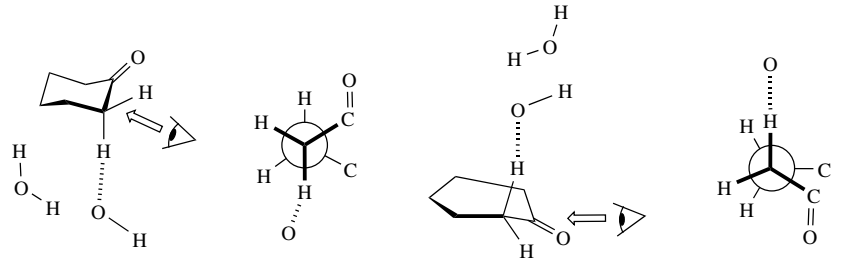
SCHEME 1. Stereoelectronic control over the orientation of the abstracted proton[17–19]

From there, theoretical descriptions of increasing sophistication were proposed to model the proton transfer. In 1985, Moreland and Dauben made the assumption that a linear relationship links the energy difference in conformation of the carbonyl compound to the activation barrier. Resorting to molecular mechanics, they established that the steric interactions occurring at the (cyclic) transition state govern the course of the stereoselection[20]. This model was improved a few years later by Xie and Saunders who proposed, on the basis of their own results and those of others, that the constraints of a cyclic structure formed during the deprotonation can overweight the stereoelectronic preference[21]. A consequence is that the angle between the CO and the departing H can be smaller than 90° (Scheme 2). Looser models in which the 90° angle is restored are to be considered in a THF–HMPA dissociating medium.



SCHEME 2. Cyclic transition structures at the deprotonation[20,21] (B = base)

More recently, Houk and coworkers have tried to address the problem of the selectivity of the deprotonation of bridged (camphor-type) or cyclic (cyclohexanone) ketones using quantum mechanical methods[22]. Using a water–hydroxy anion complex to model the solvated base, they established that the overlap effect is essential to the deprotonation, but cannot account for the selectivity in favor of the axial proton observed experimentally.



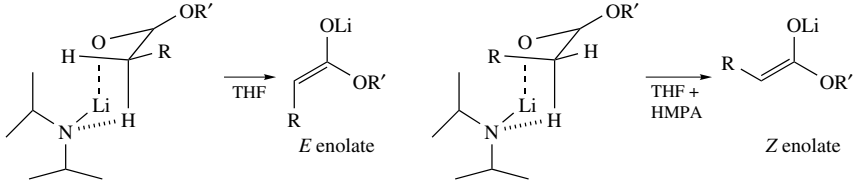
Deprotonation of the axial H:
almost perfectly staggered situation

Deprotonation of the equatorial H:
almost eclipsed situation

SCHEME 3. Calculated transition structures for the deprotonation of the axial (left) and equatorial (right) proton of cyclohexanone[22]

Torsional effects (linked to the preference for staggered arrangements at the transition state) are more likely to be at the origin of this selectivity (Scheme 3).

The models become more complex when they take the structure of the base into account. A simple and very popular hypothesis was proposed for esters by Ireland and coworkers in pioneering work[23]. This model supposes that a monomeric LDA is the active species and that the lithium–carbonyl interaction leads to a six-membered cyclic Zimmerman–Traxler chair-like transition state[24], at which a more-or-less concerted proton transfer occurs. The resulting preference for the *E* enolate observed in THF and the *Z* preference in THF–HMPA mixtures, an issue discussed in more detail below, could even be accounted through steric considerations (Scheme 4).



The tight O–Li interaction renders
the carbonyl 'bulky' in THF

The O–Li interaction decreases in the presence of HMPA:
OR′ becomes the bulkiest group

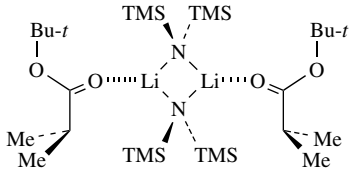
SCHEME 4. The Ireland model to explain the *E* selectivity in THF (left) and the *Z* preference in THF/HMPA mixtures (right) during the deprotonation of an ester by LDA[23]

This model received widespread attention for its predictive power. However, unrealistic features were pointed out in Ireland's description, such as its nonlinear C-to-N proton transfer[25] and the poor orientation of the leaving proton with respect to the carbonyl. These discrepancies were partly resolved by a semiempirical study on the deprotonation of acetaldehyde by a monomeric lithium amide published later by McKee[26]. A relatively flat six-membered transition state (exhibiting an almost linear C−H−N arrangement) was found to be favored, in overall agreement with Ireland's hypothesis, except for the chair topology. Note that an eight-membered transition state built on the same type of interactions has been proposed to account for the stereoselectivity of the deprotonation of α,β-unsaturated carboxamides[27].

The chair model has been increasingly challenged when the possible intervention of various types of aggregates of the lithiated species in solution was evidenced[28]. The

aggregation level of the intermediates and their involvement in the deprotonation sequence remains a matter of persistent debate since rate studies often reveal fractional reaction orders consistent with fragmentations such as deaggregation. The lack of structural detail in most solutions explains why these questions are generally impossible to untangle. In addition, the species observable in solution by NMR or other spectroscopic techniques are not necessarily those that are directly involved in the reactions. All these facts explain why computational methods have become almost compulsory in any in-depth analysis of reactions involving organolithium compounds.

It is generally admitted that a preliminary complex ('pre-enolization' or 'pre-transition state' complex) resulting from the docking of the oxygen of the carbonyl on the (or one of the) lithium cation(s) of the base[29,30], acting as a Lewis acid[31], is formed by partial desolvation. Such a complex has been identified in particular for carbamates[32] or carboxamides[33] by IR or NMR[34], and the energy of interaction between its components evaluated by *ab initio* calculations (for instance 37.5 kcal mol^{-1} for MeLi + $MeCONH_2$)[35]. An aggregate between *t*-butyl isobutyrate and the dimer of lithium bis(trimethylsilyl)amide (LiHMDS) has also been crystallized, demonstrating the capacity of the oxygen of the carbonyl to dock on the lithium (Scheme 5)[36].

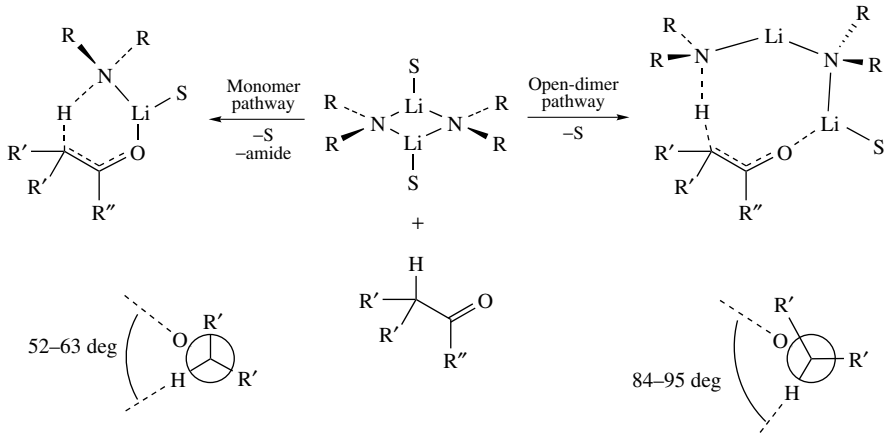


SCHEME 5. Pre-enolization complex between $(LiHMDS)_2$ and two molecules of *t*-butyl isobutyrate[36]

The structure in solution of popular lithiated bases such as LDA, LiHMDS or lithium 2,2,6,6-tetramethylpiperidin-1-ide (LiTMP) in usual solvents (ether, THF, toluene ...), alone or in interaction with frequently used ligands (HMPA, TMEDA, NEt_3 ...), has been extensively studied. These spectroscopic and theoretical efforts, in particular by Collum's group[37,38], offered a remarkably detailed panorama of the field. The central role played by dimers of these usual lithium dialkylamides is often pointed out[39,40]. When steric constraints allow it, these dimers organize around a N−Li−N−Li lozenge core that keeps the strong N−Li dipoles antiparallel to each other. In equilibrium with their monomer[41], the dimers are now considered as the key players in the deprotonation sequence[42].

The possible occurrence of an open dimer, resulting from the fragmentation of the central Li−N core upon docking of the carbonyl, was introduced progressively in the 1990s, on the basis of spectroscopic, theoretical[43,44] and crystallographic data[45]. This model, somewhat comparable to the one proposed previously for the addition of dimeric methyllithium on aldehydes[46], presents the advantage of allowing both the substrate activation by Lewis acidic precomplexation of the carbonyl and the liberation of a potentially basic lone pair for reaction of one lithium amide without intervening deaggregation. The partial core cleavage would also allow a subsequent proton transfer along a favorable eight-membered cyclic transition state.

The dimer-based mechanistic pathways in the deprotonation of ketones and imines have been carefully studied by theoretical (MNDO) methods, particularly for LDA and pinacolone, microsolvated by various solvents (Scheme 6)[47]. The results suggest that, even if no general rule can be drawn, the open dimer mechanism is expected to dominate under all circumstances, and particularly with increasing amide and solvent steric



SCHEME 6. Monomer *vs.* open-dimer pathways in the aldol reaction (S = solvent)[47]

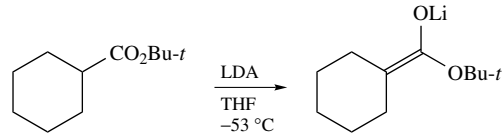
demands. However, increased ketone bulk is expected to strengthen the competitiveness of the monomer pathway.

After the proton transfer completion, the enolates tend to merge in (1:1) mixed aggregates with the excess lithium amide[34]. These species have so far been the object of relatively little attention[48]. Then, as the enolization proceeds to completion, the aggregated enolates form at the expense of the mixed dimers. Another aspect to be considered is the interaction between the lithium enolate and the amine released after protonation of the amide[49]. This phenomenon will be discussed in the section dedicated to the enantioselective reactions of enolates.

Taking the solvation into account in such models is both very difficult and necessary for the best possible understanding of these exceedingly complex phenomena. The disolvation of the amides dimer (one solvent per lithium in THF, THF + HMPA or THF + DMPU)[50] seems to be indicated, while trisolvated dimers appear relatively unstable. However, a very extensive semiempirical theoretical (MNDO) study on the various cyclic and open mixed aggregates formed by LDA and LiTMP with LiCl or three different enolates, solvated by discrete molecules of THF or HMPA, showed that general conclusions are almost impossible to draw[48]. A complex interplay of steric effects, induced by the partners of the aggregate and the solvent, seems to be the dominant influence on the relative stabilities of the species characterized.

The mechanism of the deprotonation of esters by LDA has been particularly detailed. A kinetic and IR spectroscopic approach to the deprotonation of *t*-butyl cyclohexylcarboxylate by LDA in THF confirmed the formation of a complex between a monomeric LDA and the ester, in fine accord with Ireland's model[51]. The data suggested that a spectroscopically invisible dimer–monomer pre-equilibrium occurred first, followed by a rate-determining proton transfer, leading to the overall rate laws reported in Scheme 7.

Actually, this system is extremely solvent-dependent, four different mechanisms being observed in pure THF (disolvated LDA monomer pathway), THF + HMPA (triple ion-based metallation), DMPU (mono- and disolvated LDA monomer) or *t*-butyl methyl ether (monosolvated LDA dimer)[33]. However, these mechanistic differences do not necessarily translate into rate differences. Note that in *t*-BuOMe, the complex between the ketone and the monosolvated LDA dimer evolves into an open dimer. In this reaction model, it was also shown, by multinuclear NMR, that the progressive formation of mixed aggregates



$$\frac{1}{2}(i\text{-Pr}_2\text{NLi}\cdot\text{THF})_2 + \text{THF} + \text{ester} \underset{}{\overset{K_{eq.}}{\rightleftharpoons}} i\text{-Pr}_2\text{NLi(THF)}_2\cdot\text{ester}$$

$$i\text{-Pr}_2\text{NLi(THF)}_2\cdot\text{ester} \xrightarrow{k} \text{enolate}$$

$$-\frac{d(\text{ester})}{dt} = k\,K_{eq.}\,[\text{THF}][(i\text{-Pr}_2\text{NLi}\cdot\text{THF})_2]^{1/2}\,[\text{ester}]$$

SCHEME 7. Kinetics of *t*-butyl cyclohexene carboxylate deprotonation[51]

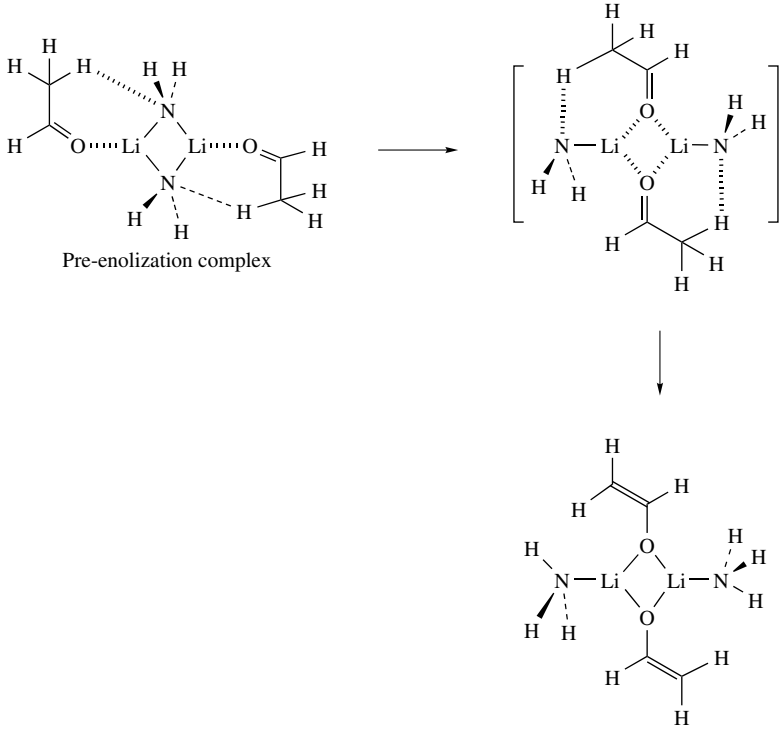
between LDA and the enolate mentioned above resulted in a progressive slowdown of the deprotonation rate[34]. This autoinhibition effect correlates with the relative stabilities of the mixed aggregates in the solvent retained. In contrast, the positive effect of a poorly coordinating ligand such as NEt_3 on the enolization of methylcyclohexanone by LiHMDS in toluene has been explained by a strong affinity of this amine for the transition structure[52]. Most highly hindered amines, such as $(i\text{-Bu})_3N$, were shown to have no effect on the rate of this same reaction[53]. These results with amines are worth highlighting with respect to the relatively moderate acceleration induced by hindered dialkyl ethers, as shown in toluene for the deprotonation of 2-methylcyclohexanone by LiHMDS[54].

Note that the deprotonation of cyclohexanone-derived imines has equally been the subject of thorough spectroscopic[55–57] and theoretical[58] studies but will not be discussed in this review. For the sake of brevity, lithium enolates derived from (di)thioesters[59] and selenoamides[60], which have also found applications in synthesis, will not be detailed here either.

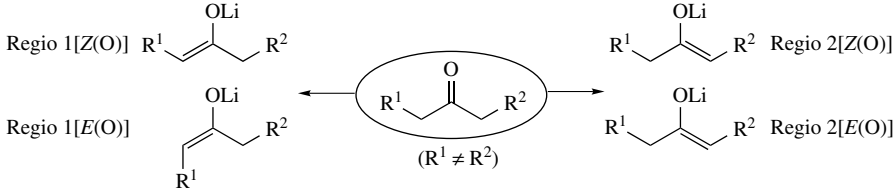
We close this section with a rather different theoretical model proposed recently by Mair and colleagues to account for the deprotonation of aldehydes. Working on the canonic $MeCHO + H_2NLi$ system, these authors reached the conclusion that a rearrangement of the original complex between the dimer of the amide and two aldehydes occurs[61]. The resulting new complex, in which the oxygen of the carbonyls adopts a bridging position (Scheme 8), lies much higher in energy than the original one, but is closer to the transition state.

2. Stereoselective generation of enolates

Controlling both the site of the proton abstraction and the configuration of the newly created double bond upon deprotomation of a ketone is a fundamental operation of organic chemistry, since the Z/E ratio of the enolate can exert a strong influence on the stereoselectivity of its reactions[62]. This explains why the identification of the parameters influencing the configuration of the double bond created upon deprotonation has been the object of many studies[7]. For esters, carboxamides, thioesters and related derivatives the regioselectivity of the deprotomation is unambiguous and, the configuration of the double bond remains the only issue of concern. In the following we will refer to the E and Z enolates as being those bearing the β-substituent with the highest CIP priority *trans* or *cis* to the OLi moiety, respectively (Scheme 9). They will be denoted by E(O) and Z(O) following Masamune's original suggestion[63]. This choice guarantees that the same description always refers to the same type of structure, regardless of whether the enolate is derived from a ketone, aldehyde or ester.



SCHEME 8. Alternative model for the deprotonation of acetaldehyde by NH_2Li[61]

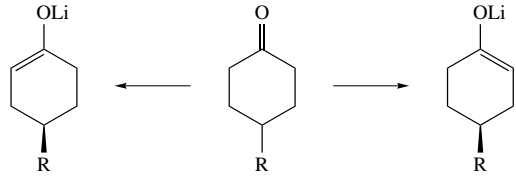


SCHEME 9. Regio- and stereochemical issues upon ketone deprotonation

In some cases, a third control to be secured is that of the enantioselectivity, such as for the deprotonation of prochiral ketones with nonracemic bases (Scheme 10).

a. Regiocontrol. It is now well established that when two different deprotonation sites are available, the thermodynamic (obtained by reversible process) and kinetic (obtained by irreversible process) enolates can be differentiated[9].

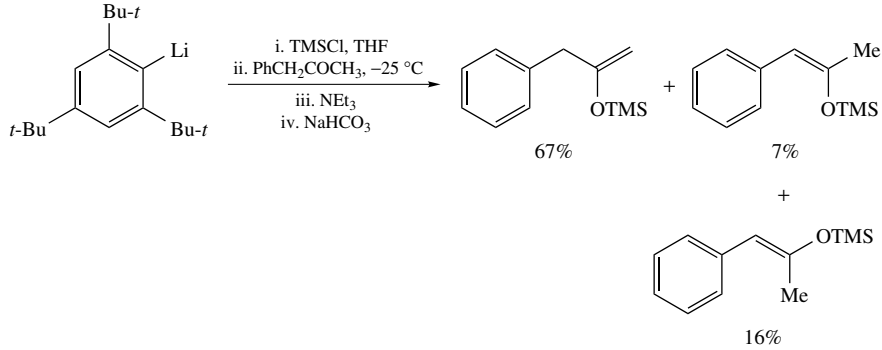
The thermodynamic enolates are generally prepared at room temperature or even at reflux of a protic solvent. In these conditions the more stable enolate is obtained, and this tends to be the more substituted or more conjugated one when the counter ion is a potassium or sodium, but with notable exceptions for lithium which can favor the less substituted enolate[3], as in the case of 2-methylpentan-3-one or 2-methylcyclopentanone[64].



SCHEME 10. Enantiocontrol issue upon prochiral ketone deprotonation

This difference was assigned to the lesser ionicity of the OLi bond when compared to the OK one. The solvent is likely to play an important role in the equilibrium as well: polar solvents seem to favor the more substituted enolate. In addition, House and Trost highlighted the fact that lithium enolates equilibrate very slowly unless a substantial excess of the free ketone is present in the solution[64]. Note that *ab initio* calculations on the naked enolates (no associated cation) of 2-butanone (Scheme 9 with $R^1 = H$ and $R^2 = Me$) suggest that the primary and Z(O) secondary isomers are almost isoenergetic,[65] while the E(O) secondary analog is less stable by more than 4 kcal mol^{-1}. Repeating these calculations for the 3-methyl-2-butanone enolates showed that the primary isomer is more stable by 4.3 kcal mol^{-1}.

In contrast, the kinetic lithium enolates are generally obtained by action of strong and hindered bases at low temperature in aprotic medium (typically LDA, −78 °C, THF), as originally established by House[5,9]. These non-equilibrating conditions favor the abstraction of the less hindered proton, the selectivity being particularly sensitive to the structure of the base. Note that when a $CH_2-CO-CH_3$ appendage is to be deprotonated, there is a statistical preference of 3:2 for reaction at methyl over reaction at methylene[18]. The presence of a substituent on the α carbon can also exert an electronic influence. For instance, a phenyl, a vinyl, a second carbonyl function, a cyano or a sulfone group will generally provide sufficient additional stabilization to control the direction of enolate formation in an unsymmetrical ketone[66]. However, the use of an extremely bulky base can counterbalance this effect, as illustrated by the kinetic deprotonation of benzyl methyl ketone (1-phenylpropan-2-one) by 2,4,6-tri-*t*-butylphenyllithium (Scheme 11)[67].



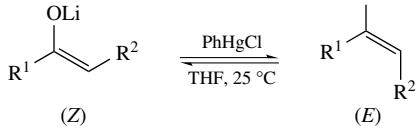
SCHEME 11. Regiocontrol during the deprotonation of benzyl methyl ketone by 2,4,6-tri-*t*-butylphenyllithium[67]

The case of α-alkoxy and α-acyloxy ketones has been the object of a recent compilation[68]. The examples gathered in this review underline that the regioselectivity of the deprotonation

is not merely driven by the enhanced kinetic acidity of the geminal protons α to the oxygen. The regioselectivity of the deprotonation of ketone-derived hydrazones by lithium amides has also been the object of careful studies[69].

The regioselectivity of the deprotonation of α,β-unsaturated carbonyl compounds deserves comment. Ketones that have protons at both the γ and α' positions are known to deprotonate selectively in α', and the resulting enolates undergo alkylation[70] or aldolisation[71] without equilibration. In contrast, when there are no enolizable protons at the α' position, an ambident enolate is obtained that can react at the α or γ positions[72]. An X-ray structure of the dienolate resulting from the autocondensation of pinacolone enolate has been obtained which shows the lithium cation lying out of the diene plane[30].

b. Stereocontrol. As mentioned above, Ireland and coworkers were among the first to investigate the effect of the solvent on the E(O) /Z(O) ratio of the kinetic enolates[23]. For esters, he found early on that the E(O) enolate predominates when obtained by deprotonation with LDA at $-78\,^{\circ}C$ in pure THF, while the Z(O) isomer becomes the major product in a 23% HMPA–THF mixture[73]. Later on, a set of data, collected at $0\,^{\circ}C$ by Rathke and coworkers, suggested that the Z(O)-enolate of 3-pentanone is the thermodynamically more stable isomer and the E(O)-enolate the kinetically more stable one, whatever the solvent employed[74]. These results were supplemented elegantly by a study on the equilibration between the E and Z enolates of five different ketones using catalytic phenylmercuric chloride in THF[75]. The results showed that there is an intrinsic thermodynamic preference for the Z(O) enolates, unless the ketone bears a bulky substituent at the β position (Scheme 12).



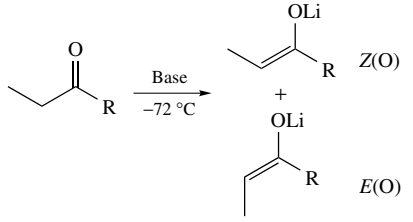
R^1	R^2	Eq. ratio (Z/E)
Me	Me	82:18
Me	*t*-Bu	20:80
t-Bu	Me	99.8:0.2
H	Me	65:35
H	*t*-Bu	3:97

SCHEME 12. Thermodynamic equilibration of the stereoisomers of enolates[75]

The influence of the structure of the base on the stereoselectivity has been studied. In 1980, the stereoselectivity of the deprotonation by LDA, LiHMDS and LiTMP of a set of ketones, esters and carboxamides at low temperature was measured after quenching with TMSCl[76]. The authors found that the proportion of the Z(O) enolate tends to increase according to the series LiTMP < LDA < LiHMDS and to the bulkiness of the R group borne by the ketone (Scheme 13). This important finding avoided the use of toxic HMPA to prepare Z(O) enolates.

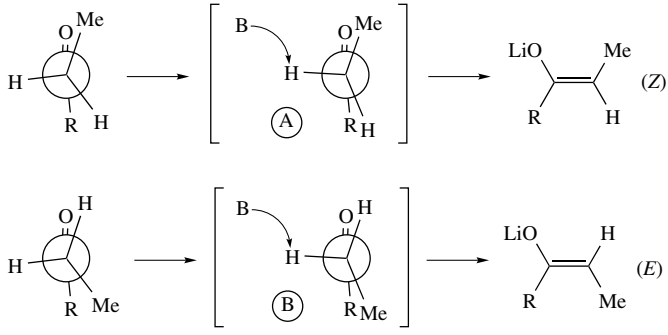
Reasoning on the transition states of the deprotonations led Heathcock and coworkers to propose an origin to these effects[76]. They suggested that situation A (Scheme 14) is probably preferred for bulky Rs, enhancing the proportion of the Z(O) isomer. The effect of the size of the base can be accounted for if this latter approaches 'over the face of the incipient enolate plane' rather than along the C–H direction. Thus, after the rotation orienting the proton perpendicular to the CO, the interaction between the base and the methyl group in situation A becomes unfavorable, depleting the Z(O) isomer population (Scheme 12). Overall, this description relies on interactions relatively similar to those taken into account in Ireland's model.

On the other hand, very cumbersome bases tend to favor E(O) enolates, as illustrated by the results of Kuwajima and coworkers[77] or of Corey and Gross[78] regarding the



R	% of Z(O) enolate		
	LiTMP	LDA	LiHMDS
MeO	-	5	-
MeS	4	8	87
Et	16	30	66
i-Pr	32	56	100
N(Pr-*i*)$_2$	52	81	-
Ph	100	100	100
t-Bu	100	100	100

SCHEME 13. Effect of the base on the stereoselectivity of the deprotonation of various carbonyl compounds[76]

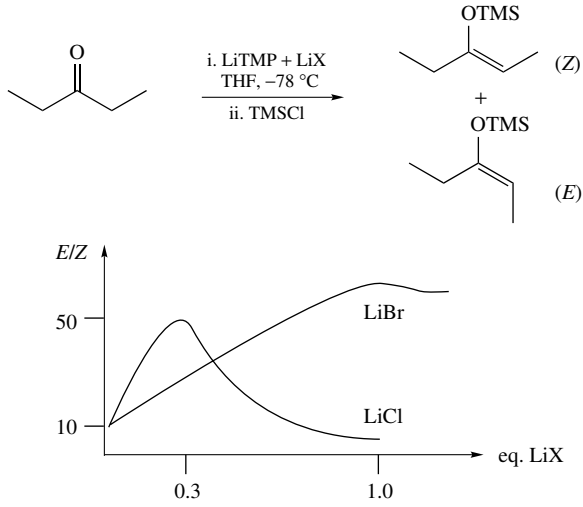


SCHEME 14. Heathcock's model to explain the influence of R on the stereoselectivity of the deprotonation[76]

deprotonation of pentan-3-one in THF. Resorting to the combination of a bulky base such as LiTMP or LOBA (lithium *t*-octyl-*t*-butylamide) and an internal quench by trimethylsilyl chloride, the latter authors enhanced the *E* selectivity significantly. High to very high *E* selectivities were also obtained recently upon deprotonation of esters with the *N*-tritylamide superhindered base[79].

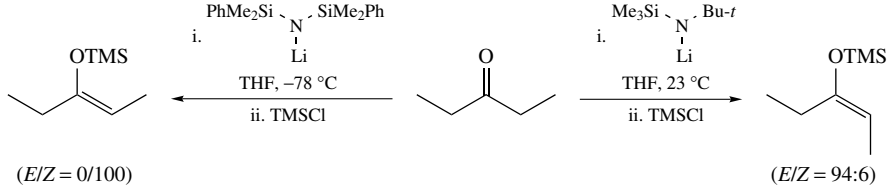
The origin of some of these good selectivities was shown to be related to the slow reaction of TMSCl with the bulky amides, generating sufficient amounts of LiCl to form mixed aggregates of the lithium amide and LiCl[80]. This hypothesis was fully confirmed by a kinetic[81], then a spectroscopic[82], study on the effect of LiCl and LiBr. In the latter case, the E/Z ratio of the enolate of 3-pentanone formed under the action of LiTMP at $-78\,^{\circ}C$ in THF and trapped *in situ* by trimethylsilyl chloride was systematically determined (Scheme 15)[82]. An optimal $E/Z > 50{:}1$ was obtained upon addition of 0.3 equivalent LiCl in the medium, after which a relatively sharp decrease in the selectivity was observed (10:1 for 1 equivalent). By contrast, LiBr led to an almost steady $E/Z \approx 60{:}1$ at 1 equivalent and above.

Interestingly, when a mixed aggregate of LiTMP and *n*-butyllithium is employed in THF, the selectivity in favor of the *E* enolate of 3-pentanone is slightly improved, particularly at low conversion rates, that is before the lithium enolate–LiTMP mixed aggregate interferes[83]. A disolvated 1:1 LiTMP–BuLi cyclic mixed dimer was shown to be the active species in THF and this aggregate is more selective than LiTMP or BuLi alone[84]. In contrast, the proportion of the *Z*(O) isomer of 4-heptanone[85] and 3-pentanone[8] lithium enolates increases in non-polar solvents such as hexane.



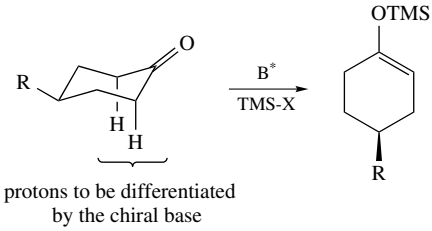
SCHEME 15. Effect of salts on the stereoselectivity of the deprotonation of 3-pentanone by LiTMP[82]

The E/Z selectivity is not easy to rationalize using the monomer/open-dimer models discussed above, the E(O) isomer of standard model enolates being invariantly preferred on the basis of MNDO semiempirical calculations, whatever the solvent included in the model[47]. However, the steric and stereoelectronic influence of the amide on the stereoselectivity of the enolates resulting from the deprotonation of ketones by different bases at various temperatures has been evaluated and rationalized resorting to the simple Ireland's model. The results showed that, on 3-pentanone, high E or Z selectivities are obtained with either lithium N-*t*-butyl(trimethylsilyl) amide at room temperature[86] or lithium N,N-di(phenyldimethylsilyl) amide[87] (or lithium N-trimethylsilyl anilide)[86] at $-78\,^{\circ}$C, respectively (Scheme 16). Remarkably high Z-selectivity was also observed resorting either to lithium anilide bearing strong electron attracting groups on the aromatic nucleus or to lithium diphenylamide[88].



SCHEME 16. Effect of the structure of the base on the stereoselectivity of the deprotonation of 3-pentanone[86, 87]

c. Enantiocontrol. The asymmetric desymmetrization of various types of prochiral substrates, and in particular of cyclic ketones, using chiral lithium amide bases is now considered as a standard tool for the synthesis of chiral enolates[89]. The first applications of chiral lithium amides to asymmetric deprotonation have been reported simultaneously by Whitesell and Feldman[90] as well as Duhamel and Plaquevent[91]. A little later Koga[92], Simpkins[93] and coworkers showed that the enantioselective deprotonation of conformationally locked

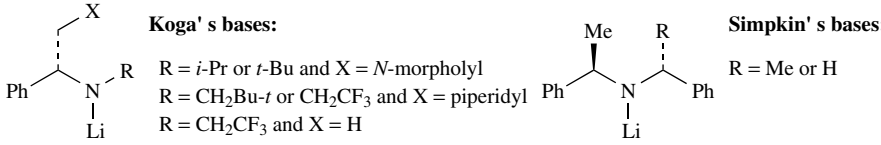


SCHEME 17. Asymmetric deprotonation of conformationally locked cyclohexanones

cyclohexanones (with the help of a bulky R substituent in position 4, Scheme 17) could be efficiently achieved employing lithium amides derived from chiral amines or diamines in well-defined conditions. Note that the stereoelectronic factors mentioned above explain why it is one of the axial protons which will be selectively removed upon deprotonation.

A review on this topic, published by O'Brien in 1998[94], was updated in 2001[95]. These two papers will give the reader an excellent account of the fundamental results in the domain as well as a list of previous compilations of literature. We just wish to summarize here the general conclusions drawn in these documents.

Benzylic chiral amines are most often employed to perform asymmetric deprotonations. Two main families have been used with the most general success up to now (Scheme 18).

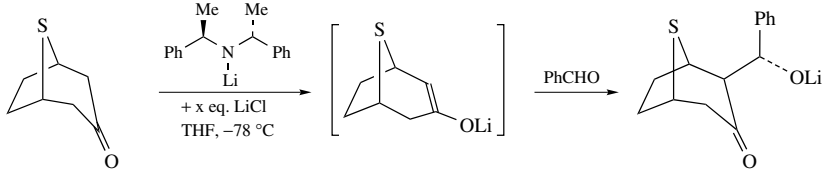


SCHEME 18. Most frequently used chiral bases in the asymmetric deprotonation of ketones[94]

It was soon noted that the best enantioselectivities were consistently obtained when an internal quench of the reaction with TMSCl was performed. Actually, the lithium chloride generated while the reaction progresses emerged as being responsible for these improved performances. Consequently, an external quench can afford high e.e. values provided 0.5 to 1 equivalent of LiCl (or larger amounts of LiBr) are added to the medium. Note that LiCl is advantageously generated *in situ* by the action of butyllithium on the amine hydrochloride. The resulting enolates can be used directly in aldol reactions toward aldehydes (Scheme 19).

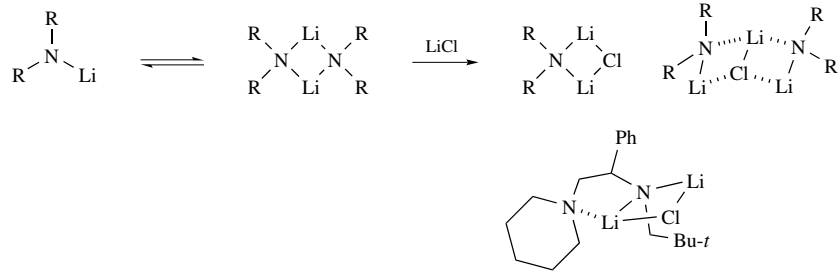
Zinc chloride has also been observed to have a significant influence on the enantioselectivity of these reactions. But several other important parameters have been pointed out, such as the temperature (best performances are obtained at very low temperatures), the solvent (HMPA is often required) or the concentration of the lithium amide[96]. As underlined above about the stereoselectivity of the deprotonation, the formation of lithium amides–lithium chloride mixed aggregates (1:1 or 2:1) has been proposed to rationalize the important salt effects (Scheme 20), the amide homogeneous dimer being supposed to provide only mediocre enantioselections. With diamines, the intramolecular chelation would provide a fairly rigid system.

Regarding the substrate, the asymmetric deprotonations are relatively tolerant as demonstrated by the synthetic applications listed in O'Brien's review. Cyclohexanones and (bridged) cycloheptanones are commonplace while cyclopentanones and cyclobutanones have been more rarely investigated.



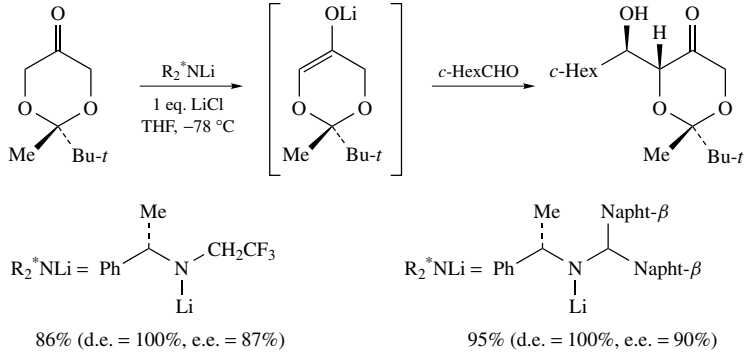
x	e.e (%)
0	16
0.1	73
0.6	86
1.0	76

SCHEME 19. Asymmetric deprotonation and external trapping of the enolate[94]



SCHEME 20. Formation of mixed aggregates of lithium amides and LiCl[94]

Applications of these reactions have been further extended lately. For instance, the acetal derived from 3,5-dihydroxycyclohexanone has been efficiently transformed into chiral 5-hydroxycyclohex-2-enone with good e.e. values resorting to Simpkins' base[97]. Bicyclic *meso* imides are also prompt to react with the same base[98]. The resulting enolates undergo both internal and external quenches in high to very high e.e. Acetals derived from 1,3-dioxan-5-ones have also been successfully transformed into the corresponding cyclic lithium enolates under the action of various original chiral lithium amides (Scheme 21)[99].



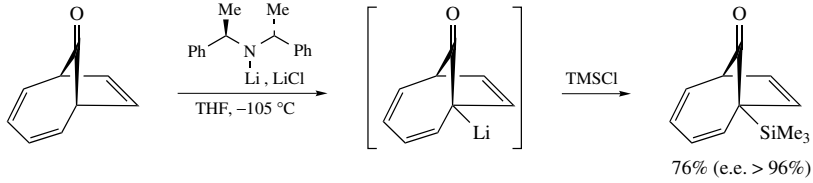
86% (d.e. = 100%, e.e. = 87%)

95% (d.e. = 100%, e.e. = 90%)

SCHEME 21. Enantioselective deprotonation of a cyclic acetal[99]

Their *in situ* trapping by cyclohexylcarboxaldehyde provided the expected aldol as a single *anti–cis* isomer exhibiting up to 90% e.e.

Also noteworthy is the spectacular application to bridgehead enolates (better described as α-keto carbanions) studied by Simpkins and coworkers[100]. A 76% yield and e.e. > 96% were returned when adding the chiral C_2 symmetrical base and LiCl to a mixture of ketone and Me_3SiCl (Scheme 22). Comparably good results were obtained with a large range of bicyclic compounds (diketones, lactones, lactams, imides) that all provided bridgehead enolates ready for silylation or alkylation[101].

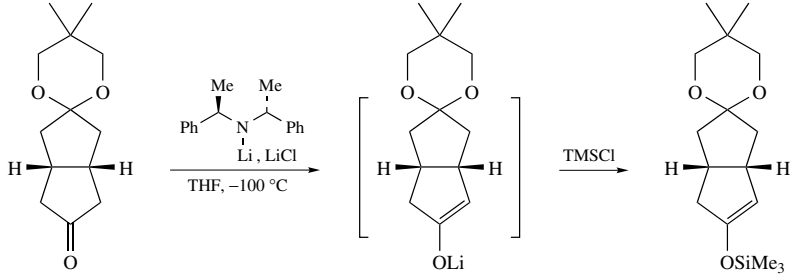


76% (e.e. > 96%)

SCHEME 22. Asymmetric synthesis of a bridgehead enolate[100]

New bases have also been proposed to extend the arsenal presented in Scheme 16. In particular, conformational constraints have been introduced on the amide. It was shown, for instance, that e.e. values up to 81% can be returned for the deprotonation of 4-*t*-butylcyclohexanone in a THF/HMPA mixture by a lithium amide derived from a tetrahydroquinoline bearing a heterocycle at C_3[102]. Note that the same ketone can be converted in its (*S*)-enolate in 90% e.e. resorting to the bulky lithium *N*-trityl-*N*-(*R*)-1-phenethylamide[79]. Interestingly, chiral lithium amides on polymeric solid support have also been successfully employed to deprotonate bridged cycloheptanones[103].

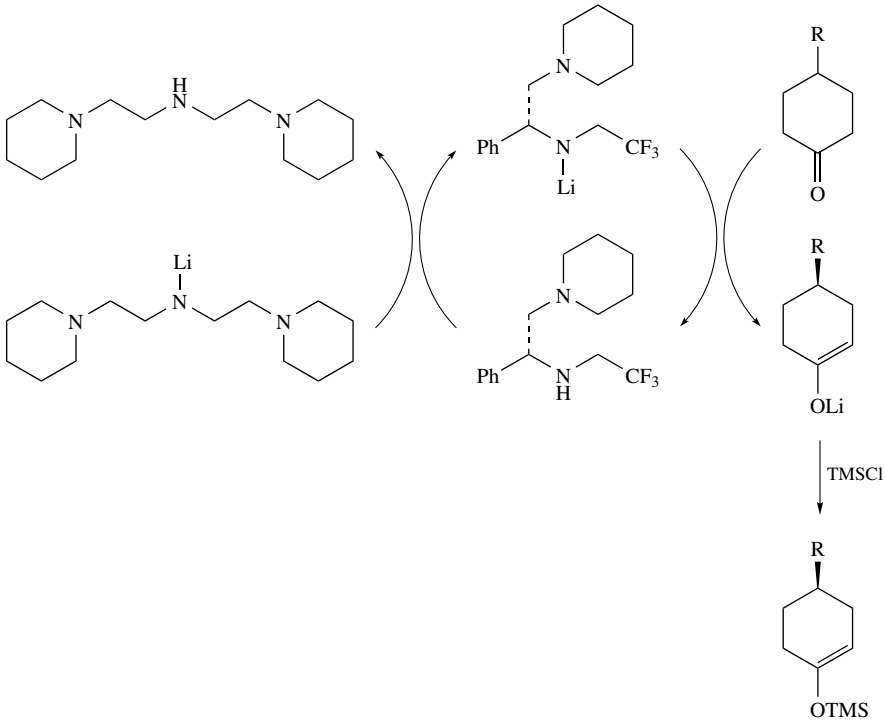
Among recent synthetic applications of chiral enolates generated by asymmetric deprotonation, we mention the synthesis of 8-oxanorcocaine and 8-oxapseudonorcocaine by Kozikowski and coworkers[104], of fragments of Scytophycin C by Hunt and Grieco[105] and of carba-prostacyclin analogues by Bergen and Gais (Scheme 23)[106].



80% (e.e. = 90%)

SCHEME 23. Asymmetric deprotonation of a cyclopentanone[106]

Catalytic versions of the asymmetric deprotonations have been conceived remarkably early[107]. High e.e. values (up to 82%) were obtained in the test reaction of *t*-butylcyclohexanone provided 2 equivalents HMPA and TMSCl were added to the medium at $-78\,^{\circ}C$. A catalytic cycle has been proposed on the basis of NMR observations (Scheme 24).



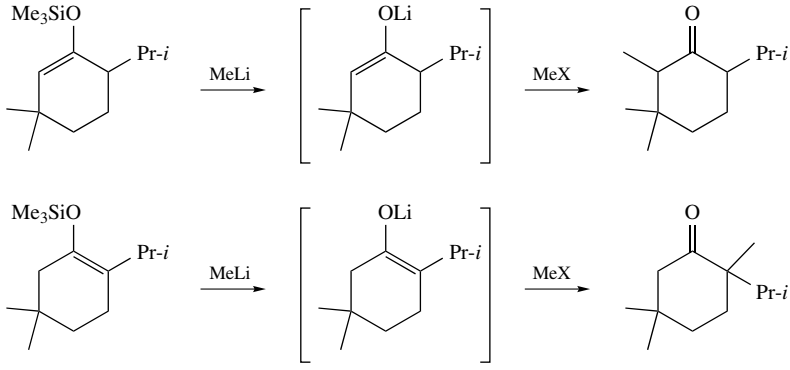
SCHEME 24. Catalytic version of an asymmetric deprotonation[107]

B. Synthesis of Enolates from Enol Ethers and Esters

An alternative to the direct α-deprotonation of a ketone is the conversion of its enol ether (in particular, TMS enol ethers) or ester (in particular, acetates) into the corresponding lithium enolate. The advantage of this detour is that the enol ethers and esters can either be prepared as a single isomer or the mixture of isomers can be separated by distillation or chromatography[108], while their conversion into enolates takes place in a regio- and stereospecific manner.

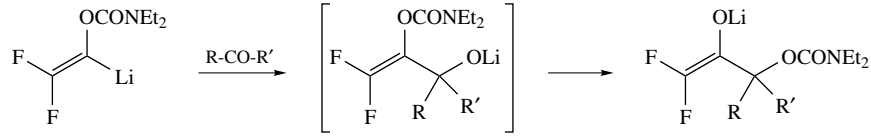
Enol acetates were used first, since they could be easily prepared by quenching the potassium or sodium enolates with acetic anhydride[3]. However, their cleavage by excess methyllithium, albeit efficient and perfectly respectful of stereochemical integrity[109], generates strongly basic lithium *t*-butylate in the medium. This latter can complicate the situation by promoting further alkylation of the initially formed product[5]. Silylenol ethers[110], which are readily accessible from the sodium enolates and trimethylsilyl chloride[108] or directly from the carbonyl compounds[111], and can be purified by distillation or chromatography, solve this problem. Upon reaction with methyllithium (a more efficient cleaving agent than butyllithium) in glyme or THF, the silylenol ethers generate the expected lithium enolates with structural integrity plus inert tetramethylsilane (Scheme 25)[112].

Actually, silylenol ethers can be cleaved off by many different nucleophiles (in particular, fluorides) to provide a large variety of enolates[113]. Hence, lithium amide in liquid ammonia[114] or alcoholates[115] transform efficiently the aldehyde silylenol ethers into the corresponding lithium enolates. To be extended to ketones silylenol ethers, this latter



SCHEME 25. Regiospecific cleavage of silylenol ethers by methyllithium[112]

method required the O−Si cleavage by potassium *t*-butoxide followed by metal exchange with 5 equivalents of lithium bromide[116]. This mild way of generating enolates has found useful applications in synthesis[117]. Note that a related intramolecular example of lithium-alcoholate-induced enol carbamate cleavage has been described to access difluoro lithium enolates (Scheme 26)[118].



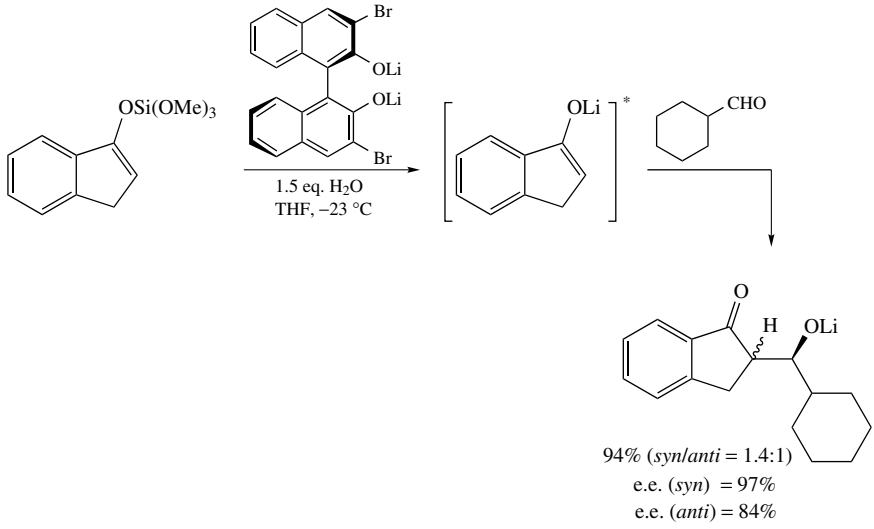
SCHEME 26. Intramolecular cleavage of an enol carbamate by a lithium alcoholate[118]

A particularly attractive version of this reaction relies on the action of a catalytic chiral lithium binaphtholate and an excess of water on trimethoxysilylenol ether[119]. The tetralone enolate thus generated was directly employed in an aldol reaction, which turned out to be poorly diastereoselective but highly enantioselective for both diastereomers (Scheme 27).

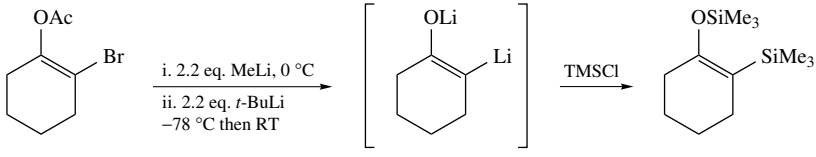
The case of α-ketodianions needs to be discussed separately. These reagents can be obtained by double deprotonation of β-dicarbonyl compounds. When NaH, then *n*-BuLi are employed, the resulting dianions react with aldehydes at the more basic site but with a weak reactivity at $-78\,^{\circ}C$[120], depending on the structure of the dianion[121]. This regioselectivity is an obvious synthetic advantage since it permits the successive functionalization of both positions of the β-dicarbonyl substrate.

An alternative to the double deprotonation consists in a cleavage, then lithium−bromine exchange on α-bromoenol acetates induced by the sequential use of methyllithium and *t*-butyllithium (Scheme 28)[122]. Obviously, the latter enol acetate can result from a conjugate addition on an enone[123]. Note that an extension of this reaction to the homologation of esters has been described by the same group[124].

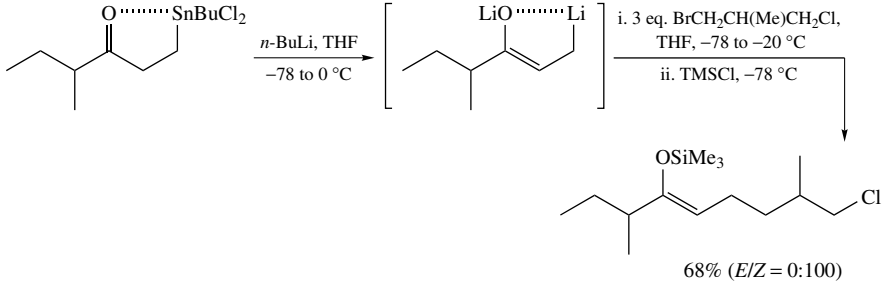
A complementary access to the α,β-dianions relying on a deprotonation/tin−lithium exchange sequence triggered on β-tributyl or β-dichlorobutylstannyl ketones was also described recently[125]. A strong coordination between the oxygen of the regioselective enolate and the β-lithium occurs. The resulting dianion can react on both its *C* and *O* sites toward trimethylsilyl chloride. But the β-position being more reactive, the *C*-trapping of carbon electrophiles (including, after transmetallation, enones[126, 127] or acyl



SCHEME 27. Catalytic cleavage of trimethoxysilylenol ether[119]



SCHEME 28. α-Ketodianions by sequential cleavage/exchange[122]



SCHEME 29. α,β-Ketodianions by sequential deprotonation/Sn–Li exchange[125]

chlorides[128]) takes place selectively on this position, giving efficiently access to *Z*-enol ethers (Scheme 29).

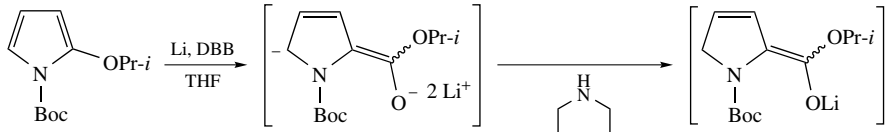
The reactivity of these species is not commented on in this section. However, we think it is interesting to mention that a set of lithium–potassium α-ketodianions or sodium–dilithium diketo trianion, prepared by sequential action of KH or NaH, then *n*- or *s*-BuLi/TMEDA[129], can be monoalkylated in good yields. Also, the one-pot cyclopropanation of enones through their lithiothioacetal lithium enolates (γ-ketodianions) has

been the object of detailed studies[130]. Finally, we mention that several reviews about the application of these dianions to cyclization reactions have been published recently[131, 132].

C. Synthesis of Enolates by Conjugate Addition to Enones

The reactions in this section cover the conjugate (Michael) addition of various lithiated nucleophiles to activated olefins such as enones and enoates. Lithium enolates are formed as intermediates during the addition process. They can be treated as such and trapped, for instance, by an electrophile to provide ketones or esters substituted both in the α and β positions. We will focus only on the most important information relevant to the intermediate enolates, and those are rarely discussed in the literature on the Michael addition. The reader can advantageously consult Chapter 14 of the first part of this volume[133], which is entirely dedicated to the organolithium additions to double bonds, for a more extensive coverage of the topic.

Stork and coworkers found long ago that enones are converted into enolates upon treatment with lithium in liquid ammonia[1, 2, 134]. However, the presence of a proton source in the reaction medium, that is necessary to generate specific enolates, limits their utility. A clever way to evade this problem has been recently proposed that relies on ammonia-free conditions[135]. Lithium di-*t*-butylbiphenyl (LiDBB) transforms aromatic esters into dianions, then the (second) more basic position is selectively quenched by bis(methoxyethyl)amine (BMEA). This amine is not acidic enough to protonate the enolate, which can be selectively reacted with classical electrophiles and furnish the expected alkylation or aldolisation products in good to high yields (Schemes 30 and 124).



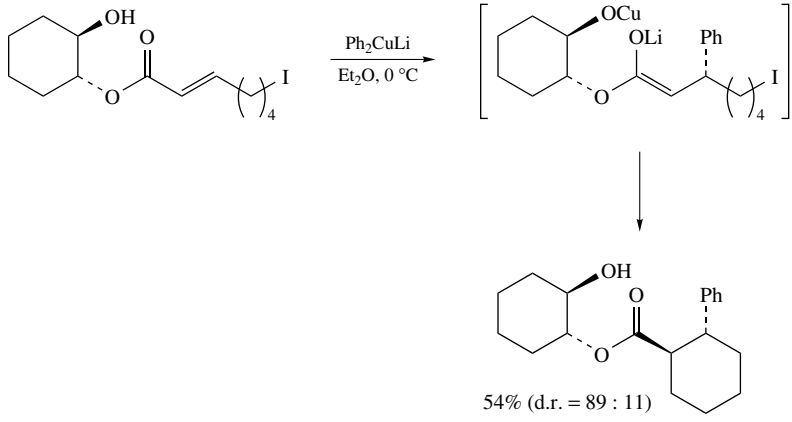
R	Yield
Bn	80%
Me	74%
H	62%
SPh	52%
PhCHOH	70%

SCHEME 30. Ammonia-free partial reduction of aromatic esters using LiDBB[135]

1. Addition of carbon nucleophiles

The conjugate addition routes to lithium enolates became increasingly busy when it was shown that the copper-catalyzed reaction of methyllithium in ether probably involves a solvated cuprate (Me_2CuLi)[136] and that the resulting species was a lithium enolate rather than a copper enolate[137, 138]. More detailed spectroscopic[139] and theoretical[140] descriptions of the lithium enolates and even of the cuprate–olefin complex formed preliminarily came later to confirm House's hypotheses. A significant solvent effect is associated to the enolates generated this way since their alkylation can be fast and regioselective, provided THF[141] or DME[142] is preferred to ether.

Asymmetric versions of this fundamental way of making carbon–carbon bonds have attracted considerable attention lately. The diastereoselective version has proven successful in terms of high inductions and versatility of the substrate (unsaturated ketones, esters, amides, sultames, oxazolidines, aldimines ...). The very large amount of data reported in this area precludes its coverage but excellent reviews are available[143–145]. The fine example displayed below, in which the intermediate enolate is trapped intramolecularly, illustrates the potency of this approach (Scheme 31)[146]. Similarly, good results were obtained with lithium enolates derived from (−)-8-phenylmenthyl esters[147].



SCHEME 31. Generation of a chiral lithium enolate by diastereocontrolled conjugate addition of an achiral nucleophile on a chiral substrate, followed by intramolecular alkylation[146]

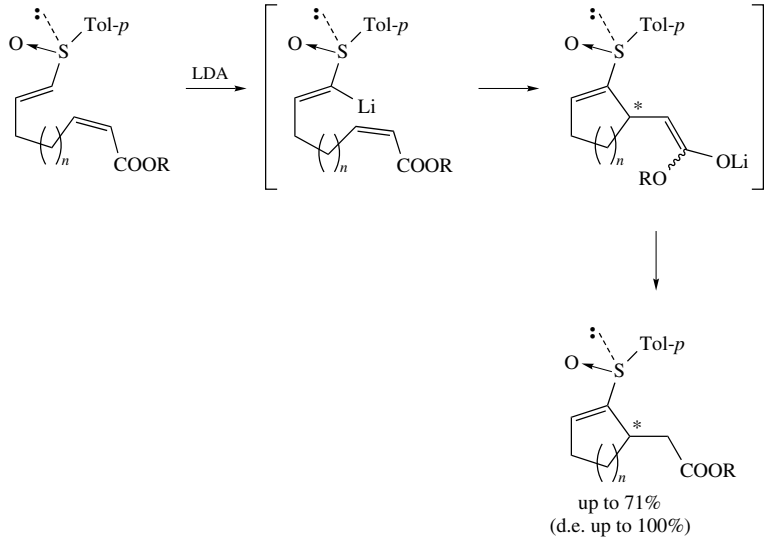
The conjugate addition step can also be intramolecular. For instance, Tanaka and coworkers studied the case of a lithiated vinyl sulfoxide that undergoes intramolecular conjugate addition in high yields and complete diastereocontrols (Scheme 32)[148].

In contrast, the de-aromatization studied recently by Clayden and coworkers (Scheme 33)[149] rather seems to go through an electrocyclic ring closure[150].

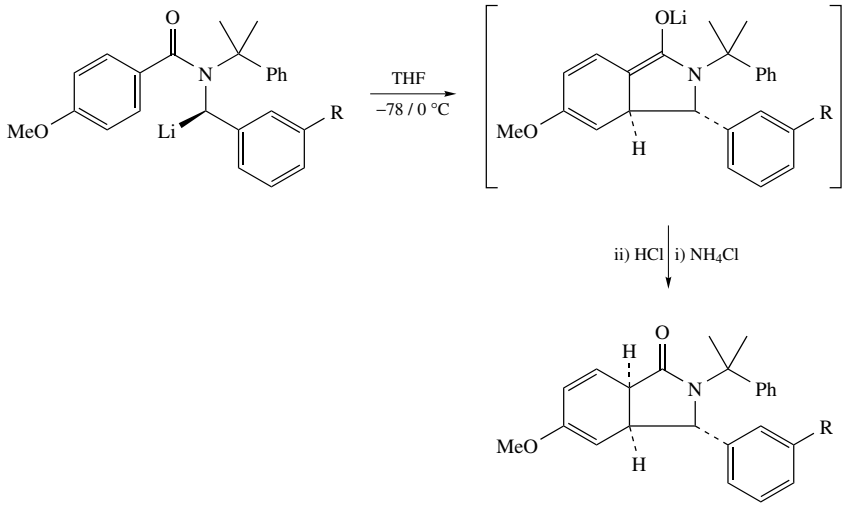
Enantioselective routes complement the above examples. They generally rely on the conjugate addition of a lithium cuprate complexed by a chiral ligand (such as an aminoether, diether ...) onto a prochiral substrate. A good overview of the most important results is given in the reviews mentioned above[143]. We thus just wish to illustrate this section with two recent examples of enantioselective additions of alkyl and aryllithium. The first one concerns chiral silylamidocuprates reacted with chalcone[151]. Extremely high e.e. values were returned upon fine tuning of the silyl group (Scheme 34).

The addition of phenyllithium on unsaturated esters of bulky butylated hydroxyanisole (BHA) is also noteworthy[152, 153]. Chiral diamines or diethers were the ligands employed in these last cases (Scheme 35).

Lithium enolates can in turn be used as the nucleophiles in conjugate additions to activated olefins. Two ketone lithium enolates have, for instance, been added 1,4 to enoates. In the presence of a well-chosen amine or amide derived from chiral diamines[49] or triamines[154], modest to high e.e. were measured on the adducts. Similarly, ester-derived lithium enolates go through a conjugate addition onto enoates[155]. Thus, the enolate of methyl phenylacetate generated by deprotonation with a chiral lithium alkoxide undergoes Michael addition on methyl acrylate, leading to the expected 1,3-diesters in variable e.e. values (Scheme 36)[156].

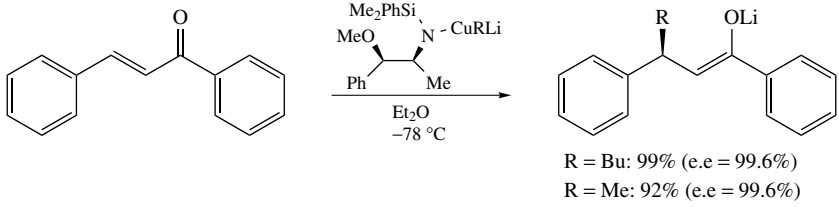


SCHEME 32. Generation of a chiral lithium enolate by intramolecular diastereocontrolled conjugate addition[148]

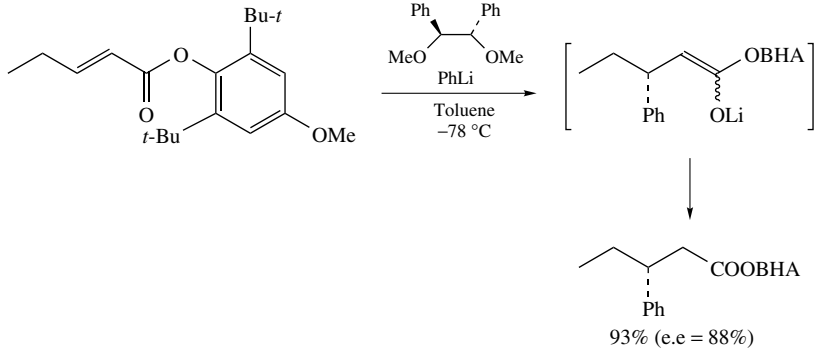


SCHEME 33. Generation of a chiral lithium enolate by diastereocontrolled electrocyclic ring closure[149]

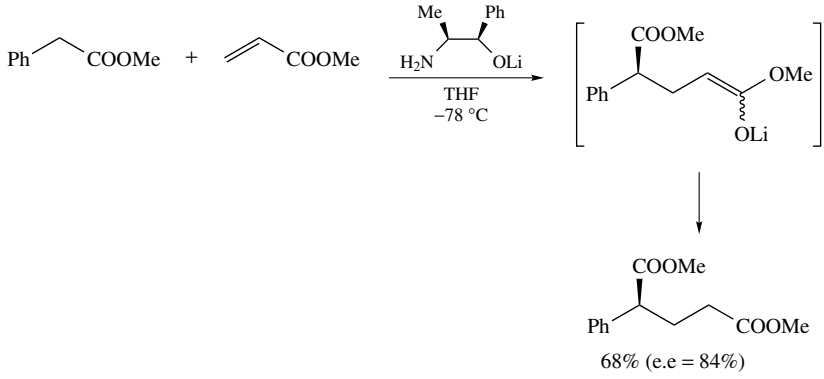
Using the type of chiral ligand depicted in Scheme 35 to complex the enolate of dimethylpentan-3-ol α-trimethylsilanylacetate during its addition to enones also affords attractive e.e. values[157]. However, the stoichiometric amounts of the metal salt and chiral ligand which usually cannot be recovered remain the major drawbacks to these methods. Another downside is the high substrate specificity: a certain chirally-modified reagent



SCHEME 34. Generation of a chiral lithium enolate by enantiocontrolled conjugate addition of chiral silylamidocuprates on chalcone[151]



SCHEME 35. Generation of a chiral lithium enolate by enantiocontrolled conjugate addition of complexed phenyllithium on an unsaturated ester[153]

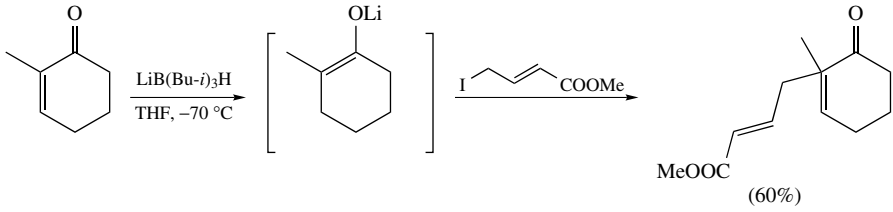


SCHEME 36. Asymmetric Michael addition of an ester enolate on an enoate[156]

often gives high selectivities with only one or very few Michael acceptors. Catalytic enantioselective versions of this reaction would open a major breakthrough. However, the recent developments in this direction rely mainly on organozinc derivatives with copper, nickel or cobalt catalysts[158], and are therefore irrelevant within the framework of this chapter.

2. Addition of hydrides

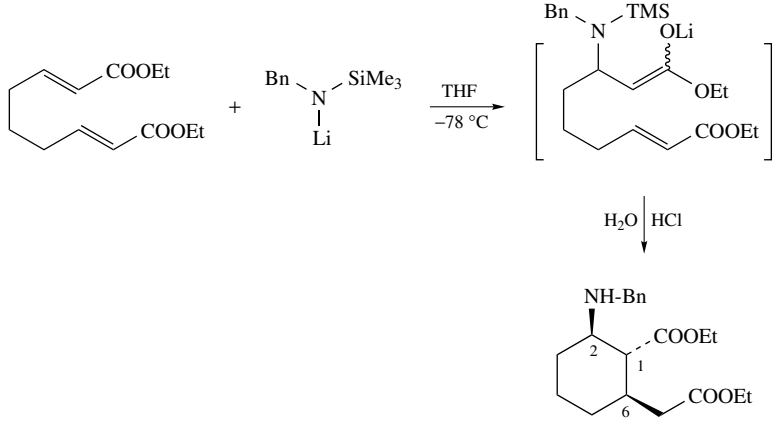
Carbon nucleophiles do not have a monopoly for the generation of enolates by conjugate addition. Bulky lithium borohydrides such as L-selectride undergo 1,4-hydride addition to enones and enoates to yield a lithium enolate that can be alkylated in THF (Scheme 37)[159]. Interestingly, the latter reductive alkylation probably goes through a lithium enolate of which geometry is largely controlled by the s-*cis*/s-*trans* conformation of the starting carbonyl derivative[160].



SCHEME 37. Reductive alkylation of an enone[159]

3. Addition of lithium amides

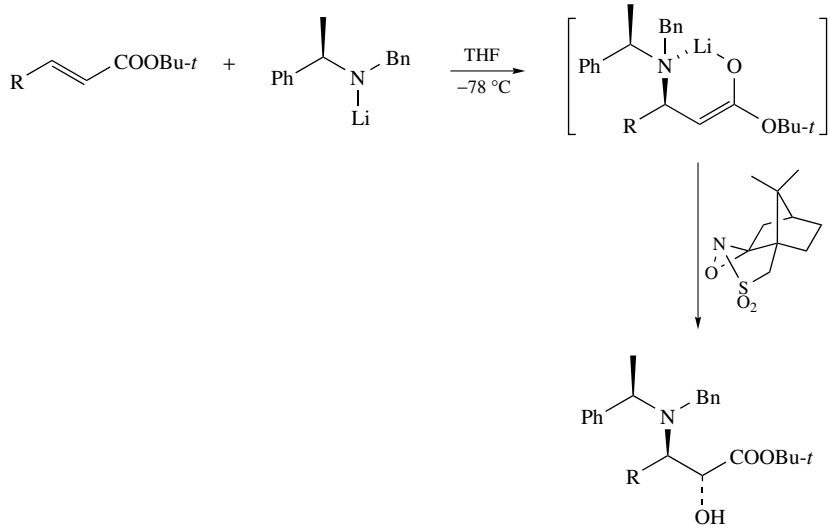
The ability of lithium amides to add on enoates to provide lithium enolates has been known for some while[161]. This reaction has found many useful synthetic applications, one of the most spectacular being the tandem, stereocontrolled, conjugate additions (Scheme 38)[162].



SCHEME 38. Tandem conjugate addition triggered by a lithium amide[162]

The relative stereocontrol of carbons 1, 2 and 6 observed in the above example has been assigned to the intramolecular chelation of the lithium of the intermediate enolate by the carbonyl of the second ester group. Note that lithium amide cuprate reagents also add efficiently to enoates and dienoates[163].

Diastereoselective versions of this reaction have been developed, the chirality being borne either by the substrate[164, 165] or by the lithium amide[166, 167]. The latter approach, in particular that relying on the readily available (*R*)- or (*S*)-*N*-benzyl-1-phenylethanamine



SCHEME 39. Diastereoselective conjugate addition of Davies' chiral lithium amide followed by diastereocontrolled oxidation of the intermediate enolate[169]

(Davies' lithium amide)[168], turned out to be particularly efficient. It has therefore found a large number of applications by Davies himself (Scheme 39)[169,170] and many others[171,172].

Actually, repeating the tandem addition of Scheme 38 with the (*R*) enantiomer of Davies' amide affords total control on the three created asymmetric centers, and provides the trisubstituted cyclohexane in 72% yield and as a single (1*R*, 2*R*, 6*R*) enantiomer (i.e. absolute configurations reported in Scheme 38)[173,174].

4. Addition of miscellaneous nucleophiles

Lithium thiolates add well to activated olefins, generating β-sulfurized lithium enolates[175]. Those can be used in tandem inter-[176] or intra-[177] molecular addition–aldolisation processes. In the presence of a catalytic amount of bi- or tridentate chiral ligands[178], this addition becomes enantioselective and the newly created asymmetric center(s) can be almost totally controlled, provided the thiolate and the enone structures are well chosen (Scheme 40)[179–182].

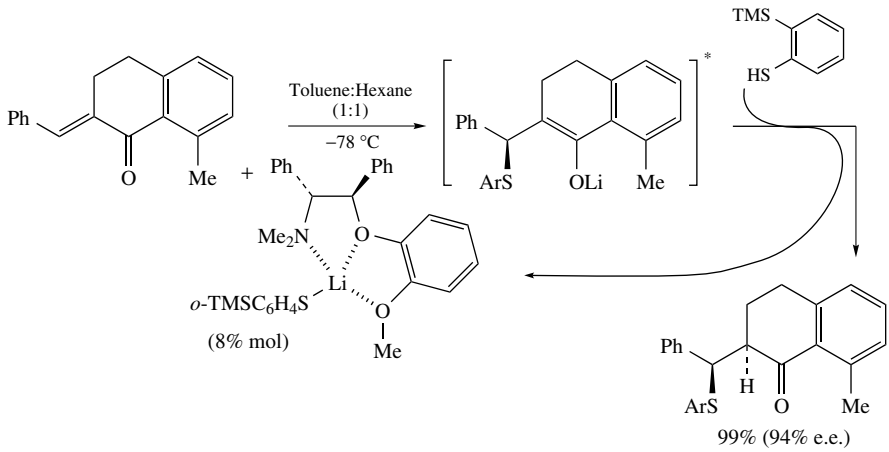
The conjugate addition of lithium peroxides on enones is a non-classical route to epoxidation. The original lithium enolate rearranges immediately *in situ*[183]. Note that a catalytic asymmetric version of this reaction was also developed (Scheme 41)[184].

Finally, R_3SnLi (R = Me, Et, *n*-Bu) can also add 1,4 to unsaturated ketones, providing the expected β-stannylated lithium enolates in good to very good yields[185]. Those can be simply hydrolyzed or transformed into the corresponding silylenol ether, or involved in subsequent aldolisation reactions.

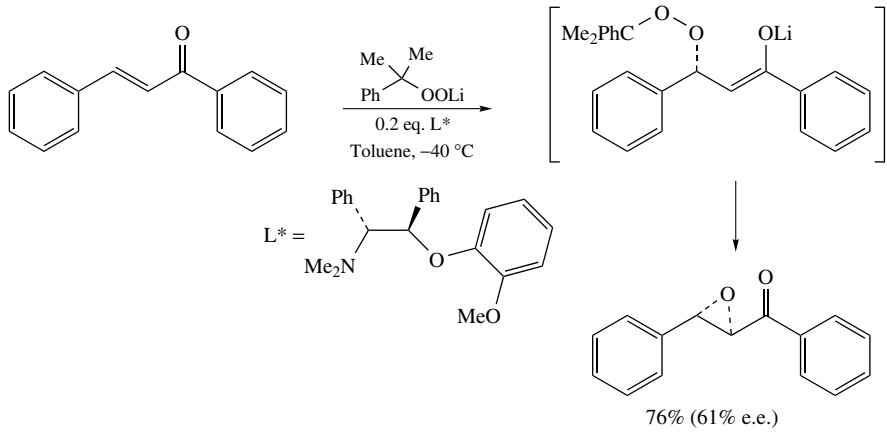
D. Synthesis of Enolates by Miscellaneous Methods

1. By addition of alkyllithium reagents

In several cases, the nucleophilic addition of an organolithium onto various substrates can yield enolates. For instance, the addition of *n*-butyllithium onto diethylketene has



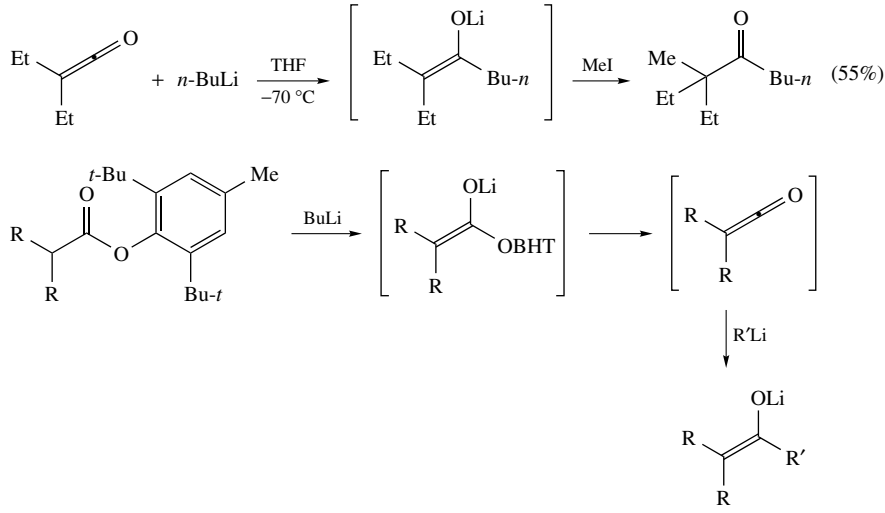
SCHEME 40. Enantioselective catalytic conjugate addition of a thiophenolate on an enone with diastereocontrolled protonation of the intermediate enolate (Ar = *o*-TMS-C_6H_4)[181]



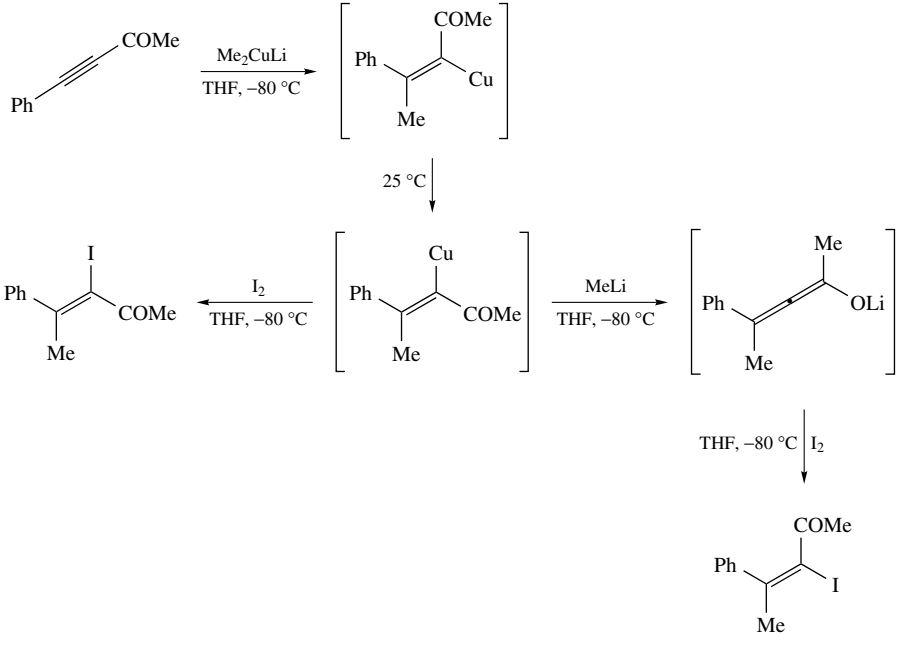
SCHEME 41. Enantioselective catalytic conjugate addition of a lithium peroxide on chalcone[184]

been shown to occur on the central (sp) carbon, furnishing the corresponding enolate, ready for alkylation by electrophiles (Scheme 42)[186]. Similarly, Seebach and colleagues have established that bulky BHT ester enolates can be regarded as ketenoids[187]. They convert into ketone enolates, probably through the RLi addition on the *in situ* generated ketene resulting from the α-elimination of the BHT-OLi phenoxide. When the starting ester bears two different R groups, the *Z*(O) enolate becomes predominant, the selectivity increasing with an increasing difference in size between the two substituents.

The treatment of vinylcopper derivatives, resulting from the conjugate addition of lithium cuprates on propargylic esters, by methyllithium is a way to prepare lithium cumulenolates (Scheme 43)[188]. Those can be trapped as the corresponding vinyl iodides. Note that the authors propose a 'naked' vinylcopper intermediate while a VinylCuMe or a $(Vinyl)_2Cu$ is more likely to be involved.



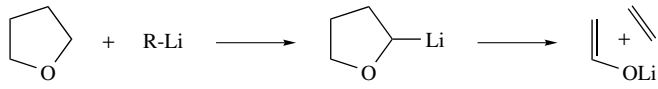
SCHEME 42. Addition of butyllithium to isolated[186] or *in situ* generated[187] dialkylketenes



SCHEME 43. Cumulenolates from vinylcopper derivatives[188]

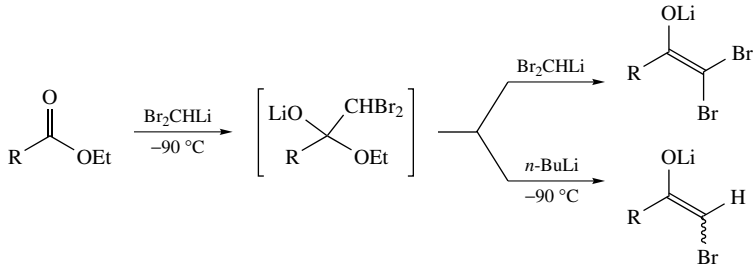
2. By elimination reactions

At least two reactions can be mentioned here that are ether cleavages resulting from deprotonations on the one hand, and the alkoxy elimination induced on an α-alkoxyalcoholate (lithium hemiaminalate) on the other. The first case has been the object of detailed studies, since it involves in particular the decomposition of THF[189]. This reaction has been proposed to go through an α-deprotonation followed by a $[\pi 4s + \pi 2s]$ cycloreversion, providing ethylene and the enolate of acetaldehyde (Scheme 44). Unfortunately, this clean method of generating enolates does not apply to larger cyclic ethers[190]. A recent investigation based on Raman and IR data as well as DFT calculations has allowed a precise description of the elementary steps of this decomposition[191].



SCHEME 44. Acetaldehyde lithium enolate obtained by deprotonation of THF[190]

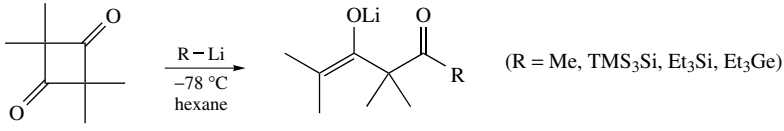
The second set of reactions results from a β-elimination, prompted either by deprotonation[192] or by a bromine–lithium exchange[193], on an α-alkoxyalcoholate (Scheme 45). It provides α-bromo or dibromo enolates.



SCHEME 45. α-Bromo and dibromo enolates generated by elimination[192,193]

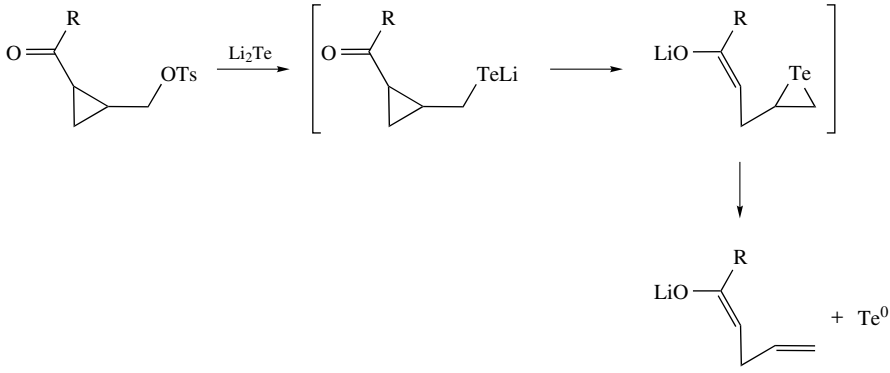
3. By ring openings

An unexpected cyclobutanedione cleavage upon addition of various R–Li was observed by Apeloig and coworkers. It leads to the enolates of β-diketones, but also to the enolates of β-ketoacylsilanes and ketoacylgermanes (Scheme 46)[194].



SCHEME 46. Enolates from β-ketoacylsilanes[194]

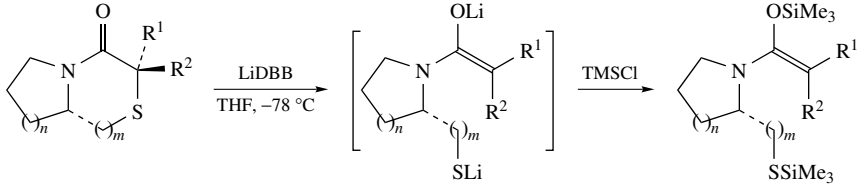
A telluride-triggered nucleophilic ring opening of monoactivated cyclopropanes has been recently described that gives access to β,γ-unsaturated enolates (Scheme 47)[195]. An intermediate epitelluride is supposed to be involved in the reaction pathway. This



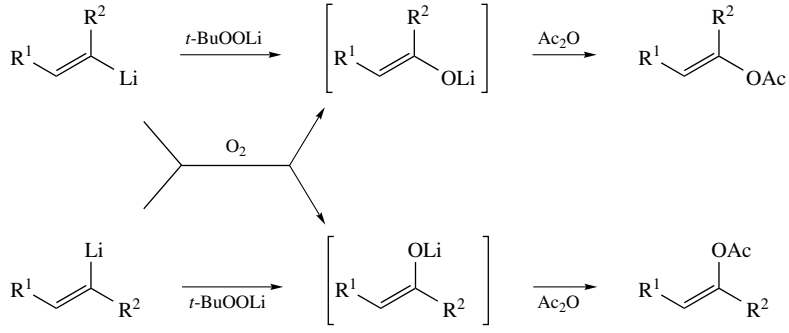
SCHEME 47. Generation of unsaturated enolates by $TeLi_2$-induced cyclopropane ring fission[195]

relatively unusual procedure presents the advantage of giving access to enolates in the absence of strong bases or Lewis acids.

A method relying on the reduction of bicyclic thioglycolate lactams by lithium di-*t*-butylbiphenylide (LiDBB) has also been proposed (Scheme 48)[196]. This route has the advantage of affording carboxamide enolates with E/Z ratios that depend directly on the stereochemistry of the starting bicyclic lactam and do not rely on the steric difference between the two substituents.



SCHEME 48. Reduction of bicyclic thioglycolate lactams by LiDBB[196]

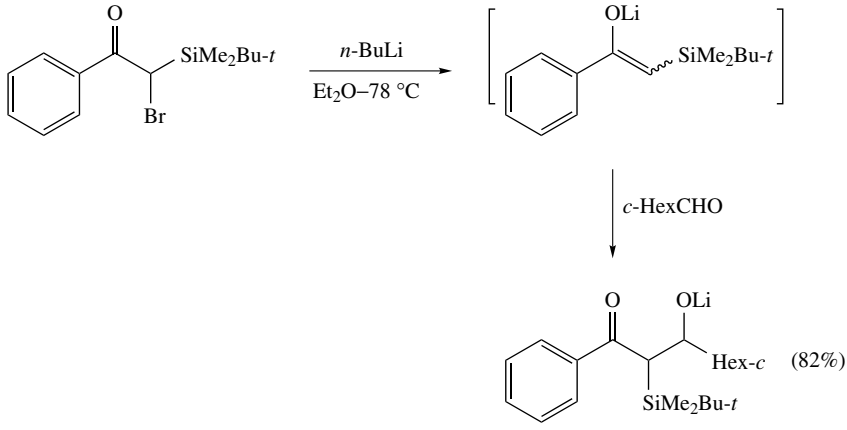


SCHEME 49. Stereospecific (with *t*-BuOOLi) or stereodivergent (with O_2) oxidation of vinyllithium derivatives[197]

4. By oxidation or reduction

The oxidation of vinyllithium by oxygen or peroxides furnishes lithium enolates[197]. Working with stereocontrolled vinyl derivatives helped to show that with oxygen, vinylic radicals are involved, while they do not seem to be relevant when *t*-butyllithium peroxide is employed (Scheme 49).

On the other hand, enolates can also be generated by halogen–lithium exchange on α-haloketones[198]. Resorting to *n*-BuLi in ether (THF is inappropriate in this case) suffices to get excellent yields (Scheme 50)[199]. However, the E/Z ratio of the enolates is not disclosed in the original publication.



SCHEME 50. Synthesis of enolates by bromine–lithium exchange[199]

III. STRUCTURE OF LITHIUM ENOLATES

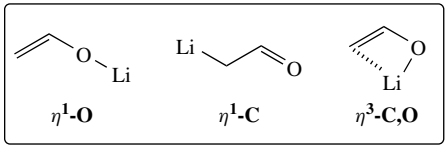
As most organometallic compounds, lithium enolates are highly polar entities susceptible to combine in various types of (eventually solvated) aggregates that undergo dynamic equilibria in solution. This phenomenon explains why enolate solutions are difficult to describe by the classical spectroscopic, physicochemical or theoretical methods, a difficulty enhanced by the sensitivity of these equilibria to many physicochemical factors such as the concentration, the temperature or the presence of complexing additives (lithium halides, amides, amines, HMPA, ...). The problems due to dynamics are avoided in the solid state where many clusters of lithium enolates, alone or co-crystallized with exogenous partners, have been identified by X-ray crystallography.

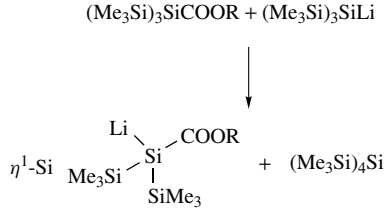
In the following, we wish to provide a brief description of the structure of a significant portion of the various lithium enolates characterized to date. Their importance as chemical reagents explains why they have been considered from many different chemical points of view. We will thus begin with the enolates *in silico*, that is as isolated entities in the gas phase or microsolvated, as handled by theoretical chemists. We will continue with the structure of enolates in the solid state to end up with the more complex 'real' situation that is the organization of these species into solution (as perceived through the UV, IR and particularly NMR spectroscopic data) where the problems linked to aggregation (homogeneous and heterogeneous) and solvation are fully relevant.

A. Lithium Enolates in silico

The structure and reactivity of lithium enolates are challenging problems to quantum chemists. The theoretical data available in 1988 were gathered by Seebach in a remarkable review presenting the state-of-the-art about enolates[200]. Since this milestone contribution, major advances have taken place, first with the spreading of modern semiempirical methods, then with the development of faster computers and of *ab initio* and DFT methods. This progress allowed the handling of larger systems, giving access to 'realistic' descriptions of aggregation and solvation phenomena, which refined knowledge about the structure and forces underlying their organization to an unprecedented level.

We have mentioned above (Section I) that the lithium in the enolates can *a priori* be located either toward the oxygen (η^1-O coordination mode), the carbon (η^1-C) or both (η^3-C,O). This property, called lithiotropy, creates structural problems, first tackled by theoreticians in the canonic case of acetaldehyde lithium enolate (lithium vinyloxide: Vinoli, Scheme 51). The (η^3-C,O) topology is that found on theoretical and experimental grounds for vinyllithium. However, a smaller tendency for bridging can be expected for lithium enolates compared with alkyllithium derivatives as a consequence of the larger electronegativity of oxygen. Note that the silicon analogues of lithium ester enolates has been shown, on a spectroscopic basis, to adopt the single η^1-Si mode (Scheme 51)[201].





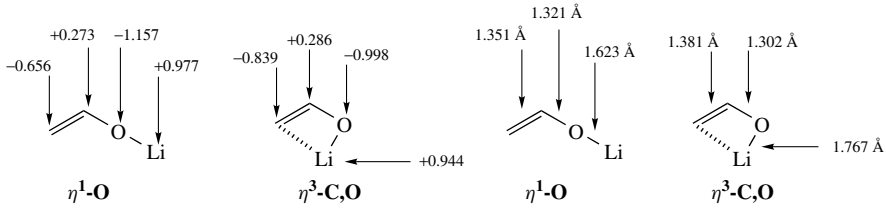
SCHEME 51. Lithium coordination modes in acetaldehyde enolate and in lithium ester silenolate[201]

As emphasized in Section IV of this chapter, the lithiotropy is of much consequence in the reactivity of enolates, the O and C sites competing toward electrophiles. This problem has been examined recently by Meneses and coworkers[202], who described a local hardness parameter that can be used as a selectivity index, in particular for a set of ketone lithium enolates.

1. Aldehyde and ketone enolates

The theoretical examination of Vinoli monomer (existing probably only in the gas phase) was undertaken at a restricted Hartree–Fock level in 1980 by Hall and coworkers[203]. Despite serious technical limitations due to the early computer capabilities, this pioneer work led to qualitatively good conclusions regarding the relative energy of the possible arrangements of this minimal system. It was indeed found that the η^3-C,O conformation is preferred by 1.4 kcal mol^{-1} with respect to the η^1-O mode (in which C, O and Li are almost aligned), provided a 'large' basis set (split valence plus polarization) on the carbons and the oxygen is considered.

Monomeric Vinoli was reconsidered later by Schleyer and coworkers[204, 205]. Using more sophisticated theoretical approaches led to similar conclusions concerning the η^3-C,O form, found to be more stable by 5.1 to 1.2 kcal mol^{-1}. A full optimization performed on the threshold conformers furnished all the geometrical characteristics as well as the natural charges (Scheme 52). The charge borne by the lithium of acetaldehyde enolate was



SCHEME 52. Natural charges (in electron) and interatomic distances (in Å) calculated (B3LYP) for threshold structures of acetaldehyde lithium enolate[205]

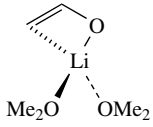
calculated to be larger than +0.9 e, suggesting that the Li−O bond is essentially ionic. As expected, a transfer of the s and p electron densities from the oxygen to the C=C double bond due to the deprotonation of the putative vinyl alcohol triggers a polarization of the double bond. Other high-level computational results, published simultaneously by Wang and coworkers[206], confirmed these data and gave access to the transition states between the coordination modes.

Comparable figures have been obtained from an extensive investigation on Vinoli in which several computational methods were compared[207]. Beyond the simple monomer, the solvation (by discrete addition of dimethyl ether) and aggregation phenomena were taken into account (Scheme 53). It was concluded from this very complete approach that:

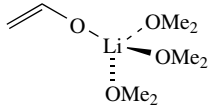
(i) geometries derived from semiempirical (PM3) optimizations are relatively fine but the corresponding energies are not trustworthy;
(ii) the lithium cation can be tetra- or tricoordinated, depending on the cumbersomeness of the ligands;
(iii) the solvation has little influence on the internal geometry of the anion but mainly affects the LiO distance;
(iv) solvating the monomer is a favored process, albeit the exothermicity associated to each incoming solvent decreases progressively (total solvation energies = −16.4/−27.9/−30.6 kcal mol^{-1} when considering 1, 2 and 3 molecules of Me_2O on the lithium, respectively, at the B3LYP/6-311+G**//PM3 level), the third Me_2O unit being particularly labile probably because of ligand–ligand repulsions;
(v) the η^3-O,C mode remains favored until three molecules of Me_2O are added (making the lithium tetracoordinated);
(vi) the oligomerization process is also decreasingly favored (total aggregation energies = −26.0/−33.5/−35.3 kcal mol^{-1} for the dimer, trimer and tetramer assembling, respectively, at the B3LYP/6-31+G*//PM3 level).

Several isomers of the dimer have been compared, then solvated by two, three and four molecules of Me_2O (Scheme 53). If the η^3-O,C coordination survives in the bare dimer, it disappears upon solvation, even by two Me_2O. A similar observation was made on the cyclic trimer, with a progressive loss of the π-cation interaction upon introduction of the solvent. When it comes to the tetramer, four isomers were identified exhibiting little energy difference until the solvent was added. The cubic tetrasolvated entity (in which each lithium reaches tetracoordination) becomes the more stable one by far, seemingly because of the more or less constant solvation energy (*ca* 10 kcal mol^{-1}) brought by each Me_2O. In the optimal spatial arrangement of the cubic structure, the repulsions between neighbor ligands are minimized.

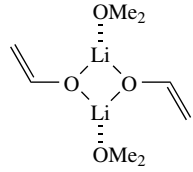
The considerable amount of data gathered in the above paper[207] suggests that the solvation has a critical influence on the aggregation processes, since the smaller entities (monomer and dimer) have a lesser tendency to form the trimer and tetramers when



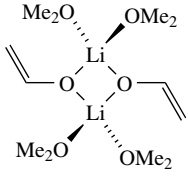
Disolvated monomer
$(CH_2{=}CHOLi)(Me_2O)_2$



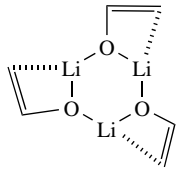
Trisolvated monomer
$(CH_2{=}CHOLi)(Me_2O)_3$



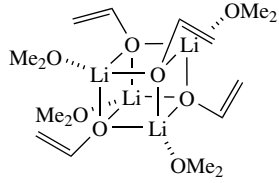
Disolvated dimer
$(CH_2{=}CHOLi)_2(Me_2O)_2$



Tetrasolvated dimer
$(CH_2{=}CHOLi)_2(Me_2O)_4$



Unsolvated trimer
$(CH_2{=}CHOLi)_3$



Tetrasolvated tetramer
$(CH_2{=}CHOLi)_4(Me_2O)_4$

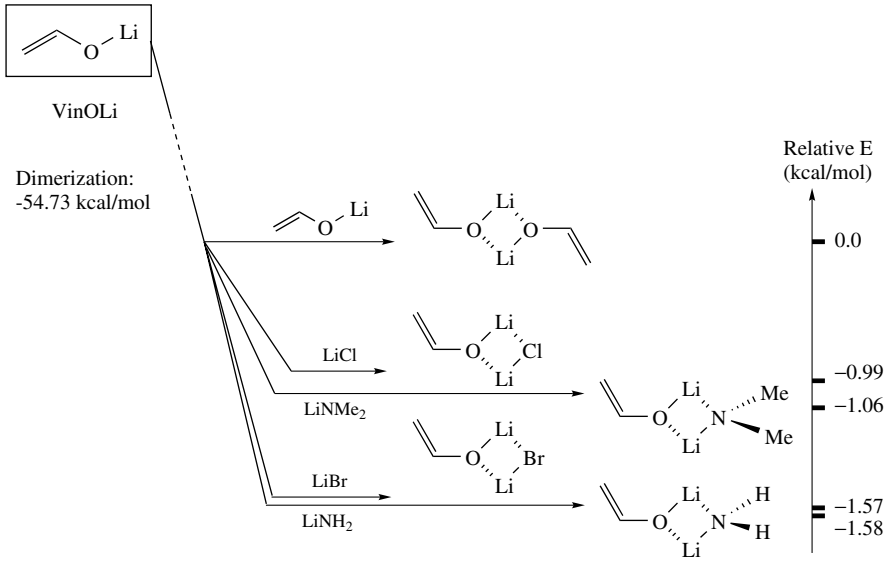
SCHEME 53. Optimal arrangements of the solvated monomer and small oligomers of acetaldehyde lithium enolate[207]

two molecules of Me_2O are included in the computation. These results parallel well the experimental data (see below). The charge calculated on the lithium seems relatively little affected by the solvation/aggregation states. Most of the above figures have been confirmed by a recent DFT study[191].

The mixed aggregation between Vinoli (monomer to trimer) and lithium halides (X = Cl or Br) or amides ($LiNH_2$ or $LiNMe_2$) was examined soon after by Williard, Schleyer and coworkers[208]. The calculated (HF) energy balance for the reaction between dimeric LiBr and dimeric Vinoli, each solvated by four NH_3 molecules (taken as model for the ether solvents), suggested that the mixed aggregation was favored by 1.5 to 0.1 kcal mol^{-1} over the homogeneous aggregation, depending on the computational level. Later on, Pratt and Streitwieser[209] generalized these results. Their HF/6-311+G* data led to the conclusion that, when starting from the Vinoli unsolvated monomer and the same ionic additives as above, the 1:1 mixed dimerization is always favored over the homogeneous one (by *ca* 1.0 to 1.6 kcal mol^{-1}, Scheme 54).

Similarly, the mixed (unsolvated) trimers (2:1 or 1:2) were found to be more stable, on theoretical grounds, than the homogeneous ones. A solvent effect superimposing a dipolar field (continuous dielectric) on the discrete ligand coordination was then taken into account. Overall, these effects decrease the exothermicity of both the homogeneous and mixed aggregations, but the entropic component makes them of little consequence on the previous disproportionation. Note that the structure of the mixed dimer formed between Vinoli and methyllithium has also been examined at the B3LYP/6-31+G* level[191].

The mixed (heterogeneous) complexes of a lithium amide (LDA or LiTMP) and a ketone lithium enolate (acetone, cyclohexanone or diisopropyl ketone) have been examined by semiempirical methods (MNDO) by Romesberg and Collum[48]. If the stabilization associated with these mixed complexes was not determined, the solvation (by THF and HMPA) of the mixed cyclic dimers and trimers was calculated to be generally exothermic (but decreasingly with the steric demand of the enolate) and led to disolvated entities. A set of solvated dimers, trimers and tetramers, cyclic or not, has thus been identified



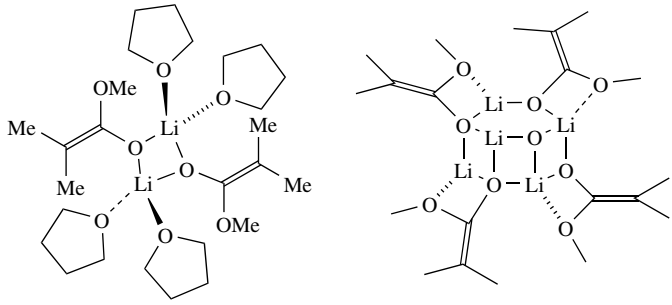
SCHEME 54. Mixed aggregations are favored over homogeneous dimerization[209]

as local minima on the MNDO potential energy surfaces. The influence of HMPA on these aggregation phenomena, a subject of many debates, is depicted as promoting mixed dimers relative to higher oligomers and eventually favoring open dimers (*vide infra*) in the case of the more hindered enolates.

2. Ester enolates

Lithium ester enolates are extremely important in polymer chemistry as initiators and active centers of the anionic polymerization of acrylic and methacrylic monomers in polar solvents. Thus, HF-SCF studies, comparable to those mentioned above, were undertaken on monomeric methyl isobutyrate (MIB) enolate[210,211]. The overall conclusions on the aggregation and solvation trends are exactly the same, the bent η^3-O,C mode being preferred over the η^1-O planar one by *ca* 3.3 kcal mol^{-1}. While the dimeric MIB enolate solvated by four molecules of THF was found to be the enthalpically most stable aggregate, the prismatic S_6 unsolvated MIB hexamer was computed as the preferred structure in non-polar solvents (Scheme 55)[212]. In the latter case, the supplementary oxygen of the ester acting as a 'side-chain' ligand for the lithium seems to explain this remarkable stability.

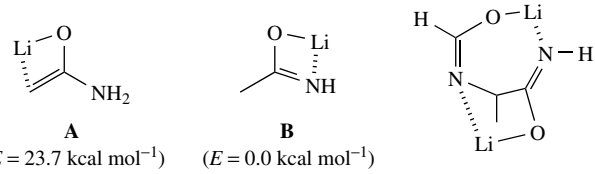
The structure of mixed aggregates involving ester enolates is also of major interest to macromolecular chemists, since ionic additives are often introduced in the polymerization medium. The more stable arrangement between lithium 2-methoxyethoxide and MIB lithium enolate was thus calculated (at the DFT level) to be a 5:1 hexagonal complex with similar O−Li lateral coordinations[212]. The same team has recently extended this study to complexes formed between the same enolate in THF and σ-ligands such as TMEDA, DME, 12-crown-4 and cryptand-2,1,1[213]. Only in the case of the latter ligand could a separate ion pair [(MIB-Li-MIB),2 THF]$^-$, Li(2,1,1)$^+$ be found as stable, still at the DFT level, as the THF solvated dimer [(MIB-Li)$_2$,4 THF].



SCHEME 55. Optimal arrangements of methyl isobutyrate (MIB) lithium enolate as a tetrasolvated dimer (left) or as an unsolvated hexamer (right, one enolate side-chain in the front and one Li−O couple in the background have been removed for clarity)[211,212]

3. Amide enolates

The importance of the electrostatic contribution to the lesser acidity of amides and esters with respect to ketones has been discussed recently[214], complementing former investigations on the origin of the enol acidity[215]. A combination of semiempirical and *ab initio* methods was retained in 1996 by Feigel and coworkers to detail the structure of acetamide lithium enolate as well as that of the azaenolate of a *N*-formylalanylamide (a model for a segment of small lithiated peptides, Scheme 56)[216]. The η^3-O,C coordination (A), calculated as the most favored conformation for a classic $CH_2{=}C(OLi)NH_2$ enolate in the absence of discrete solvent, is by far less stable than the corresponding CH_3-C(OLi)=NH (B) azaenolate (by *ca* 25 kcal mol^{-1} at various *ab initio* levels of calculation). This preference for the azaenolate form, buttressed by an intramolecular coordination, was also found in the peptide model.



SCHEME 56. Left: lithium enolate (**A**) and azaenolate (**B**) of acetamide (energies at the MP2/ZPE level). Right: intramolecular chelation scheme in lithium diazaenolate of H_2NCO-$CH(CH_3)$NH-CHO[216]

A high-level *ab initio* treatment of small enolates derived from acetamide (CH_3CONH_2) but also acetylphosphine (CH_3COPH_2) and acetophenone (CH_3COPh) was undertaken soon after at the SCF-MP2 level using a double- or triple-ζ basis set, eventually augmented with polarization functions[217]. Sgamellotti and coworkers have thus found that, for these three unsolvated monomers, the η^1-O and η^3-O,C coordination modes of the lithium are more or less isoenergetic while the η^1-C mode is disfavored by around 20 kcal mol^{-1}. Interestingly, when three molecules of water, the smallest possible model of an ether, are taken into account to simulate the first solvation shell of the cation, the η^1-C and η^1-O coordinations become isoenergetic. This is to be emphasized keeping in mind that the comparison between calculated and experimental ^{13}C NMR chemical shifts of the acetaldehyde lithium enolate suggests that the η^3-O,C arrangement does not exist in solution in

THF[205]. More recently, the acetamide $AcNH_2$ bare enolate has been re-inspected by DFT methods[218]. In particular, a 5–7 kcal mol^{-1} rotation barrier of the pyramidalized NH_2 group has been computed (in agreement with experiment), for the monomer as well as for the mixed aggregate with LiOH.

As shown below (Section IV), the lithium enolates are remarkable vectors of asymmetry. Indeed, the development of many chiral auxiliaries has been associated (in particular through their ester derivatives) with the enolate chemistry. We conclude this section with the contribution of a group of mathematical chemists who have tried to quantify the desymmetrization induced on enolate orbitals by common chiral auxiliaries[219]. This unusual viewpoint suggests that when the allylic stereogenic center is in the β position, the (Z) isomer has more chirality content than its (E) counterpart. This paper also concludes that in the enolates derived from Meyers' oxazolines, the lithium cation distorts the structure but has little influence on its chirality.

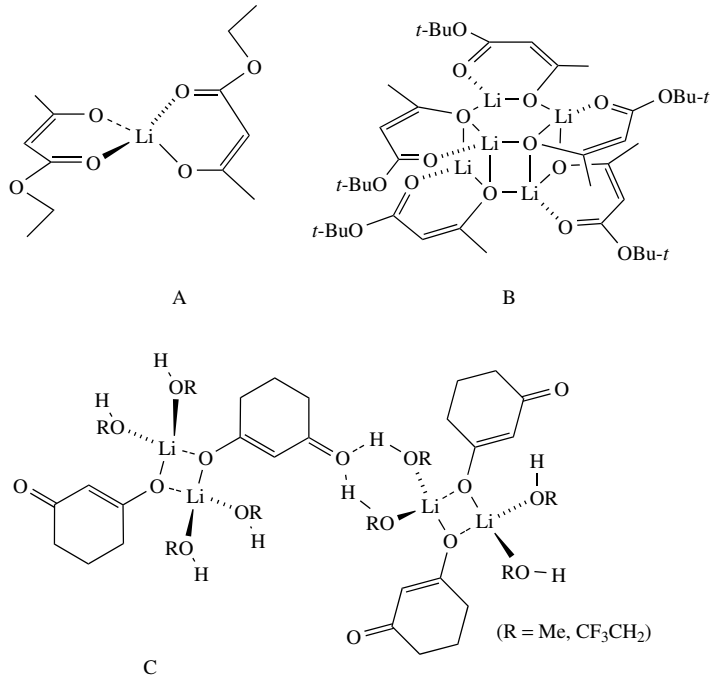
B. Lithium Enolates in the Solid State

A fine early account of the relevant information on this topic is featured in Seebach's 1988 review[200]. Enolates seem to crystallize only as even aggregates (from dimers to octamers). Actually, it has been known for a while that ester enolates are stable crystalline solids[220], but it took many efforts to obtain and handle crystals of a quality sufficient to achieve X-ray crystallography. Indeed, they tend to decompose into ketene and alkoxide, even in the crystalline state[221].

1. Ketone enolates

The stability of enolates derived from β-ketocarbonyl compounds, due to their intramolecular chelation, explains why these species were crystallized first. A triple anion of ethyl acetoacetate lithium enolate, obtained in a CH_2Cl_2/AcOEt mixture containing 1 equivalent of cryptand (2,1,1), was observed as an unsolvated dimer as early as 1979[222]. It featured an almost tetrahedral arrangement of oxygens around the lithium cation (Scheme 57A). The *t*-butyl derivative was also obtained as an unsolvated hexamer exhibiting six lateral coordinations by the oxygen of the ester carbonyl group (Scheme 57B)[223]. The stability of this enolate is such that it allowed for mass spectrometry and photoelectron spectroscopy. Oligomers up to the tetramer could thus be observed in the gas phase. The 1,3-cyclohexanedione lithium enolate could also be crystallized as a dimer tetrasolvated by 4 molecules of methanol or 2,2,2-trifluoroethanol[224]. Interestingly, both O–Li and O–H coordinations could be shown in this structure (Scheme 57C). The 2-oxopropyl-2-oxopropylidenediphenylphosphorane lithium enolate structure was also elucidated by X-ray crystallography[225]. The crystals, obtained in THF, showed a dimeric disolvated structure with two intramolecular O–Li coordinations. The lithium enolate of a β-ketoacylsilane, prepared by ring fission of tetramethyl-1,3-cyclobutanedione under the action of TMS_3SiLi–3 THF, could equally be characterized in the solid state[194]. The X-ray crystallography exhibited a cubic tetramer with four intramolecular O–Li coordinations.

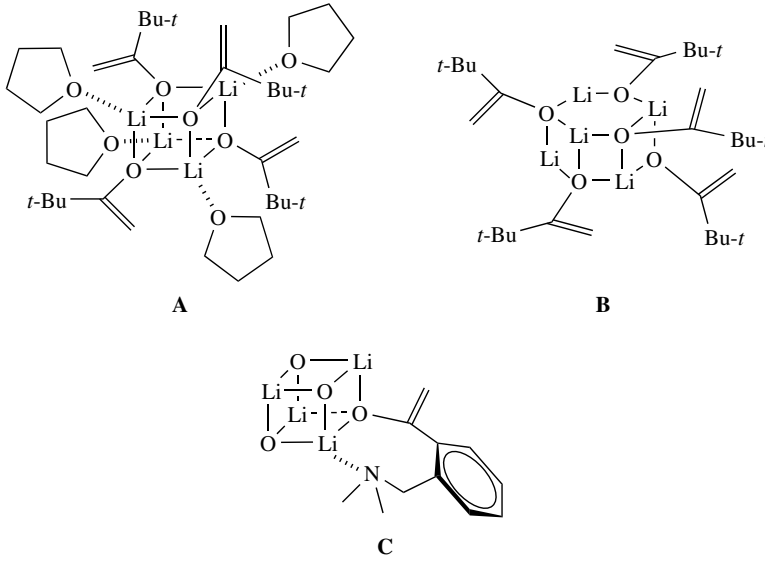
Seebach, Dunitz and coworkers reported, in 1981[226], the first crystal structures of lithium enolates of simple ketones, obtained in THF from pinacolone (3,3-dimethyl-2-butanone) and cyclopentanone. Both were arranged as tetrasolvated cubic tetramers, one THF molecule capping each lithium cation (Scheme 58A). Note that pinacolone enolate can also be crystallized, from heptane at $-20\,^{\circ}C$, as a prismatic unsolvated hexamer exhibiting an approximate S_6 symmetry and six slight π-cation interactions[227, 228] (Scheme 58B) or as a dimer in the presence of 2 molecules of TriMEDA[29]. Similarly,



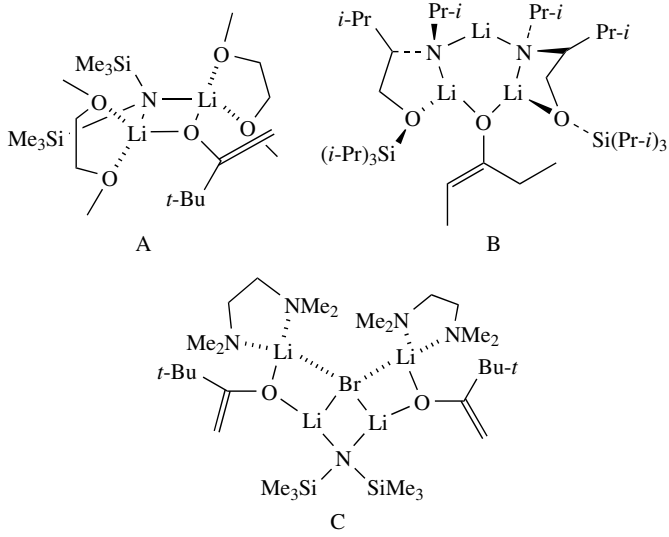
SCHEME 57. Various types of solid-state aggregation of β-ketocarbonyl compounds: (A) unsolvated dimer $[(CH_3C(OLi)CH\text{-}COOEt]_2]$[222]; (B) unsolvated hexameric $[(CH_3C(OLi)CHCOOBu\text{-}t]_6$[223]; (C) tetrasolvated dimer of 1,3-cyclohexanedione lithium enolate exhibiting both O−Li and O−H coordinations[224]

the lithium dienolate of the α,β-unsaturated ketone 2,2,5,6,6-pentamethylhept-4-en-3-one (the self-condensation product of pinacolone) crystallized as a dimer with two DMPU molecules[30]. By contrast, and probably because of strong Li−N intra-aggregate coordinations, a solvent-free cubic arrangement was obtained for the lithium enolate of 2-[(dimethylamino)methyl]acetophenone (Scheme 58C)[229].

Mixed aggregates involving ketone enolates have been equally characterized by X-ray crystallography. One of the simplest heterogeneous complexes was obtained co-crystallizing LiBr or LiI and diisopropyl ketone lithium enolate[208]. A 1:1 mixed dimer with one TMEDA chelating each lithium was thus obtained. Of major significance in light of the aldolisation reaction mechanism was the identification, in Williard's laboratories, of 1:1 and 2:2 heterogeneous complexes between ketone lithium enolates and LiHMDS[230] (Scheme 59A) or LDA[231], respectively. Interestingly, the same group recently co-crystallized the lithium enolate of 3-pentanone with a lithium amide derived from (*S*)-*N*-isopropyl-*O*-triisopropylsilyl valinol and obtained a 1:2 aggregate organized around a roughly hexagonal NLiOLiNLi core, one of the cations being dicoordinated (Scheme 59B)[232]. Three mixed aggregates of pinacolone lithium enolate were also obtained involving either: (i) potassium *tert*-butoxide (4:4 + 1 KOH + 5 THF) as a crown-shaped complex[233]; (ii) pinacolone sodium enolate (4:4 + *i*-Pr_2NH) as an 'open triple-stack' structure[234]; or (iii) LiBr and LiHMDS (2:1:1 + 2 TMEDA) as a triple anion complex exhibiting two three-coordinate (trigonal planar) and two four-coordinate (tetrahedral) lithium types (Scheme 59C)[235].



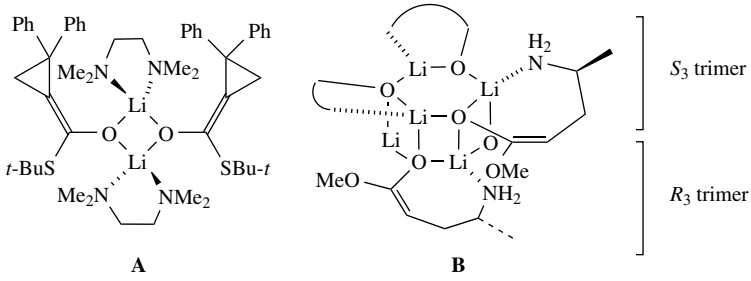
SCHEME 58. Various types of solid-state aggregation of ketone enolates: (A) tetrasolvated cubic $[(CH_2C(OLi)Bu\text{-}t]_4$, 4 THF][226]; (B) unsolvated hexameric $[(CH_2C(OLi)Bu\text{-}t]_6$[228]; (C) intramolecular chelated *o*-$[(CH_2C(OLi)C_6H_4CH_2N(CH_3)_2]_4$[229]



SCHEME 59. Various types of solid-state mixed aggregates involving ketone lithium enolates: (A) pinacolone enolate/lithium amide [LiHMDS/$CH_2C(OLi)Bu\text{-}t$, 2 DME][230]; (B) pentan-3-one enolate/2 chiral lithium amide[232]; (C) pinacolone enolate/lithium amide/LiBr [LiHMDS/2 $CH_2C(OLi)Bu\text{-}t$/LiBr, 2 TMEDA][235]

2. Ester enolates

The solid-state structure of ester lithium enolates has been extensively studied by Seebach and coworkers. Three examples (enolates derived from *t*-butyl propionate, *t*-butyl isobutyrate and methyl 3,3-dimethylbutanoate) were disclosed simultaneously[221]. The latter was obtained as a solvated tetramer comparable to those prepared from ketones, while the two former esters gave rise to dimers solvated by two TMEDA molecules. The dimers exhibited LiOLiO more or less planar cores, alike those described above from computational results. Each of the two TMEDA molecules coordinate as a bidentate chelate to one lithium atom. Note that these enolates, prepared in pure THF, have a (*Z*) double bond, as expected from Ireland's rules (*vide supra*). The same team was able to get an X-ray crystal analysis of the lithium enolate of a cyclopropane thioester[236]. Despite the obvious stress undergone by the three-membered ring, a dimer, organized around the same LiOLiO core, was crystallized with two TMEDA ligands (Scheme 60A). The lithium enolate of *t*-butyl α-cyanoacetate, crystallized with two TMEDA, adopts a dimeric arrangement due to an intermolecular N−Li coordination with the nitrogen of the nitrile appendage[237]. The important case of α-aminoester enolates has been studied by van Koten and coworkers[238], who reported a hexameric arrangement for the (*E*) enolate of ethyl *N*,*N*-diethylglycinate exhibiting Li−N intra-aggregate coordinations. A tetrameric X-ray structure was obtained from two β-enaminoesters exhibiting an intramolecular N−Li coordination[239] while an unsolvated hexamer (consisting of a face-to-face arrangement of a R_3 and a S_3 trimer, Scheme 60B) was disclosed more recently in the case of a racemic primary β-aminoester[240].

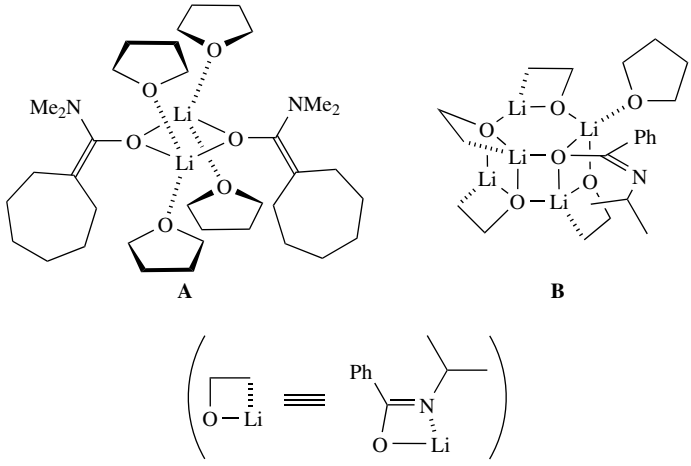


SCHEME 60. Solid-state aggregation of (thio)ester lithium enolates: (A) chelated dimer [(*c*-Pr=C(OLi)SBu-*t*)$_2$, 2 TMEDA][236]; (B) chelated hexamer of racemic [$NH_2CH(Me)CH_2CH{=}C(OMe)OLi]_6$[240]

3. Amide enolates

Lithium enolates derived from carboxamides are more stable and therefore easier to study. The X-ray crystal structure analysis of lithium enolates derived from tertiary [(*N*,*N*-dimethylpropionamide)[29], (*N*,*N*-dimethylamino)-8-heptafulvenamide[241], also studied by cryoscopy in THF[242]] and secondary [(*N*-isopropylbenzamide)[243]] amides have been obtained by Seebach's group. The two first ones both crystallized as dimers including either two TriMEDA or four THF (Scheme 61A), respectively. Note that neither the nitrogen atom nor the π-systems are involved in the coordination. The secondary amide structure was more challenging, since the acidic NH proton is abstracted first and thus the resulting lithium cation can *a priori* reside on the oxygen (azaenolate), the nitrogen or both. The azaenolate, favored on theoretical grounds (*vide supra*), was found experimentally. It crystallizes from THF/hexane (and one equivalent of TMEDA) as a

prismatic hexamer (Scheme 61B) with four intramolecular N−Li chelations, two THF to complete the lithium coordination spheres and a third THF incorporated in a disordered fashion. Note that the four-membered chelates formed between the COLiN atoms imply the chelating azaenolates are (*E*), while the two remaining 'pending' units are (*Z*). In similar experimental conditions, this same species provided also another type of crystal that X-ray crystallography revealed to be made out of an unsolvated octamer in which the lithums are capped either by the lateral nitrogen chelation, as described above, or by a phenyl group[244].



SCHEME 61. Solid-state aggregation of amide lithium enolates: (A) tetrasolvated dimer [(*C*-$C_7H_{12}C(OLi)NMe_2)_2$, 4 THF][241]; (B) intramolecular chelated [(PhC(OLi)=NPr-*i*)$_6$, 2 THF][243]

C. Lithium Enolates in Solution

Because the vast majority of the reactions in organic chemistry are conducted in solution, getting an insight on the structure and behavior of lithium enolates in their 'natural' environment gives access to the most relevant information on the subject. Not too surprisingly, a considerable number of publications describes the solvation and aggregation phenomena undergone by these species in various solvents, resorting to physicochemical measurements obtained from colligative, kinetic or spectroscopic (and, in particular, UV-visible and NMR) methods. A review by Jackman and Bortiatynski, published in 1992, gives a good account of the main techniques available to determine the parameters characteristic of the lithium enolates (and phenolates, considered as models) in solution, in particular by magnetic resonance methods[245]. The main results obtained from cryoscopy, a technique which seems to be no longer used, are presented in this review and will not be detailed here. Note that a recent review on the solvation effects on organolithium compounds in general is also available[246].

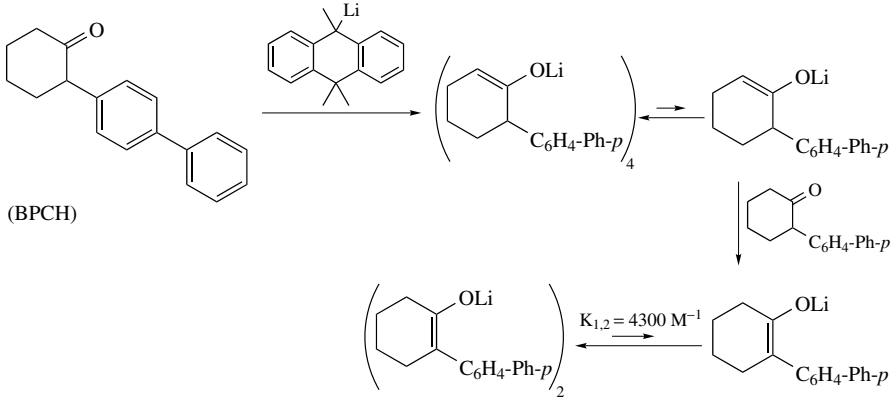
1. Data from UV-visible measurements

Ion-pair acidity is an important parameter to probe highly diluted solutions, as demonstrated by the sophisticated visible or near-UV absorption methods developed mainly by Streitwieser and coworkers. This analytical approach afforded the pK_a values and aggregation states of a large set of cesium and lithium enolates. Its principle relies

either on a 'single-indicator technique'[247] or on a linear-algebraic method based on the variations of UV-absorptions with concentration and called 'singular-value decomposition' (SVD)[248]. Applied to a global absorption spectrum, this deconvolution provides a sum of single species contributions. Important parameters characterizing the solution could thus be determined, provided the observed enolate (i) bears good chromophores (in general, conjugated aryl nuclei) and (ii) is sufficiently inert to avoid self-condensation problems.

It has, for instance, been shown with these methods that the dependence of the pK_a of the lithium enolate of *o*-methoxyacetophenone on the concentration in diluted THF was a consequence of its aggregation, and that an important internal solvation effect of the lithium cation by the oxygen of the methoxy appendage was taking place in the dimer[249].

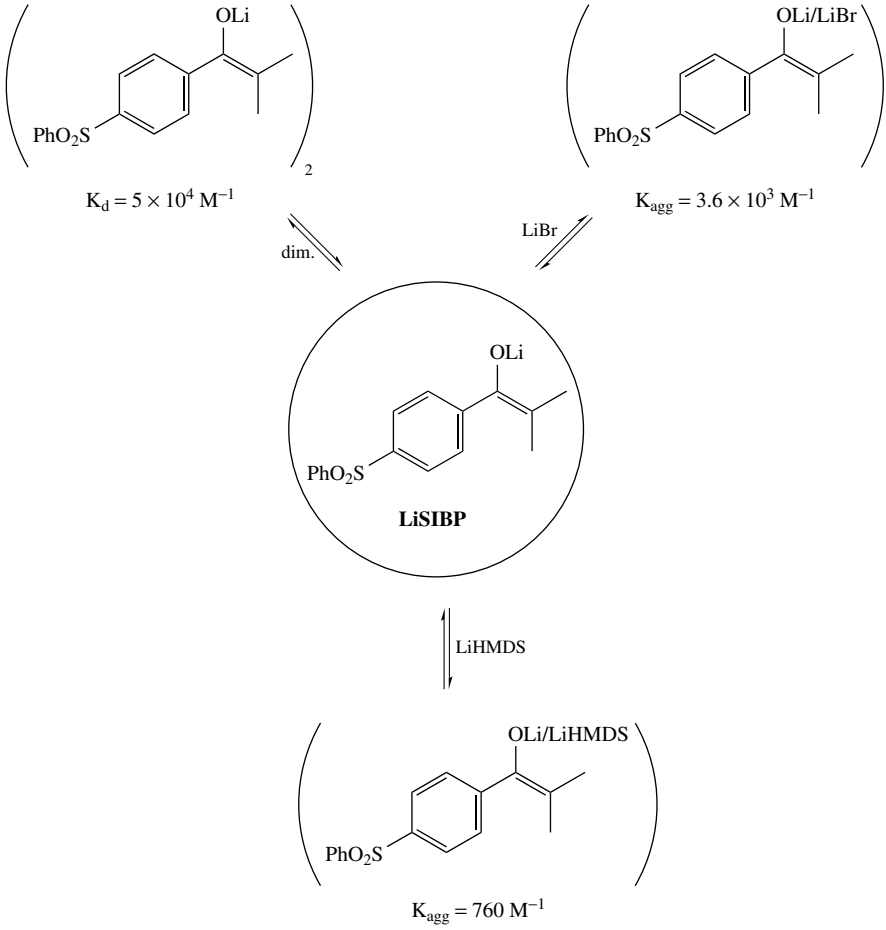
These spectroscopic approaches also shed light on the fundamental point of the equilibration between regioisomeric enolates[250]. The case study was that of 2-biphenylcyclohexanone (BPCH) deprotonated by 9-lithio-9,10,10-trimethyldihydroanthracene (LiTMDA) in THF at room temperature (Scheme 62). The less substituted (kinetic) enolate was first obtained dominantly as a tetramer. The data showed that the conversion of this latter into its conjugated (thermodynamic) isomer occurs gradually, through the monomer of the kinetic enolate which reacts with the starting ketone to give the thermodynamic isomer. This latter is present as a monomer–dimer mixture with $K_{1,2} = 4300\ M^{-1}$.



SCHEME 62. From the kinetic to the thermodynamic enolate of BPCH[250]

Abbotto and Streitwieser have shown that the lithium enolate of *p*-phenylisobutyrophenone (PhIBP) evolves from a monomer at high dilution (*ca* 10^{-4} M) to a tetramer at 10^{-2} M. Note that the monomer contribution is still in the 1–5% range in 0.1–1.0 M solutions[251]. The study of the influence of the ethereal solvent on the aggregation of this very enolate has led to the conclusion that it can be found as a pure monomer (in DME) or a pure tetramer (in MTBE), as well as a mixture of both (in THF)[252]. Upon addition of HMPA, the tetramer dissociates to monomers solvated by 1–2 molecules of HMPA[253].

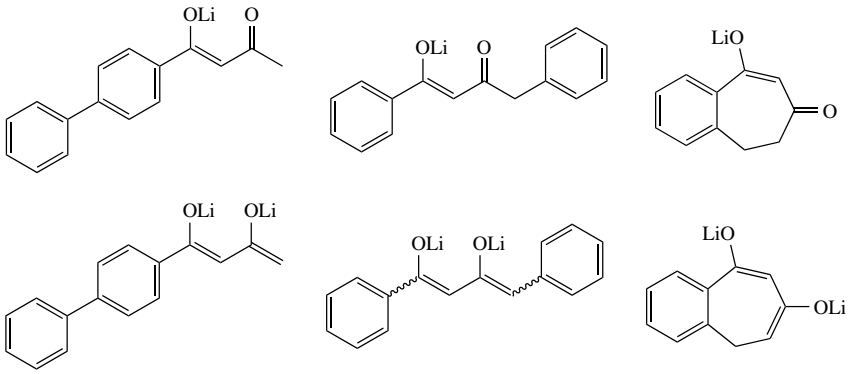
By comparison, the lithium enolate of *p*-(phenylsulfonyl)isobutyrophenone (SIBP) was found mainly dimeric in THF, in equilibrium with its very reactive monomer ($K_d = 5 \times 10^4\ M^{-1}$)[254]. In the presence of lithium bromide, this dimer gave birth to a well-characterized 1:1 LiSIBP–LiBr mixed aggregate[255]. Similarly, a 1:1 LiSIBP–LiHMDS was demonstrated upon addition of lithium hexamethyldisilazide (Scheme 63)[256].



SCHEME 63. Aggregation of LiSIBP in THF, alone, with LiBr or LiHMDS[254–256]

The THF solution of enolates derived from 2-phenyl- and 2,6-diphenyl-α-tetralone have also been investigated by SVD analysis of their UV spectra[257]. In the 10^{-3}–10^{-5} M range, they appeared as a mixture of monomer and dimer with $K_{1,2} = 2650$ and 1930 M^{-1}, respectively. By contrast, a monomer–tetramer equilibrium (displaced on the monomer side under the influence of HMPA) was obtained for the lithium enolate of 6-phenyl-α-tetralone[258]. Interestingly, dibenzyl ketone (DBK) gave access to both the enolate and the corresponding dianion. In THF, the standard lithium enolate was found to form dimerized ($K_d = 4.2 \times 10^2$ M^{-1}) contact ion pairs while the dianion exhibited two types of triple ions: one in which both cations are in contact with the DBK dianion and one in which one cation is solvent-separated[259].

The second acidity of three β-diketones was determined from ion-pair UV-vis absorption spectra (Scheme 64)[260]. The aggregation levels determined from the pK_a values suggested that both the monolithium and dilithium salts are dimers in THF solutions at concentrations >0.01 M.



SCHEME 64. Mono- and dilithium enolates forming dimers in THF[260]

A set of seven amide lithium enolates has been analyzed by the same techniques[261]. The pK_a measured for the corresponding ion-pairs were found to be in the 20s range in THF at 25 °C, a value increasing under the influence of intramolecular chelation. All these enolates were found essentially monomeric when in 10^{-6}–10^{-3} M solution in the same solvent.

We complete this section with a study of the effect of TMEDA on the polymerization of methyl methacrylate lithium enolate in THF[262]. It was concluded that TMEDA hardly affects the kinetics of the polymerization and therefore the monomer–dimer equilibrium. From these figures, TMEDA does not seem to be a better ligand for lithium ester enolates than THF, in line with previous observations by Collum on other organolithium compounds[263].

2. Data from IR and NMR spectroscopy

Infrared spectroscopy has found little application to the characterization of lithium enolates, albeit some useful data could be collected in various cases (*vide infra*), particularly thanks to the recent development of *in situ* measurement techniques. In contrast, nuclear magnetic resonance, which is probably the most potent spectroscopy in the field, is particularly good for probing the structure and organization of aggregated species in solution. In particular, NMR is the tool of choice to study alkyllithiums or lithium amides because of the direct ^{13}C or ^{15}N–^{7}Li or ^{6}Li coupling observations. In the case of enolates, indirect methods have been proposed, such as the line shape analysis (developed in particular by Fraenkel[264]) and quadrupole splitting constant (QSC) on ^{7}Li which can provide valuable information on the degree of aggregation and the level of solvation of the species[265]. The ^{13}C NMR spectroscopy is also an appropriate tool to follow enolates in solution through two parameters. First, the π electron density on a carbon atom is known to be strongly correlated to its ^{13}C chemical shift. Therefore, the presence of between one and four lithium cations when going from the monomer to the tetramer is expected to progressively shift the conjugated carbons to lower field. Advantage can be taken of these effects, but attention should be paid to structural or ligation/solvation effects before comparing data. Second, ^{13}C spin–lattice relaxation time can be used to identify partners in equilibrium, provided the systems of interest are separately observable by ^{13}C NMR and have half-life for exchange which is long compared with relaxation times. A general presentation of the theoretical and experimental aspects of these techniques is available in Jackman and

Bortiatynski's review[245]. Note that whatever the technique retained, low temperatures are generally required for both stability and rapid interaggregate exchange issues.

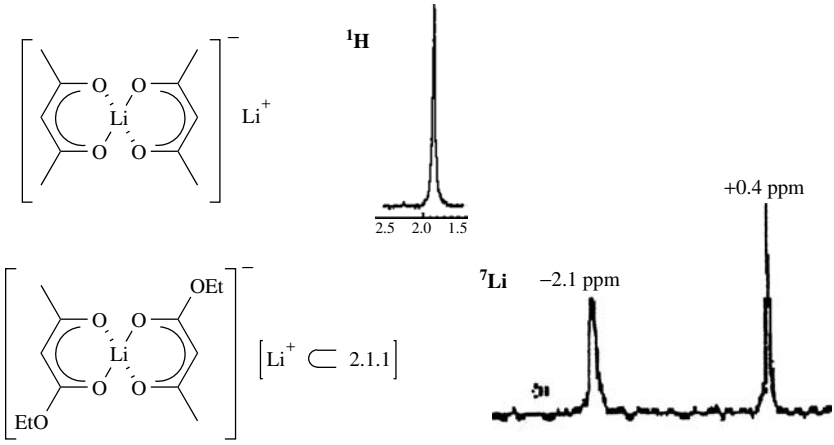
a. Aldehyde and ketone enolates. Relatively little is known about aldehyde enolates. Acetaldehyde lithium enolate has been studied by Wen and Grutzner who found two types of tetramers in THF, differing probably by their level of solvation[266]. Collum and coworkers showed that the deprotonation of cyclohexanecarboxaldehyde by LDA leads to a complex mixture[8].

In contrast, the first IR and NMR recordings of ketone enolates were carried out in the early 1970s by a few pioneer teams. Jackman and Haddon showed that no rotation around the double bond of isobutyrophenone enolate occurs in six different solvents and up to 200 °C ($E > 27$ kcal mol^{-1})! Two types of homogeneous aggregates were observed in solution in dioxolane, as well as heterogeneous aggregates with LiCl and LiBr[267]. Simultaneously, House and coworkers were able to establish that various α-mercurated ketones exhibit covalent C−Hg bonds while the corresponding lithium enolates are mostly under their OLi form in solvents such as DME, THF or DEE[268]. Soon after, Jackman and Szeverenyi demonstrated by a ^{1}H, ^{7}Li, ^{13}C triple nuclei NMR study plus quadrupole splitting constant measurement on ^{7}Li that the prototypic isobutyrophenone lithium enolate undergoes a dimer–tetramer equilibrium in solution in ethers[269]. This investigation also led to the conclusion that the dimer was disolvated in DME and that a mixed aggregate $Li_4Cl(enol)_3$ formed in the presence of LiCl. A relatively large set of ^{13}C NMR data was collected on ketone-derived enolates[270]. As mentioned above, the drifts undergone by the ^{13}C chemical shifts upon addition of cryptands or HMPA give access to the effect of the cation or the solvent on the polarization of the C=C double bond[271]. The 2-alkyltetralone lithium enolates were also studied in great detail by Jackman and Bortiatynski[245]. It was shown, for instance, that these species participate in a tetramer–dimer equilibrium which is slow at room temperature and markedly displaced toward the dimer for bulky alkyl groups.

The particular case of lithium acetylacetonate (acac), a canonic example of β-diketone enolate, was also examined early. It was shown that its chelated (Z,Z) conformation was almost exclusive in methanol at −60 °C and that dimers were probably formed in which one of the two lithium cations would be chelated by the two acac anions[272]. A somewhat similar dimer, obtained from the lithium enolate of ethyl acetoacetate complexed by a 2.1.1 cryptate, was characterized in one of the first ^{7}Li NMR studies of enolates (Scheme 65)[273]. Note that the structure of the three β-diketone mono- and dilithium enolates displayed in Scheme 64 has been studied, despite their poor solubility, in both THF-d_8 and DMSO-d_6 by ^{13}C NMR[260]. The data obtained for the monoenolates are consistent with rapidly equilibrating dimers, while the dimers of dienolates seem to form slowly on the NMR time scale.

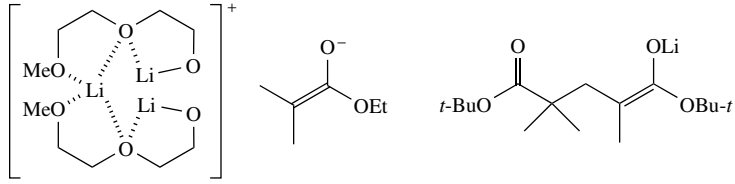
Interestingly, a ^{13}C NMR study indicated that the lithium enolate derived from cyclopentadienyl methyl ketone is planar and configurationally stable between −60 and +55 °C[274]. By contrast, the cyclopentadienyl t-butyl ketone enolate exhibits dynamic rotation at room temperature. Recently, the fate of cyclopentanone lithium enolate in solution in three ethereal solvents (Me_2O, Et_2O, THF) containing increasing amounts of HMPA has been the object of a ^{7}Li,^{13}C,^{31}P NMR study[275]. The results led to the conclusion that this enolate is involved in a tetramer (solvated by 4 HMPA)—dimer (solvated by 2 ether molecules and 2 HMPA) equilibrium that is almost fully displaced toward the dimer when at least two equivalents of HMPA are added[276].

b. Ester and amide enolates. Regarding enolates of esters, original observations were published by Rathke, first for the lithium enolates of t-butyl acetate in benzene[277], then of N,N-dimethylacetamide in pyridine[278].



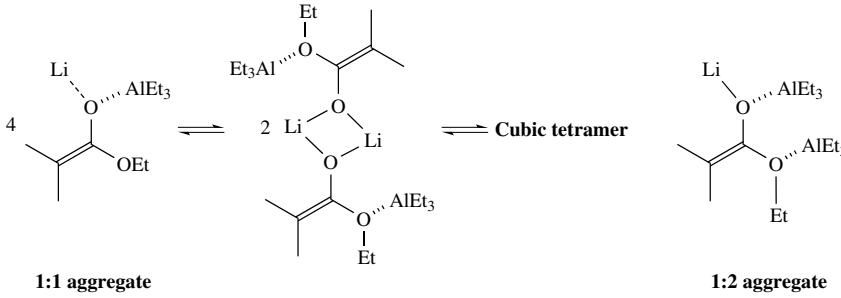
SCHEME 65. NMR spectrum of lithium acetylacetonate (^{1}H, 60 MHz, top) and of ethyl acetoacetate lithium enolate (^{7}Li with $LiClO_4$ in water as external reference, 35 MHz, bottom); 2.1.1 cryptate = 4,7,13,18-tetraoxa-1,l0-diazabicyclo[8.5.5]eicosane[272, 273]

The structure of the methyl lithioisobutyrate (MIBLi) in THF has been the object of a series of detailed ^{7}Li/^{13}C NMR investigations owing to its possible importance as a model for the living poly(methyl methacrylate) chain occurring during anionic polymerizations. Thus, the ^{13}C chemical shifts were collected on a series of butyrate enolates[279]. An equilibrium between the tetramer and solvated dimer of MIBLi was demonstrated in THF and the effects of the temperature and concentration were determined[280]. The tetramer and dimer of this same enolate were also shown to form 1:1 and 1:2 mixed complexes with LiCl upon addition of 1 or 2 equivalents of this salt, respectively[281]. Actually, the MIBLi dimer population was shown to increase upon addition of cation complexing agents in the medium, while addition of cryptand 211 shifted the equilibrium toward a single monomeric K211-complexed species[282]. Upon addition of lithium *t*-butoxide, a series of $[(MIBLi)_x(t\text{-BuOLi})_{4-x}]$ tetramers, identified by ^{13}C NMR, is formed in THF at $-40\,^{\circ}C$, whatever the MIBLi/*t*-BuOLi ratio[283]. Interestingly, the addition of lithium 2-(2-methoxyethoxy)ethoxide, an alcoholate bearing a chelating appendage, to a solution of the same ester enolate, in THF or THF/toluene mixtures, leads to a loose mixed complex between two alcoholates and three lithium cations on one side and the MIB enolate on the other (Scheme 66, left)[284]. Note that a more sophisticated dimeric entity (di-*t*-butyl 2-lithio-2,4,4-trimethylglutarate, Scheme 66, right) has also been investigated by ^{1}H,^{7}Li, and ^{13}C NMR in THF/toluene mixtures as a model for the propagation center of the anionic polymerization[285].



SCHEME 66. Aggregates formed between MIBLi and lithium 2-(2-methoxyethoxy)ethoxide (left)[284] and di-*t*-butyl 2-lithio-2,4,4-trimethylglutarate (right)[285]

The favorable effect of trialkylaluminium on the anionic polymerization of acrylic monomers induced by organolithium compounds prompted a DFT theoretical and ^{6}Li,^{13}C NMR study on the interaction between $AlEt_3$ and ethyl lithioisobutyrate (EIBLi) in toluene at $-20\,^{\circ}C$. Monomers, dimers and tetramers of 1:1 or 1:2 enolate and $AlEt_3$ aggregates were identified (Scheme 67)[286].



SCHEME 67. 1:1 (left) and 1:2 (right) aggregates formed between EIBLi-$AlEt_3$ and their complexes[286]

Note that other ester and amide enolates have been examined by NMR methods[8]. For instance, the lithium enolate of a β-amino-α,β-unsaturated ester was shown to provide a highly twisted dienic skeleton[287]. More recently, the organization of chiral and racemic β-aminoester enolates in a THF/toluene mixture was investigated. Its results, supported by X-ray data, suggested that a dynamic equilibrium between heterochiral hexamers was taking place[240], but that the balanced heterochiral R_3S_3 form (Scheme 60B) was markedly more stable[288]. The lithium enolate derived from methyl cyclopentylcarboxylate was shown to freely rotate around its double bond, as mentioned above in the case of the cyclopentyl *t*-butyl ketone enolate[274], an interesting result with regard to that obtained for two lithium heptafulvenolates[289]. Conjugating an enolate double bond to an aromatic ring can be of consequence in its configuration and aggregation, as observed by IR and ^{13}C NMR in the cases of methyl and *t*-butyl phenylacetate enolates[290]. In these cases surprisingly low aggregation degrees (monomers + dimers) were observed.

The deprotonation of acyldiphenylphosphines using BuLi provides α-phosphino enolates, isolated as a white solid and characterized by NMR as a tetrasolvated dimer in THF[291].

c. Mixed aggregates. The strong tendency of enolates to form mixed aggregates in solution is of chemical importance, as emphasized in a recent review[292]. For instance, the aggregation of ketone lithium enolates and lithium amides has a significant influence on the enolization itself as this association implies that the basic partner evolves along the reaction course. Thus, the mechanisms operating at early conversion are not necessarily the same as those at the latter stages of the reaction. The mixed aggregation phenomena have been the object of in-depth studies, conducted mainly by Collum's group. In particular, the problem was addressed by a ^{1}H, ^{6}Li, ^{15}N triple nuclei NMR investigation[293]. Mixed 1:1 dimers and 2:1 trimers (2 amides + 1 enolate) formed between LiTMP and lithium cyclohexenolate were proposed and their proportions were shown to depend on equilibria influenced by the bulkiness of the partners, their relative concentration as well as the concentration of the sample studied. Hence, only 1:1 dimers could be identified with cumbersome amides such as *t*-Bu_2NLi[293] or lithium bis(2-adamantyl)amide[294], while neither LDA[293,295] nor lithium dicyclohexylamide[296] aggregated with lithium cyclohexenolate.

In the presence of HMPA, 1:1 dimers were observed with both lithium cyclohexenolate or 2,4-dimethylpentanolate and [^{6}Li,^{15}N]LDA or [^{6}Li,^{15}N]LiTMP[297]. The β-aminoester enolate presented above (Scheme 60B) was also shown to provide a 1:1 mixed aggregate with LiHMDS in THF[288].

We end this section with the mixed aggregates formed between lithium enolates and enolates of other metals such as zinc or magnesium. These have been obtained by addition of $ZnBr_2$ or $MgBr_2$ to the lithium enolate of 2,2-dimethylpentan-3-one and characterized by ^{13}C NMR and infrared spectroscopies[298]. The influence of this different type of mixed aggregation on the reactivity has also been studied[299].

IV. REACTIVITY OF LITHIUM ENOLATES

Although the development of stable latent enolates and their analogs became progressively prominent[300–303], preformed lithium enolates are still widely encountered as key intermediates in the elaboration of a number of natural products. The pioneering works reported in Section II have allowed an almost complete control over the preformed lithium enolates, which are now available regioselectively and with a predictable stereochemistry. These results were among the seminal achievements that ultimately led to the overwhelming development of the chemistry of lithium enolates and, in the same way, to the supramolecular approach now spread over modern organic chemistry[304]. Moreover, their low stability and complex aggregated structures have dictated the development of sensitive and rapid time-resolved analytical techniques to confront the mechanistic aspects of their reactivity.

In this fourth part we outline some aspects of the reaction of lithium enolates with electrophilic reagents and their nucleophilic addition onto saturated carbonyl groups. Two significant problems associated with these reactions are: (i) the site (C/O) selectivity due to the ambident character of enolates, and (ii) the facial discrimination which controls the stereochemistry of the overall process.

Recent molecular orbital calculations in the gas phase have confirmed the C−C(−O) bond-length shortening and the charge transfer to the oxygen atom on going from the parent carbonyl to the enolate[305]. The reactivity of enolates toward electrophiles has long been associated with their ambiphilic character. The regioisomeric ratio is very sensitive to the nature of the electrophilic reagent and has been rationalized by the fundamental Klopman–Pearson's HSAB principle[306, 307]. Basically, the selective solvation of the metal of the enolate results in a local external perturbation, enhancing the reactivity on the carbon atom that can be appreciated in terms of non-local reactivity[308]. Thus, the nature of the solvent and the degree of aggregation are expected to influence the rate, the regiochemistry and the stereochemical control. The reaction at the oxygen atom would be favored owing to the oxophilicity of the reagent, thus silylation remains a powerful method for quenching lithium kinetic enolates, providing a synthetically useful access to silylated enol ethers and silylated ketene acetals. This same property is used in the transmetallation of preformed lithium enolates.

In the following, the stereofacial differentiation will be considered in a classical way (Figure 1). Thus, if the direct precursor of the prochiral enolate and/or the reacting electrophile is covalently linked to the source of asymmetry, we will classify the transformation in the category of the diastereospecific reactions. In contrast, if achiral (or racemic) structures are employed and the asymmetry is introduced via the use of non-covalently bonded chiral ligands, we will refer to enantiospecific reactions.

A. Protonation of Preformed Lithium Enolates

The trivial protonation step ending many organic reactions is of utmost importance in controlling the final stereochemistry of the experimental sketch of a reaction sequence

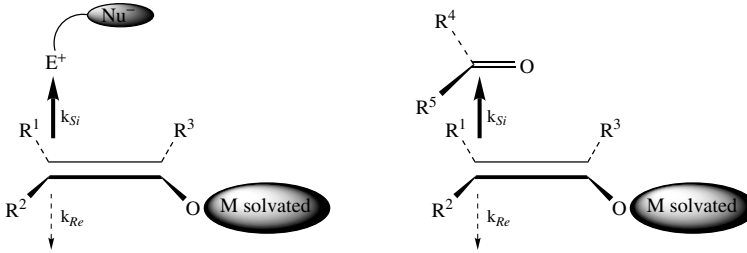


FIGURE 1. Stereoface differentiation during the electrophilic substitution and nucleophilic addition of preformed lithium enolate

involving the transformation of a prochiral sp^2 enolate (or enol) to the parent carbonyl compound. The proton transfer generally involves solvated protons[309,310], and factors affecting the stereoselectivity of the protonation of the enolate include the nature of the protonating agents[311,312] as well as parameters that influence the structural behavior of the reactive center such as steric, electronic substituent effects as well as aggregation state[180]. Since screening is still a favorite way to find the best proton source for a particular enolate, some rules for the design of the protonating agents have progressively emerged and it is amazing that most of the results accumulated on this reaction come from enantioselective protonation studies. Interestingly, these results are prone to be applied to the development of efficient strategies for direct incorporation of non-radioactive isotopic labels within organic molecules.

1. Conditions for the kinetically controlled C-protonation

The question of whether kinetic O-protonation is followed or not by a proton-relayed transfer to yield the C-protonated product still remains open. The large degree of charge transfer, which occurs in the gas phase, from the carbanionic center to the oxygen atom of the enolate, sustains the assumption that protonation will occur first at the more electronegative oxygen atom[313–316]. The calculated ion–dipole complexes, for the protonation of acetaldehyde enolate in the gas phase by the very weak methyl acidic protons of acetaldehyde, are best described by a head-to-tail orientation and only at a high level of calculation are the distances between the incoming proton and both the α carbon and the oxygen centers of the enolate equal in length[317].

A short O---H distance (1.9 Å) was found by Boche and coworkers for the weak ammonium enolate ($pK_{BH} = 24.3$ in acetonitrile) derived from *t*-butyl α-acetoacetate[237], and recently, clearly well-shaped crystals of 1,3-cyclohexanedione lithium enolate (LiCHD) solvated by two molecules of methanol or 2,2,2-trifluoroethanol have been isolated by slow evaporation of a methanol solution of LiCHD. In the aggregate pattern, both oxygens have intramolecular contacts at all available *syn* or *anti* lone-pair positions (Figure 2)[224].

On the other hand, the kinetically controlled protonation, by chiral aminoalcohols, of transient photoenols generated by 1,4-addition of thioacids onto substituted acrolein[318] or by a Norrish type II rearrangement of conjugated esters[319], has been reported. The enantioselectivity of the reaction strongly suggests the participation of the chiral alcohol in the 1,3-proton shift and probably the synergy of both the amino and the hydroxy groups in a relay mechanism (Figure 3)[320].

However, except when stabilized by either electron attracting or sterically demanding groups, the net result of the protonation of an enolate is the formation of the thermodynamically stable parent carbonyl. For example, on treatment of the lithium enolate

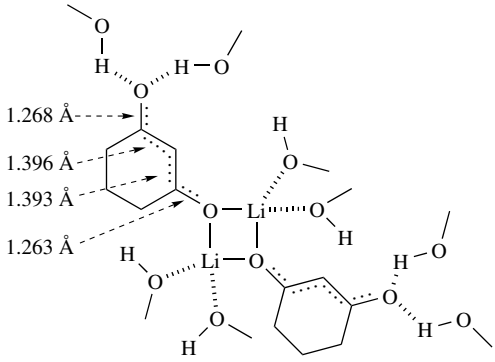


FIGURE 2. Molecular arrangement of methanol solvated lithium enolate of 1,3-cyclohexanedione (LiCHD)[224]

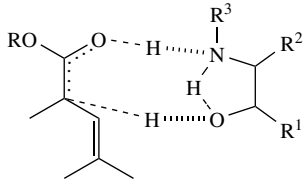


FIGURE 3. Possible relay mechanism in the protonation of an enol

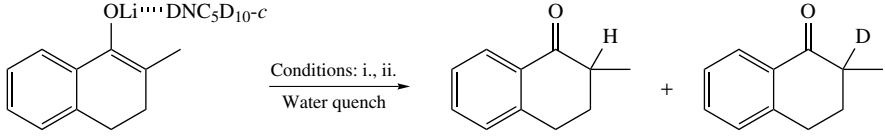
of isobutyraldehyde with an excess of water, a rapid proton transfer yields the enol ($\lambda_{max} = 200–220$ nm) which slowly isomerizes to the carbonyl compound. The reaction is a first-order general acid-catalyzed process ($k_E^{H+} = 5.45 \times 10^{-3}$ $M^{-1}\,s^{-1}$) with a kinetic isotope effect ($k_{H^+}/k_{D^+} = 2.8$) strongly suggesting that the proton transfer is rate-determining[321]. From the comparison of the rate of ketonization of enol and enolate, it was concluded that under weak acidic conditions, the enolate is *C*-protonated up to 10^8 times faster than the corresponding enol.

Thermodynamic control is usually observed when the protonation is conducted with strong acids at room temperature. Complete protonation requires that the thermodynamic acidity of the proton donor in the complex proton source–substrate is higher than that of the product[322]. Moreover, the structural reorganization that takes place upon the C-protonation of an enolate affects the rate of the process and a face differentiation is likely to occur. Then, the stereochemical control of the *C*-protonation would be best achieved under kinetically controlled conditions (careful protonation at low temperature) using weakly acid protonating agent ($pK_a = 15–20$) to allow a better transition state discrimination[323]. It should also contain electron-rich groups to ensure a conformational rigidity in the transition state; another criteria to be taken into account is the possibility of introducing a chiral environment[324].

Solvation has a critical role in determining the relative energies of aggregated species of the nucleophilic reagent; the negative charge on C_β decreases from a monomer to higher aggregates. However, upon solvation, the effective positive charge on the lithium atom decreases but without significant change for the oxygen charge population of the enolate moiety[207]. In these conditions, a direct protonation by a weak acid is unlikely to

occur since rearrangement in the aggregation state will probably operate before transfer of the proton.

The incomplete deuteriation of lithium enolates, generated by lithium amide deprotonation[325–328], was explained by Seebach[329] as a competitive protonation by the amine within the lithium enolate aggregate since transformation of this amine to lithium amide, before deuteriation, led to a completely deuteriated product[330, 200]. The orientation of the N–H bond toward the enolate carbanionic center in the solid state, found for the lithium enolate of pinacolone, solvated by trimethylethylenediamine, can accommodate this intramolecular proton transfer[29]. Alternatively, Hünig proposed that the amine, close to the lithium ion, mediates a rapid proton/deuterium exchange with the protonating agent[331]. In a study of factors affecting the C-deuteriation, the lithium anion of 2-methyltetralone generated by cleavage of the corresponding silyl enol ether in THF was reacted with fully deuteriated piperidine in the presence (or not) of Lewis acid[332, 333]. The measure of H/D ratios confirms the role of the amine as well as the role of added Lewis acid, especially Me_3SiCl[334], in assisting the deuterium transfer process (Scheme 68).



Conditions	i. CD_3CO_2D ii. Me_3SiCl	i. CD_3CO_2H ii. Me_3SiCl	i. Me_3SiCl	i. LiBr ii. Me_3SiCl	i. H_2O
Yield (H%/D%)	72% (5:95)	71% (91:9)	59% (70:30)	51% (40:60)	60% (98:2)

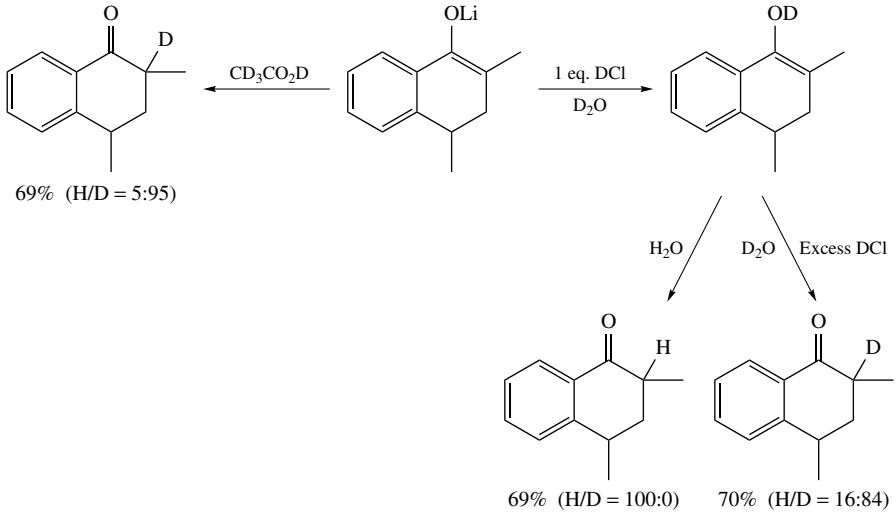
SCHEME 68. Influence of the experimental conditions on the deuteriation of 3-methyltetralone lithium enolate[333, 334]

Besides its use as a mechanistic probe, deuteriation of anions under kinetically controlled conditions is a potentially promising way to access deuteriated molecules in a regio- and stereo- controlled manner, in opposition to the thermodynamic equilibration in the presence of an excess of deuterium donor. Thus, treatment of the lithium anion of 2-methyltetralone ($pK^E = 7.31$, $pK^E{}_a = 10.8$, $pK^K{}_a = 18.1$ in water)[335], by one equivalent of a solution of deuterium chloride in deuterium oxide, generates the intermediate *O*-deuteriated enol whose reaction with water or with an excess of deuterium chloride in deuterium oxide conducts to, respectively, the tetralone or the deuteriated tetralone (Scheme 69)[336].

A careful study of the *C*-deuteriation of a series of preformed endocyclic[337] and acyclic or exocyclic lithium enolates has recently been carried out by Eames and coworkers[338], extending their previous observations on protonation[339].

2. Diastereoselective protonation of lithium enolates

The formation of the less favored diasteomer, resulting from the kinetic diastereoselective protonation[340] of rigid cyclic and exocyclic enolates, has been interpreted by Zimmerman as an exothermic proton transfer to the less hindered side of the enolate in an early reactant-like transition state[341–344]. This diastereoface selection can be rationalized by considering the proton, which is delivered at the less hindered face as a very large pseudosubstituent (solvated or aggregated proton donor) in the transition state[345]. The dominant steric influence of the substrate is clearly expressed during the kinetic



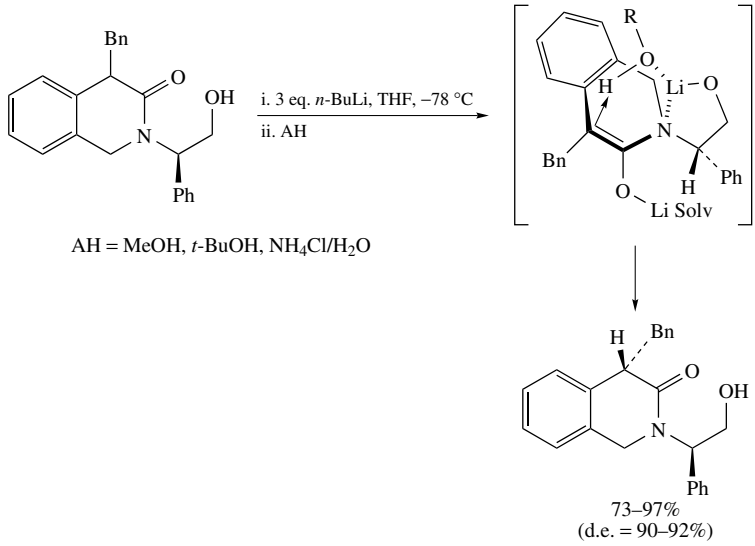
SCHEME 69. Effect of the acidity on the protonation and deuteriation of the 2,4-dimethyltetralone lithium enolate[336]

protonation of a series of 1,3-dioxolan-4-ones and 1,3-oxazolidin-4-ones by a variety of weak proton sources leading to 70–90% of the *cis* major isomer[346]. Alternatively, the exchange of the cation from lithium to potassium or the addition of Lewis acids does not affect this ratio. However, some deviations from this general tendency have been observed and the presence of long chains or substituents acting as internal proton source can be critical[347, 348].

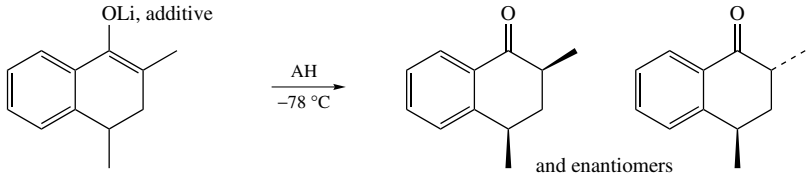
The opposite diastereoface discrimination, compared to the corresponding alkylation, observed from the diastereoselective protonation of the non-racemic 4(*S*)-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one, derived from (*R*)-phenylglycinol[349], was explained as a lithium-directed protonation by considering the five-membered ring chelate formed between the lithium alkoxide and the nitrogen lone pair (Scheme 70)[350]. In the same way, the reversal from the antiperiplanar electrophilic addition during the deuteriation (or protonation) under ion pairing and non-pairing conditions was reported for a series of 3-hydroxy- and 3-alkoxy- butyric acid esters[351].

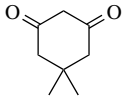
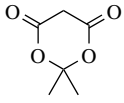
The kinetic reprotonation by a series of carbonyl-based acids, of the lithium enolate obtained from 2,4-dimethyltetralone either by LDA-mediated deprotonation or by cleavage of its silyl enol ether, was studied by Eames (Scheme 71)[352]. The diastereoselective ratio, close to the thermodynamic value, obtained with methanol ($pK_a = 29$ in DMSO) is probably due to equilibration. The difference observed in the presence of an additive was interpreted as the result of a fine balance between the coordinating ability, the intrinsic acidity, and probably the concentration of the enolic form of the cyclic and linear dicarbonyl acidic compounds.

For weak acids, the proton is directly transferred from the acid to the substrate in a reagent-controlled manner and, in order to increase the selectivity, extremely shielded 2′-substituted *m*-terphenyls have been developed as concave protonating reagents inspired by the geometry of enzymes. Thus, the diastereoselective protonation by a series of substituted phenols of endocyclic keto enolates, obtained by the stereocontrolled 1,4-addition of lithiocuprates onto substituted cyclohexenones, was reported by Krause and coworkers[354, 355] and applied to the synthesis of racemic methyl dihydroepijasmonate[356].



SCHEME 70. Lithium relay in the diastereoselective protonation of (*R*)-phenylglycinol-derived 4-(*S*)-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one[349]

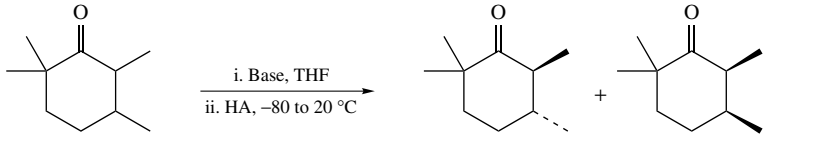


AH	Enol[a]	pK_a (DMSO)	additive	*syn*	*anti*
AcOH		12.6	free/***i*-Pr$_2$NH**/LiBr	95/**85**/95	5/**15**/5
Ac_2CH_2	92 (92)	13.3	-	80/**94**/98	20/**6**/2
$AcCH_2CO_2Et$	50 (30)	14.2	-	70/**95**/90	30/**5**/10
$CH_2(CO_2Et)_2$		16.4	-	-/**52**/-	-/**48**/-
	10 (90)	11.2	-	90/**74**/87	10/**26**/13
		7.3	-	74/**79**/70	26/**21**/30
MeOH		29	-	-/**60**/-	-/**40**/-

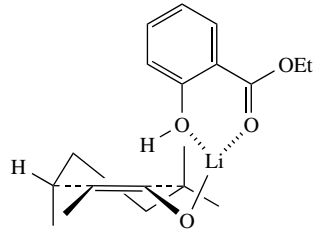
[a]Percentage of enol form in AH in cyclohexane or diethyl ether (Et_2O)[353].

SCHEME 71. *Syn* vs. *anti* protonation of the lithium enolate of 2,4-dimethyltetralone by carbonyl-based acids under kinetic conditions[352]

Careful variation of the substituents indicates that, when an excess of salicylate is used, particularly high *cis*-diastereoselectivities are obtained regardless of the ring size and substitution pattern. The formation of a rigid chelate was proposed to account for these results (Scheme 72, bottom structure).



Base	*trans*	*cis*
LDA	71	29
LDA/*n*-BuLi	22	78
$KN(SiMe_3)_2$	16	84
KH	16	84



SCHEME 72. Influence of the nature of the base and possible intermediate during the protonation of 2,3,6,6-tetramethyltetralone using ethyl salicylate[354, 355]

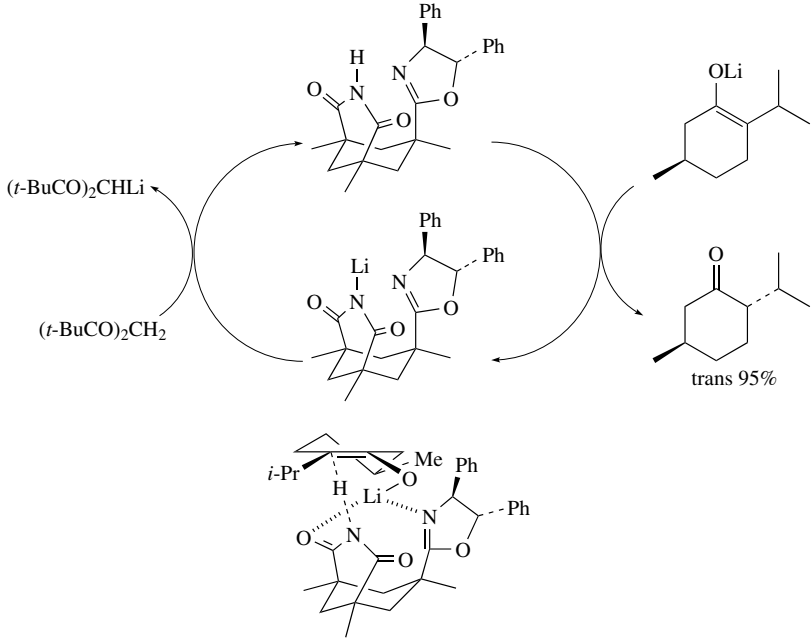
The effect of the diisopropylamine formed upon the deprotonation is again particularly important, since a complete reversal of the selectivity is observed on going from free diisopropylamine to its lithium salt or to hexamethyldisilazane. On the other hand, there is a strong dependence of the stereoselectivity of the proton transfer on both the nature of the cation and the ligands attached to the metal, though lithium iodide present with the cuprate has no noticeable effect.

Double stereodifferentiation was effective in the protonation of the lithium enolate of (−)-menthone using chiral imides derived from Kemp's triacid. This protonating agent gathers both the chelation with the chiral oxazoline and a cumbersome protonating imide site. Moreover, a catalytic version was set up using 0.1 equivalent of the chiral imide in the presence of a non-chiral proton source (Scheme 73)[357, 358].

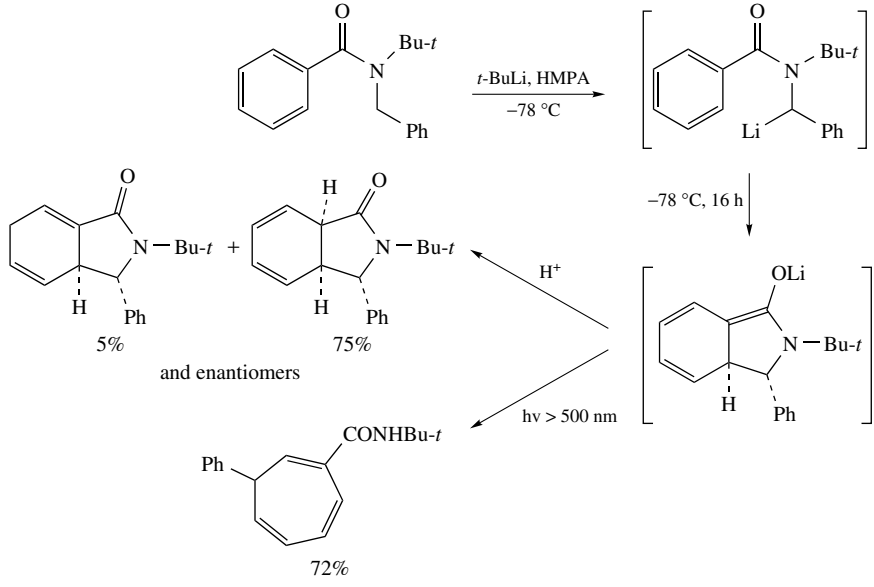
3. Regio- and diastereoselective protonation of extended enolates

Formation of intermediate extended enolates is an attractive strategy commonly used for the synthesis of functionalized six-membered ring compounds[359,360]. The rearrangement of the anion generated by deprotonation α to the nitrogen of the *N*-benzylbenzamide (Scheme 74) gave a cyclized enolate which, upon protonation, led to a mixture of α- and γ-protonated tetrahydroisoindolinones and, upon irradiation, to a rearranged product[361, 362]. The nature of the deprotonating reagent influences the ratio of α- and γ-protonated products[363], whereas the introduction of chirality into the starting material offered new potential for diastereospecific synthesis of chiral five-, six- and seven-membered ring systems[362].

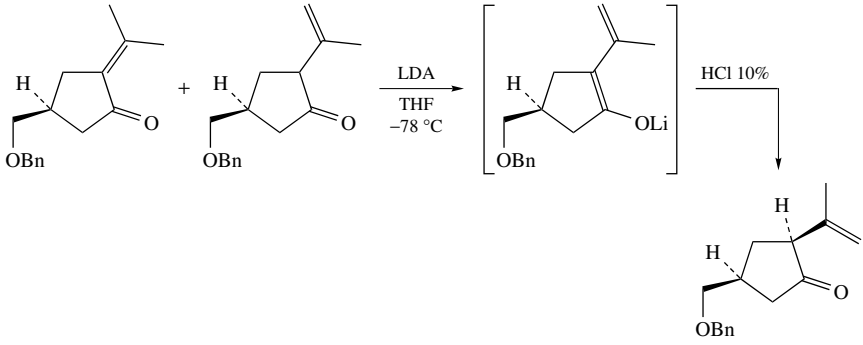
The deprotonation by LDA of the mixture of lactones derived from (*R*)-benzylglycerol followed by kinetic protonation (Scheme 75) provided a regio- and stereospecific access to a key intermediate in the synthesis of irregular monoterpenes. This regioselectivity has been observed for the protonation of many steroidal dienolates[364, 365].



SCHEME 73. Catalytic cycle in the protonation of 2-isopropyl-5-methyl cyclohexanone lithium enolate using Kemp's acid imide derivative as a catalyst[357,358]

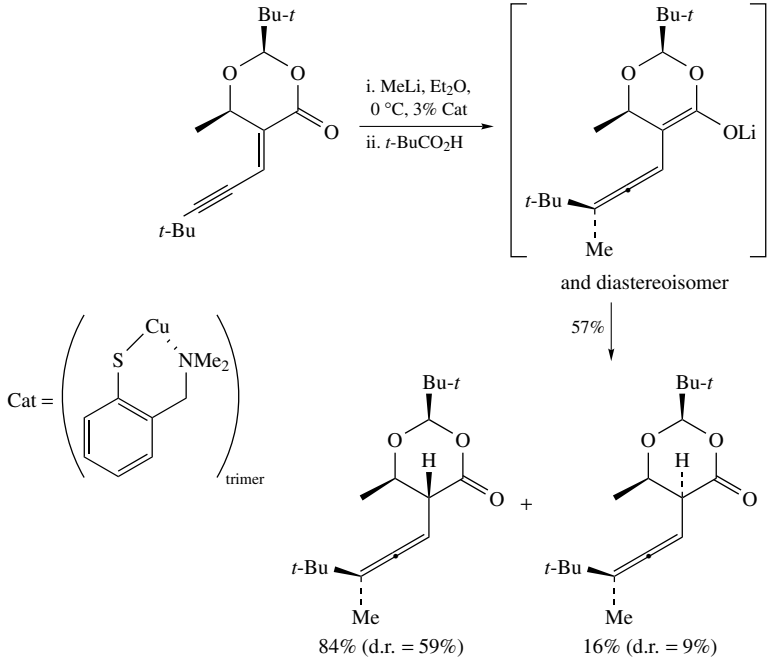


SCHEME 74. Kinetic protonation of extended enolate formed by intramolecular addition of lithium anion[362]



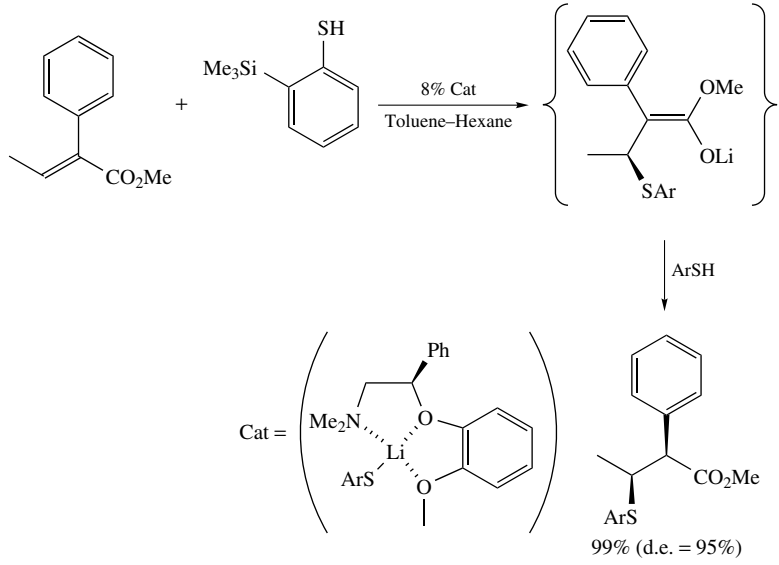
SCHEME 75. Regio- and stereoselective kinetic protonation of a mixture of unsaturated lactones[364, 365]

The regioselective protonation of the enolate formed under strictly controlled conditions, by diastereoselective copper-mediated 1,6-addition of methyllithium to non-racemic substituted enynes acceptors, gives the corresponding allenes in a 84:16 diastereomeric excess[366]. The effect of the copper aggregates on the protonation step seems to be limited, since stoichiometric addition of Me_2CuLi,LiI gives the same almost 4:1 diastereomeric excess though with a better 78% yield (Scheme 76)[367].



SCHEME 76. Regio- and stereoselective protonation of the lithium anion generated by 1,6-catalyzed addition of methyllithium onto (2*R*,6*R*)-6-methyl-(4′,4′ dimethylpent-2′-yn)-yliden-2-(l,l-dimethyl-ethyl)-l,3-dioxan-4-one[366]

Finally, the generation of enolate by addition of lithium thiolate to unsaturated acyclic trisubstituted carboxylic acid derivatives, in the presence of the corresponding thiol in excess, was studied by Naito and coworkers[368]. For esters, variations of the experimental conditions led to the conclusion that a catalytic amount of the base is sufficient while an excess of the thiol, which acts as the protonating agent, is necessary. In addition, the nature of the countercation does not affect the selectivity. The Michael addition to 2,3-substituted crotonates proceeds through the *s*-cis conformation and steric hindrance, at the site opposite to the reacting olefin moiety, is critical. The protonation step is mainly governed by the conformation of the enolate and takes place *anti* to the newly generated C−S bond[369]. Enantioselective addition, catalyzed by non-racemic chiral amino ether lithium thiolate complex, led to elevated diastereomeric excesses (Scheme 77).

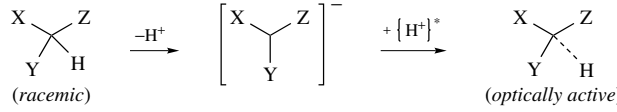


SCHEME 77. Tandem lithium thiolate enantioselective Michael addition kinetic protonation[181]

4. Enantioselective protonation of lithium enolates

The concept of asymmetric protonation was first introduced by L. Duhamel, who coined the term 'deracemization' in 1976[370]. This technique, widely used today, consists in converting an electron-rich prostereogenic center into its stereogenic equivalent through a kinetically controlled transfer of proton. The source of chirality can be the protonating agent itself or another external auxiliary in interaction with one of the two reactive partners. The main advantage of this method over the more classical resolution techniques is that it allows the conversion of up to 100% of the racemic starting material into one single enantiomer (Scheme 78). Thus, the asymmetric protonation (transfer of H^+) complements the long-known hydride (transfer of H^-) and hydrogen (transfer of $H^\bullet$) asymmetric reductions.

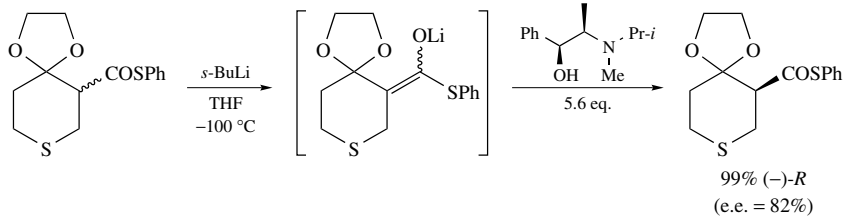
Actually, most asymmetric protonations concern lithium enolates, although increased e.e. values have been reported when swapping from Li to Mg or Zn enolates. It would therefore be far beyond the scope of this section to list the numerous examples already described in the literature. Furthermore, an excellent review was published at the end of



SCHEME 78. Deracemization of a racemic substrate by asymmetric protonation[370]

2004 which gives an extensive list of substrates, reagents and conditions published to date as well as the main rationale underlying the conception of new chiral protonating agents (CPA)[371]. In particular, this paper discusses the important requirements for the CPA to allow good enantiomeric excesses. Thus, general trends on the efficient structures are pointed out, the most important being that one proton-donor and one proton-acceptor site must be oriented *syn* one to the other to rigidify the interaction between the CPA and the enolate. The acidity of the CPA is another critical parameter. Its pK_a values range from 5 to 25, but caution should be paid to the kinetic and thermodynamic acidities[372] as well as to the 'internal proton return' phenomenon[200]. The influence of (i) the structure of the substrate (and, in particular, the issue of the homogeneous vs. heterogeneous aggregation), (ii) the E/Z configuration of the enolate (with a summary on the Reaction Site Control and Neighboring Site Control concept), (iii) the presence of an amine interacting with the enolate, and (iv) the temperature, on the asymmetric protonation, are also addressed. The review ends with a section dedicated to the catalytic enantioselective protonation of enolates. The reader is thus strongly recommended to look at this paper, which lists previous reviews on the subject and gives a fine account of the state-of-the-art in the domain.

Among the very few papers published after the above review appeared, two deserve some comment. The asymmetric protonation of the lithium enolate of a thiopyranic thioester by an ephedrine-derived chiral aminoalcohol described by Ward and coworkers leads to the desired enantiomer in 99% yield and 82% e.e., provided the reaction was performed in carefully designed conditions (Scheme 79)[373].

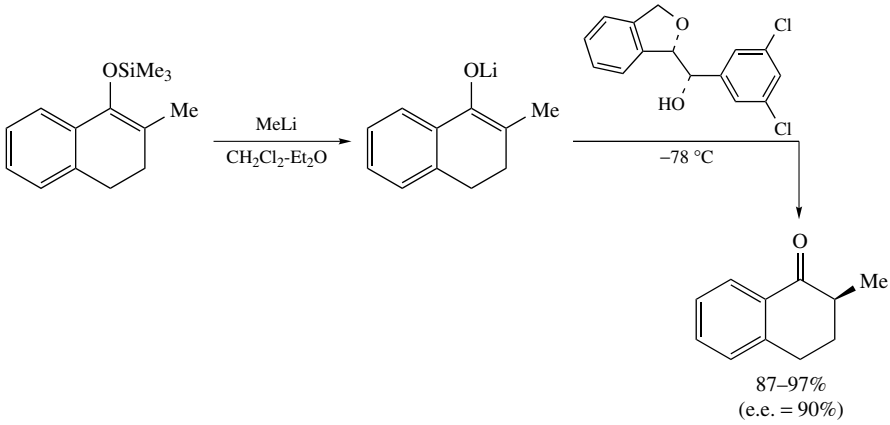


SCHEME 79. Deracemization of thiopyranic thioester by asymmetric protonation[373]

Kim and coworkers have evaluated the performance of a set of β-hydroxyethers in the asymmetric protonation of the lithium enolate of 2-methyltetralone[374]. Their best results were obtained with a salt-free enolate (generated by adding methyllithium in ether to the corresponding silylenol ether in methylene chloride), and using a dichlorobenzylic alcohol as CPA, at any temperature between -25 and $-98\,^{\circ}C$ (Scheme 80).

B. Alkylation and Acylation of Preformed Lithium Enolates

The alkylation of enolates offers one a most common way to simply introduce one carbon–carbon bond α to a carbonyl functionality. The acylation would be briefly treated as well, since the formation of the C–C bond in the final product formally represents the displacement of a nucleofugal group by the incoming nucleophilic enolate.



SCHEME 80. Deracemization of methyltetralone by asymmetric protonation of the lithium enolate generated by cleavage of the corresponding enolether[374]

1. Chemoselectivity of alkylations

In the gas phase as in solution, the *C*-alkylated product is thermodynamically more stable than the *O*-alkylated one[375]. Kinetically, however, the *O*-alkylation is normally the preferred issue in the gas phase, first and foremost due to the endoergic rehybridization of the carbon center[376]. In solution, the alkylation at the carbon site is generally favored and the *O*-alkylation of lithium enolates is strongly dependent on the degree of ion pairing, which in turn depends on the polarity of the solvent, the aggregation state and the reactivity of the electrophilic reagents.

The results, reported in Table 1 for the ethylation of salts of ethylacetoacetate in DME, emphasize the assumption that factors affecting the dual alkylation of ambident enolates are: (i) the nature of the solvent, (ii) the nature of the cation and (iii) the nature of the electrophilic reagent and its associated nucleofugal group[377,378]. Obviously, the C/O ratio decreased and the rate constants increased on going from lithium to cesium and to the naked ammonium salt. Moreover, concentration and added salts affect the magnitude of the kinetic order. Thus from kinetic measurements in DMSO, Zook and Miller found a second-order rate for the reaction of a series of substituted acetophenones with alkyl bromides and iodides or allyl chloride. On the contrary, alkyl chlorides gave a rapid reaction over the first 30% reaction followed by a first-order rate, independent of the concentration of the alkyl halide[379]. Interestingly, the addition of LiCl at the beginning of

TABLE 1. Rate constants and product ratios for the ethylation of salts of ethylacetoacetate in DME

	EtBr		EtI		EtTos	
Cation	k_{obs} [a]	C/O	k_{obs} [a]	C/O	k_{obs} [a]	C/O
Li	0.011	73	0.266	100	0.005	2.2
Na	0.67	60	16	100	0.38	6.0
K	2.3	41	42.5	100	1.1	4.7
Cs		10.3		43		1.7
NBu_4	510	2.9	5420	8.4	180	0.26

[a] k_{obs} is defined as $k_C + k_O$.

the reaction suppressed the first rapid stage and the result was explained by the formation of a less reactive enolate aggregated species (En−LiCl).

Jackman and coworkers directed attention to factors affecting the C *vs.* O reactivity for the alkylation of enolates and presented evidence that the lithium tosylate, formed during the reaction of the lithium enolate of isobutyrophenone with methyl tosylate in dioxolane, acts as a lithium-sequestrating agent and generates mixed aggregates, lowering the C/O methylation ratio[380,381]. A recent report by Streitwieser and coworkers corroborated this observation (addition of external $LiClO_4$ salts) and it was proposed that the more reactive enolate dimer $(EnLi)_2$ was transformed to a mixed tetramer $Li_4En_3ClO_4$ that became the reacting species[271]. The same dependence was observed when methyl tosylate was reacted with the lithium enolate of 4-phenylisobutyrophenone[254]. On the other hand, this chemical behavior and the solvent effect have been recently evaluated within the local viewpoint of the hard and soft acids and bases (HSAB) principle by theoretical calculations in the context of density functional theory.[307]

Acylation also gives mixtures of *C*- and *O*- acylated products and House and coworkers[268] early reported interesting features in a thorough study of cyclopentanone cyclohexanone and phenylaceto phenone enolates under kinetic conditions. Reagents, stereochemistry of the enolate, nature of the metal and conditions of the reaction (solvent, temperature, additives) have all been shown to influence the regioselectivity. Particularly, factors that help to maintain intimately bond enolates will favor the *C*-acylation and, interestingly, the LiCl formed during the reaction of acetyl chloride was supposed to be at the origin of an increased ratio of the *C*-acylated product. A plethora of *C*-acylating reagents has been designed including acid chlorides[382], acid chalcogenides (anhydrides, *N*-acylimidazoles, 1-acylbenzotriazoles[383], chloroesters[384]), ketenes[385], formates[386] and Weinreb amides[387,388]. Finally, Zayia recently reported a modification of the thermodynamic Claisen formylation reaction using the reactive 2,2,2-trifluoroethyl formate (TFEF)[389]. The preformed lithium enolate of ketones reacted in a regio- and chemo- selective manner, in good overall yield (60−80%), provided non-dissociating conditions are used (Li > K; Et_2O > THF > DME > HMPA). On the other hand, under those kinetic conditions, 3-methylcyclohexenone gave the α-formyl ketone exclusively.

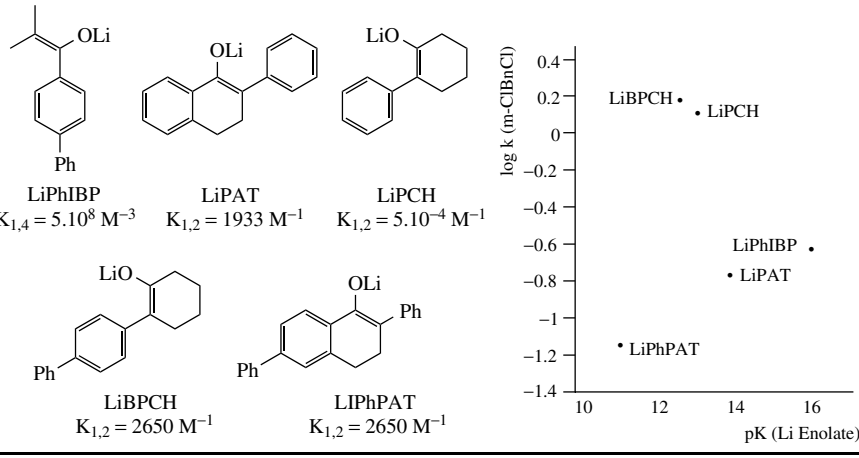
Under strictly kinetic conditions, the regioselectivity of the alkylation of non-symmetrical ketones is related to the regiodirected synthesis of their enolates (*vide supra*). Interestingly, significant deviation from the normal α-alkylation of lithium 2-butenoic acid dienediolate was observed[390]. Especially, the nature of the leaving group increased the α/γ ratio on going from the chloride to the iodide because of two opposite effects during the progress of the reaction. On the one hand, the formation of the lithium halide favors the α-alkylation, while on the other the resulting lithium carboxylate favors the γ-alkylation.

2. Mechanistic considerations

a. Kinetic approach of the aggregation effect. Recently, Streitwieser's group reported on the role of enolate aggregates in their reaction with electrophiles by monitoring the C-alkylation of 4-phenylsulfonyl- and 4-phenyl- isobutyrophenone (LiIPB and LiPhIPB) with *p*-tert-butylbenzyl bromide using UV-spectroscopy and SDV analysis of their results.

Although they found a dramatic change in the aggregation state of LiSIPB in THF, on going from 10^{-5} M to 10^{-2} M (the average ion pair numbers vary from 1.8 to 3.4)[254], their results put into evidence that the monomer (1 to 5%) is the reactive species even in the presence of a large excess of dimer in the range of 0.1 M to 1 M[251,391]. On the other hand, LiPhBP is a contact ion pair present as a mixture of monomer and tetramer in THF (λ_{max} = 352 and 329 nm, respectively), depending on the concentration (the average

TABLE 2. Dissociation constants (left) of the aggregates ($K_{aggregate,monomer}$) and rate of enolate with *m*-chlorobenzyl bromide compared to the enolate pKs (right) for a series of monomeric Li-Enolates (LiEn) in THF measured by UV–visible spectroscopy[391b]



$K_{1,4}$ = [tetramer]/[monomer]^4; $K_{1,2}$ = [dimer]/[monomer]^2

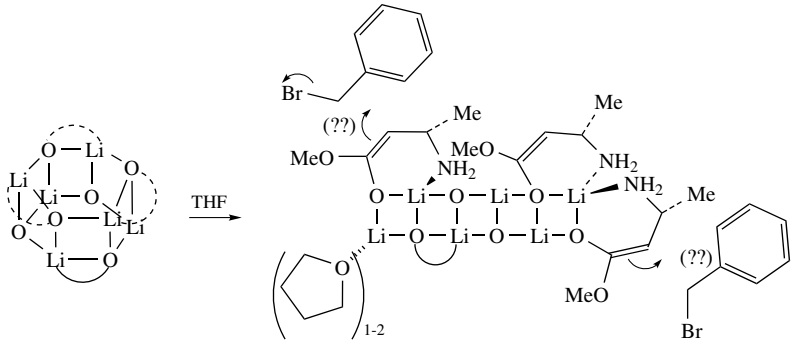
aggregation number is 3.9 for a 0.1 M solution), while the same cesium salt is a mixture of monomer ($\lambda_{max} = 420$ nm), dimer and tetramer. Again, kinetic studies clearly indicate the monomer as the true reactant with a second-order rate constant (0.141 $M^{-1}\,s^{-1}$) invariant with the concentration and the same order of magnitude was measured for benzyl-, *m*-chlorobenzyl-, *o*-chlorobenzyl- and *o*-methylbenzyl bromides[391].

Conclusively, the lithium salts presented in Table 2 (left) are solvent-separated ion pairs and their monomers (this is true for the cesium salts as well) are the reacting species.

Interestingly, no correlation could be observed from their monomer ion-pair acidities (pK_0 in THF) and the second-order rate constant for the monomer in their reaction with *m*-chlorobenzyl bromide (Table 2, right), a linear relationship occurs when the corresponding cesium salts are alkylated with methyl tosylate. On the other hand according to the authors, this accounts for the fact that the lithium cation is as important as the basicity of the enolate.

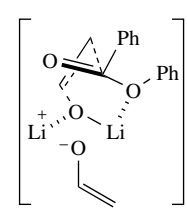
Finally, the alkylation of the hexameric di-solvated lithium enolate of methyl 3-amino-butyrate with benzyl bromide in THF shows a conversion-dependent deceleration attributed to the formation of LiBr (this is relevant for NMR results). Interestingly, the side dibenzylated product results from the alkylation of the enolate formed by deprotonation of the *syn* isomer ($k_{syn}/k_{anti} = 7$)[288]. Kinetic studies performed under pseudo-first-order conditions reveal approximate first-order dependencies in THF ($n = 1.3$) and enolate. The idealized rate law implicates a direct alkylation of the hexamer without deaggregation. Moreover, the hypothesis of an *anti* alkylation taking place at either end of the open form of the hexamer (Scheme 81), although unusual, was not excluded by MNDO calculations.

Interestingly, the same kind of experimental work led to completely different results when the role of aggregates was considered for the Claisen acylation. Access to the aggregation numbers, in the reaction of a series of *p*-substituted benzoates with LiPhIPB and LiSIPB (Scheme 82), indicates the monomer not to be the only reactive species ($k_{tetramer}/k_{monomer} = 1.3$ and $k_{dimer}/k_{monomer} = 0.09$, respectively, with phenyl benzoate)[392].



SCHEME 81. Possible representation of the alkylation of the hexameric methyl-3-amino-butyrate lithium enolate in THF[288]

	m-ClPhCO-OPh	PhCO-SPh	PhCO–N
$10^2\ k_M\ (M^{-1}\ s^{-1})$	1.96	37.8	811
$10^2\ k_D\ (M^{-1}\ s^{-1})$	0.17	0	136
k_D/k_M	0.086	0	0.17



SCHEME 82. Reactivities of the monomer (M) and of dimer (D) of LiSIPB with benzoyl substituted phenol, thiophenol and, imidazole and the possible transition state model for the benzoate[392]

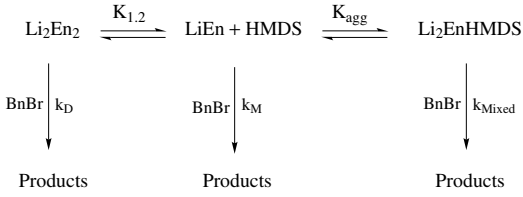
The consequence of this finding on the reaction is that at synthesis concentration, the aggregates are the dominant species.

According to the authors, the coordination of both oxygens with two lithium cations in the aggregate framework could be responsible for these results (Scheme 81, right). Then, comparing the value in Scheme 81 (left) for LiSIBP to a series of acylating reagents, sustains the idea that the more chelated the lithium, the more reactive the aggregate[393].

Besides contact ion-pair self-aggregation, the role of the solvent and the role of added (or formed) salts is of utmost importance for alkylation, as already mentioned. Thus, LiSIBP led to a dimer $LiEn_2Br$ ($K_{agg} = 3.6 \times 10^3\ M^{-1}$) upon incremental addition of LiBr in tetrahydrofuran. Then, the rate law corresponding to the reaction of LiSIBP with *p-tert*-butylbenzyl bromide must be corrected since LiBr decreases the initial rate. Thus, although the reaction still proceeds through the monomer, the contribution of Li_2EnBr becomes substantial for high LiBr concentrations (equation 1)[255].

$$-\mathrm{d}[Li_2EnBr]/dt = k_{Mixed}[Li_2EnBr][RX] + k_M[Li_2EnBr][RX]/K_{agg}[LiBr] \qquad (1)$$

The same approach was used with LiSIBP and LiBnPAT, upon incremental addition of LiHMDS in THF solution, as a potential model for the study of the alkylation of chiral amide-enolate aggregates. From the average values for K_{agg} (respectively, 560 and 760 M^{-1}) and the values of the ratio k_{mixed}/k_M (respectively, 100 and 20), the initial alkylation was estimated to involve 40% of monomeric enolate (although it represents less than 1% of the species in solution), a situation unsuitable for asymmetric synthesis (Scheme 83)[256].



SCHEME 83. Li Enolate (LiEn) aggregates and LiHMDS mixed aggregate in their reaction with benzyl bromide (rate/[BnBr][Li_2EnHMDS] = $k_{Mixed} + k_M/K_{agg}$[LiHMDS])[256]

The potential of the SDV method for determining the ion-pair acidities and aggregation constant in dilute solution was used to tackle the problem of polyalkylation. The benzylation of 6-phenyl-α-tetralone (PAT) was used as a model[397]. Thus, the monomeric enolate derived from the alkylation product (2-benzyl-6-phenyl-α-tetralone) LiBnPAT ($pK_0 = 13.96$, $K_{1,2} = 3791\ M^{-3}$,) is slightly less basic than the unsubstituted monomeric enolate LiPAT ($pK_0 = 14.22$, $K_{1,4} = 4.4 \times 10^{10} M^{-3}$;). It is also less aggregated and 1.8 times more reactive. These results support House's explanation that the competitive polyalkylation can stem from a difference in the aggregation state of the two enolates[6].

b. Solvent effect. Equilibration of enolates derived from unsymmetrical ketones depends strongly on the associated counter ion[141, 394]. Accordingly, alkylation of lithium enolates often results in a loss of regioselectivity and in polyalkylation. But a markedly increased rate and regioselectivity observed when reactive electrophiles or lithium complexing agents were used (Table 3)[395].

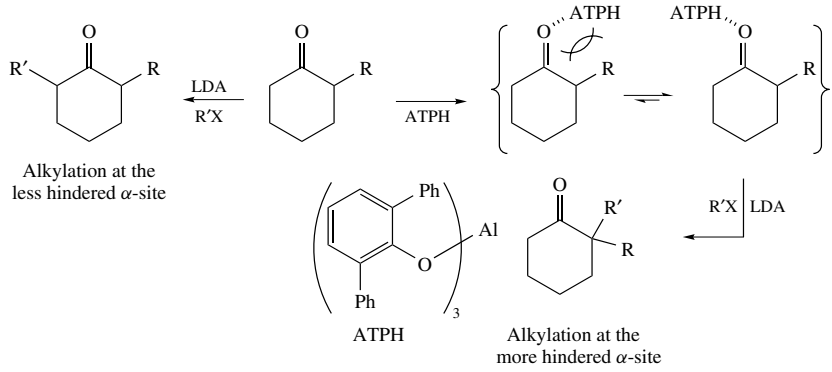
Similarly, precomplexation of the unsymmetrical ketone by a bulky Lewis acid prior to deprotonation results in the inversion of the regioselectivity by alkylation at the more hindered site, probably via a preferred coordination with one of the lone pairs *anti* to the more hindered side of the ketone (Scheme 84)[396]. Interestingly, an aldehyde in the same conditions is not deprotonated (*vide infra*).

The solvent effect has long been recognized as an important factor in that it affects the lithium–oxygen bond polarization but also the electrophilic reagent[380, 398]. The effect on aggregation was evaluated by measurement and comparison of the reactivities of monomeric, dimeric and tetrameric forms of LiPhIBP and LiPhAT or LiPhIBP in various ethers[252]. In the less polar solvent methyl-tert-butyl ether, lithium enolates are tetrameric and do not react with benzyl bromide. On the contrary, with added HMPA the dissociation of the tetrameric LiPhIBP is accompanied by solvation of each monomer by 1–2

TABLE 3. External vs internal benzylation and butylation of lithium enolate derived from heptan-2-one [a]

Electrophile	Additive (equivalents)	Reaction time	External/Internal
BnBr	none	30 min	26:39
	Benzo-14-C-4 (1.6)	30 min	45:10
	HMPA (4.9)	30 min	77:7
BuI		1 min	2:0.3
	none	10 min	8:2
		3 h	8:21
	HMPA (10)	1 min	44:14
		2 h	36:24

[a] Reaction performed in DME, enolate ratio (terminal/internal) = 87/13.



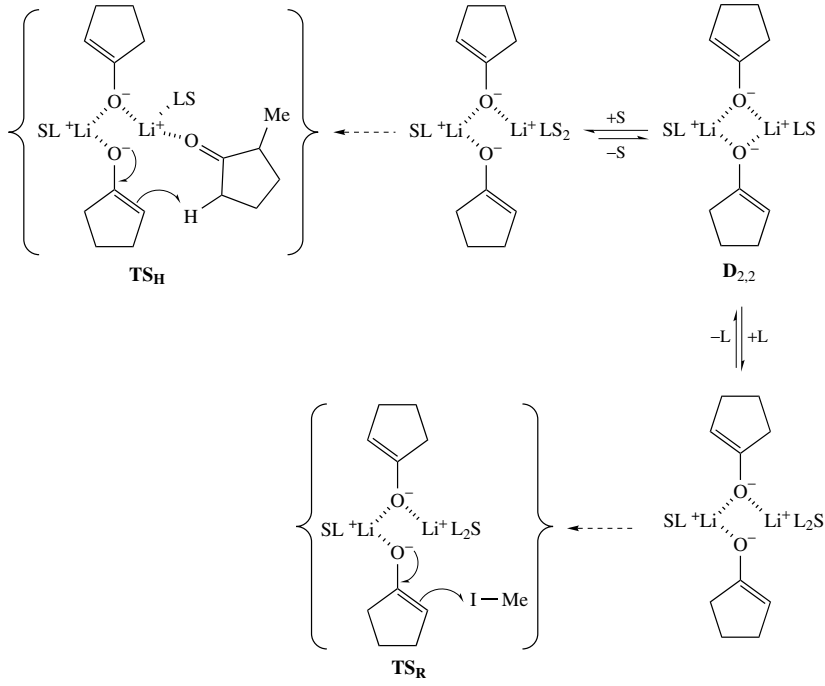
SCHEME 84. Regioselective alkylation of substituted cyclohexanone[396]

molecules of HMPA, producing a separated ion pair which dramatically increased the rates of the alkylation with a first-order rate in monomer and HMPA[253].

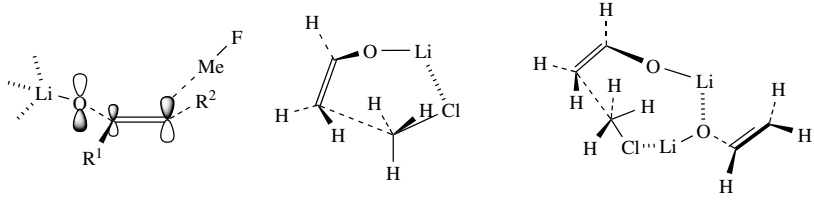
The rates for the methylation of cyclopentanone and for the proton abstraction from 2-methylcyclopentanone were significantly increased by a factor of 7500 and 5, respectively, when six equivalents of HMPA were added to the reaction. Using ^{31}P, ^{7}Li and ^{13}C NMR spectroscopy, Suzuki and Noyori found that the tetrasolvated $\mathbf{D_{2,2}}$ dimer was exclusively generated from the tetrameric ($\mathbf{T_{0,4}}$) and dimeric ($\mathbf{D_{0,4}}$) tetrasolvated lithium amine-free enolate of cyclopentanone (0.16 M in THF, $-100\,^{\circ}C$, ratio 2/3)[275]. Kinetic analysis gave a first-order reaction in dimer and HMPA for the reaction with a modulation for free HMPA[33], and a first-order reaction in dimer for deprotonation, independent of HMPA. Possible transition state structures for alkylation and proton abstraction are drawn in Scheme 85.

In addition, Koga and coworkers claimed a spectacular rate enhancement adding either 1,1,4,7,10,10-hexamethyltriethylenetetramine or ureas (such as *N*,*N*′-dimethyl-*N*,*N*′-propylene urea or *N*,*N*′-dimethyl-*N*,*N*′-ethylene urea) as a substitute for HMPA during the alkylation of tetralone lithium salt in DME[399]. Interestingly, in the case of secondary alkyl halides, a kinetic resolution occurred in some particular cases with fair[400] to excellent enantioselectivities[401].

c. Mechanism. From the huge amount of data available, it should be remembered that most alkylations of ambident enolates are kinetically controlled and are thought to generally involve a S_N2 process, although the transition state can be closer to a S_N1 type according to the site which undergoes the attack. The reaction is strongly exoergic and the transition state closely resembles the reactants[402]. The S_N2 mechanism implies an quasi-perpendicular approach of the electrophile to the plane of the enolate to maintain a maximum orbital overlap between the developing C−C bond and the π-orbital of the carbonyl in the transition state[403]. 3-21G *ab initio* calculations for the alkylation of the lithium enolate of acetaldehyde with methyl fluoride in the gas phase[375] revealed that the angle of approach of the electrophile to the enolate carbon is 106°, close to the Burgi–Dunitz angle (Scheme 86, left). However, an acute trajectory has been calculated more recently for the alkylation of the lithium enolate of spiro-γ-lactones[404]. The participation of the nucleofuge is taken into account in a cyclic transition state model for the monomer and for the open dimer (Scheme 86, right) in recent refinements[405]. For an open-chain structure, this selectivity is generally opposite to the nucleophilic addition onto the corresponding carbonyl and in the same direction as protonation[406–408]. The π-facial



SCHEME 85. Possible transition state structures for competitive alkylation (TS_R) and proton abstraction (TS_H) reactions; (S = THF, L = HMPA; $D_{x,y} = D_{xL,yS}$)[275]



SCHEME 86. Trajectory of the approach[403] and transition state models for the reaction of monomeric and dimeric lithium enolate of acetaldehyde with MeCl[405]

stereoselectivity of preformed enolates, containing one (or more) proximal resident chiral (or non-chiral) center(s), in their reaction with electrophiles is governed by substituent effects and have to be considered in terms of steric (often prevailing) and stereoelectronic effects[17, 409].

3. Diastereoselective alkylation

Hereinafter, the extra- and intra- annular chirality transfer (CT) classification defined by Evans[402] will be employed provided the original stereocenter is linked to the enol moiety by one or two points of anchorage, with the possibility of chelate-enforced chirality transfer due to internal chelation with heteroatoms (Figure 4)[410].

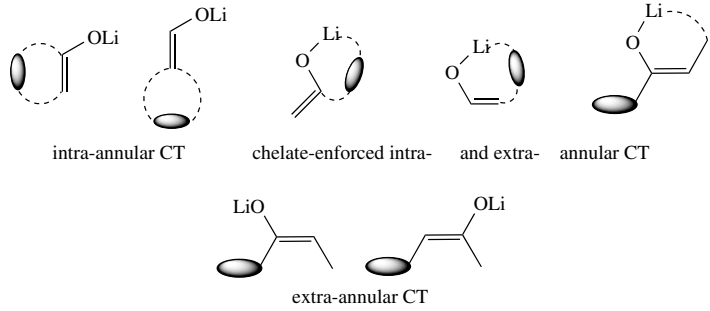


FIGURE 4. Intra-, extra-annular and chelate-enforced chirality transfer (CT; the symbol ⬬ represents the chiral information)[410]

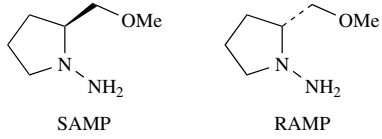
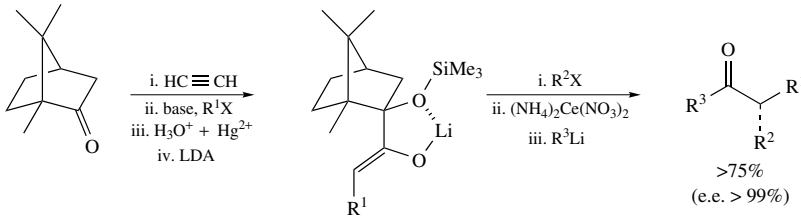


FIGURE 5. Classical SAM and RAMP chiral vectors used for azaenolates alkylation[410]

a. Alkylation of ketones. Since substantial side reactions such as competitive regioisomerization, Z/E equilibration, aldolization and polyalkylation are commonly observed during the reaction of simple carbonyl enolates, the closely related azaenolates have received widespread applications and structural investigations[57,411,412]. Azaenolates are significantly more nucleophilic than ketone or aldehyde enolates and, more importantly, they allow the introduction of temporary covalently-bonded chiral ligands and their potential ability for chiral induction[301,413,414]. Thus, alkylation of SAMP and RAMP hydrazones of aldehydes and ketones followed by ozonolytic cleavage have defined one of the standards in the field (Figure 5)[415–417].

On the other hand, lithium enolates derived from substituted endocyclic ketones have largely been exploited in the synthesis of steroids since the regioselectivity of their deprotonation can be controlled and high levels of 1,2- and 1,3-stereoselection occur[9,418]. The control is steric rather than electronic, with the attack directed to the less substituted π-face of the enolate for conformationally rigid cyclopentanones, whereas stereoelectronic control becomes significant for the more flexible cyclohexanones. Finally, an asymmetric variant of the formation of α-branched ketones by hydration of camphor-derived alkynes followed by sequential alkylation with reactive alkyl halides of the resulting ketones was recently reported (Scheme 87)[419].

b. Alkylation of carboxylic acid derivatives. i. Extra-annular chirality transfer (ECT). Nonbonding interactions (such as a steric effect or π-stacking) that restrict conformational motion are necessary for high selectivities. However, the difficulty of controlling the deprotonating sequence associated with side reactions, such as racemization, ketene formation or Claisen condensation, makes the results difficult to predict[420,421]. Typically, the alkylation of the lithium enolate of 8-phenylmenthylphenyl acetate (Figure 6A) produces arylacetic esters with poor diastereoselectivities. The role of aggregation was put forward in this latter case using dissociating solvent (DBU) or cation-free enolate (prepared with Schwesinger's base t-Bu$-$P$_4$). The expected alkylated esters were recovered,



SCHEME 87. Alkylation of camphor-based lithium enolate[419]

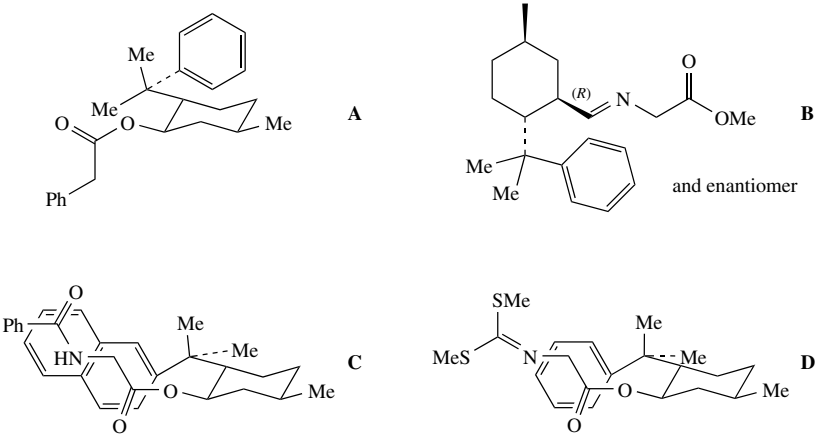
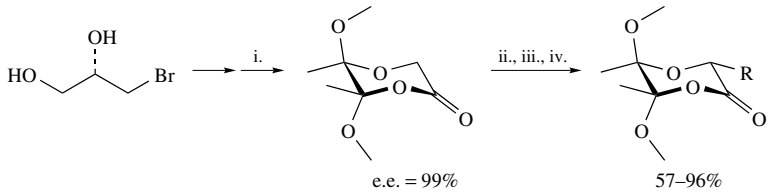


FIGURE 6. Synthons for phenylmenthyl-based extra-annular alkylations

exhibiting d.e. in the 84–96% range[422,423]. Much better results were obtained by Duhamel and coworkers, taking advantage of similar through-space interactions in compact structures, associated with extra-annular chelate-enforced chirality transfer. Thus, the lithium enolates of iminoesters derived from 1-(*R*)- or 1-(*S*)-formyl-2-(*S*)-dimethylbenzyl-5-(*R*)-methylcyclohexane (Figure 6B) gave access to the (*R*) or (*S*) alkylated amino acids, by simply switching the asymmetric center bearing the C=N from the (*R*) to the (*S*) configuration[424]. A further successful application of 8-arylmenthols was proposed by Berkowitz and coworkers[425] for the synthesis of tetrasubstituted-α-vinyl amino acids[426]. A careful structure–stereoselectivity relationship rationalized by semiempirical calculations led to the alkylation of the chelate-enforced chiral vinylglycine-derived dilithiodienolates (Figure 6C) with high diastereomeric inductions. However, further work on related structures (Figure 6D) clearly showed that the substituent on the nitrogen influences the stereodifferentiating process[427].

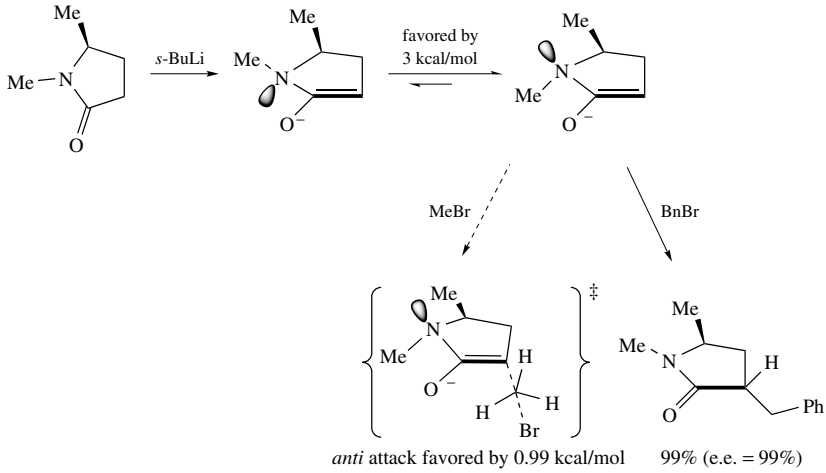
ii. Intra-annular chirality transfer. The synthesis of such important synthons as non proteinogenic and unnatural amino acids or α-hydroxyacids is undoubtedly associated with the new concepts and new auxiliaries developed for the asymmetric alkylation of heterosubstituted enolates. The stereodifferentiation in intra-annular CT is essentially structure-directed, so external factors such as aggregation, solvent or ligand effect would be less, if not important for the stereoselection process. Nevertheless, they clearly interfere with the rate of the reaction.

For instance, the reaction of alkyl halides with the lithium enolate derived from the chiral glycolate designed by Ley and coworkers[428] takes place from the side opposite to the 1,3-related axial methoxy group, giving excellent diastereoselections (Scheme 88)[429]. Another striking example is the benzylation of 1,5-dimethylpyrrolidin-2-one lithium enolate, which takes place *anti* to the nitrogen lone pair of the pseudo-planar enolate and leads to a 99/1 *anti* selectivity, close to the value predicted by *ab initio* calculations for the methylation (Scheme 89). Additionally, a second alkylation also led to an α attack, though with a slightly lower selectivity[430].



i. *a*) $(MeCO)_2$, CSA, $CH(OMe)_3$; *b*) KHMDS; *c*) O_3 then PPh_3
ii. LHMDS, THF, −78 °C
iii. RX, −78 to −30 °C
iv. AcOH

SCHEME 88. Synthesis of BDA-desymmetrized glycolic acid and alkylation[429]



SCHEME 89. Benzylation of 1,5-dimethylpyrrolidin-2-one lithium enolate and the computed transition state for the methylation[430]

In the absence of any chelating or steric interaction, the preferred diastereoselectivity was currently attributed to a stereoelectronic effect. However, according to Itaka and Tomoda, it could also depend on the π-facial environment of the most stable enolate species C_{t-endo} in THF (Figure 7)[431,432].

The incorporation of the chiral auxiliary into chiral non-racemic bicyclic lactams, proposed by Meyers and coworkers, is of major interest in the asymmetric construction of

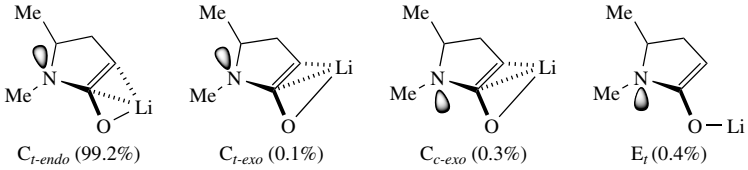


FIGURE 7. DFT calculated structures and population of 1,5-dimethyl-2-oxazolidinone lithium enolate[431,432]

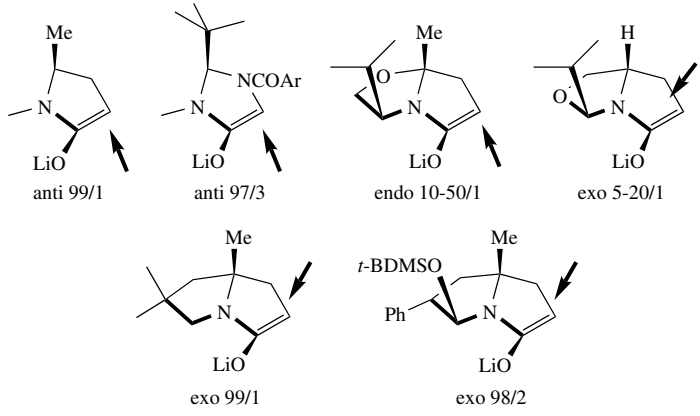
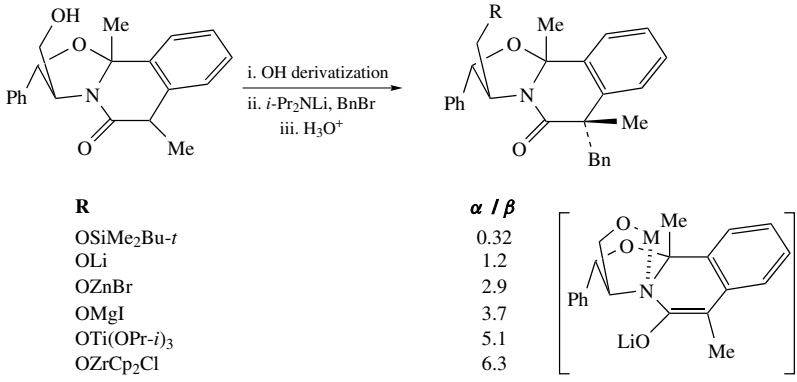


FIGURE 8. Effect of structural variation on the alkylation of the lithium salt of oxazolidinones[436]

highly stereocontrolled tertiary and quaternary carbon centers[433–435]. The alkylation of their lithium salts, generated by proton abstraction mediated by either lithium amides or organolithiums, results in excellent *endo* or *exo* diastereoselectivities, depending on subtle remote variations in the substitution pattern (Figure 8). The π-facial selectivity can be explained by a combination of torsional and steric effects[436].

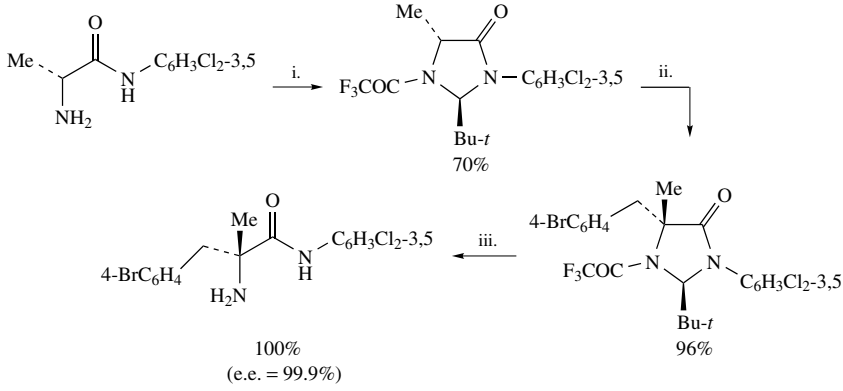
Additional chelation in these systems proved to be helpful since the diastereoface discrimination, relative to benzyl bromide (Scheme 90), was greatly improved on going from the ether to a metal alcoholate, and this difference was associated to the chelation of the bulky metal ion system with the lone pair of the pyramidalized nitrogen atom[437].

The self-regeneration of stereocenters (SRS), a concept introduced by Seebach and coworkers[438–440], provides an alternative and potent methodology for the alkylation of chiral non-racemic heterosubstituted carboxylic acids. The basic idea relies on the formation of a new transient diastereogenic center during the formation of a temporary cyclic intermediate. Then, the bulky substituent of the new stereogenic center enables the control of both the geometry of the strained enolate, obtained after removal of the first stereogenic center by proton abstraction, and its subsequent π-facial differentiation. This concept has found numerous applications based on the natural 'chiral pool'. A recent illustration of this methodology is the diastereoselective nucleophilic aromatic substitution of *o*- and *p*-fluoronitrobenzenes, based on mandelic acid transient induction[441]. Also, the SRS strategy was recently transposed on an industrial scale for the synthesis of a precursor of leukointegrin LFA-1 antagonist BIRT-377 (Scheme 91)[442]. This compound presents potential therapeutic utilities in the treatment of a variety of inflammatory and immune disorders.



R	α / β
$OSiMe_2Bu$-*t*	0.32
OLi	1.2
OZnBr	2.9
OMgI	3.7
$OTi(OPr\text{-}i)_3$	5.1
$OZrCp_2Cl$	6.3

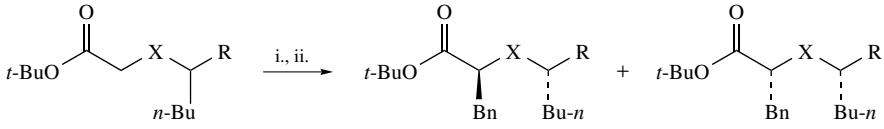
SCHEME 90. Influence of a distal alkoxy group and of the nature of the associated metal[437]



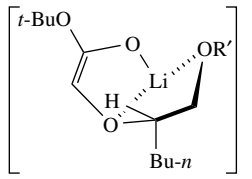
i. *a*) *t*-BuCHO, *b*) TFAA, NEt_3
ii. *a*) LHMDS, *b*) $4\text{-}BrC_6H_4CH_2Br$
iii. a) *n*-$BuNMe_3OH$ / 50% NaOH, b) HCl 6M

SCHEME 91. The self-regeneration of stereocenters (SRS) strategy applied to the synthesis of BIRT-377 precursor[442]

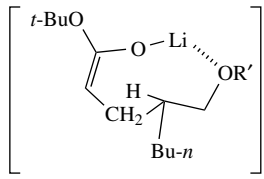
iii. Chelate-enforced chirality transfer. As already mentioned, the possibility of chelation of the counter ion, leading to compact intermediates, influences the stereochemistry of the enolization step and the subsequent π-facial discrimination. Consequently, the ability of the lithium cation to promote intramolecular chelation played a prominent role in the development of numerous chelate-enforced chirality transfer auxiliaries[443]. An eight-membered intramolecular chelate was postulated by Ukaji and Narasaka to account for the high *anti* diastereoselectivity resulting from the alkylation of γ-substituted- ω-hydroxycarboxylic acid derivatives (Scheme 92)[444]. This remote chelation still operates for the corresponding glycolates (X = O), but was dramatically affected, with a bidentate chelation control leading to a predominant *syn* selectivity[445].On the other hand, recent results by Kim and co-workers using (*S*)-(4-methoxyphenyl)-[4(R)—2,2-dimethyl-1,3-dioxolan-4-yl]-methanol claimed stereoselectivities up to 300/1 using Li HMDS as a base[445b].



i. $LiN(CH_2)_4$-*c*, THF / HMPA, −100 °C
ii. BnX



B

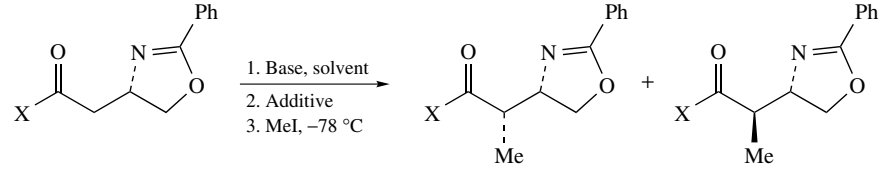


A

	anti	*syn*
X = CH_2, R = CH_2OH[444]	major	-
X = O, R = CH_2OSiEt_3[445a]	1	0.9
X = O, R = CH_2OH	1	2.7
X = O, R = $CH(OCH_2CH_2O)$	1	6.0

SCHEME 92. Proposed transition state models for Chelation-controlled benzylation of 5-hydroxy-4-n-butylpentanoïc ester and the corresponding glycolic ether derivatives[444,445a]

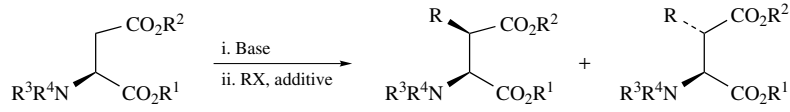
Having in mind the influence of remote substituents on the stereoselective outcome of the alkylation of enolate[446], β-heterosubstituted carboxylates are of particular interest since they can be easily synthesized in their pure, non-racemic form[447]. The stereofacial differentiation of their preformed enolates is generally efficient for heterosubstituents such as hydroxy-[448,449], amino-[450,451], or silyl[452]-substituted groups. However, competing steric, stereoelectronic and chelating factors are operating. Thus, the reversal of the stereofacial selection observed by McGarvey and coworkers (Scheme 93) during the methylation of β-aminoenolates was explained by the disruption of the internal chelation of the enolate due to the presence of the strongly solvating HMPA, leading to a switch from a chelate-controlled model to a stereoelectronic-controlled one[453].



		syn	***anti***
X = NMe_2	$LiNEt_2$, THF	16%	84%
X = NMe_2	$LiNEt_2$, THF; additive: HMPA	33%	67%
X = *t*-BuS	NaHMDS, THF	5%	95%
X = *t*-BuS	NaHMDS, THF; additive: HMPA	86%	14%

SCHEME 93. Effect of cation and additive on the methylation of β-substituted aminoenolate[453]

The regiospecific alkylation of aspartate enolates provides a valuable basis for the stereocontrolled access to α-substituted β-amino acid derivatives[454,455]. The nature of the cation appears to control the geometry of the enolate, as established by trapping experiments: the *E*(O) enolate prevails for the lithium cation, while the *Z*(O) enolate is the current isomer for potassium[456]. Thus, high diastereoselectivities could be achieved



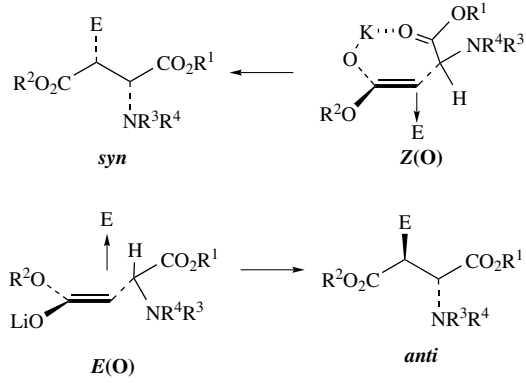
$R^1 = R^2 = Me$, $R^3 = H$, $R^4 = PhF1$[(a)]	KMDS; MeI	No additive	2	:	1^{456}
$R^1 = R^2 = Me$, $R^3 = Bn$, $R^4 = PhF1$	LiMDS; MeI	"	50	:	4
	KMDS; AllylI	"	1	:	10
	LiMDS; AllylI	"	23	:	1
$R^1 = R^2 = Me$, $R^3 = H$, $R^4 = Cbz$[(b)]	LiMDS; AllylBr	"	99	:	1^{457}
$R^1 = t$-Bu, $R^2 = Bn$, $R^3 = Bn$, $R^4 = PhF1$	KMDS; BnBr	"	1	:	50^{470}
	LiMDS; BnBr	"	50	:	11
$R^1 = t$-Bu, $R^2 = Bn$, $R^3 = Bn$, $R^4 = PhF1$	KMDS; BnI	HMPA	25	:	1.5
$R^1 = Me$, $R^2 = Bn$, $R^3 = Bn$, $R^4 = PhF1$	KMDS; BnI	HMPA	1	:	1^{458}
$R^1 = t$-Bu, $R^2 = Me$, $R^3 = H$, $R^4 = Cbz$	LiMDS; $ClCO_2Bu$-t	No additive	99	:	1
	LiMDS; $ClCO_2Bu$-t	1–10 eq. LiCl	99	:	1

(a) PhF1 = 9-Phenylfluoren-9-yl; (b) Cbz = benzyloxycarbonyl

SCHEME 94. Substituents and cation effect on aspartate alkylation[454–458]

with preformed enolates, depending on the reactivity of the electrophile, and it was shown that the steric bulk of R^1 as well as the nitrogen substituents are of paramount importance (Scheme 94).

For the *E*(O) enolate, the stereoselection is best understood in terms of stereoelectronic effect. The most stable conformation of the 2,3-allylic bond of an acyclic enolate corresponds to the smallest substituent eclipsing the double bond whatever the geometry of the enolate ($A^{1,3}$ strain)[459]. Then, in the transition state, the maximum overlap of the better allylic σ-donor and the π-orbital of the enolate directs the antiperiplanar attack of the electrophile (Scheme 95).



SCHEME 95. Chelation vs. stereoelectronic control in the alkylation of potassium and lithium aspartate enolates

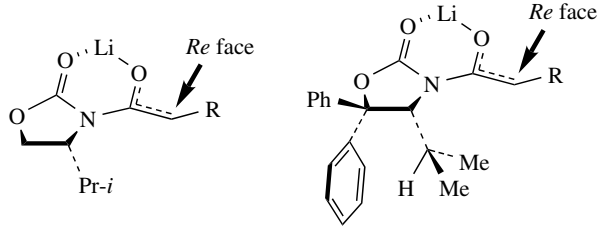
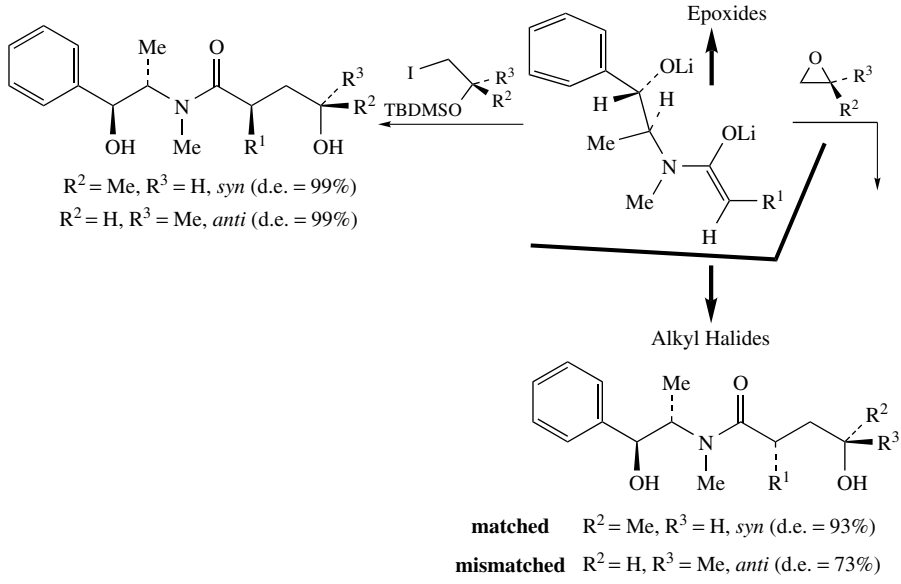


FIGURE 9. The conformational effect introduced by added phenyl substituents on (*S*)-4-isopropyloxazolidin-2-one enhance the *Re* face selectivity[462]

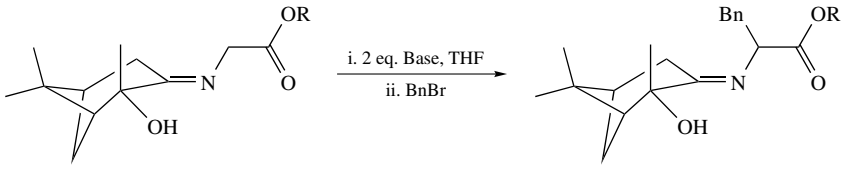
(*S*)-Valinol- and (1*S*,2*R*)-norephedrine-derived oxazolidinones introduced by Evans are to be regarded as a milestone in the development of temporarily attached chiral auxiliaries[460,461]. Although Evans and coworkers reported significantly better yields using sodium enolates relatively to their lithium counterparts, this appears not to be a general rule moreover, diastereoselectivities are generally improved with the latter. Further structural variants exhibit excellent and predictable diastereoselectivities, avoiding formation and hydrolysis drawbacks. The efficiency of these auxiliaries can be understood in light of the crystallographic results reported by Seebach and coworkers[462] for a series of *N*-acyl derivatives of 4-isopropyl-5,5-diphenyloxazolidin-2-one. The data demonstrated that the methine H-atom of the *i*-Pr group points toward the *cis*-Ph group, causing a buttressing effect in the face selectivity of the reaction of enolates with electrophiles (Figure 9)[462].

The presence of a free hydroxyl group close to the double bond generally introduces some interesting conformational bias. This is illustrated by the results of Myers and coworkers, who focused on the amides derived from commercially available pseudoephedrine. This method allows the asymmetric alkylation of simple carboxylic acids, but also of glycine or sarcosine, with a high diastereoselectivity under strictly controlled conditions[463–467]. The use of 6 equivalents of LiCl is necessary in both latter cases and, remarkably, there is no need to protect the amino group of the glycine precursor[465]. On the contrary, when epoxides are used as electrophiles, the π-facial selectivity is reversed, though it is modulated by the stereochemistry of the epoxide itself, giving matched and mismatched combinations (Scheme 96). This method was extended efficiently to the synthesis of chiral α-alkyl-β-amino acids[469]. It complemented earlier reports on prolinol-derived amide lithium enolates exhibiting a striking reversal of stereoselection from the *Si* to the *Re* face on going from the lithium alkoxide to their ethers and from alkyl halides to epoxides[470–472]. A non-chelated model[473,474], in which one face of the π-system is locked by the solvated lithium alkoxide, was proposed to account for the *anti* selectivity, by analogy with Meyers' report[437].

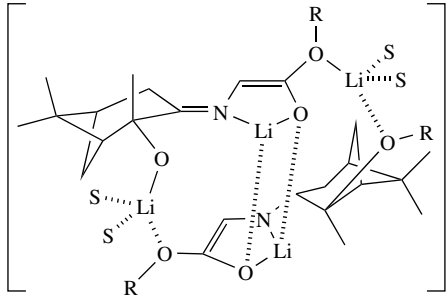
The alkylation of a folded dimeric aggregate was postulated to account for the high diastereoface selection and for the *S* absolute configuration of the amino acid resulting from the alkylation of the lithium and potassium enolates of the iminoester of glycine derived from 2-hydroxypinan-3-one[475,476]. Addition of magnesium bromide, especially to the potassium enolate, might enforce the formation of the dimer, thus favoring the outer approach of the alkylating agent. On the other hand, a marked decrease in the diastereoselectivity was observed upon addition of TBAF, probably due to the cleavage of the intermolecular O−Li bond (Scheme 97) by the ammonium salt.



SCHEME 96. Ephedrine-directed alkylation of carboxylic acid[468]



Base	*S*:*R*
LDA	96 : 4
LDA + TBAF	32 : 68
t-BuOLi	84 : 16
t-BuOK	80 : 20
t-BuOK + $MgBr_2$	93 : 7



SCHEME 97. Hydroxypinan-3-one-directed alkylation of glycine lithium and potassium enolates and proposed structure for the dimer of the lithium enolate (S = solvent)[475,476]

Alternatively, similar results were explained on the assumption of a monomeric cluster model (Figure 10, left)[477–479]. More recently, it was proposed that the *meso* dimer (Figure 10, right), probably more stable than each homochiral dimer, could be the reacting species in the alkylation of the iminoester derived from the racemic 2-hydroxypinan-3-one. This hypothesis is further supported by the observation that the starting imine and

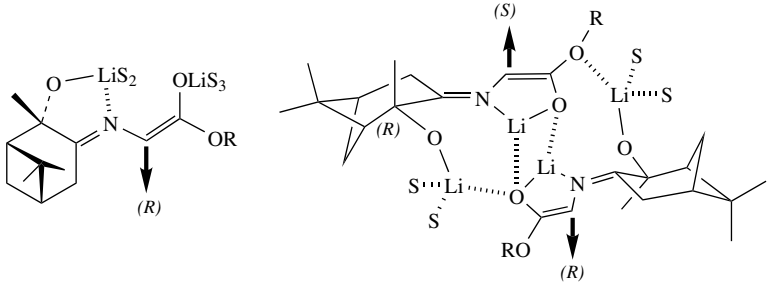
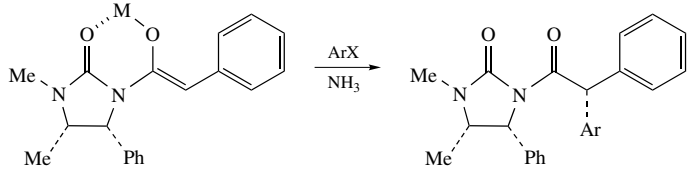


FIGURE 10. Monomeric cluster (left) and meso dimer (right) structures proposed for the hydroxypinan-3-one-directed alkylation of glycine lithium enolate[477–479]

the alkylated racemic products are crystalline C*i*-symmetric dimers connected by two hydrogen bonds, while the corresponding optically pure compounds are liquids[480].

The backbone modification of dedicated peptides through the regio- and stereoselective alkylation of their polylithiated enolates was essentially addressed by Seebach's group[200,481–483]. Critical to the success of this procedure was the ability to solubilize the peptides and their polylithio derivatives in THF by the addition of lithium salts.

Finally, the $S_{RN}1$ photostimulated diastereoselective C-arylation of the lithium, sodium and potassium salts of (4*R*,5*S*)-1,5-dimethyl-4-phenyl-3-(2′-phenylacetyl)-imidazolin-2-one was recently reported[484]. Interestingly, the best results were obtained with the lithium salt in liquid ammonia at low temperature (Scheme 98).



M	*T*(°C)	Ratio	Yield (%)
Li	−33	89 : 11	43
Li	−78	98 : 2	57
Na	−33	70 : 30	47
Na	−78	78 : 22	5
K	−33	64 : 36	29
K+$TiCl_4$	−33	98 : 2	43

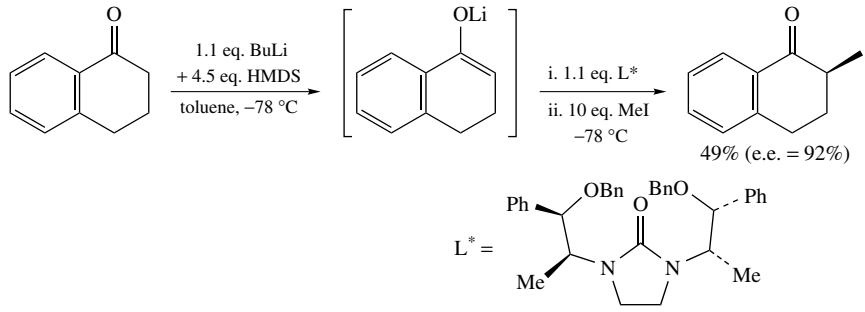
SCHEME 98. Metal and temperature effects on the C-arylation of prochiral enolates by photostimulated $S_{RN}1$ reaction (Ar = 1-naphthyl)[484]

4. Enantioselective alkylation

The enantioselective versions of the alkylation of lithium enolates rely on the complexation of the cation by a chiral ligand, which can be in stoichiometric or sub-stoichiometric (catalytic) amounts.

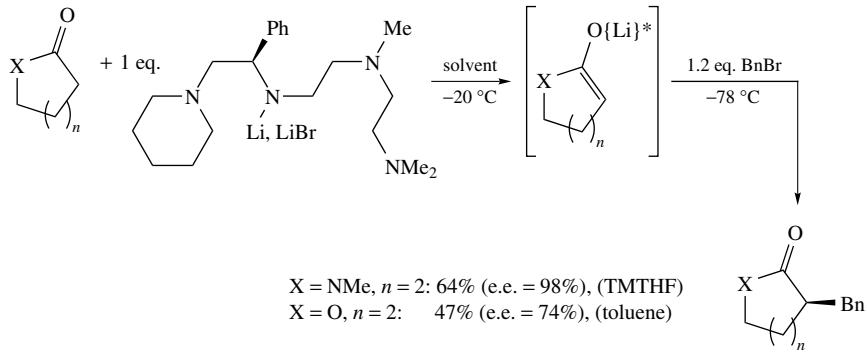
Apart from this example, the ligands retained for this purpose are mainly di- and polyamines and aminoethers. An elegant solution built around a set of C_2-symmetrical

cyclic urea derivatives was proposed by Koga and coworkers. This group studied the methylation of the enolate of 1-tetralone in the presence of 1.1 equivalents of these chiral ligands and found that e.e. values up to 92% can be reached provided HMDS is added to the medium (Scheme 99)[485]. The ligands are easily accessible from (1*R*,2*S*)-norephedrine.



SCHEME 99. Enantioselective benzylation of 1-tetralone lithium enolate in the presence of a stoichiometric amount of chiral cyclic urea[485]

Cyclohexanone is another substrate of choice for the enantioselective alkylation. A chiral aminodiether[486] or a set of lithium amides[487] was employed to generate the corresponding chelated enolate which was benzylated, in some cases in the presence of LiBr, in high to very high enantiomeric excesses[488]. Application to the enantioselective alkylation of the lithium enolates of lactams and lactones has been reported (Scheme 100)[489]. The solvent turned out to have a major influence on the selectivity, the highest e.e. values being obtained for the lactams in the rather unusual 2,2,5,5-tetramethyl-THF (TMTHF).

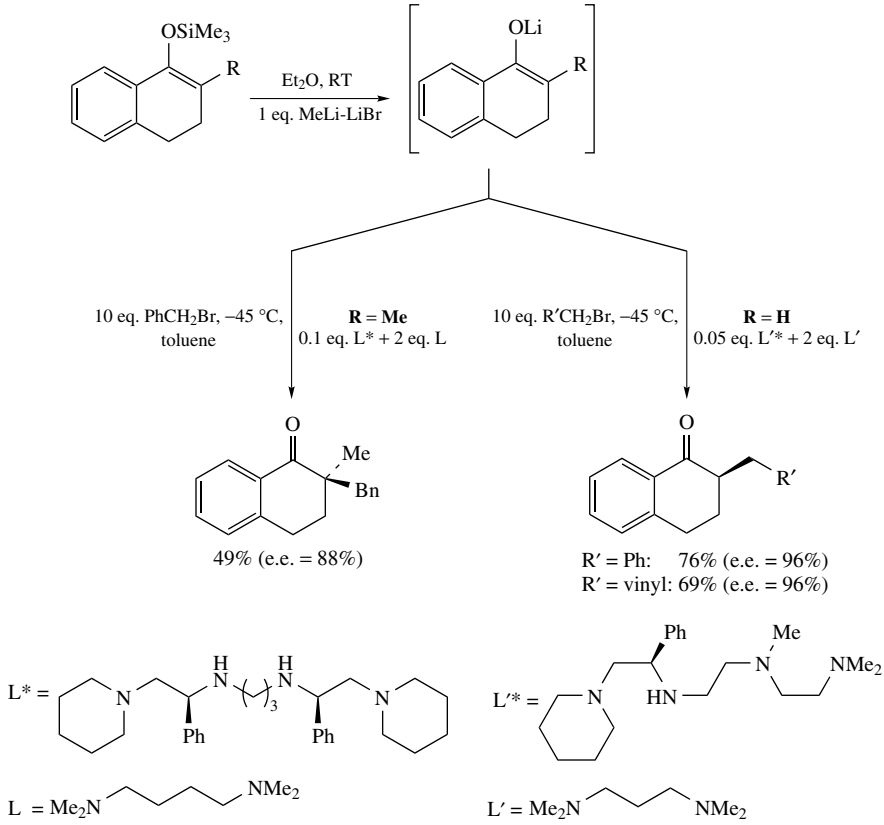


SCHEME 100. Enantioselective benzylation of lithium enolates of lactams and lactones in the presence of a stoichiometric amount of chiral tetramine[489]

The dilithium salt of phenylacetic acid has also been alkylated at its α position in excellent yields and medium to good e.e. values (up to 68%) when the preliminary deprotonation was accomplished in the presence of a chiral β-amino lithium amide[490].

The catalytic routes to the asymmetric alkylation have been difficult to describe since the lithium enolates are reactive entities that can hardly be channeled through a pathway involving exclusively their aggregate with a chiral partner present in substoichiometric amounts. Nevertheless, solutions have emerged progressively following Koga and

coworkers' findings that the benzylation of the tetralone model enolate occurs in high yields and e.e. values (up to 96%), even in the presence of 0.01 equivalents of a chiral tetramine[491,492]. The addition of LiBr, mixed with the methyllithium employed to transform the starting silylenol ether into the corresponding enolate, and of 2 equivalents of TMPDA (*N*,*N*-tetramethylpropanediamine) together with the chiral ligand were shown to be necessary for the chemical and stereochemical efficiency of this system (Scheme 101). Comparable results were obtained in similar conditions for the allylation of the same enolate[493]. The enantiocontrolled construction of quaternary centers can also be performed following an analogous strategy relying this time on a C_2-symmetrical ligand, both the stoichiometric and catalytic versions (also in the presence of 2 equivalents of an achiral diamine, Scheme 101) being documented[494].

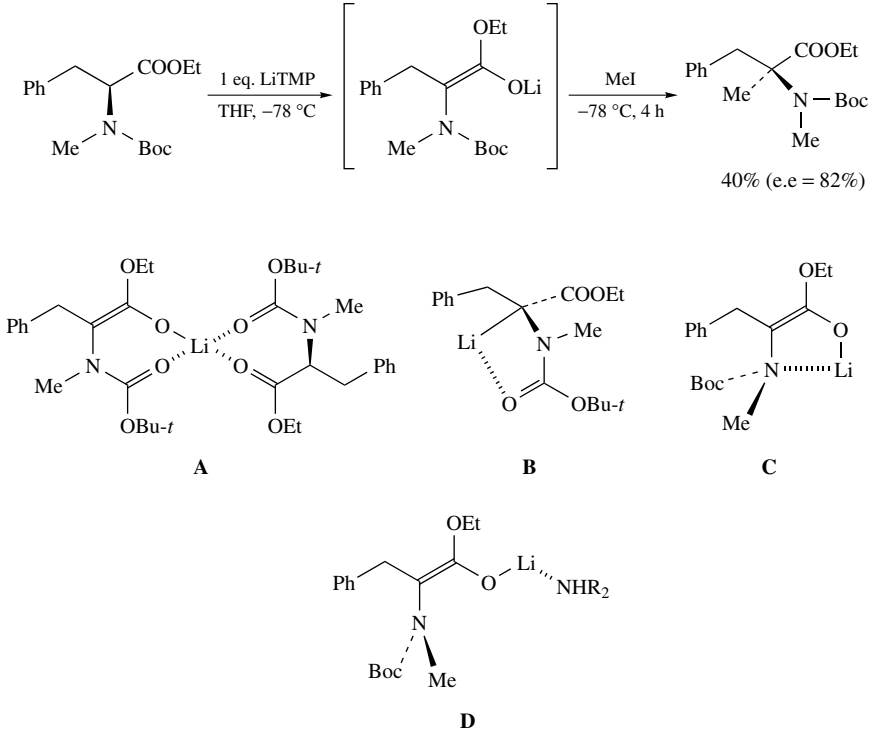


SCHEME 101. Enantioselective benzylation of tetralones lithium enolates in the presence of catalytic amounts of chiral tetramines[494]

The enantioselective α-benzylation of the lithium enolate of acyclic carboxamides, such as propionamides and butyramides, generated with CLA derived from original pentamines bearing several asymmetric centers has been reported[495]. Complementary, cyclic carboxamides such as perhydropyrimidinones lithium enolates, obtained from more classic Simpkins-type CLAs, were methylated or benzylated in toluene at $-78\,^{\circ}C$ in the

presence of LiBr. Relatively modest enantioselectivities, inferior to those obtained with (−)-sparteine, were measured[496].

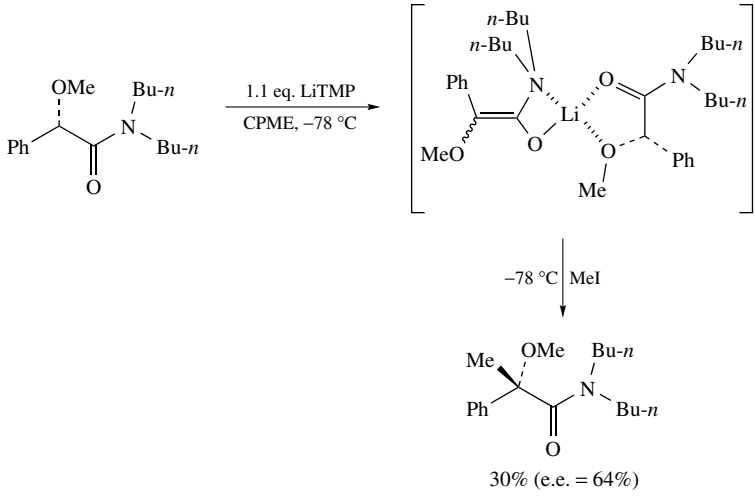
Interestingly, the alkylation of an enolate can occur in an enantioselective way in the absence of any external source of chirality. This striking phenomenon, which can be regarded as an enantioselective version of Seebach's SRS strategy (see above), was first described as the *memory of chirality* by Kawabata, Fuji and coworkers[497]. It has been observed with the enolates derived from carbonyl derivatives such as ketones, α-aminoesters[498] (including a remarkable cyclization process[499]) or carboxamides[500]. Note that the more spectacular results in this area were obtained with potassium enolates, which are not relevant here. Nevertheless, the lithium enolate of phenylalanine derivatives, apparently devoid of any element of chirality, undergoes α-methylation in THF with e.e. values up to 82% (Scheme 102)[501].



SCHEME 102. Memory of chirality: enantioselective methylation of a phenylalanine derivative lithium enolate in the presence of no external source of chirality[501]

The origin of the chiral information in these systems seems still unclear. Several hypothesis have been evoked[502] (Scheme 102), including the formation of an intermediate mixed aggregate such as **A** (the yields of these alkylations tend to be modest), or of a configurationally stable carbanion **B** stabilized by the Boc group, or a chelation of the lithium by the chiral nitrogen **C**, or also of an enolate **D** presenting a chiral C−N axis made due to a rotation impairment imposed by the solvated lithium cation. However, recent results on the alkylation of symmetrically *N*,*N*-disubstituted amides (such as that obtained condensing (*S*)-*O*-methyl mandelic acid and *N*,*N*-dibutylamine or pyrrolidine), which can be

achieved in decent e.e. values, suggest that an **A**-type aggregation phenomenon is likely to be involved in this reaction (Scheme 103)[503]. Interestingly, in THF the latter reaction provides the racemic product, the best inductions being observed in *t*-butyl methyl ether (TBME) or cylopentyl methyl ether (CPME).



SCHEME 103. Enantioselective methylation of a phenylalanine derivative lithium enolate in the presence of no external source of chirality[503]

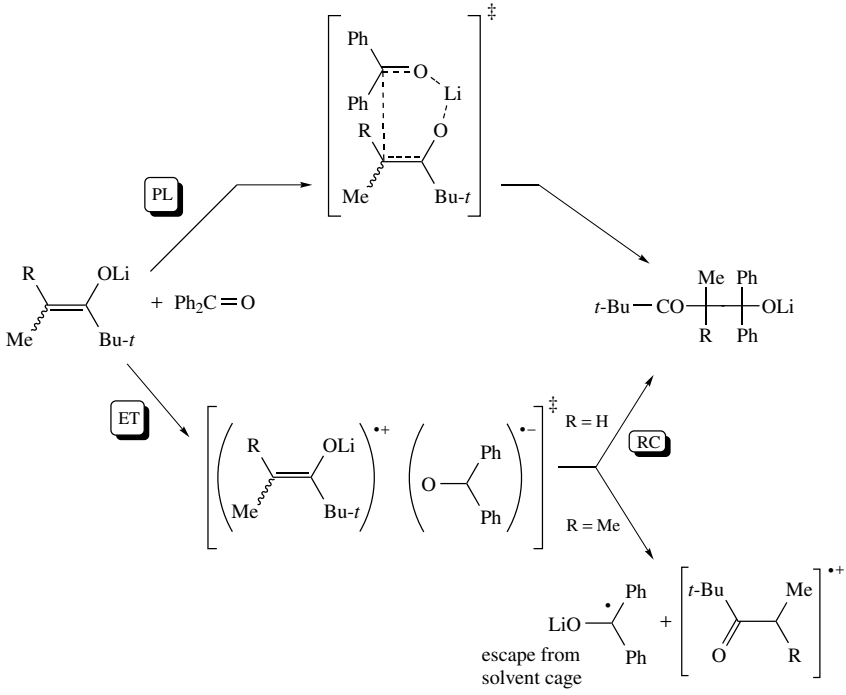
C. Directed Aldol Reaction

The aldol reaction is one of the most fundamental tools in organic chemistry, and it still remains an open field for new ideas and developments[504–509]. Among the many reviews dedicated to this subject, the reader should refer, for a more referenced survey, to Heathcock[7,11] and more recently to Braun's articles[510] devoted specifically to the preformed metal enolates of group I–II. The Mannich reaction (the aza-equivalent of the aldol reaction) is a subject on its own and will be only partially treated here.

1. Mechanism and reaction pathways

The kinetically controlled nucleophilic addition of preformed lithium enolates onto carbonyl compounds is reversible with a low activation barrier, and the thermal conditions are likely to have a major impact on the stereoisomeric ratio of the final aldols through the retroaldolization and the thermodynamic equilibration of lithium enolates[76]. The tendency of aldolates to undergo retroaldolization increases with the stability of enolates, and when going from lithium to potassium. On the other hand, boron enolates usually undergo completely irreversible aldol reaction[511,512].

a. Polar vs. electron transfer mechanism. The distinction between the two possible pathways for the nucleophilic addition to the carbonyl function, i.e. a polar mechanism (PL) vs. an electron transfer–radical coupling [(ET)–(RC)] sequence (Scheme 104), is not straight forward[513]. The ability of lithium enolates derived from alkyl and aryl ketones to transfer a single electron was early recognized by Russel and coworkers[514]. Later,



SCHEME 104. Aldol condensation: polar vs. electron transfer pathways

Ashby and coworkers reported spectroscopic EPR evidence that aldol condensation might take place by an electron transfer mechanism[515]. Hence, when 2,2-dimethyl-3-pentanone lithium enolate was treated with benzophenone, no aldol was formed, but a blue persistent colored solution developed ($\lambda_{max} = 632$ nm) and a well-resolved EPR spectrum was recorded similar to that of an authentic sample of diphenylketyl radical. In sharp contrast, 2,2-dimethylbutanone yielded 90% of the aldol together with a non-resolved faintly persistent EPR signal (maximum concentration 0.1% after 18 h) whose first-order rate decay ($k_{decay} = 2.3 \times 10^{-5}$ s^{-1}) parallels the rate of formation of the aldol, the overall reaction being second order ($k_{decay} = 2.3 \times 10^{-5}$ s^{-1}, and $k_{overall} = 4.5 \times 10^{-5}$ s^{-1} at 25 °C). However, the rate of the reaction in the presence of light, radical scavengers or dicyclohexylphosphine was unaffected and, moreover, the benzophenone ketyl radical generated independently in THF was unable to react with the lithium enolate, ruling out the possibility of a $S_{RN}1$ mechanism.

More recently, the distinction between the PL/ET or RC/ET rate-determining step was evaluated by measuring the carbonyl–carbon kinetic isotope effect (KIE) as a probe, since the value of the carbonyl–carbon KIE reflects the C–C bond-forming process and its contribution to the reaction coordinate vibrationae motion at the rate-determining transition state[516]. Thus, isotope effects have been evaluated (Table 4) for the reaction of pinacolone lithium enolate with C_6D_5CHO *vs* C_6H_5CHO and $C_6H_5^{13}CHO$ *vs* C_6D_5CHO under kinetic conditions (0°C, contact 10s)[516]. The small positive experimental carbonyl-^{13}C KIE value ($^{12}k_C/^{13}k_C = 1.019$) suggests a PL or RC rate-determining step. Additionally, this value, larger than the computed equilibrium KIE at carbonyl—^{13}C for benzaldehyde

TABLE 4. Kinetic and equilibrium isotope effects for the reaction of benzaldehyde with various organolithium reagents[12]

Li reagent/Solvent	Hammett's	k_H/k_{D5}	$k_{D5}/^{13}k$	$^{12}k/^{14}k$ [b]	Step	ΔH_{gas} [c]
PhLi/Cyclohexane–Et_2O	0.13			0.998	ET	400.8
AllylLi/Et_2O	0.21			0.994	ET	390.7
$LiCH_2CN$/THF	0.14	1.021	0.976	0.992 [a]	ET	372.8
Pinacolone Li enolate/THF	1.16	1.031 (1.094) [a]	0.988	1.039 (1.006) [a]	PL	368.0

[a] (computed equilibrium IE) values.
[b] Values of $^{12}k/^{13}k$ corrected to $^{12}k/^{14}k$.
[c] Intrinsic acidities estimated from the heat of formation in the gas phase (in kcal mol^{-1}).

($^{12}k_C/^{13}k_C = 1.006$), indicates that the carbonyl–carbon KIE is of primary nature and that the bonding is changing at the rate-determining transition state. Measured and computed secondary deuterium kinetic isotope effect (SDKIE) for benzaldehyde d_5 suggests that the transition state is reached at about one third along the reaction coordinate for a PL mechanism.

Complementarily, competitive experiments for the reaction of lithium 3,3-dimethyl-2-butanone enolate with a set of substituted benzaldehydes, under kinetic conditions (0°C, contact 10 s), gave access to the relative reactivities k_X/k_H[517]. The magnitude of the electronic substituent effect ($\rho = 1.16$), clearly different from those of other RLi reagents (see Table 4), strongly suggests a rate-determining step different from an ET. Finally, neither the isomerization of (*Z*)-2,2,6-tetramethylhept-4-en-3-one nor the dehalogenation of *o*-iodobenzophenone used as chemical probes was observed, definitively ruling out the ET pathway.

b. Aggregation and solvent effects. Another point of concern is the exact structure of the reacting enolates through their aggregation and solvation states. Correlations of thermodynamic data between the solid state and solution structures have been reported by Arnett and coworkers using a multi-experimental technics approach (vapor pressure osmometry, cryoscopy and rapid injection NMR), for the reaction between lithium pinacolate and pivalaldehyde or a series of substituted benzaldehydes[518–521]. The results underline a large contribution from the energies of solvation and a high dependency of the aggregation number on the nature of the ligand (Table 5). In addition, for substituted benzaldehydes, the heat of reaction recorded in different solvents (THF, CH_3CN or THF/$LiClO_4$), are similar with a good linear correlation with the Hammett values ($\rho = 3.4$). Again, consistent with a non-ET mechanism, cyclizable probe experiments are negative[521].

Modification of the reaction medium corresponds to a change in the intimate microscopic solute to solution interactions. Hence, the influence of the solvent on the selectivity is a function of enthalpy and entropy contributions[522]. Thus, Eyring plots (diastereomeric excess vs. temperature) for the reaction of the lithium enolate of *t*-butylacetate with racemic 2-phenylpropanal gave $\Delta\Delta H^{\#} = -0.70$ kcal mol^{-1} and $\Delta\Delta S^{\#} = -0.10$ cal mol^{-1} K in *n*-hexane and $\Delta\Delta H^{\#} = -0.59$ kcal mol^{-1} and $\Delta\Delta S^{\#} = +1.7$ cal mol^{-1} K in THF. The

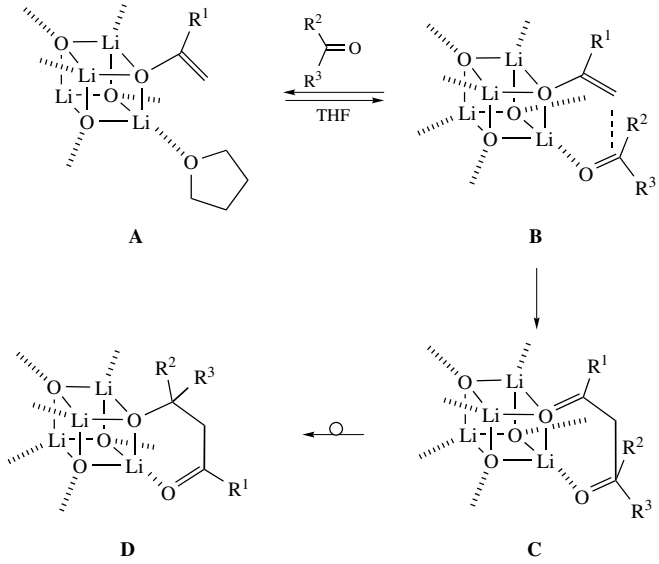
TABLE 5. Heats of reaction and solvation, and aggregation numbers for the reaction of lithium pinacolate with pivalaldehyde at 6 °C in cyclohexane[519,520]

Ligand	Cyclohexane	DME	TMEDA	THF
$\Delta H_{reaction}$ (kcal mol^{-1})	−21.59	−19.52	−19.49	−16.35
$\Delta H_{solvation}$ (kcal mol^{-1})	—	−3.52	−2.98	−6.17
Aggregation number	6.4	5.5	5.2	4.5

same authors found similar solvent effects in the addition of *n*-BuLi to *O*-protected α-hydroxyaldehydes[523]. Since entropy control is associated with processes where weak interactions are dominant[524], the origin of the switch from enthalpy control in THF to entropy control in hexane, although speculative, might reflect a change to a preorganized state through the docking step[525].

Regardless of increasing structural data on both the solution and the solid state, the question concerning the exact structure of the reacting species in solution remains ambiguous. Wei and Bakthavatchalam[526] argued that in the solid state, for a heterogeneous reaction, the absence of solvation should preserve an enolate from dissociation and therefore it should be the primary reactant. Thus, they compared the results of the reaction of the lithium enolate of methyl 3,3-dimethylbutanoate in the solid state, with the same reaction in the usual solution conditions at different temperatures. In the solid state, a set of solid and liquid aldehydes were mixed and grounded under argon with the enolate; everything being equal, the aldol reaction was conducted in THF for the same period. Although the yields are lower for the solid state (corresponding to a lower conversion of the aldehydes), the *syn*/*anti* ratio is almost the same and independent of the reaction temperature, at low temperature, but strongly dependent at higher temperature with $T_{inv} = 273$ K. Moreover, the initially formed kinetic aldolate equilibrates reversibly to the thermodynamically more stable one with aging of the aldolate. These results strongly suggest that the same reacting species and transition state operate in both the solid and solution conditions, although it is difficult to substantiate whether the reaction is truly heterogeneous at the microscopic level in the solid state reaction.

From the tetrameric THF-tetrasolvated enolates[221], whose structures have been substantiated by the accumulation of experimental data, Seebach, Dunitz and coworkers proposed a scheme in which the stereoselection is considered in a supramolecular context[527]. Later completed by Williard and coworkers[45,208], this proposal accounts for the formation of a mixed tetrameric aggregated enolate **A** incorporating ligands (Scheme 105)[380]. The



SCHEME 105. A possible supramolecular pathway for the aldolization of a tetrameric lithium enolate[36,529]

docking of the carbonyl is then supposed to replace one molecule of the solvent, yielding a tetraketone-solvated tetrameric enolate (aggregate **B**)[528]. Finally, an intramolecular reaction takes place yielding the tetrameric aldolate **D** (Scheme 105)[36,529].

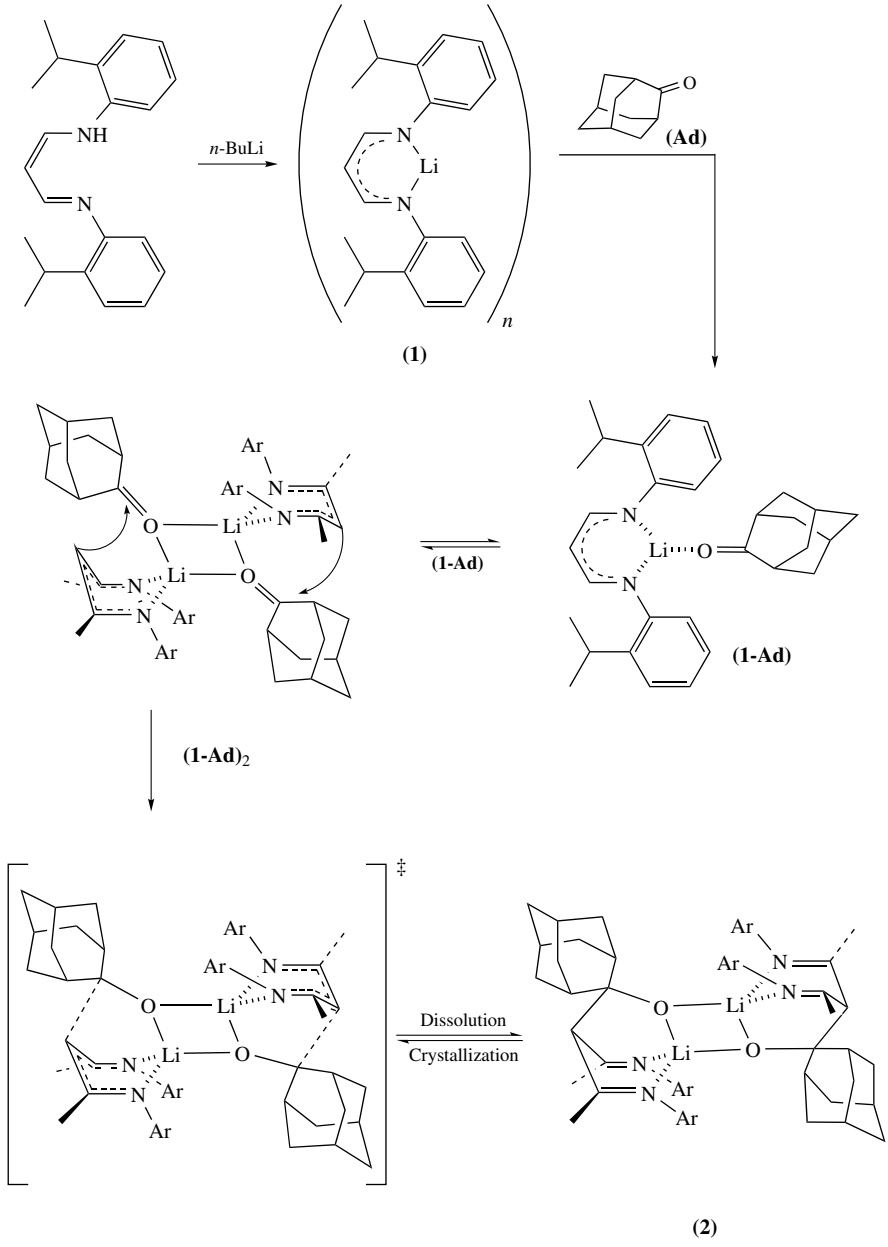
At this point, the direct formation of the tetrameric aldolate seems questionable since: (i) it could be the result of the aggregation of monomeric or dimeric aldolates resulting from the reaction of a monomeric or a dimeric enolate (alcoholates are often tetrameric); (ii) the above model implies the simultaneous reaction of the four enolates within the tetramer framework without any stereochemical incidence for each other; (iii) each oxygen switch in **C** needs a complete rearrangement of the OLi core of the aggregate. Actually, these comments are substantiated by Streitwieser's report that the cubic tetramer of a lithium enolate cannot normally compete with the simple addition of monomer, even at synthetic concentration[393].

Interestingly, a crystallized aza-analogue of an aldolate close to structure **C** (Scheme 106) **(2)**], was recently isolated and structurally characterized by Mair and coworkers during the reaction of the *N*, *N*′-diaryl-1,5-diazapentadienyl lithium anion **(1)**[530] with adamantanone **(Ad)**. X-Ray analysis demonstrated a dimeric structure built around a O-Li core, with a 1.35 Å short C-O bonding and a 1.64 Å distance for the new C-C bond. Retroaldolization occurs by simply dissolving the aldolate in hexane or benzene and cryoscopic experiments strongly support the presence of the monomeric **1Ad**, suggesting a ground state in which the steric bulk of each reagent and the stability of the 1,5-diazapentadienyllithium anion results in a very small energetic barrier between reagents and product. Thus, it was postulated that the coupling is the result of the dimerization, the greater polarization of the carbonyl in $(\mathbf{1Ad})_2$ and the closer proximity of the reagents facilitating the carbanion attack. Additionally, the viability of such a dimer had already been supported on computational grounds[61].

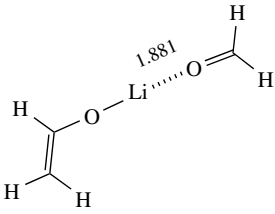
c. Theoretical aspects of the aldolization reaction. Transition structures in the gas phase have been located, for the aldol reaction of the monomeric lithium enolate of acetaldehyde with formaldehyde, at the RHF 3-21G level of calculation[532,533]. In these two papers, the first step is the formation of a linear η^1 complex (Figure 11, left) by dipole interaction between the oxygen of the aldehyde and the lithium atom of the planar enolate. However, recent calculation refinements located a η^3 out-of-plane enolate as the most stable[534] (by 1.7 kcal mol^{-1}) structure compared to the linear η^1 in-plane enolate. Note that the C=O---Li interaction is likely to be due to a limited basis set artefact, as found in the case of the methyllithium formaldehyde interaction[535]. Similar results have been obtained for the reaction of the lithium enolates of acetone and acetaldehyde and these are not affected by taking the solvent into account. Then, according to Leung-Toung and Tidwell[533], the calculated C vs. O bond formation gave two possible transition states TS_{oxygen} and TS_{carbon} very close in energy to the complex and the C−C bond formation is the favored pathway (Scheme 107).

In this latter case, a single transition state was located at which 30% of the C−C bond was completed. The arrangement at the six-membered transition state can be described as an approximate half-chair, with the lithium cation lying approximately in the plane of the four adjacent atoms. The direction of the C−C arising bond lies at *ca* 93° with respect to the enolate plane (smaller than the value for the metal-free enolate), and at 107° with respect to the aldehyde plane. This latter value is in fine agreement with the Bürgi–Dunitz[536] attack angle theory and is similar to that calculated for other nucleophilic attacks to carbonyls[537]. The deviation on the C−C=C−O torsion angle, from $\theta = 69°$ in the TS to 48° in the aldol, accounts for the difference in the steric and electronic effects on both cation free and lithium enolates.

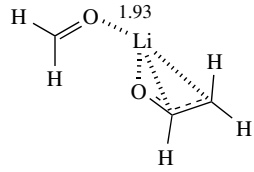
Recently, two diastereoisomeric transition states have been located by *ab initio* calculations at the MP2/6-31G*/HF/6-31G* level, for the reaction of the *Z*(O) lithium enolate



SCHEME 106. Mechanism of the nucleophilic addition of *N*,*N*′-aryl-1,5-diazapentadienyllithium anion with norbornanone. Influence of the dimer (Ar = 2-*i*-PrC_6H_4)[531]

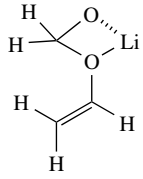


RHF 3-21G optimized in-plane η^1 complex

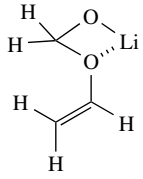


HF 6-31G** optimized out-of-plane η^3 complex

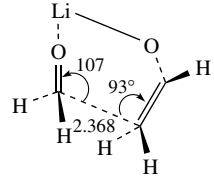
FIGURE 11. Ab initio calculated transition structures in the gas phase for the aldol reaction of the monomeric enolate



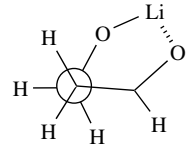
TS_{oxygen} −29.5 kcal mol^{-1}



−22.9 kcal mol^{-1}



TS_{carbon} −26.0 kcal mol^{-1}



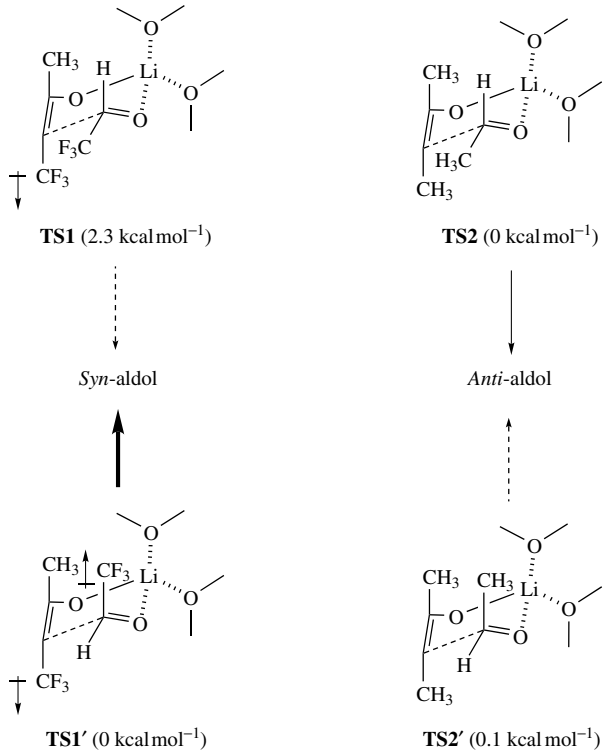
−40.2 kcal mol^{-1}

SCHEME 107. Relative energies and geometries for the O- and C-addition transition state calculated for the addition of formaldehyde to the lithium enolate of acetaldehyde and the preferred conformations of aldol[535]

of 1,1,1-trifluoropropan-2-one with trifluoroethanone. The same reaction involving non-fluorinated molecules was then compared, dimethyl ether being set as the solvent[538]. Interestingly, while the non-fluorinated diastereoisomers are isoenergetic with a small preference for the *syn* aldol by 0.1 kcal mol^{-1}, the fluorinated TS differ by 2.3 kcal mol^{-1}, giving anomalously the *anti* aldol as the major product. This result is explained by the efficiency of the strong dipole interaction in directing the sterically more demanding CF_3 group to the axial orientation (Scheme 108, TS1′).

2. Stereofacial selectivity

a. Simple diastereoselection. The approach of the carbonyl from one of the two faces of the enolate is associated with the geometry of the (prochiral) enolate (simple diastereoselection). On the other hand, the approach of the carbonyl from one of its enantiotopic faces (diastereofacial selectivity) is related to steric and electronic requirements. Considering a monomeric enolate, both a closed model and an open model rationalize the stereochemical outcome of the addition. The closed transition state model is preferred for covalently bonded oxophilic metals such as Li, Mg, Al, Zn and implies a synclinal relationship between the enolate and the carbonyl moieties[539]. Consequently, the approach of the enolate to the carbonyl center along the Bürgi–Dunitz trajectory takes place quasi-perpendicular to the C=C bond. Then, due to the intramolecular coordination of the metal to the oxygen atoms, the minimization of the steric repulsion between R^4 and R^1 or/and between R^3 and R^4 in (Scheme 109) enforces a modification of the θ (O=C−C=C) dihedral angle (Figure 12).



SCHEME 108. Transition states models for the reaction of the *Z*(O) lithium enolate of 1,1,1-trifluoropropan-2-one with acetaldehyde and trifluoroethanal[538]

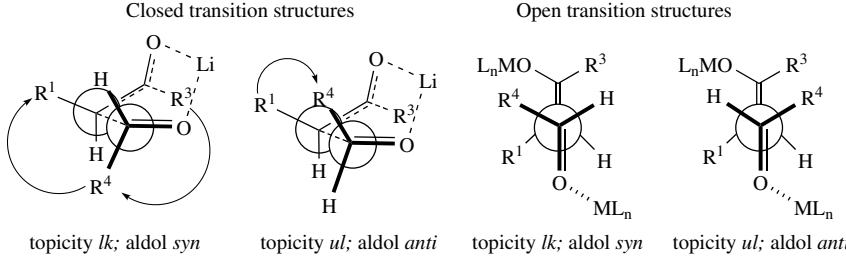
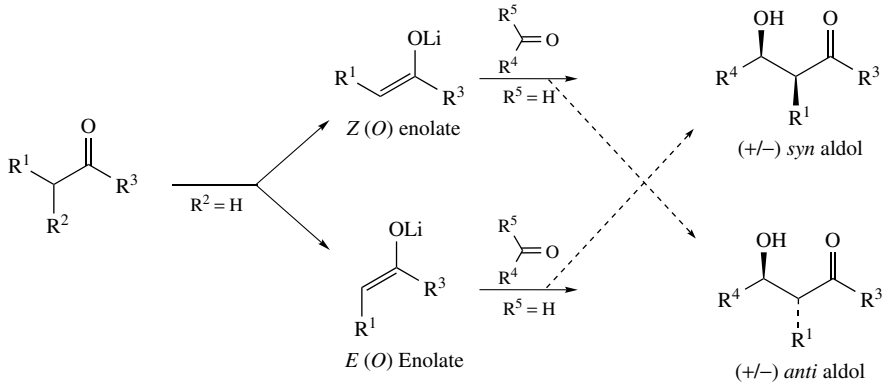


FIGURE 12. Closed and open transition state models for the aldol reaction of a *Z*(O) enolate ($R^2 = R^5 = H$)

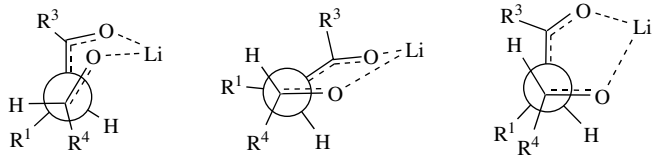
Generally speaking, *Z*(O) enolates are associated with *syn* aldols and, to a smaller extent, *E*(O) enolates with *anti* aldol products (Scheme 109)[540]. However, deviations from this idealistic situation are often encountered, depending on the substitution patterns, and much of recent research studies has focused on delineating the conditions under which the relationship between the *E*(O) vs. *Z*(O) enolate geometry and *syn* vs. *anti* aldol configuration is the most strongly expressed.



SCHEME 109. Relationship between the enolate geometry and the aldol structure[540]

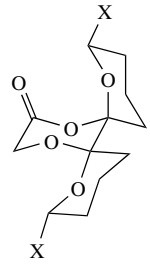
The numerous literature data already collected for the lithium enolates[541] substantiate that the steric interactions between R^3, R^4 and R^1 are of utmost importance in directing the stereochemical outcome of the reaction in the case where $R^2 = R^5 = H$. Accordingly, under kinetic control: (i) the diastereoselectivity for the *Z*(O) enolate (*syn* aldol) is greater than that for the *E*(O) enolate (*anti* aldol); (ii) the *Z*(O) enolate is highly *syn*-selective when R^3 is sterically demanding whereas it is *anti*-selective when R^1 is large; (iii) the *E*(*O*) enolate is highly *anti*-selective only when R^3 is strongly sterically demanding[542]; (iv) the effect of the metal and its ligands is crucial; (v) the presence of heteroatom has a profound influence on both the rate of the reaction and its selectivity[543].

A consequence of the regulation of the *syn*- vs. *anti*- selectivity, through the geometry of the enolate, is the propensity of acyclic ketones and amides to produce *anti*-selective aldols, while *syn*-selective aldols rely on esters and thioesters. Most of these data have been rationalized on the basis of a pericyclic chair like six-membered ring transition state model (Zimmerman–Traxler model, $\theta = 60°$)[24]; alternatively, a boat ($\theta = 0°$) or a skewed model ($\theta = 90°$) has been considered (Scheme 110)[11]. Note that use of Lewis acids or transmetallation of lithium enolates is a frequently used strategy to invert or to gain higher stereoselectivities[544].



SCHEME 110. Boat, pericyclic and skewed transition state models for *E*(O) enolate leading to the *anti* isomer (topicity[545] *lk*)

b. Absolute diastereoselection. Since optically active *syn*- and *anti*- 1,3-diols, 3-hydroxycarbonyl and 3-hydroxy-2-methylcarbonyl units are ubiquitous structural motifs in many important biologically active compounds, the efficiency of the stereocontrol in aldol assembly sequences is still a challenging endeavor as reported by Schinzer, taking



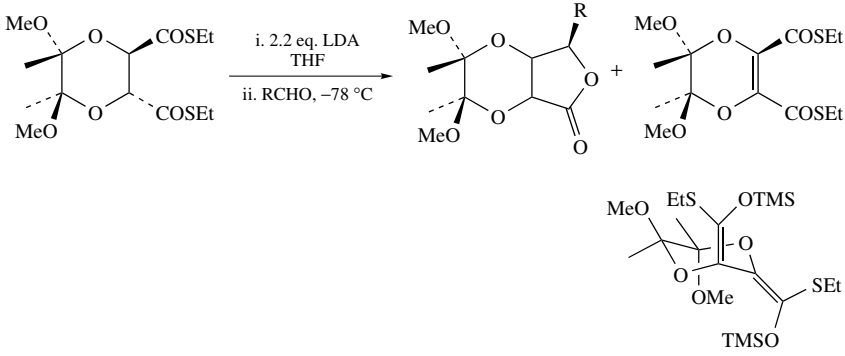
A (X = H, CH_2SPh)

FIGURE 13. Non racemic glycolic acid-derived spiroketals **A**[550, 551]

the 'epothilone story' as an example[546, 547]. A chiral center in the close spatial proximity to the prostereogenic reacting center will influence the diastereoface recognition, and three cases are to be considered depending on its location on: (i) the enolate, (ii) the substrate or (iii) both of them.

i. Chiral enolate and auxiliary-induced diastereoselectivity. There has been significant effort to build up chiral ketones, esters and amides of which enolates could be able to promote high diastereofacial selectivity. However, variation of the metal is often a much better promise of success. Indeed, the lithium cation proved to be stereochemically efficient only in some particular cases, including the previously mentioned Seebach's self-reproduction strategy based on 1,3-dioxolanone units[548], although failure to these results was recently reported[549]. The spiroketals **A** (Figure 13), derived from glycolic acid, proved to be convenient synthons: their aldol condensation leading to enantioselectivities up to 98%[550, 551].

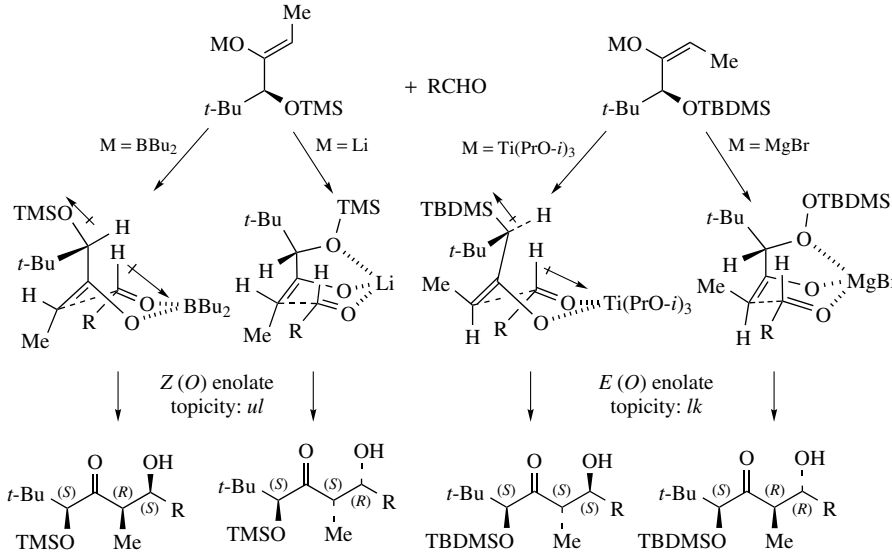
The synthesis of γ-lactones from acetals derived from a tartaric acid dithioester was recently reported[552]. Quenching the readily obtained lithium dienolate (analyzed as its bis-silylketen acetal, Scheme 111, bottom structure) with a series of aldehydes gave only one diastereomeric lactone, generally in *ca* 60% yield, along with a variable amount of oxidized diester depending on steric factors (Scheme 111). An intramolecular complexation of the lithium atom is assumed to favor the C_2-symmetric *Z,Z* non-planar chelated



SCHEME 111. Synthesis of γ-lactones from tartaric-derived bis-thioester by aldol reaction and the bis-thioketene acetal obtained by silylation of the intermediate bis-enolate[552]

intermediate. Interestingly, the retroaldolization is prevented by the lactonization of the *cis*-aldol.

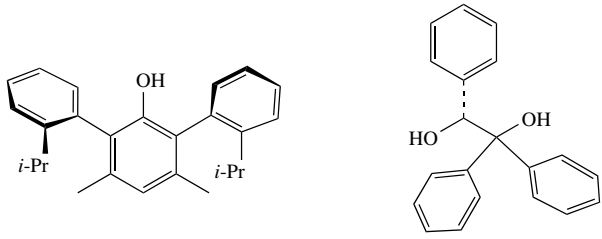
The possibility to control the absolute configuration of all four diastereomers, through a judicious combination of the nature of the metal and the geometry of the chiral enolate, was reported in a remarkably didactic example by Heathcock[553]. In this particular case, the chelating (or non-chelating) of the silyloxy moiety by the sterically demanding R group helps to perfectly control the 2,3-relationship and assume a nearly total stereofacial control over the aldehyde ($Si/Re = 95/5$) (Scheme 112).



SCHEME 112. Synthesis of all four diastereomers by substrate and metal-induced diastereoselective aldol reactions[553]

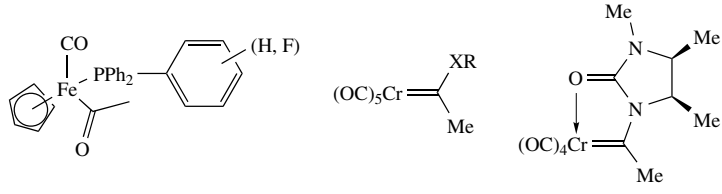
One of the most difficult problems encountered in asymmetric aldol reaction was, by far, achieving high induction with α-unsubstituted enolates[554]. Recent solutions came with the auxiliary controlled addition of enolate derived from the acetate of the sterically demanding 2,6-*diiso*-propylphenyl-3,5-dimethylphenol (axial chirality) (Figure 14). Good yields and high enantiomeric excesses have been reported only when using LDA as a base[555]. On the other hand, the double deprotonation of the acetate of the easily available Braun reagent (HYTRA) gave high diastereoselectivities provided very low temperature is used ($-130\,^{\circ}C$) and magnesium salts are added[556].

Other solutions have been proposed to avoid this problem, such as using acetate equivalents, typically acetyl iron complex **A** or Fischer carbene complexes **B** and **C** (Figure 15). The chiral iron acyl derivatives failed to promote highly stereoselective aldol condensation through the lithium enolate of their acetyl derivative[401]. Notwithstanding the possibility of circumventing this closure by transmetallation or using pentafluorophenyldiphenylphosphine as a ligand[557], the difficulty in obtaining these acyl complexes optically pure precludes their use as synthetic tools. On the other hand, the variation of the organic ligands of the readily prepared Fischer carbene complexes **B** is relatively easy. Thus, fruitful investigations of their aldol reactions have been achieved. Especially high stereoselectivities have been obtained with imidazolidinone-derived carbene **C**[558] when LDA,



2,6-diisopropylphenyl-3,5-dimethyl-phenol HYTRA

FIGURE 14. Selected sterically demanding non racemic alcohols allowing high diastereoselectivities in the aldol reaction of their lithium enol acetates[555, 556]



A **B** **C**

$[XR = OMe, NR'_2]$

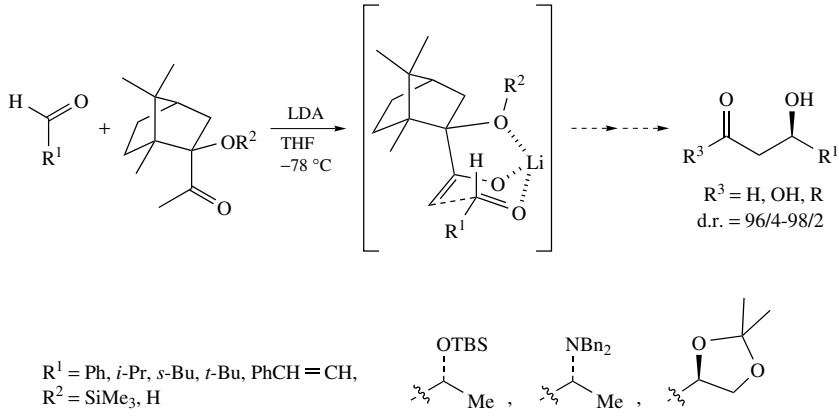
FIGURE 15. Chiral iron acetyl complex **A**[557] and chromium Fischer carbene complexes **B** and **C**[558] as chiral acetate equivalents

n-BuLi or LiHMDS are used as a base. Nevertheless, a marked cation dependence was observed and the outcome of the reaction was found to be profoundly affected by such parameters as the solvent, cosolvent (HMPA), ligand (LiCl) or temperature. The formation of aggregates is supposed to be at the origin of this dependency[559].

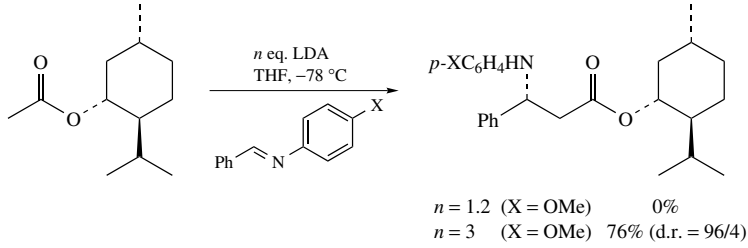
Finally, an organic variant of acyl-protected compounds was recently proposed by Palomo and coworkers, who introduced the camphor-masked acyl lithium-mediated enolate to produce β-hydroxyketones or acids in 70 to 80% yield and high enantiomeric excesses (Scheme 113)[560, 561]. Interestingly, for unprotected camphor derivatives (R^2 = H), the stereoselectivity was dramatically improved by adding six equivalents of lithium chloride.

Compared to the preceding statements, the addition of the lithium enolate of menthyl acetate to *p*-substituted phenylaldimines is of significant value, since it furnishes β-amino acids in good yields and with diastereomeric ratios up to 94%. Using 1.2 equivalent of LDA to generate the enolate led to unparalleled diastereoselectivities when increasing the Hammett ρ constant values of the 4-substituents of the aniline moieties. Alternatively, in the case of a methoxy substituent, a spectacular d.r. enhancement has been obtained when using 3 equivalents of LDA, probably as a consequence of the formation of a more selective new binary LDA–enolate complex (Scheme 114)[562].

ii. Substrate-induced diastereoselectivity. Results collected in the literature indicate the general tendency of lithium enolates to react with alkyl-substituted chiral aldehydes with moderate diastereofacial selectivities unless enolates with bulky substituents are used[563]. The diastereofacial selectivity of the reaction of non-chiral boron or lithium enolates with



SCHEME 113. Camphor-mediated diastereoselective synthesis of α-unsubstituted β-hydroxycarboxylic acids, aldehydes and ketones[560,561]

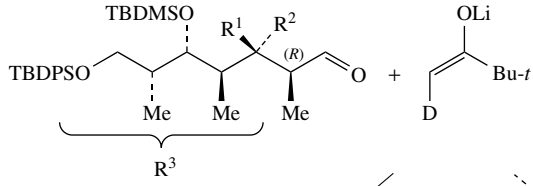


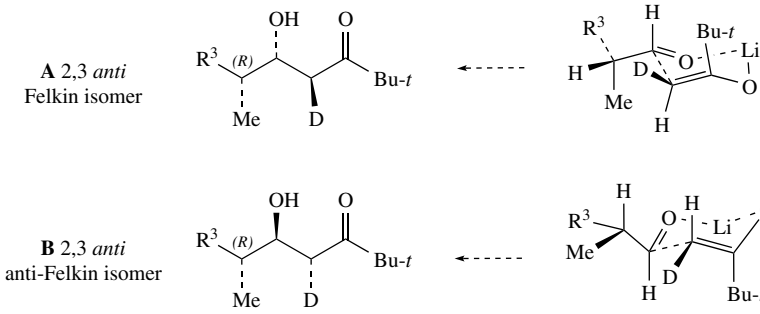
SCHEME 114. Influence of the ternary reagent concept on a Mannich-type reaction[562]

a series of chiral α-methylaldehydes has been the object of *ab initio* calculations by Roush[564]. The conclusion of his paper was that 'the dominant stereocontrol element that determines aldehyde diastereoselectivity is the minimization of gauche pentane interactions in the competing cyclic, chair-like transition state'.

On the other hand, with heterosubstituted chiral aldehydes, the product distribution for the reaction with methyl ketone enolates is strongly influenced by the nature of the metal, the nature of the heteroatom and its position within the molecule. A chair-like transition state explained the formation of the Felkin adduct, while a boat-like transition state was invoked for the formation of the anti-Felkin adduct. However, this assumption was recently challenged by Roush and coworkers using deuterated pinacolone lithium enolate[565]. Performing a set of aldolizations with chiral and non chiral aldehydes led these authors to show that the isomeric purity of the enolate correlates almost perfectly with the ratio and pattern of deuterium labeling in the 2,3-*anti*-aldol formed consistent with a highly favoured chair-like transition state (Scheme 115).

On the other hand, chelation-controlled aldol reactions usually provide the *anti*-Cram aldol. This has been early illustrated by Heathcock and coworkers[76] who reported that the proportion of the exclusive *syn* condensation products **B** and **C** (>98%) of the bulky enolate **A** (Scheme 116) was completely reversed when a chelating group was present on the aldehyde backbone (although the chelating ability of the *t*-butyl dimethylsilyloxy group is questionable[566]).





	Enol		**A**	**B**
	E (D)/*Z* (D)/(H)	ds	*anti* (D)/syn (D)/(H)	*anti* (D)/syn (D)/(H)
R^1 = OMOM; R^2 = H	89/6/5	95/5	major (91/5/4)	minor (maj/min/ND)[(a)]
R^1 = H; R^2 = OMOM	85/10/5	7/93	minor (81/11/8)	major (74/18/8)

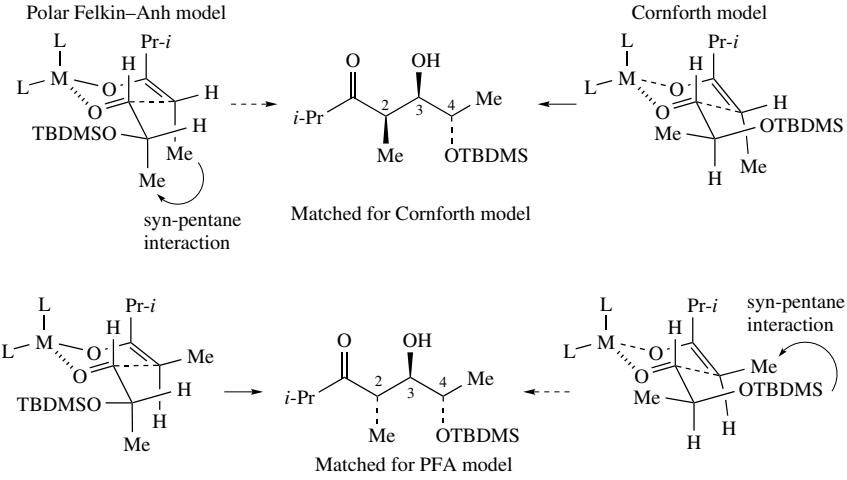
(a) qualitative or not determined due to tiny quantities of product

SCHEME 115. Chair-like transition states and product distribution for the aldol reaction of deuterium-labeled pinacolone lithium enolate with a 3-hetero-substituted chiral aldehyde[565]

	B	**C**
R = Ph	81%	19%
R = CH_2OBn	33%	67%
R = $CH_2OTBDMS$	21%	79%

SCHEME 116. Stereoface differentiation in chelated vs non-chelated model[76]

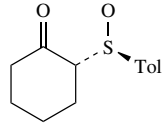
In the absence of chelation, comparison of the destabilizing *syn*-pentane interactions recently encouraged Evans and coworkers to use the Cornforth model to justify the exalted 3,4-*anti* selectivity observed for a series of chiral α-oxygenated aldehydes reacting with the Z(O) boron and lithium enolates of 2-methyl-3-pentanone (Scheme 117)[568]. Complementarily, the corresponding E(O) isomers showed, as expected, a striking difference in their 2,3-selectivities, while the 3,4 *anti*-selectivity was lowered in both cases: a finding inconsistent with the PFA model.



SCHEME 117. Comparative chair-like transition states using the polar Felkin–Anh and Cornforth models for Z(O)[568]

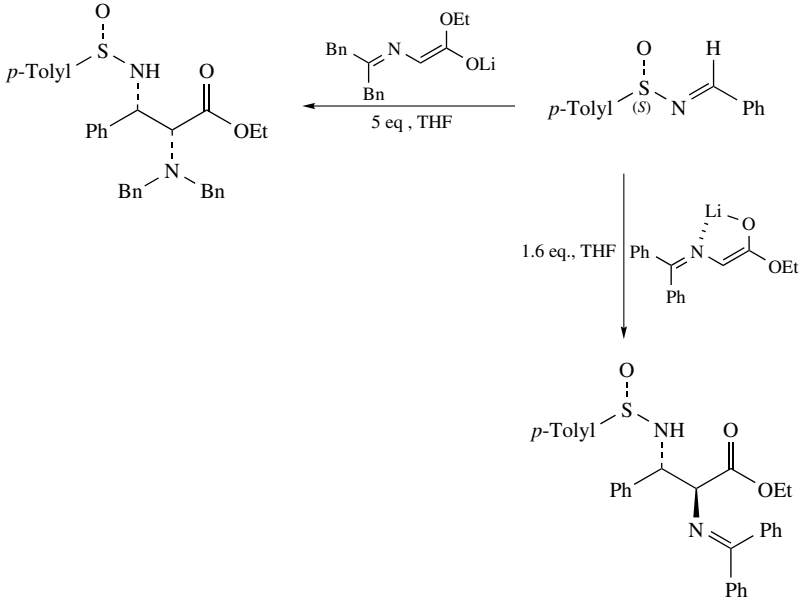
The stereoselective chelation-controlled aldol reaction of unsubstituted lithium ester enolates with (R_S)-2-(*p*-tolylsulfinyl) cyclohexanone **A** (Figure 16) led to a high enantioface differentiation (> 90:< 10), while the simple diastereoselection was rather low for prochiral enolates[567]. The role of the lithium cation acting as a template is here essential, since sodium, potassium, HMPA or even added $ZnCl_2$ resulted in decreased yield and selectivity.

Concerning imine derivatives, the addition of the non-chiral lithium enolates of glycinates onto (*S*)-*N*-(benzylidene)-*p*-toluenesulfinamide provide access to chiral, either *syn*- or *anti*-, alpha,beta-diaminophenylpropanoic acids in good overall yields (Scheme 118). The reaction is essentially directed by the nature of the amino-protecting groups via their E(O) non-chelated vs. Z(O) chelated enolates. It requires an excess of anion, relative to the enantiopure sulfimine, to go to completion[569]. The absolute configuration was determined by NMR spectroscopy on the corresponding imidazolidin-2-one derivatives.



(R_S) **A**

FIGURE 16. (R_S)-2-(*p*-tolylsulfinyl)-cyclohexanone **A**



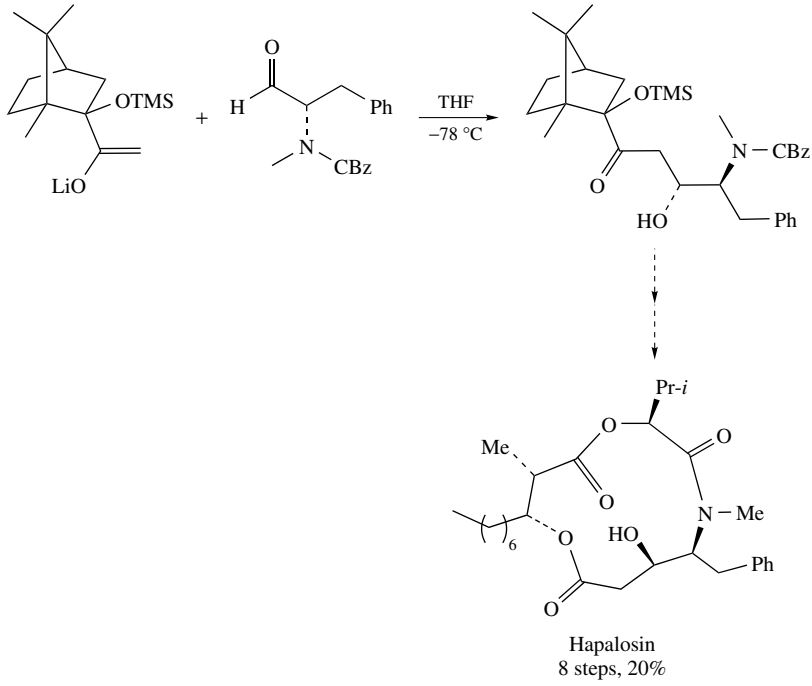
SCHEME 118. Reaction of (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide with glycine enolates at −78 °C[569]

iii. Double diastereoselection. So far, we have been concerned with the reactivity of relatively simple synthons and reagents with separate sources of chirality. The union of more complex homochiral fragments being required in the synthesis of natural products, the necessity to delineate a relationship between stereogenic centers on both substrates became obvious. The cumulative effects of two auxiliaries was first recognized and named 'double induction' by Horeau, Kagan and Vigneron[570], and a recent report on modern multiple stereochemistry aspects[571] completed Masamune's early review on double asymmetric synthesis[572].

The chiral camphor-masked acyllithium enolate already mentioned[561] was recently used by Palomo and coworkers to synthesize the twelve-membered cyclic depsipeptide Hapalosin[573]. In agreement with the preceding results, the aldol condensation takes place on the *Si*-face of the *N*,*N*-protected chiral α-aminoaldehydes, independently of the nature of the aldehyde, the chiral information of the camphor moiety overwhelming that of the aldehyde (Scheme 119).

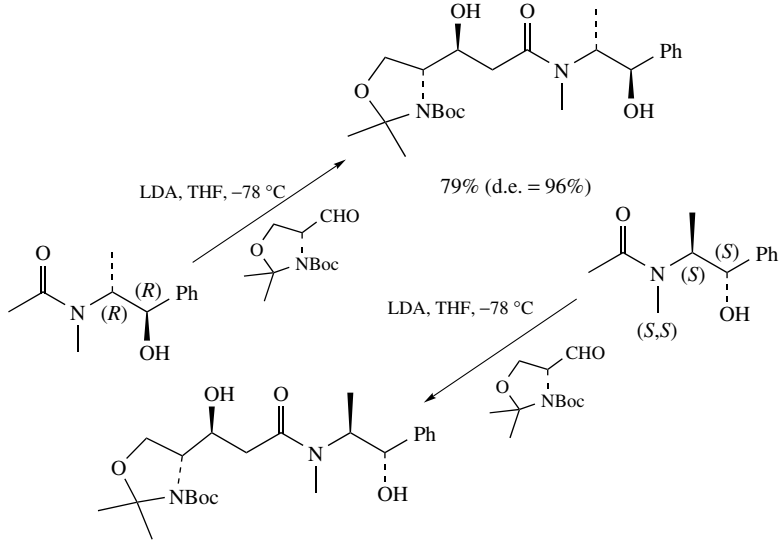
On the other hand, the condensation of Garner's aldehyde[574] with the non-chiral lithium enolate of diethylacetamide in non-chelating conditions occurs preferentially on the *Si*-face with a moderate 37% d.e. The same reaction using the enolate of (*R*,*R*)- or (*S*,*S*)-pseudoephedrine acetamides resulted in identical *anti* aldol adducts, but with an amplification of the face recognition of the aldehyde for the matched (*R*,*R*)-pseudoephedrine (d.e. = 96%). On the other hand, the mismatched (*S*,*S*)-pseudoephedrine gave only 12% d.e. (Scheme 120)[575].

The same double stereoselection was observed by Young and coworkers when both enantiomers of the glyceraldehyde acetonide were reacted with the lithium enolate of pyroglutamic esters. The (*R*)-enantiomer gave only the (*S*,*S*) adduct while the (*S*)-enantiomer gave a mixture of diastereomers (Scheme 121)[576].



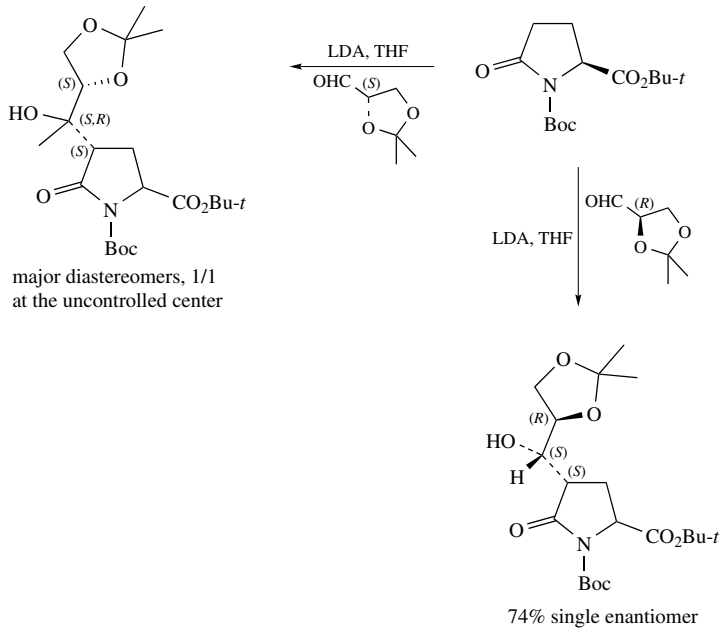
Hapalosin
8 steps, 20%

SCHEME 119. Chiral enolate directing aldol condensation synthesis of Hapalosin[573]



61% (d.e. = 12%)

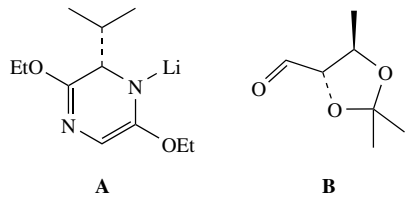
SCHEME 120. Diastereoselective addition of pseudoephedrine acetamide lithium enolates on (*R*)-Garner's aldehyde[575]



SCHEME 121. Double stereoselection in aldol reaction of pyroglutamic ester[576]

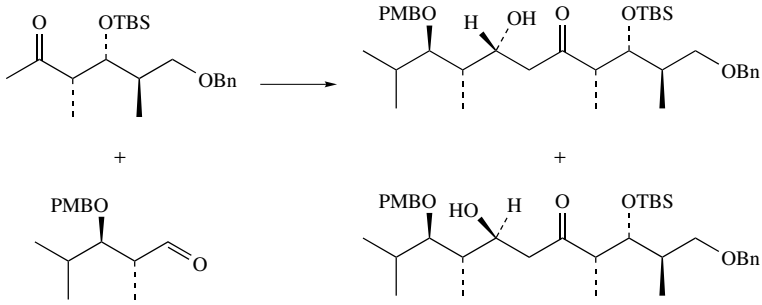
The influence of a β-methyl substituent on the aldehyde *trans* to the carbonyl group was recently found by computational study to reinforce the *syn*−*syn* stereoselection in the aldol reaction between Schöllkopf's bis-lactim ether azaenolate **A** and aldehyde **B** (Figure 17)[302].

In a more complex scenario, the β-substituents were also found to participate in partially matched or mismatched reactions[577]. Examples of double induction pave the route of polypropionate and polyketide synthesis and it was emphasized that the relative influence of the enolate or aldehyde component may be enhanced, depending on the coordinating metal employed in the double stereodifferentiating aldol reaction. Thus, it was found that, in spite of their modest *syn*/*anti* selectivity, lithium enolates are effective in double stereodifferentiating aldol reaction[578]. In the matched and partially matched cases, lithium enolate face selectivity is opposite to that which is found for their boron or titanium counterparts. This is perfectly illustrated in a recent work by Roush and coworkers reporting a partial synthesis of Bafilomycin A_1 (Scheme 122)[579].



A **B**

FIGURE 17. Schöllkopf's bis-Lactim etherlithiumazaenolate **A** and 2,2,4-trimethyl-3 formyl-1,3-dioxolane **B**



Conditions[(a)]	Yield (%)	Ratio 3,4(*syn*/*anti*)
LiHMDS, THF, –78 °C	90	10 : 1
LiHMDS, THF-HMPA, –78 °C	66	1 : 1.2
NaHMDS, THF, –78 °C	51	1 : 1
Bu_2BOTf, NEt_3, CH_2Cl_2, –40 °C	65	1.2 : 1
(–)-Ipc_2BOTf, NEt_3, CH_2Cl_2, –40 °C	72	1 : 1

[(a)] PMB = p-methoxyphenyl; Ipc = isopinocampheyl

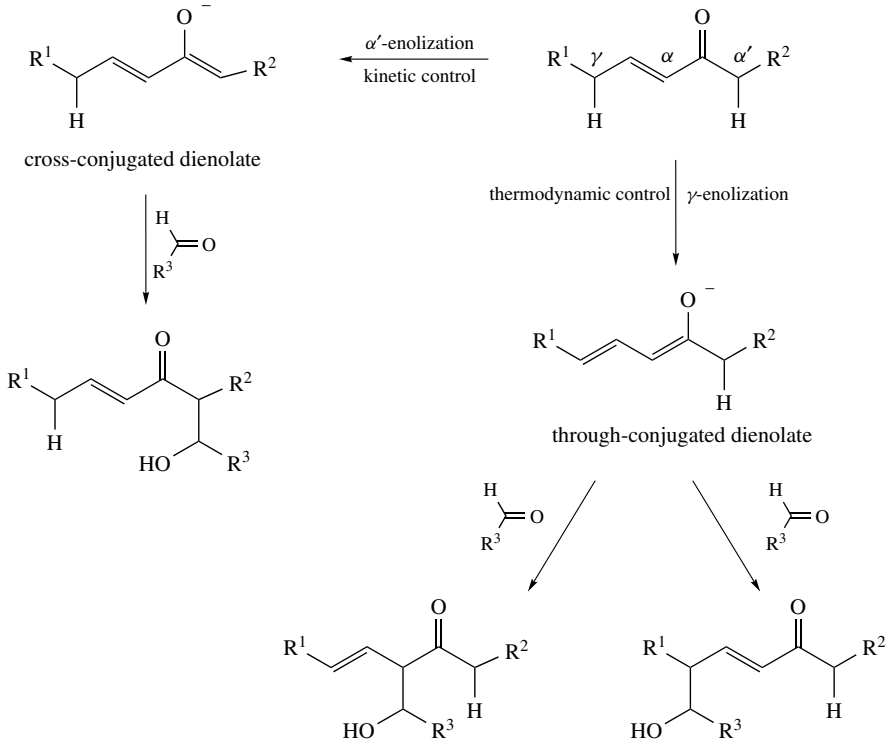
SCHEME 122. Double stereoselection as a function of the metal[579]

3. 'Complex' aldol reactions

a. Vinylogous aldol reaction. Despite their synthetic potentialities, α,β-unsaturated carbonyl compounds have been little employed as dienolate precursors, probably because of the superimposed complexity of the regio- and stereoselectivities to the inherent intricacy of the aldol condensation (Scheme 123). Under kinetic conditions (stoichiometric amounts of lithium base, THF, low temperature), the lithium cross-conjugated dienolate is usually obtained and the resulting α'-aldol is the normal product. Alternatively, the thermodynamic extended dienolate is rather difficult to obtain and its alkylation proceeds at either the α- or the γ-carbon atom, depending on the structure and reaction conditions.

For other stabilized vinylogous carbanions derived from aldehydes or esters and amides, only the α- vs. γ-alkylation is to be considered, with the α-alkylation being favored under kinetic conditions and the γ-alkylation under thermodynamic and equilibrating conditions[580]. Lately, Yamamoto and coworkers proposed a cunning and elegant solution for the γ-alkylation of unsaturated aldehydes, ketones and esters, based on a provisional protection with a bowl-shaped Lewis acid host, allowing a regioselective deprotonation and condensation[581,582]. This conceptually new strategy, using ATPH [aluminum-*tris*-(2,6-diphenyl phenoxide)] ensures the protection at the carbon α to the carbonyl group of the nucleophile, with the consequence of an exclusive attack at the γ-position. Alternatively[583], it also allows the possibility to react enolizable electrophilic carbonyl compounds. Finally, the nucleophilic addition to unsaturated carbonyl electrophiles takes place exclusively α to the carbonyl[584–586]. Conversely, Bellassoued and coworkers recently reported the exclusive α-alkylation of α,β-unsaturated trimethylsilyl ester lithium enolates with aldehydes and ketones[587].

Particular cases of regiodirected reactions involving unsaturated enolate are related to the partial reduction of electron-deficient pyrroles, furans or benzenoids by solvated electrons[588]. Thus, the *Z*(O) enolates (probably stabilized by chelation) generated under

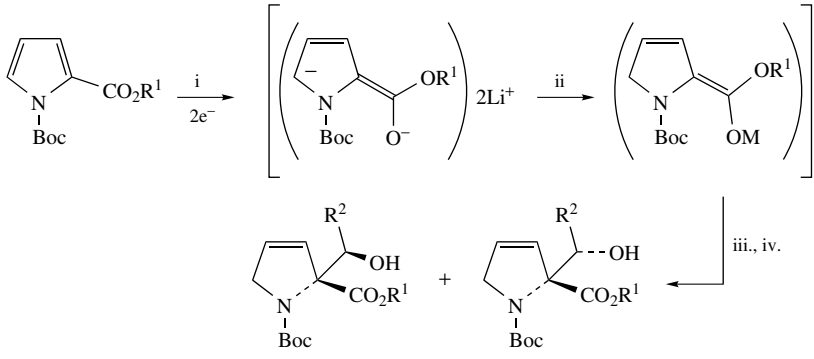


SCHEME 123. Alternative pathways for the aldol condensation of the enolates of an α,β-unsaturated ketone[580]

ammonia-free conditions undergo an aldol reaction with aromatic and aliphatic aldehydes with a preference for the *anti* isomer, depending on the structure of R^3 on the aldehyde. The selectivity can be dramatically increased by transmetallation using $MgBr_2$ (Scheme 124)[589].

b. Tandem reactions including an aldol reaction. The aldol-Titshchenko reaction, featuring an aldol reaction followed by the *in situ* reduction of the carbonyl group by a second molecule of an aromatic aldehyde, is likely to conduct directly to a 1,3-diol in a stereocontrolled manner[590].

Interestingly, the *in situ* formation of suitably functionalized aldols can be the departure to rearranged products such as lactones, epoxides or substituted carbocycles. It has been reported lately that the *syn* vs. *anti* ratio obtained in the aldol condensation of lithium enolate derived from vinylogous urethanes is definitely related to the structure of the amine, although there is no remarkable difference in their X-ray and NMR data[239]. Taking advantage of these results, Schlessinger and coworkers developed a synthetic methodology, which provides efficiently, and with very high diastereoselectivities, useful γ-alkoxy-δ-lactone synthons using substituted prolinol ethers[591]. These results are best explained by the pyramidalization of the nitrogen and the exclusive γ-attack of the aldehyde (*ul* topicity) antiperiplanar to the N−Li bond.

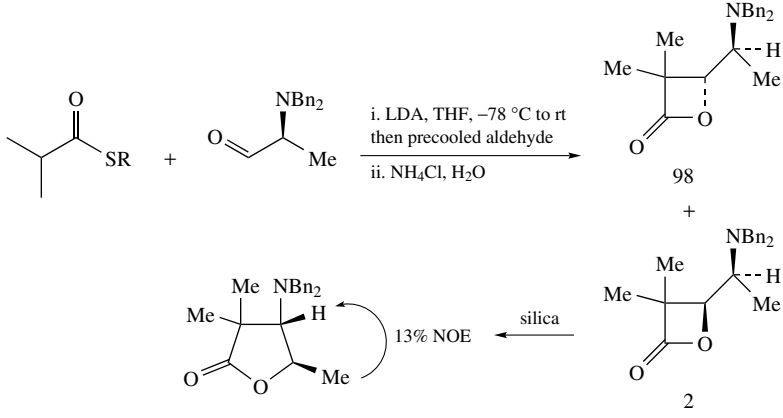


i. LDBB, BMEA, THF, −78 °C
ii. $Br(CH_2)_2Br$
iii. $MgBr_2$ (if any)
iv. R^2CHO then NH_4Cl

R^4	M = Li (MgBr)	
	anti	*syn*
Ph	1.8 (1.5)	1
Me	1.8 (7.6)	1
i-Pr	8 (20)	1
t-Bu	5.3 (7.4)	1

SCHEME 124. Reductive aldol reaction on electrodeficient furans[588]. BMEA = bis(methoxyethyl) amine

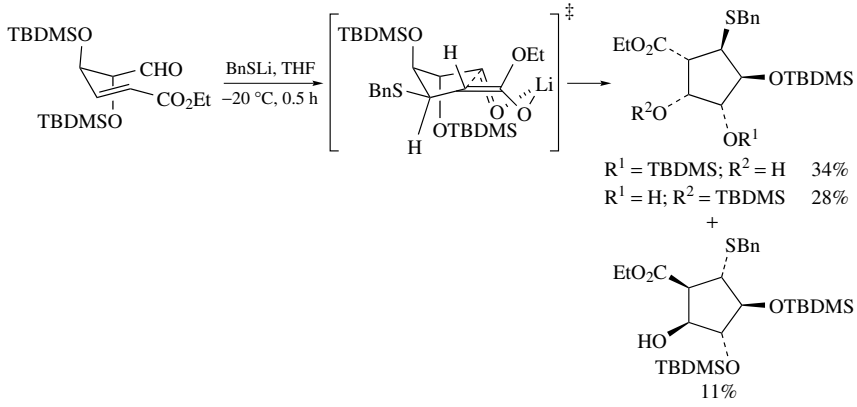
Danheiser and coworkers described a convenient preparation of oxetanones via the condensation of thioester lithium enolates with carbonyl compounds and subsequent lactonization under proper conditions[592]. The asymmetric version was reported later[593], the configuration of the new chiral center being established by a stereospecific dyotropic rearrangement to the γ-butyrolactone (Scheme 125)[594].



SCHEME 125. Stereocontrolled aldol reaction and lactone formation[594]

A remarkable example of tandem conjugate addition–aldol reaction has been recently reported by Tomioka and coworkers. The transient lithium enolate, generated by 1,4-addition of benzyl lithium thiolate onto the corresponding α,β-unsaturated ester[182,595], is followed by an intramolecular aldol tandem cyclization, resulting in a five-membered

carbocycle precursor of Neplanocin, a carbonucleoside with S-adenosylhomocystein hydrolase inhibitory activity (Scheme 126)[177]. The stereochemistry of the addition of the thiol is controlled either by the structure of the ester or by the structure of the added thiol[176].



SCHEME 126. Stereoselective Michael–aldol tandem cyclization reaction[177]

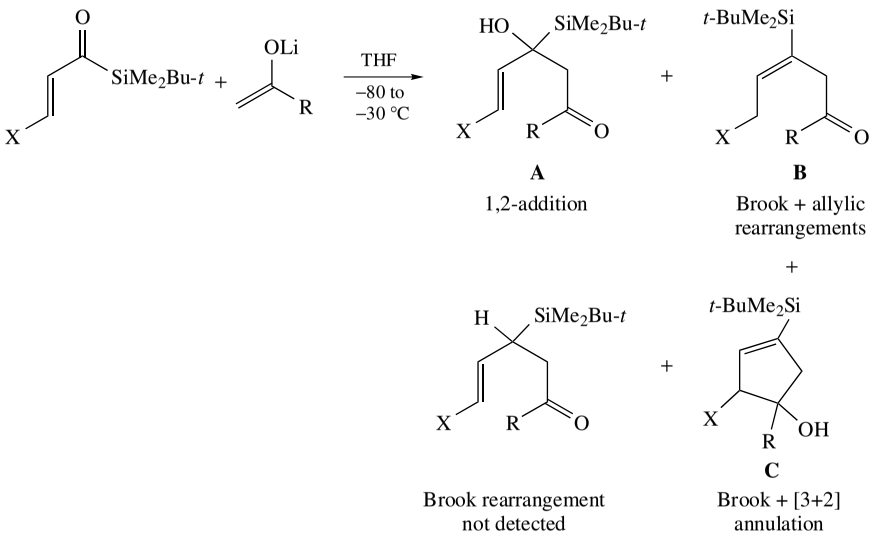
Similarly, the 1,2-addition of a lithium enolate onto β-heterosubstituted α-unsaturated acylsilanes, recently described by Takeda and coworkers[596], provides the basis of a [3 + 2] annulation giving **C** based on a Brook rearrangement. Alternatively, the product corresponding to the Brook rearrangement was not detected but the rearranged allylic product **B** was found. The distribution of the products resulting from the simple addition of lithium enolates to acylsilanes is highly dependent on the temperature and on the nature of the substituents (Scheme 127)[597].

Likewise, the application of this methodology to α,β-unsaturated methyl ketones using (*E*)-3-trimethylsilyl-1-[dimethyl-(1,1-dimethylethyl)]silyl-2-propen-1-one led to the formation of seven-membered rings by a *cis* stereoselective [3 + 4] annulation even in the case of aromatic methyl ketones[598]. Rationalization of the stereochemistry involves a multi-step mechanism implicating a tandem 1,2-addition and the concerted anionic oxy-Cope rearrangement of the *cis*-1,2-divinylcyclopropanediolate resulting from the intramolecular 1,3-cyclization of the anion formed by the Brook rearrangement (Scheme 128)[599].

Finally, it was reported that dianions derived from dicarbonyl compounds react in a straightforward manner with dielectrophiles derived from oxalic acids, yielding interesting γ-alkylidene butenolides or their aza counterparts. However, hydrolysis conditions are critical in the case of the aza derivatives[600,601].

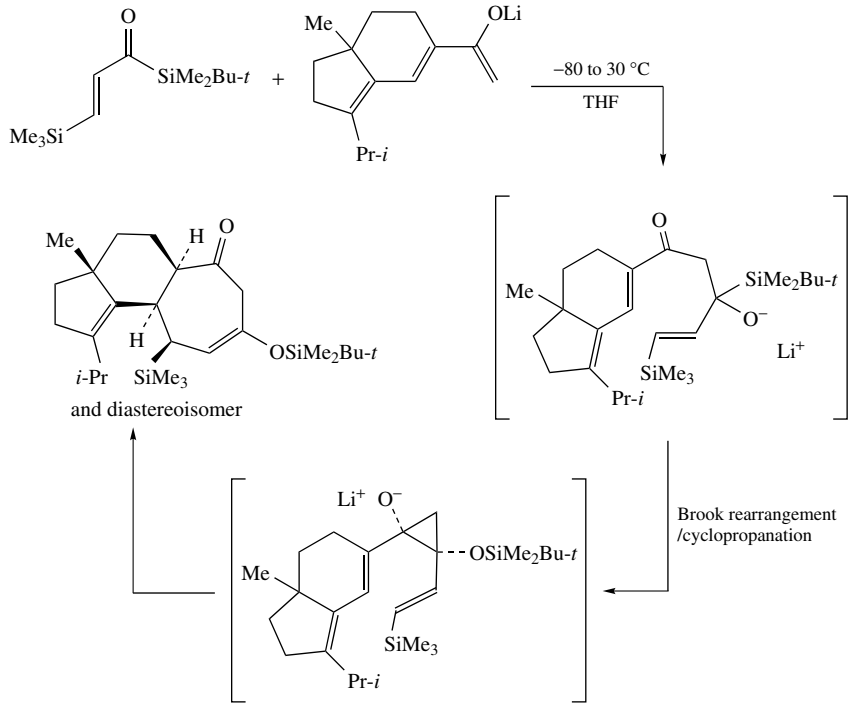
4. Enantioselective aldol reaction

Because the aldol reaction is such a cornerstone in the C–C bond formation, its enantioselective version has been a major focus in organic chemistry during the last decades of the twentieth century. Many successful results were obtained resorting to the combined handling of a chiral Lewis acid and silyl enol ethers. In contrast, relatively little attention has been paid to the lithium enolates[602]. Actually, upgrading the classical aldol route to its enantioselective version is a challenging goal. It requires a quasi-perfect control of the reaction between two highly reactive partners that are the lithium enolate on the one



X	R	**A**	**B**	**C**
$SiMe_3$ (*Z*)	*i*-Pr	-	21%	51%
$SiMe_3$ (*E*)	*i*-Pr	-	63%	14%
SPh (*Z*/*E*)	*i*-Pr	-	-	74%
$SiMe_3$ (*Z*)	OBu-*t*	54–68%	32–46%	-
SPh (*E*)	OBu-*t*	0–50%	100–50%	-
Me (*E*)	OBu-*t*	100%	-	-

SCHEME 127. Product distribution for the nucleophilic addition of lithium enolates to acylsilanes[597]

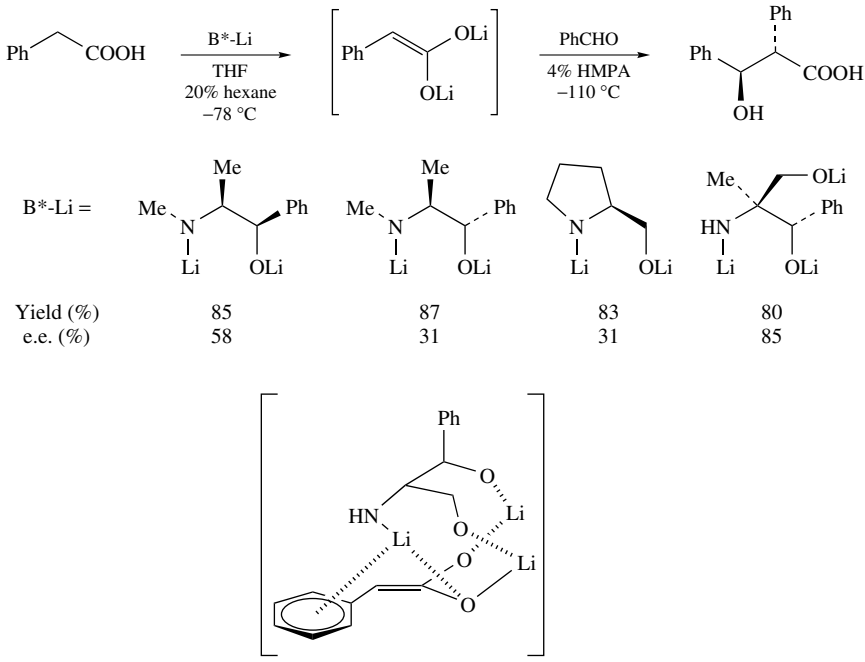


SCHEME 128. Construction of the tricyclic core of cyathins by a Brook mediated [3 + 4] annulation[599]

hand, and the aldehyde on the other. The problem becomes somewhat simpler with milder electrophiles, such as imines. Anyway, tight non-covalent interactions between the chiral moiety and the partners are the key to success. The main routes explored to date are based on the chelation of the lithium cation or on the creation of hydrogen bonding with the anionic moiety.

a. Condensation of enolates with aldehydes and ketones. In the first review on this topic, Seebach and coworkers gave a fine overview on the applications of enolates in the presence of chiral amines, amides or alcoholates to the aldol and Michael additions[49]. The data presented in their paper suggest that lithium amides are the best chiral inductors for the aldol condensation, particularly when used in excess (3 equivalents). The effect of these additives on the relative and absolute control of the stereogenic centers is discussed in terms of the formation of mixed aggregates with the enolate tetramers and dimers. In this context, the early results obtained by Mulzer and coworkers deserve special comment. These authors found that the deprotonation of phenylacetic acid by two equivalents of various chiral lithium alkoxide amides leads to a dianion that can be reacted with benzaldehyde. In well-defined conditions (THF/hexane/HMPA mixture at $-110\,^{\circ}C$), the expected β-hydroxyacid was recovered in high yields and e.e. values up to 85% resorting to a dialkoxide lithium amide[603]. A model describing the amide–enolate interaction was suggested to justify the observed results (Scheme 129).

Simultaneously, Koga and coworkers explored the effects of various chiral lithium amides on the d.e. and/or e.e. of the reaction between a set of enolates and selected



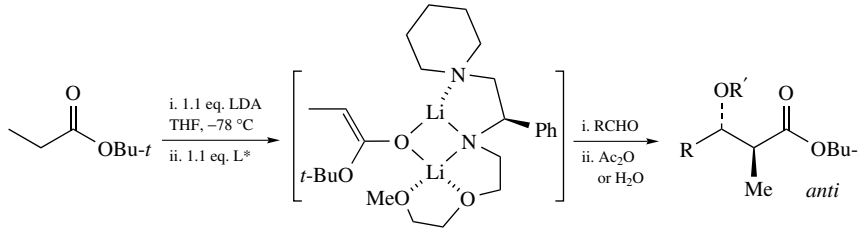
SCHEME 129. Enantioselective condensation of phenylacetic acid lithium enolate with benzaldehyde and the proposed transition state model[603]

aldehydes. Simply chelated lithium amides were employed with the lithium enolates of 2,2-dimethyl-3-pentanone[604] or of acetophenone and pinacolone[605] while tri- and tetradentate lithium amides were preferred for the enolate of *t*-butyl propionate[606]. In the latter case, best results were obtained resorting to a tetradentate lithium amide in which the coordinating sites are one ethylene unit apart. Remarkably high enantioselectivities were obtained for the major *anti* aldol products (Scheme 130), generally isolated after acetylation.

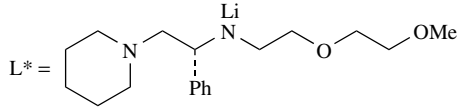
Using a chiral lithium amide to generate an ester enolate does not interfere with the usual diastereocontrol afforded by the ester group modulation. Thus, condensing enolates of various bulky esters on model aldehydes led to the *syn* or *anti* aldols in relatively high enantioselectivities[607]. Note that an autoinductive effect can operate due to the *in situ* formation of mixed aggregates between the enolate and the alcoholate resulting from the addition. This phenomenon has been clearly demonstrated in the reaction between ethyl acetate lithium enolate and benzaldehyde[608].

Chiral di- and tetraethers were also employed successfully in the aldol reaction. The best results were obtained with imines (*vide infra*), albeit significant e.e. were also reported reacting the lithium enolates of BHA esters with benzaldehyde[609]. An example of (−)-sparteine-mediated asymmetric aldolization between a protected glycine lithium enolate and a set of aldehydes was also reported not too long ago (Scheme 131). Medium to good yields and e.e. values were measured[610].

Catalytic versions of the asymmetric aldol reaction using simple lithium enolates and substoichiometric amounts of a chiral catalyst are rare[611]. The bimetallic system proposed by Shibasaki and coworkers deserve to be mentioned at this point. The combination of a

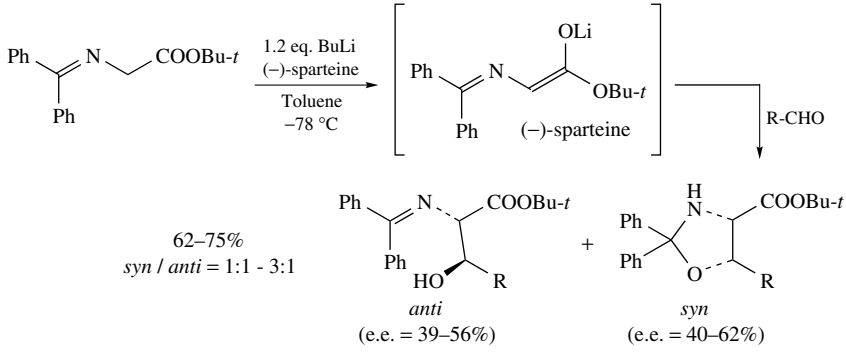


L* =



R	R′	Yield (%)	e.e. (%)
i-Pr	Ac	76	94
t-Bu	H	66	96
c-Hex	Ac	83	93
Ph	Ac	80	94

SCHEME 130. Enantioselective condensation of *t*-butyl propionate lithium enolate with various aldehydes[606]

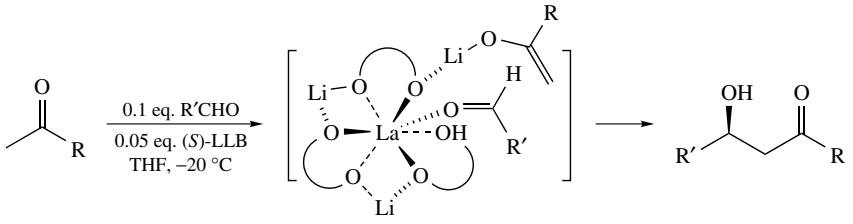


SCHEME 131. Enantioselective condensation of a protected glycine lithium enolate on various aldehydes in presence of sparteine (Ref. 609)

Brönsted base [the lithium binaphthoxides] and of a Lewis acid [La(III)] sitting side by side at the heart of the LLB multifunctional catalyst evokes the active site of aldolases and probably explains why simple unmodified ketones and primary aldehydes can be used[504]. The examples in Scheme 132 illustrate the performance of this system[612].

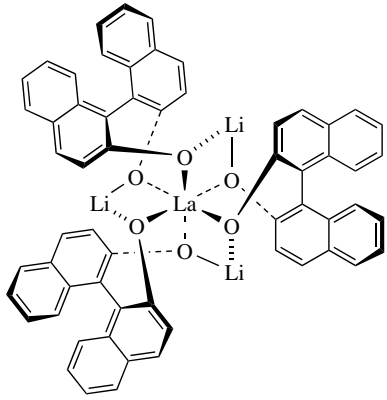
The sluggishness of the above reaction (in the examples of Scheme 132 the reaction time extends from 90 to 270 h), despite the large excess of ketone employed, constitutes a drawback to this method. Adding one equivalent of a base (such as KHMDS or KOH) to LLB greatly enhances the efficiency of the catalyst, the resulting tight complex being more efficient chemically and stereochemically speaking. Thus, the condensation of 2-hydroxyacetophenone on a series of primary aldehydes led, in the presence of a small amount such as 3% catalyst, to the expected diols, mainly as their *syn* diastereomer in very high e.e. values[613]. However, the intermediate generated in these conditions is likely to be a potassium enolate and therefore falls outside the scope of this review.

Ketones are rarely used as electrophiles in the enantioselective aldolization while they find application to enantioselective olefination reactions such as the Horner–Wadsworth–Emmons or the Peterson reaction. For instance, the deprotonation of an achiral phosphonoacetate by a set of chiral 2-aminoalkoxides led to the corresponding enolate that



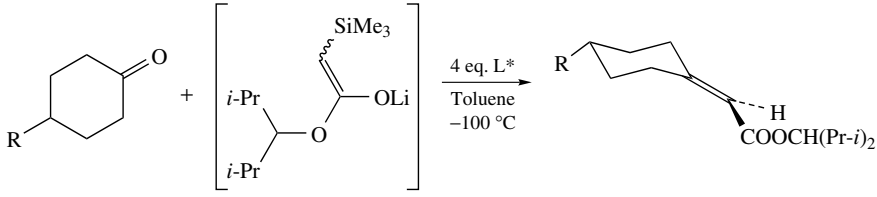
R	R′	Yield (%)	e.e. (%)
t-Bu	Ph	81	91
c-Hex	Ph	72	44
t-Bu	Me	53	73

(S)-LLB =

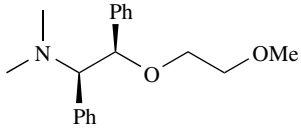


SCHEME 132. Substoichiometric catalytic version of the enantioselective aldol reaction using LLB[612]

provided, after condensation with 4-*t*-butylcyclohexanone, the expected chiral cyclohexylidene derivative in very good yields and e.e. values up to 52%[614]. Another representative example is the addition of 3-substituted or 4,5-disubstituted *meso*-cyclohexanones to the enolate derived from an α-trimethylsilyl acetate in the presence of a chiral triether. This reaction led to the expected axially chiral olefins in good e.e. values in toluene (Scheme 133)[615]. A negative influence of the lithium silanoxide released in the medium was noted during the course of this study.



L* =

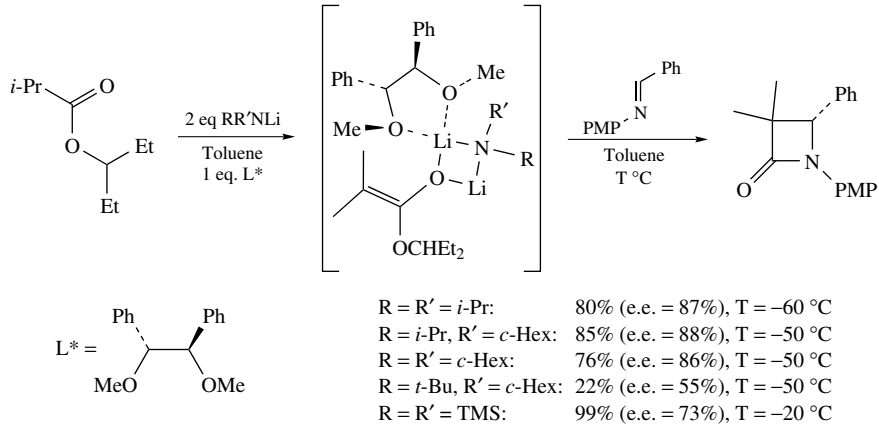


R	Yield (%)	e.e. (%)
t-Bu	95	85 (*R*)
Ph	95	76 (*R*)
Me	95	70 (*R*)

SCHEME 133. Enantioselective Peterson olefination in the presence of a chiral amino diether[615]

b. Condensation of enolates with aldimines. Imines are much less reactive than carbonyl compounds toward organolithium reagents[616,617]. This dimmed electrophilicity is an asset when it comes to the enantiocontrol of the newly created asymmetric center by external chiral ligands. Tomioka and coworkers took advantage of these characteristics to condense a set of complexes between lithium enolates of esters and various chiral ligands on a variety of imines. This reaction furnishes directly the expected β-lactams in high e.e. in several cases.

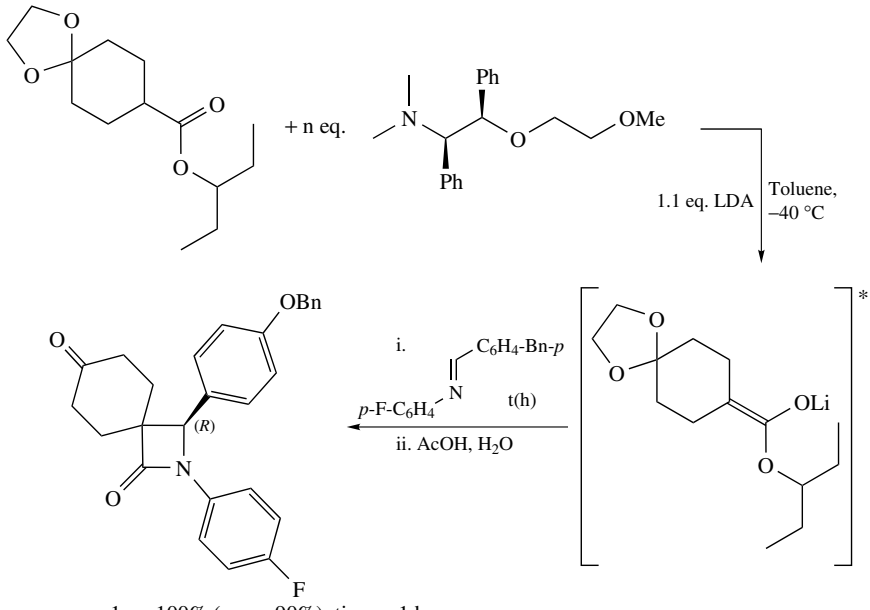
The original system considered by this group involved the lithium enolate and a chiral diether. The results suggest that the presence of an excess of the achiral lithium amide used to deprotonate the ester improves the induction level (Scheme 134)[618]. Remarkably, employing substoichiometric amounts (20 mol%) of the chiral ligand led to a marginal decrease in the e.e. value. The authors proposed that the formation of an intermediate ternary complex between the enolate, the excess lithium amide and the chiral diether could be responsible for the observed enantiomeric excesses.



SCHEME 134. Enantioselective condensation of a lithium ester enolate on an imine in the presence of a chiral diether[618]

Soon after, the exact structure of the ester was shown to exert a dramatic influence on the e.e. of this reaction[619]. The best results were obtained using extremely cumbersome esters such as 2,4-dimethylpentan-3-oyl isobutyrate and an excess of lithium isopropylcyclohexylamide (LICA) in toluene at $-45\,^{\circ}C$. The influence of the structure of the chiral ligand on the e.e. was the object of a simultaneous investigation[620]. An amino diether in which the heteroelements are two carbons apart turned out to give the highest e.e. values, even in catalytic amounts and for a relatively large set of imines. A synthetic application of this methodology, published at the same time, concerned the cholesterol absorption inhibitor Sch 58053 (Scheme 135)[621].

Diamino ethers can also trigger very good inductions, particularly if one of the amino groups is secondary. In this case, the lithium amide formed avoids the use of an excess of base, a binary complex between the enolate and the chiral lithium amide being supposed to arise and be at the origin of the induction[622]. More recently, the same group has shown that replacing the diether ligand by a chiral bisoxazoline (box) in stoichiometric[623], or even catalytic[624], amounts affords comparable e.e. values with comparable imines. A binary complex would operate in these cases.



SCHEME 135. Formal synthesis of cholesterol absorption inhibitor Sch 58053[621]

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CHAPTER 9

Chemistry of ketone dilithio dianions

ILHYONG RYU

Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599–8531, Japan
Fax: +81 72 254 9695; e-mail: ryu@c.s.osakafu-u.ac.jp

and

HIROYUKI NAKAHIRA

Chemistry Research Laboratories, Research Division, Sumitomo Pharmaceuticals, Osaka 554-0022, Japan
Fax: +81 66 466 5483; e-mail: nakahira@sumitomopharm.co.jp

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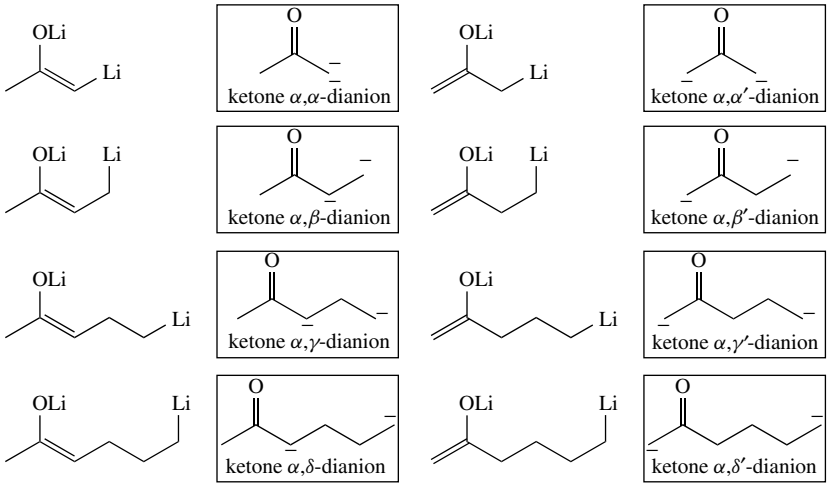
I. INTRODUCTION

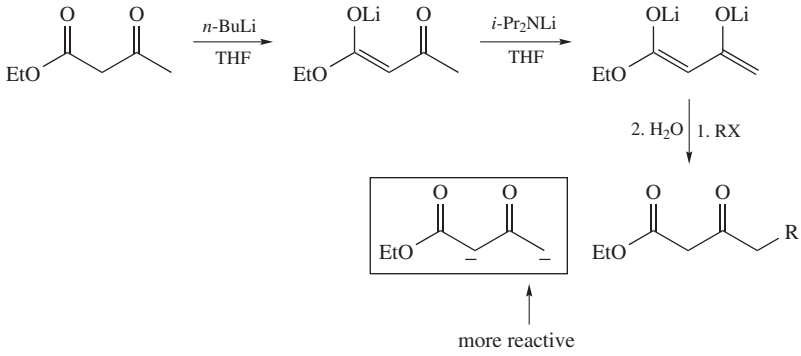
One of the advantages of organolithium chemistry is the relatively facile generation and control of dilithio dianion species[1,2]. This is in distinct contrast with biradical species and dication species, in which discrete intermediates are controlled with great difficulty in synthetic reactions. Because hydrogens, when attached to carbons α to the carbonyl group of ketones, are generally more acidic than those attached to the other carbons, the dilithium dianionic species of ketones inherently have lithium enolate structures containing an additional carbon–lithium center. This chapter reviews the method of generating and the reactivity of dilithio species of ketones. For simplicity, the terminology used throughout this chapter to define the dilithio species will be ketone α,(n)-dianions. Examples are shown in Scheme 1.



SCHEME 1

Looking back on the history of ketone dianion chemistry, one soon notices that dianion species, derived from β-keto esters, have been in continuous steady use in organic synthesis[3,4], as shown in Scheme 2. Thus, ethyl acetoacetate can be converted to the corresponding ketone α,α'-dianion via consecutive proton abstraction reactions. The resulting dienolate anion reacts with a variety of alkyl halides to give products, resulting from exclusive attack at the terminal enolate anions.

In 1976, Dimmel and coworkers reported the reaction of phenyl allyl ether and excess amounts of n-BuLi in DME[5]. After quenching the reaction mixture with methyl iodide,



SCHEME 2

they found that α-methylbutyrophenone was formed in the reaction. This fact strongly suggested the formation of the α,β-dianion of propiophenone in this reaction system. It is proposed that the initially formed 1-phenoxyallyllithium undergoes a 1,2-Wittig rearrangement, resulting in the formation of 1-lithioxy-1-phenylpropene. The subsequent proton abstraction of the lithioxypropene by *n*-BuLi then takes place, leading to the formation of the dianion. Unfortunately, the system was too complex to permit the efficient generation of the dianion. In 1977, Trost and Latimer reported on the clean generation of a ketone α,β-dianion, which involved the dual abstraction of protons from indanone by two equivalents of LDA[6].

The year 1980 was very fruitful in ketone dianion chemistry. Indeed, ketone α,α'-dianions which do not possess stabilizing substituents were reported by Harris and Hubbard[7]. In the same year, the first example of ketone α,α-dianions was reported by Kowalski and coworkers[8], and the first example of ketone α,β'-dianions was reported by Goswami[9]. In the late 1980s, Cohen and coworkers investigated ketone α,β'-dianions having a cyclopropyllithium moiety[10]. In their work, ketone α,γ-dianions having phenylsulfur groups at the γ-position were also treated as carbene precursors.

The simplest dilithio species of ketone α,β-dianions appeared in 1991 and was reported by Ryu, Sonoda and their coworkers[11]. They found that readily accessible β-tributylstannyl ketones and β-dichlorobutylstannyl ketones serve nicely as precursors for dianions[12, 13]. Recent work demonstrated that the vinylogous extension of ketone α,β-dianions can lead to the generation of ketone α,δ-dianions[14].

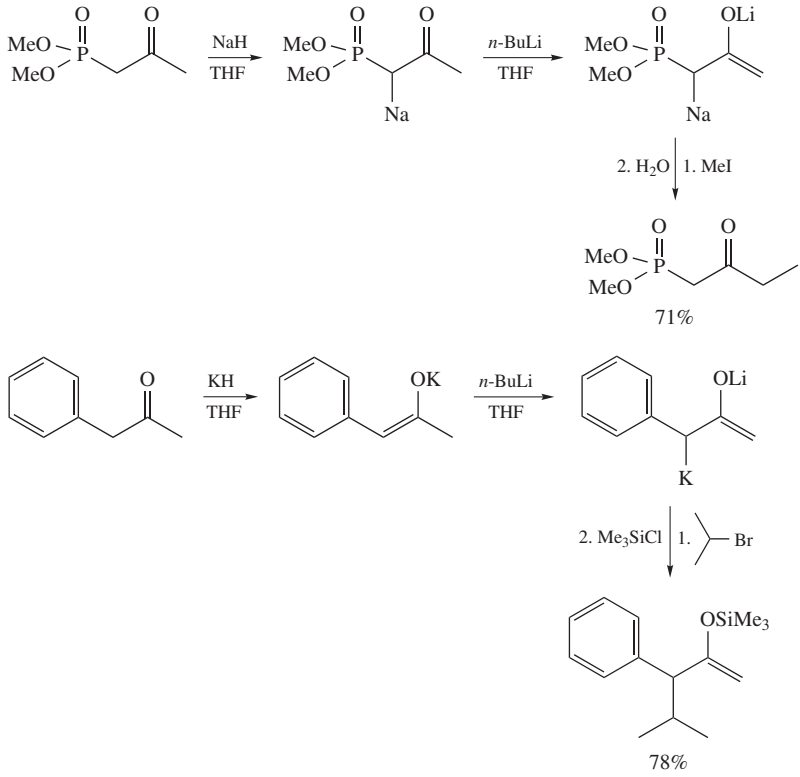
The aim of this chapter is to review the current state of the art of ketone dianion chemistry. Concerning the reactivity of ketone dianions toward electrophiles, the enolate portion generally exhibits a lower reactivity than the carbanion. This is important from a synthetic point of view, since selective alkylation at the carbanion center leads to the formation of lithium enolates, for which a tremendous number of useful synthetic transformations are now available[15, 16]. Thus, all ketone dilithium dianions have the potential to serve as a unique platform for lithium enolates. In the following second section of this chapter, methods for the generation of ketone dilithio dianions are discussed with a minimum of examples of reactions and, in the third section, synthetic reactions using ketone dianions are described with numerous examples. Because of the closely related propensity, ketone dianions containing some other cations, such as potassium ion or sodium ions, are also dealt with in some cases and, in the reaction part, C−C bond-forming reactions via transmetallation into copper and zinc species are also given.

II. METHODS FOR THE GENERATION OF KETONE DILITHIO DIANIONS

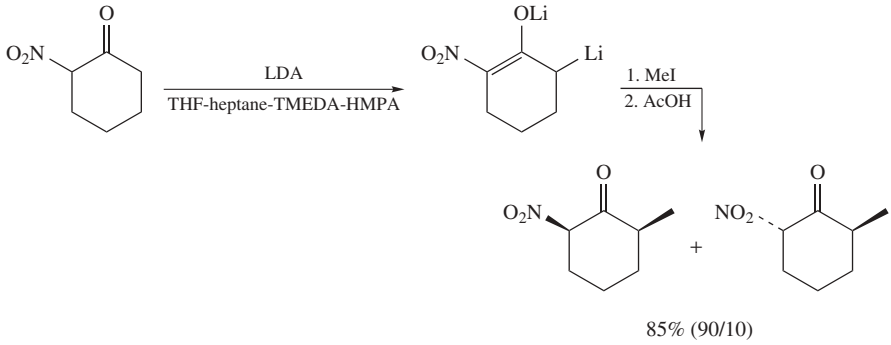
A. Ketone α,α′-Dianions

Grieco and Pogonowski reported on the generation of ketone α,α'-dianions derived from β-ketophosphonate esters by successive treatment with NaH and *n*-BuLi (Scheme 3, first equation)[17]. The dianion underwent preferential alkylation at the terminal position. Trimitsis and coworkers reported the generation of an α,α'-dianion from benzyl methyl ketone (Scheme 3, second equation)[18]. Potassium hydride was used for the proton-abstraction at the benzylic position. The second deprotonation of the resulting enolate was carried out by using *n*-BuLi. In the example given in the second equation, the reaction of the ketone α,α'-dianion with isopropyl bromide took place at the benzylic position to give a terminal enolate anion, which was then quenched by trimethylsilyl chloride (TMSCl) to give the enol silyl ether without conjugation with the benzene ring. The third equation of Scheme 3 demonstrates that α-nitro-substituted dianion can be generated from the corresponding α-nitro ketones by dual proton-abstraction with two equivalents of LDA. Alkylation took place selectively at the α'-position[19].

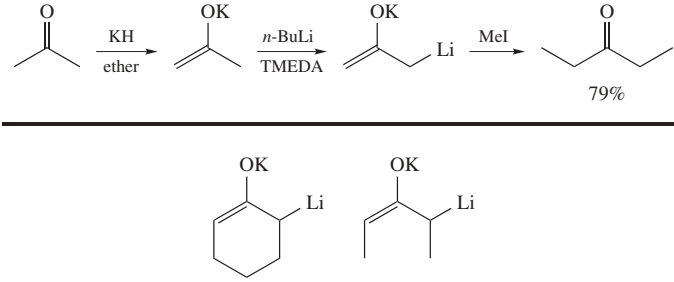
Similar conditions to the second example (Scheme 3) but with a different set of solvents (ether and then TMEDA) can also be used for the generation of ketone α,α'-dianions



SCHEME 3



SCHEME 3. (*continued*)



SCHEME 4

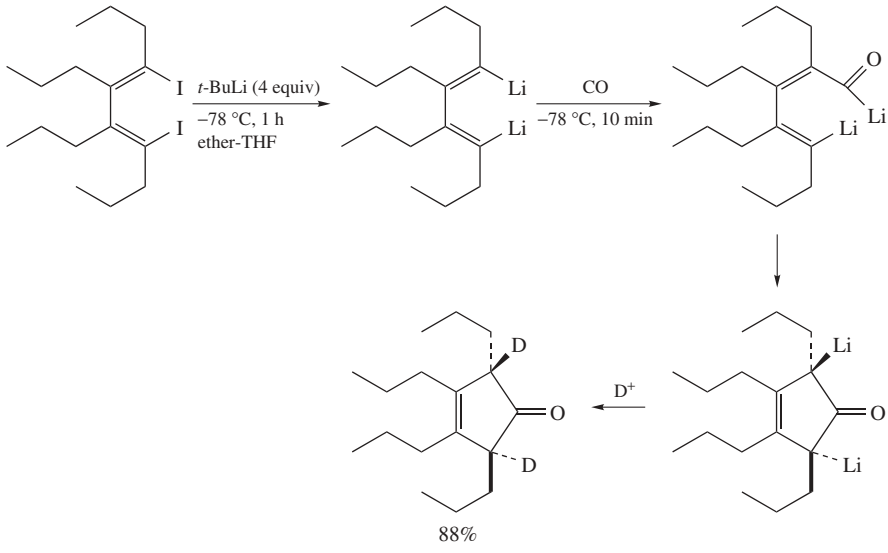
of ordinary aliphatic ketones. Using this procedure, ketone α,α'-dianions of acetone, cyclohexanone and 3-pentanone (Scheme 4) can be generated efficiently[7].

A unique carbonylation method for generating the α,α'-dianion of a 3-cyclopentenone was reported by Xi and coworkers[20]. The 1,4-dilithio-1,3-dienes are generated in situ from the diiodo compounds and 4 equiv of *t*-BuLi. The reaction of 1,4-dilithio-1,3-dienes with carbon monoxide gives an α,α'-dianion having a cyclopentene structure (Scheme 5). The cyclization step may occur by nucleophilic attack of the vinyllithium at the carbonyl group of the acyllithium, although the actual position of the lithium atoms in the resulting dianions has not been elucidated.

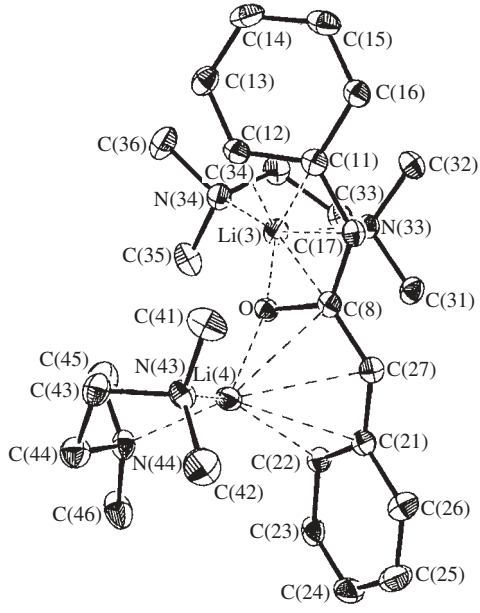
The X-ray structure of a monomeric 1,3-dilithiodibenzyl ketone complex with two molecules of TMEDA is reported to adopt an *exo*, *exo* orientation (Scheme 6)[21]. The structure can be regarded as two fused enolate units with a common C−O bond. It should be also noted that the NMR data for the dianion in THF indicate that the dianion exists as a 65:35 mixture of *exo*, *endo*- and *exo*, *exo*-isomers.

B. Ketone α,α-Dianions

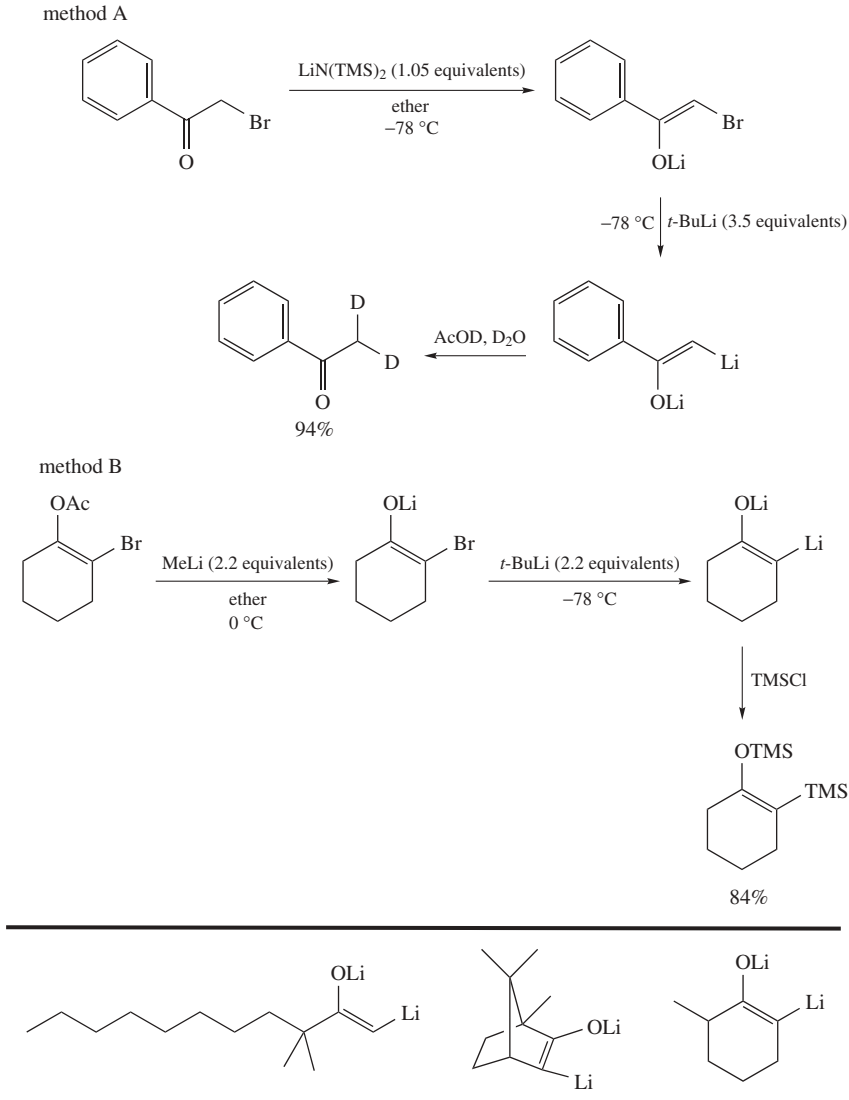
Kowalski and coworkers reported that lithium enolates of α-bromo ketones can be converted to the corresponding ketone dilithio α,α-dianions by Li−Br exchange with *t*-BuLi (Scheme 7)[8]. To generate lithium enolates of α-bromo ketones, either method A or B can be used: deprotonation of α-bromo ketones by one equivalent of lithium hexamethyldisilazide (LHMDS) (method A) or deacetylation of enol acetates of α-bromo



SCHEME 5



SCHEME 6. X-ray crystal structure of 1,3-dilithiobenzyl ketone•$(TMEDA)_2$. Reproduced with permission of Wiley-VCH Verlag from Reference 21



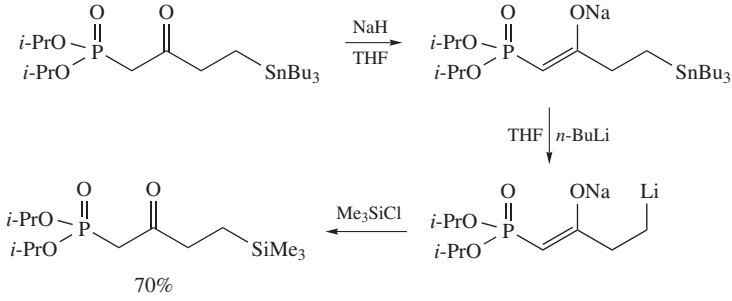
SCHEME 7

ketones by two equivalents of methyllithium (method B). Method B results in an amine-free solution. Concerning the Li−Br exchange reaction described in method A, three equivalents of *t*-BuLi are needed: one equivalent is used for the Li−Br exchange, one to quench the resulting *t*-BuBr into isobutene and lithium bromide, and the last equivalent is used to convert hexamethyldisilazane to LHMDS. In method B, two equivalents of *t*-BuLi are required. These procedures are also applicable to the corresponding α-iodo ketones. In such cases, interestingly, the second Li−I exchange reaction takes place easily, even when MeLi is used instead of *t*-BuLi. Concerning the stability of the dianions, cyclic

dianions are fairly stable at room temperature in ether. On the other hand, the dianion of acetophenone decomposes into acetylenic products within 10 min in this solvent. In THF solution, however, little decomposition is observed even after 20 min at room temperature.

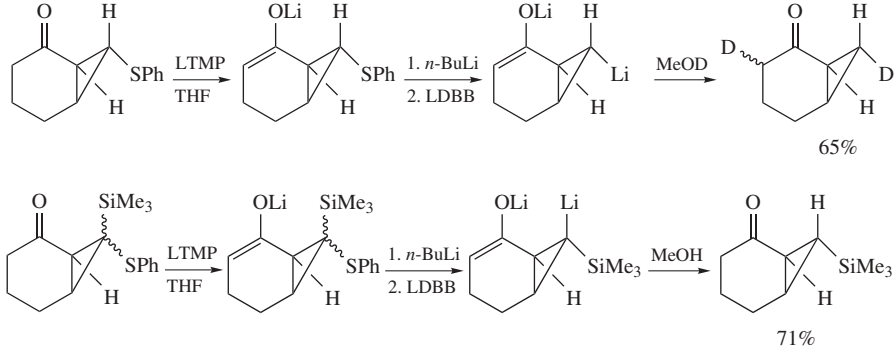
C. Ketone α,β'-Dianions

Goswami reported that a β-ketophosphonate ester, having a tributyltin substituent β to a carbonyl, can serve as a precursor for the corresponding ketone α,β-dianions (Scheme 8)[9]. The first deprotonation step was carried out by adding NaH, while the second involved a tin–lithium exchange reaction using *n*-BuLi.



SCHEME 8

Cohen and coworkers reported on dilithio species of ketone α,β'-dianions, in which cyclopropyllithium constitutes the β-carbanion portion[10]. In the examples given in Scheme 9, the first lithium enolate was produced by proton-abstraction with lithium 2,2,5,5-tetramethylpiperidide (LTMP), and the second involved the reductive cleavage of the carbon–sulfur bond by lithium 4,4′-di-*tert*-butylbiphenylide (LDBB).

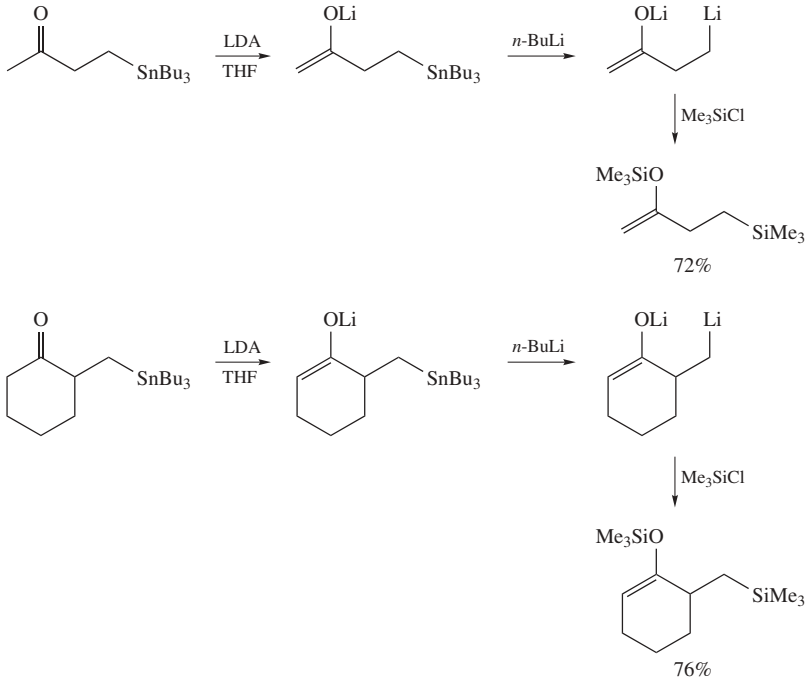


LTMP = lithium 2,2,5,5-tetramethylpiperidide
LDBB = lithium 4,4′-di-*tert*-butylbiphenylide

SCHEME 9

The β-tributylstannyl ketones are conveniently prepared by the chemoselective Grignard alkylation at the Sn atom of the corresponding β-trichlorostannyl ketones, which

are readily available from the ring-opening reaction of siloxycyclopropanes with tin tetrachloride[22] or the hydrotrichlorostannylation of enones[23,24]. Ryu, Sonoda and coworkers reported that simple ketone α,β'-dianions can be generated from β-tributylstannyl ketones by consecutive treatment of the ketones with lithium diisopropylamide (LDA) and *n*-BuLi[11,13]. In the examples shown in Scheme 10, the first lithium enolate formation proceeds regioselectively via proton-abstraction at the less hindered site to result in the homoallyltin structures. The second tin–lithium exchange step requires 3 h at 0 °C for completion. The resulting dilithio ketone α,β'-dianions were transformed into the corresponding bis-silylated products.

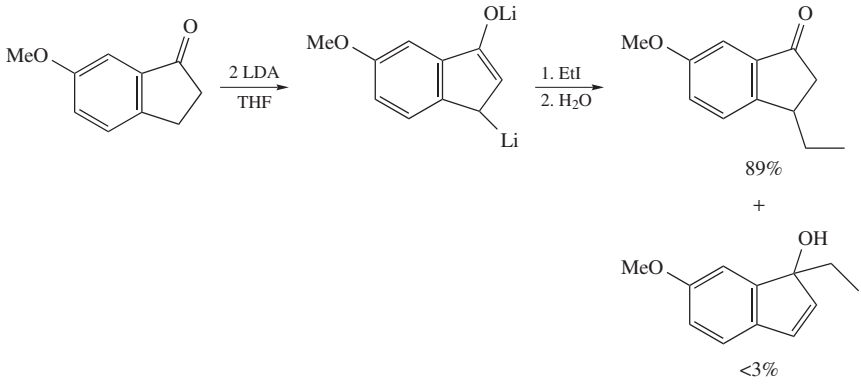


SCHEME 10

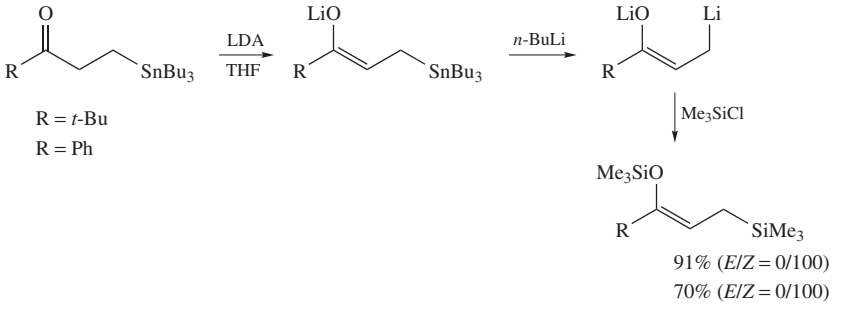
D. Ketone α,β-Dianions

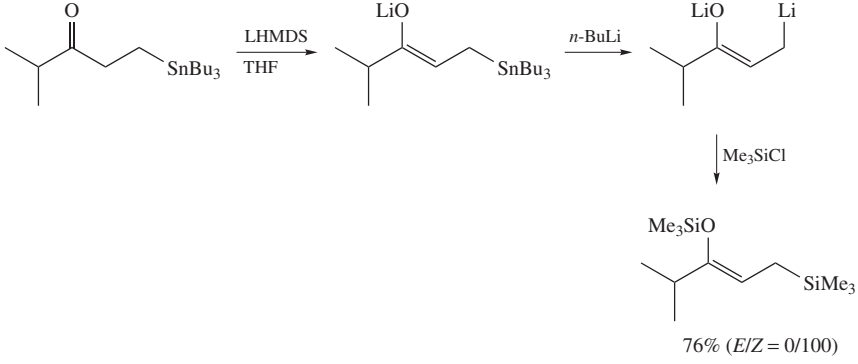
Trost and Latimer reported the clean generation of ketone α,β-dianion of 6-methoxyindanone. They used two equivalents of LDA as a base and THF as a solvent[6]. Alkylation with one equivalent of ethyl iodide gave 89% yield of 3-ethyl-6-methoxy-1-indanone. For the alkylation, the ambident character of the dianion was evident, although negligible, since the formation of 3-ethyl-3-hydroxy-6-methoxy-1-indene was confirmed (Scheme 11).

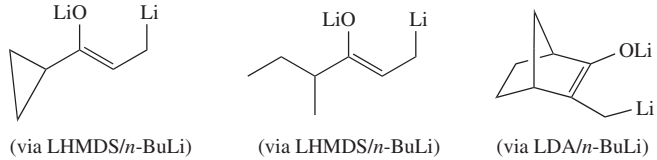
The lithium enolate formation using LDA, when applied to *t*-butyl 2-(tributylstannyl)ethyl ketone, gave the lithium enolate of β-stannyl ketone, having a (*Z*)-allyl structure, stereoselectively[11,13]. The subsequent Sn–Li exchange reaction with *n*-BuLi proceeded smoothly (0 °C, 30 min), leading to the dilithio ketone α,β-dianion (Scheme 12). The second example shown in Scheme 12 is the same α,β-dianion that Dimmel and coworkers examined using the reaction of phenyl allyl ether and *n*-BuLi[5]. In the third



SCHEME 11



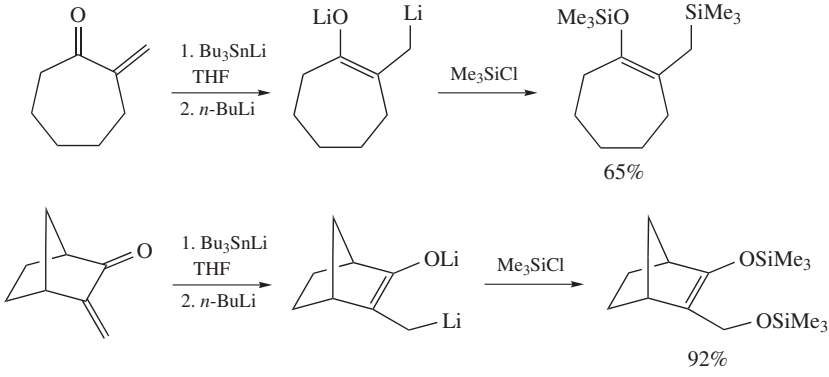




SCHEME 12

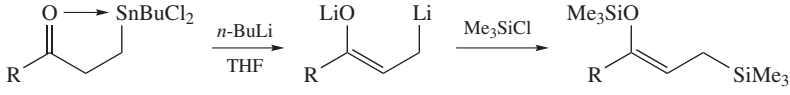
example, a bulkier base, LHMDS, was used in the first step to avoid contamination by lithium enolates having an (*E*)-allyl structure and a homoallyl structure. In contrast, the tin–lithium exchange reaction of the (*E*)-enolate was very sluggish. This suggests the importance of the coordination of the lithium alkoxide to another lithium atom in order to facilitate the tin–lithium exchange reaction.

A Michael addition reaction of Bu_3SnLi to enones can be used for the generation of lithium enolates of β-tributylstannyl ketones. The two examples shown in Scheme 13 employed such a route for the generation of ketone α,β-dianions[13].



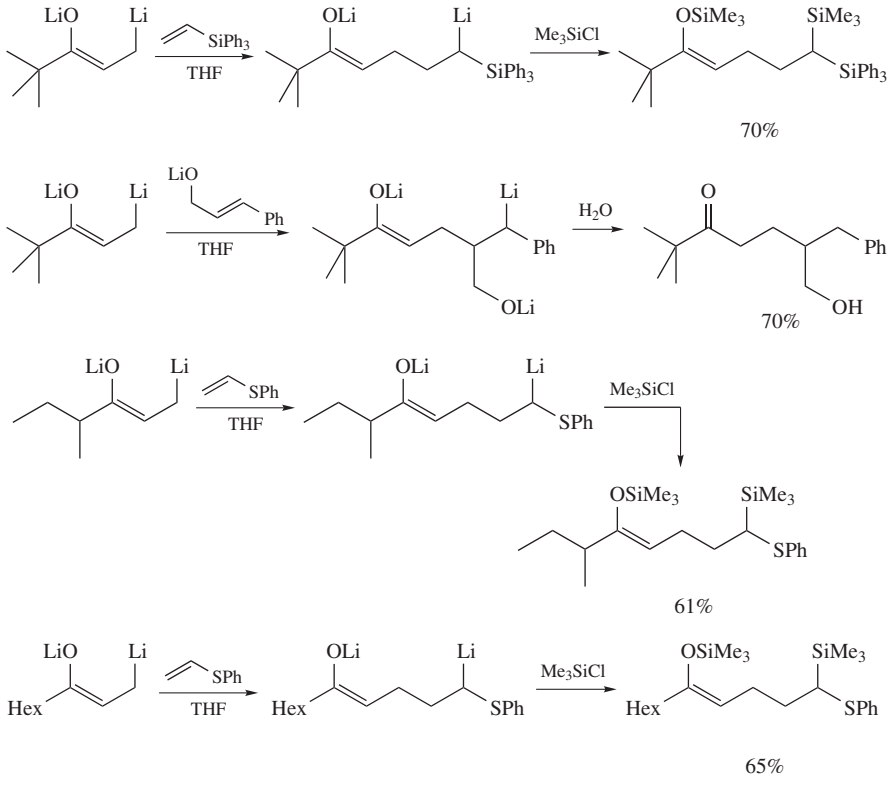
SCHEME 13

A convenient and clean approach to stereo- and regioselective dianion formation was developed, which employed chelated tin compounds (Scheme 14)[12, 13]. The simple procedure involves the treatment of β-butyl(dichloro)stannyl ketones[22] with four equivalents of *n*-BuLi in THF. The precursor for the dianion is, again, the lithium enolate of β-tributylstannyl ketone. This was confirmed by an experiment using three equivalents of *n*-BuLi, which gives exclusively the (*Z*)-enol silyl ether of the corresponding β-tributylstannyl ketone upon quenching with TMSCl. The fifth example of a substrate having two methylene groups α and α' to the carbonyl is remarkable, since α-regioselective deprotonation occurred. This 'one operation' route has the advantage of being an amine-free system, which allows transmetallation reactions of dianions as discussed in the next section.



R = *t*-Bu	90% (*E*/*Z* = 0/100)
R = *i*-Pr	84% (*E*/*Z* = 0/100)
R = Ph	78% (*E*/*Z* = 0/100)
R = *s*-Bu	81% (*E*/*Z* = 0/100)
R = Hex	76% (*E*/*Z* = 0/100)

SCHEME 14



SCHEME 15

E. Ketone α,δ-Dianions

Carbolithiation reactions of ketone α,β-dianions, generated by the above amine-free method with several alkenes, such as styrenyl derivatives, vinyl sulfides and vinylsilanes, can lead to the generation of ketone α,δ-dianions (Scheme 15)[14]. For example, when one equivalents of triphenylvinylsilane was treated with a ketone α,β-dianion, in THF, at 0 °C for 1 h and the resulting reaction mixture was quenched by 2.2 mol equivalents of trimethylchlorosilane, the corresponding bis-silylated enol silyl ether was obtained. Substituted styrenyl derivatives, such as 1,1-diphenylethylene and cinnamyl alcohol, also underwent a smooth carbolithiation to give the corresponding ketone α,δ-dianions. Similar addition reactions of ketone α,β-dianions to vinyl phenyl sulfide took place smoothly to give α,δ-dianions with a sulfur attached in the δ-position.

The generation and reaction of a ketone α,δ-dianion attached to sulfoxide will be referred to in Section III.C.1.

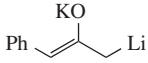
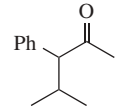
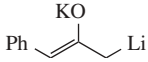
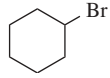
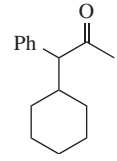
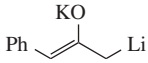
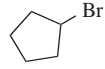
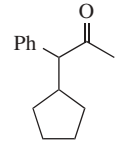
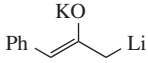
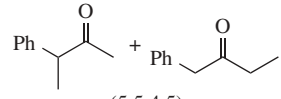
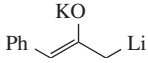
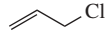
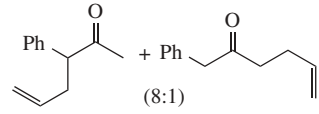
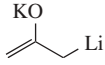
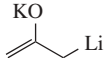
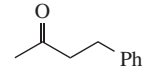
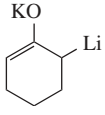
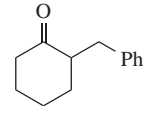
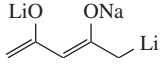
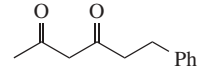
III. REACTIONS OF KETONE DILITHIO DIANIONS

A. Single C−C Bond-forming Reactions

1. Reaction with alkylating agents

Regioselectivity in the alkylation of α,α'-dianion of ketones differs depending on the structures of the dianions and the alkylating agents employed. The dianion derived from

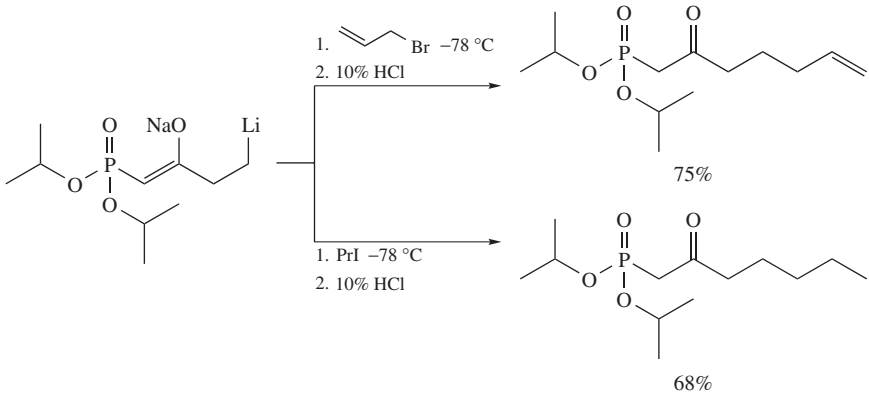
TABLE 1. Reaction of ketone α,α'-dianions with alkylating agents

Dianion	Reagent	Product	Yield (%)	References
			63	18
			61	18
			65	18
	MeI	 (5.5:4.5)	62	18
		 (8:1)	66	18
	MeI		79	7
	$PhCH_2Cl$		72	7
	$PhCH_2Cl$		67	7
	$PhCH_2Cl$		62	7

1-phenyl-2-propanone exhibited a different regioselectivity depending on the alkyl halides used (Table 1). The reaction of the dianion with methyl iodide and allyl chloride resulted in mixtures of α and α' alkylation products, whereas the reaction with secondary alkyl halides gave products that were alkylated at a benzylic position exclusively. The alkylation of α,α'-dianions of acetone and cyclohexanone with iodomethane, and benzyl chloride

gave the corresponding monoalkylation products in good yields. It is possible to generate the 1,3,5-trianion from 2,4-pentanedione by the successive addition of NaH and 2 equivalents of *sec*-BuLi. Alkylation of the trianion with 1 equivalents of benzyl chloride gave 1-phenyl-3,5-hexanedione in 62% yield. The reaction is clean with respect to the regiochemistry, and neither 1,3- nor 1,5-dialkylation is observed.

Selective β-allylation and β-alkylation was observed when Goswami's dianion was reacted with allyl bromide and propyl iodide (Scheme 16)[9]. The dianion undergoes isomerization to the α,α'-dianion at 0 °C and, as a result, the reaction must be conducted carefully at low temperatures.



SCHEME 16

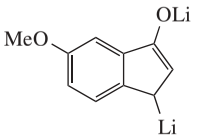
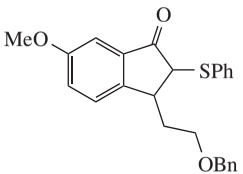
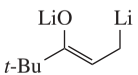
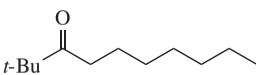
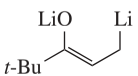
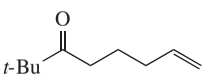
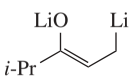
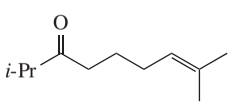
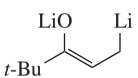
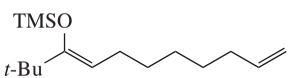
Table 2 lists examples of monoalkylation reactions of ketone α,β-dianions. The dianions always react with alkylating agents at the β-carbon atom to generate the corresponding lithium enolates, which can be quenched by water or electrophiles such as TMSCl and PhSSPh. The last two examples demonstrate the results of the single alkylation reaction of a ketone α,δ-dianion with hexyl and allyl bromides, which occurs at the δ-position to give lithium *Z*-enolates.

2. Reaction with carbonyl compounds and epoxides

Ketone dianions react smoothly with a variety of carbonyl compounds and epoxides. Examples are listed in Table 3.

Acylation of the α,α'-dianion of acetone with the sodium salt of ethyl benzoylacetate gave 1-phenyl-1,3,5-hexanetrione in 68% yield[7]. The condensation of the dianion with ethyl propionate or benzaldehyde proceeded at −78 °C to give the acylated product and the aldol product, respectively. The reaction of the α,α'-dianion of cyclohexanone with propylene oxide gave the 4-hydroxy ketone, in which the nucleophilic attack took place at the sterically less hindered carbon of the epoxide. Goswami's dianion behaves again as a β-acylcarbanion, even toward carbonyl compounds, giving rise to products via C−C bond formation at the terminal carbon[9]. The last example demonstrates the reaction of a ketone α,β-dianion with valeraldehyde, which gave a 47% yield of the homoaldol product[13]. Interestingly, a small amount of 1,2-diol was formed as byproduct, consistent with the ambident allyl anion character of the dianion. Such an ambident behavior toward aldehydes is quite similar to that of 1-silyloxyallyl anions[25].

TABLE 2. Monoalkylation of ketone α,β- and α,δ-dianions

Dianion	Reagent/Conditions	Product	Yield (%)	References
	1. $BnOCH_2CH_2I$ $-10\,^{\circ}C$ to r.t. 2. PhSSPh/HMPA r.t.		84	6
	1. n-$C_5H_{11}Br$ -78 to $-20\,^{\circ}C$ 2. H_2O		71	13
	1. $CH_2{=}CHCH_2Br$ $-78\,^{\circ}C$ 2. H_2O		62	13
	1. $Me_2C{=}CHCH_2Br$ $-78\,^{\circ}C$ 2. H_2O		53	13
	1. $CH_2{=}CH(CH_2)_4Br$ -78 to $-20\,^{\circ}C$ 2. TMSCl $-78\,^{\circ}C$		69	13

(*continued overleaf*)

TABLE 2 (*continued*)

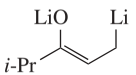
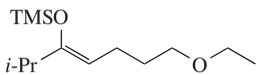
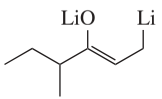
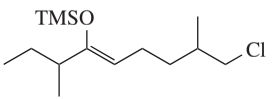
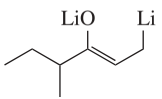
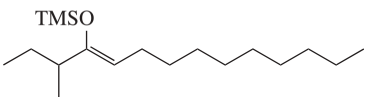
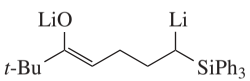
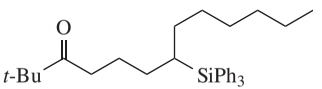
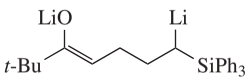
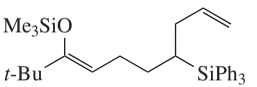
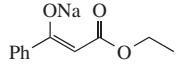
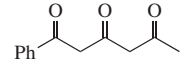
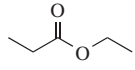
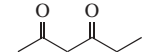
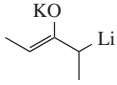
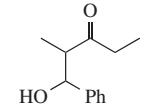
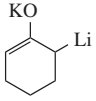
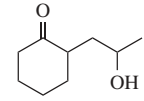
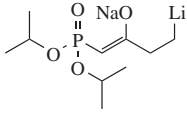
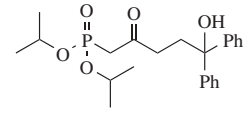
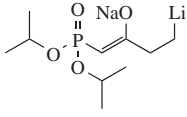
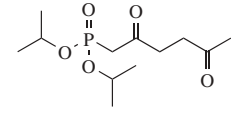
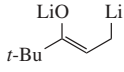
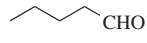
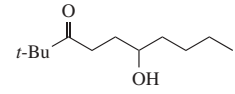
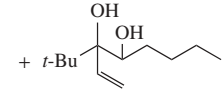
Dianion	Reagent/Conditions	Product	Yield (%)	References
	1. $EtO(CH_2)_2Br$ -78 to $-20\,^{\circ}C$ 2. TMSCl $-78\,^{\circ}C$		72	13
	1. $BrCH_2CH(Me)CH_2Cl$ -78 to $-20\,^{\circ}C$ 2. TMSCl $-78\,^{\circ}C$		68	13
	1. n-$C_8H_{17}Br$ -78 to $-20\,^{\circ}C$ 2. TMSCl $-78\,^{\circ}C$		81	13
	1. n-$C_6H_{13}Br$ -78 to $-20\,^{\circ}C$ 2. MeOH $-20\,^{\circ}C$		63	14
	1. $CH_2{=}CHCH_2Br$ $-78\,^{\circ}C$ 2. TMSCl -78 to $0\,^{\circ}C$		63	14

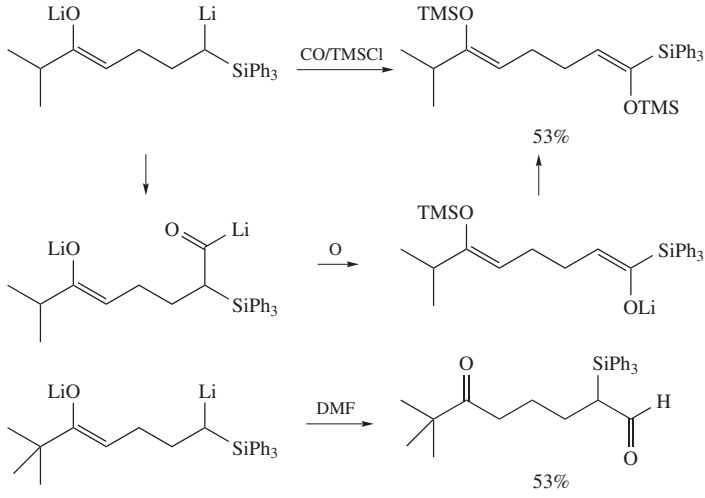
TABLE 3. Reaction of ketone α,α'-dianions with carbonyl and epoxide derivatives

Dianion	Reagent	Conditions	Product	Yield (%)	References
 (2 equiv)		THF 0 °C		68	7
 (2 equiv)		Et_2O −78 °C		58	7
	PhCHO	Et_2O −78 °C		92	7
		Et_2O 0 °C		47	7
		THF −78 °C to r.t.		72	9
		THF −78 °C to r.t.		52	9
		THF 0 °C		47	13
				4	

Carbon monoxide is generally inert toward lithium enolates, but reacts with 1-silylalkyllithium compounds[26,27]. The one-carbon homologation of the ketone α,δ-dianion was carried out in the presence of CO at atmospheric pressure, which gave the corresponding dienol disilyl ether after quenching with TMSCl (first equation of Scheme 17)[14]. The conversion of acyllithium to lithium enolate is accompanied by an anionic 1,2-silicon shift[26]. On the other hand, treatment of the ketone α,δ-dianion with DMF gave the δ-formylated product without being accompanied by such a silicon migration (second equation of Scheme 17).

3. Reaction with acyl chlorides after transmetallation reactions with copper(I)

Cuprates derived from the reaction of ketone α,β-dianions with CuCN were shown to be acylated regioselectively by acyl chlorides at the β-carbon atom to give 1,4-diketones



SCHEME 17

TABLE 4. Reactions of dianionic cuprates with acyl chlorides

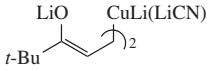
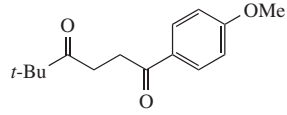
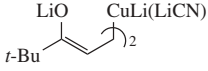
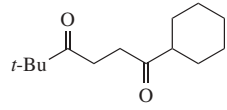
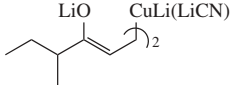
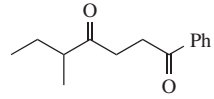
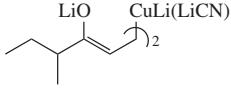
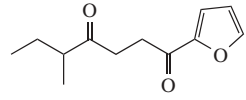
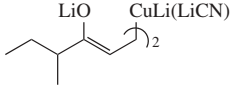
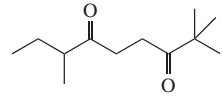
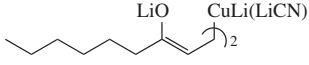
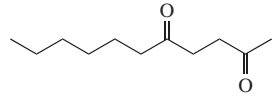
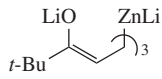
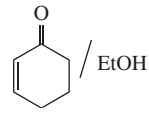
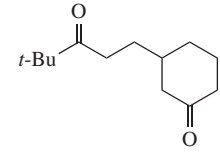
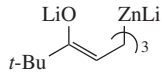
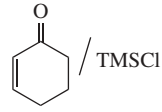
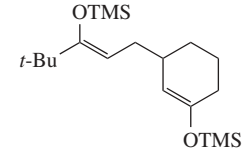
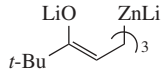
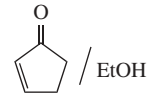
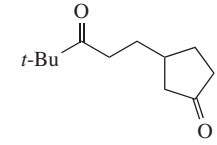
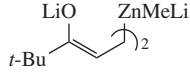
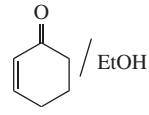
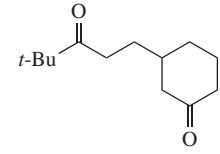
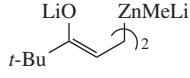
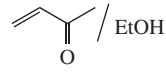
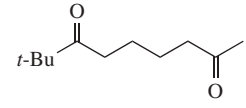
Dianionic cuprates	Reagent	Product	Yield (%)
	*p*-$MeOC_6H_4COCl$		64
	*c*-HexCOCl		53
	PhCOCl		76
	2-FurylCOCl		68
	*t*-BuCOCl		43
	AcCl		49

TABLE 5. Reaction of dianionic zincates with enone derivatives

Dianionic zincates	Reagent	Product	Yield (%)
			67
			62
			77
			70
			53

(Table 4)[28]. Mixed cuprates from α,β-dianions and 2-thienylCu(CN)Li were also found to give unsymmetrical ketones in modest yields.

4. Reaction with α,β-unsaturated ketones after transmetallation reactions with zinc(II)

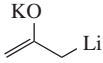
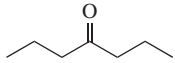
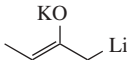
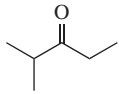
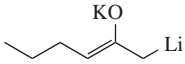
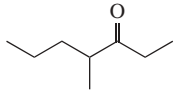
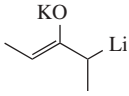
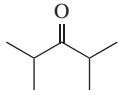
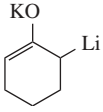
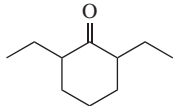
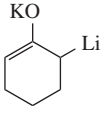
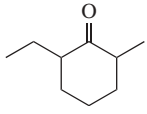
Zincates derived from the ketone α,β-dianions react with enones, affording unsymmetrical 1,6-diketones (Table 5)[29]. As shown in the second example of Table 5, quenching with TMSCl gave the corresponding dienol disilyl ether. A mixed zincate consisting of the dianion and methyllithium in a 2:1 ratio gave comparable results to the symmetrical zincate.

B. Double C−C Bond-forming Reactions

1. Reaction with alkylating agents

Bates and Taylor reported the dialkylation of ketone α,α'-dianions using alkyl triflates (Table 6)[30]. Reactions of the dianions with methyl and ethyl triflates gave α,α'-alkylated

TABLE 6. Dialkylation of ketone α,α'-dianions

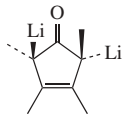
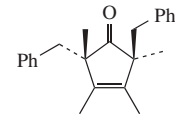
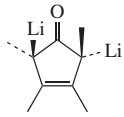
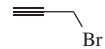
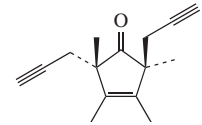
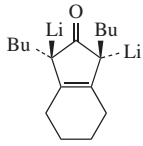
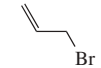
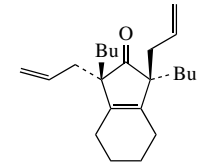
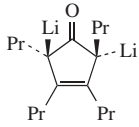
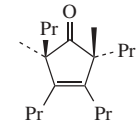
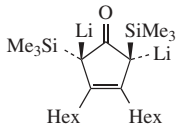
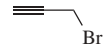
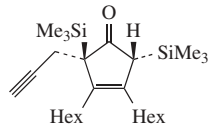
Dianion	Reagent	Product	Yield (%)
	EtOTf		49
	MeOTf		60
	MeOTf		66
	MeOTf		58
	EtOTf		70
	MeI, then EtOTf		58

products in good yields. They also exploited the dialkylation of the dianions using two different alkylating agents. The first alkylating agent cannot be an alkyl triflate since it rapidly delivers the alkyl group to the resulting enolate. Thus, as demonstrated in the last example of Table 6, consecutive treatment with MeI and EtOTf gave 2-ethyl-6-methylcyclohexanone.

Cyclic ketone dianions obtained by the condensation of 1,4-dilithio-1,3-dienes with carbon monoxide can be used for the one-pot synthesis of a variety of 3-cyclopentenone derivatives[20]. Treatment of the dilithio species with 2 equivalents of benzyl bromide gave the corresponding 2,5-dibenzyl 3-cyclopentenone in 73% yield. A single-crystal structure analysis revealed that the two benzyl groups are in a *trans* orientation. Several examples of the one-pot synthesis of 3-cyclopentenone derivatives using this method are summarized in Table 7.

The more reactive β-carbon atom of ketone α,β-dianions can be regiospecifically coupled with alkyl halides to give first lithium enolates, which are then trapped by more reactive carbon electrophiles such as allylic halides. The first example shown in Table 8 deals with the sequential β-alkylation and α-allylation of a ketone α,β-dianion[11,13]. Thus, the dianion underwent regioselective alkylation at the β carbon with *n*-pentyl bromide and then allylation with allyl bromide at the α carbon. When an excess of allyl bromide is reacted with the α,β-dianion, the diallylated product is obtained in a good yield, whereas a threefold excess of pentyl bromide only resulted in the formation of the β-alkylation product. Similar consecutive alkyl/allyl-type reactions are also possible for ketone α,δ-dianions[14].

TABLE 7. Reaction of cyclopentenone dianions with electrophiles

Dianion	Reagent	Product	Yield (%)
	$PhCH_2Br$		73
			65
			58
	Me_2SO_4		86
			66

2. Reaction with acylating agents

Single acylation reactions of dianionic cuprates have already been shown in Table 4. After the acylation reactions of these cuprates with one equivalent of an acyl chloride, the resulting lithium enolates can be subjected to a second acylation or alkylation[28]. The first example shown in Scheme 18 demonstrates such a case, in which the second acylation using benzoyl chloride gave a triketone (Scheme 18). The second example deals with the treatment of the enolate with iodomethane, which resulted in the corresponding 2-methyl-1,4-diketone.

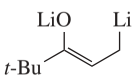
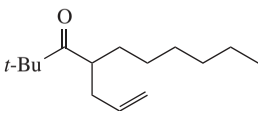
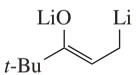
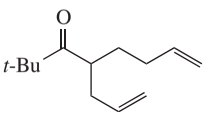
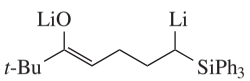
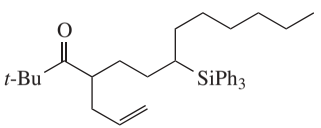
C. Annulation Reactions

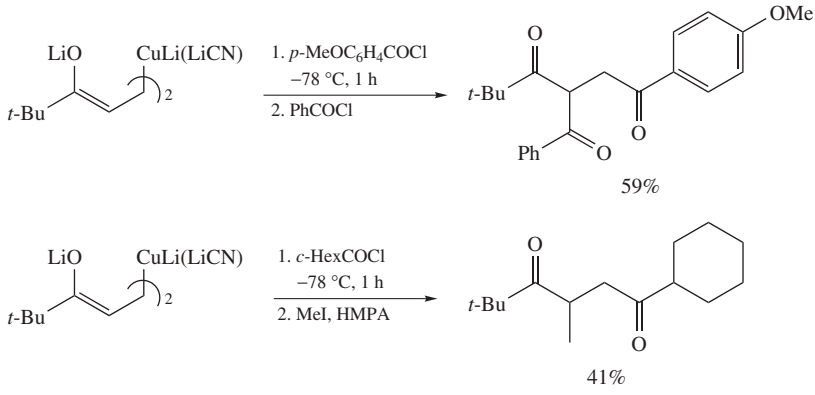
1. Reaction with dihaloalkanes

Clark and coworkers reported a successful annulation reaction between the diphenylacetone dianion and 1,3-dibromopropane, which led to the synthesis of a cyclohexanone ring (Scheme 19)[31]. On the other hand, neither 1,2-dichloroethane nor 1,2-dibromoethane gave the corresponding cyclic product. In these reactions, the ethylene-bridged compound and the dimerized compound were obtained, respectively.

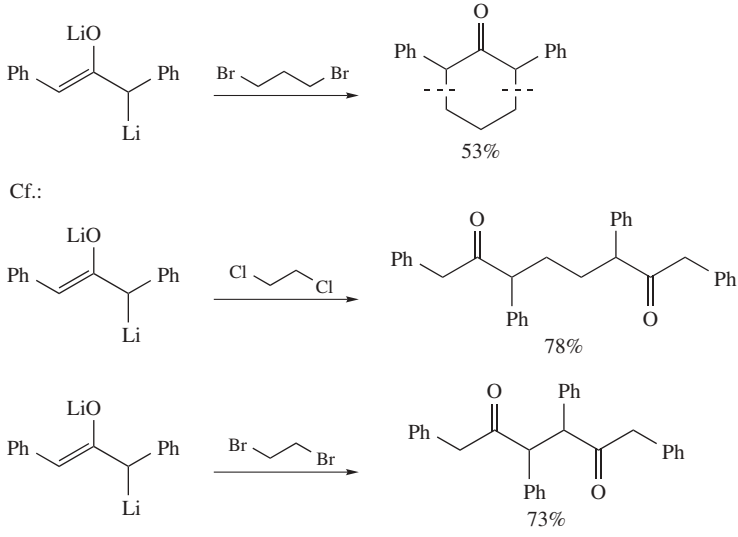
The reaction of the α,δ-dianion of the cyclic ketosulfone with dichloroisobutene results in formation of the bridged $[3 + 4]$-type cycloaddition product in good yield (Scheme 20)[32].

TABLE 8. Dialkylation of ketone α,β- and α,δ-dianions

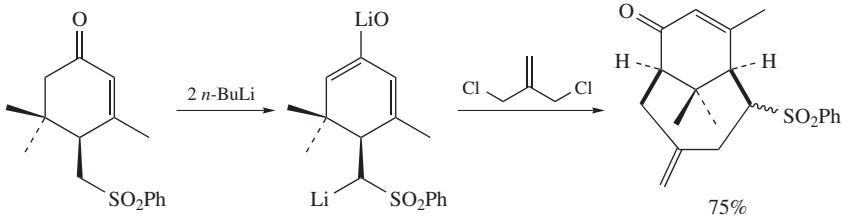
Dianion	Reagent/Conditions	Product	Yield (%)	References
	1. n-$C_5H_{11}Br$ −78 to −20 °C, 1 h 2. $CH_2{=}CHCH_2Br$ −78 to 25 °C, 1 h		70	13
	$CH_2{=}CHCH_2Br$ −78 to −25 °C, 1 h		74	13
	1. n-$C_6H_{13}Br$ −78 to −20 °C 2. $CH_2{=}CHCH_2Br$ −78 to 20 °C		62 (60/40)	14



SCHEME 18



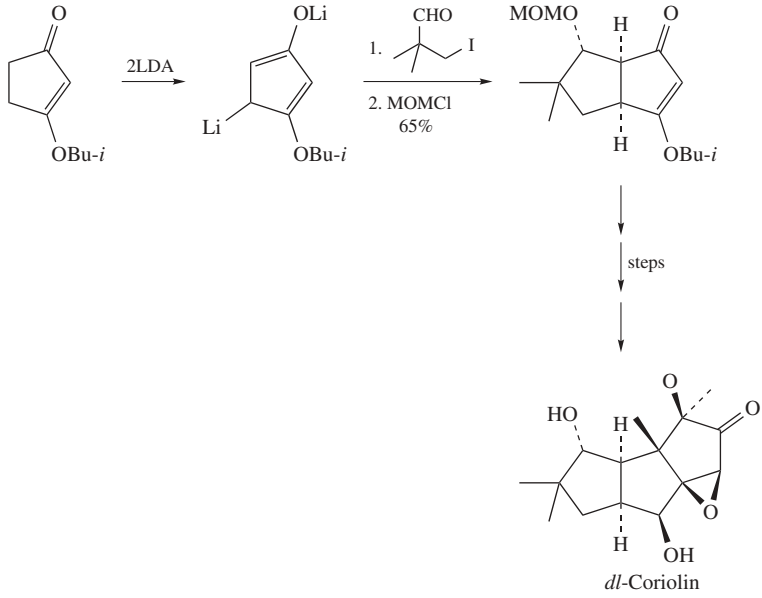
SCHEME 19



SCHEME 20

2. Reaction with 3-iodo-2,2-dimethylpropanal

Koreeda and Mislankar reported that the reaction of the dianion of 3-isobutoxycyclopent-2-en-1-one with 3-iodo-2,2-dimethylpropanal leads to a dual C−C bond-forming reaction at both the C4 and C5 carbons, giving the corresponding bicyclic compound (Scheme 21)[33]. This [3 + 3]-type annulation product was used as a key building block in the synthesis of *dl*-Coriolin.



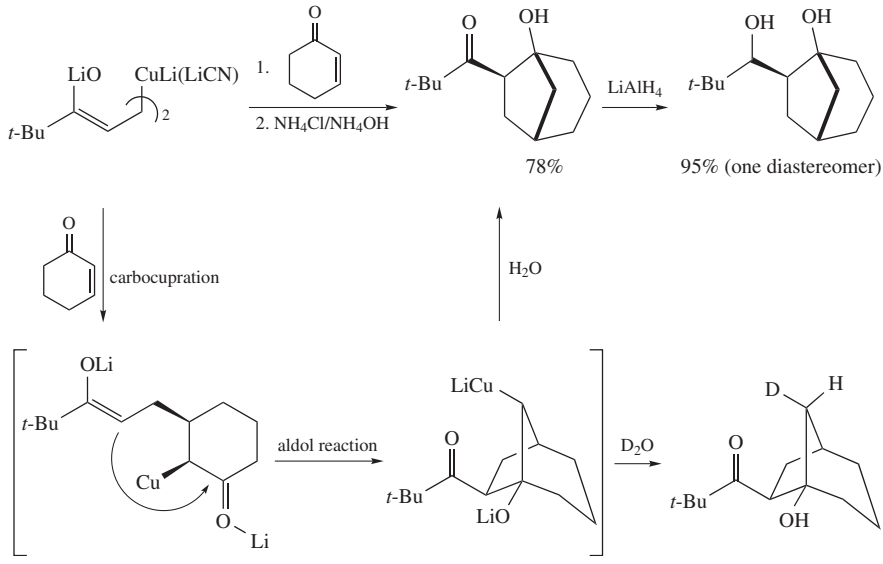
SCHEME 21

3. Reaction with α,β-unsaturated ketones after transmetallation reactions with copper(I)

When the dianion cuprate was treated with cyclohexenone at −78 °C and then warmed to 0 °C, the keto alcohol having a bicyclo[3.2.1]octane structure was formed in good yield (Scheme 22)[12]. The keto alcohol was obtained as a single stereoisomer and its *exo*-structure was determined by an X-ray analysis of the reduced diol. The mechanism of this unusual [3 + 2]-type annulation may involve the formation of α-cuprio ketone as an initial intermediate, which may be formed by carbocupration of the C−C double bond of cyclohexenone[34]. The subsequent reaction with the internal lithium enolate portion would lead to the formation of the functionalized organocuprate. In support of the intermediacy, quenching the reaction mixture with dideuterium oxide gave a single stereoisomer of mono-deuteriated product at the bridged carbon.

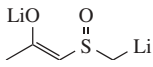
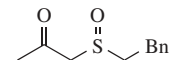
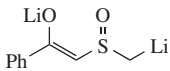
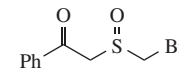
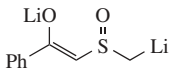
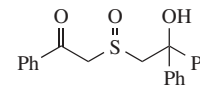
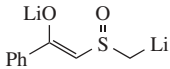
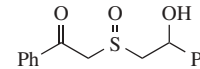
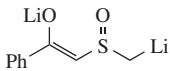
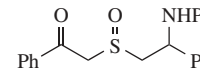
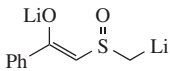
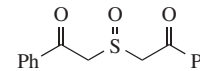
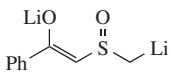
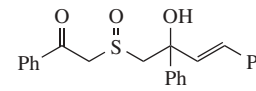
D. Miscellaneous Reactions

Tamura and coworkers investigated the reaction of dianions of β-ketosulfoxides with electrophiles (Table 9)[35]. They found that the reaction of the dianions with benzyl bromide, benzophenone, benzaldehyde, benzalaniline, ethyl benzoate and benzalacetophenone resulted in the exclusive formation of α-substituted β-ketosulfoxides.



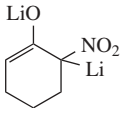
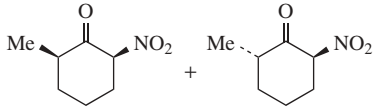
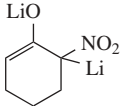
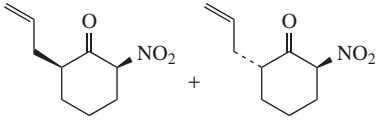
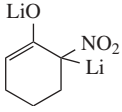
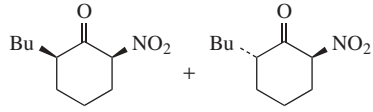
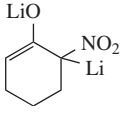
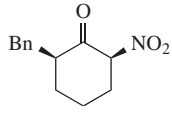
SCHEME 22

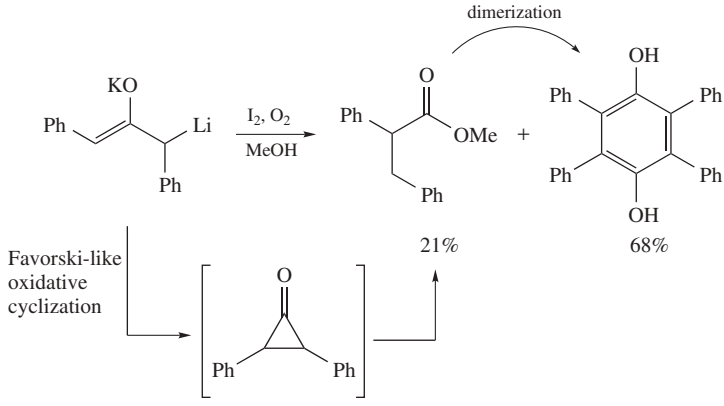
TABLE 9. Reaction of dianions of β-keto sulfoxides with electrophiles[35]

Dianion	Reagent	Product	Yield (%)
	BnBr		43
	BnBr		95
	PhCOPh		70
	PhCHO		71 [a]
	PhCH=NPh		75 [b]
	$PhCO_2Et$		52
	PhCOCH=CHPh		75 [a]

[a] A diastereomeric mixture (*ca* 1:1).
[b] Only one diastereomer.

TABLE 10. Reaction of dianion of 2-nitrocyclohexanone with alkylating agents[19]

Dianion	Reagent	Product	Yield (%)
	MeI	 (90:10)	85
	CH_2=CHCH_2Br	 (84:16)	60
	BuBr	 (95:5)	60
	BnBr		75



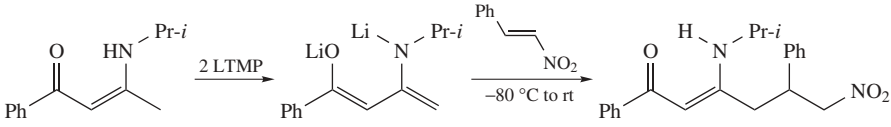
SCHEME 23

Nitro-attached ketone dianions generally suffer from rapid proton transfer during the alkylation process. However, the reaction conditions have been optimized by using HMPA or TMEDA, which enhanced the reactivity of the dianions toward the alkylating agents[19]. Examples are shown in Table 10.

Fox and Chen reported the oxidation of ketone α,α'-dianions (Scheme 23)[36]. It was speculated that diphenylcyclopropanone would be formed as the first intermediate via

a Favorski-like oxidative cyclization, which would then undergo methanolysis to give methyl 2,3-diphenylpropionate. The major product, tetraphenylhydroquinone, is then formed by ionic dimerization of the ester and subsequent oxidative aromatization.

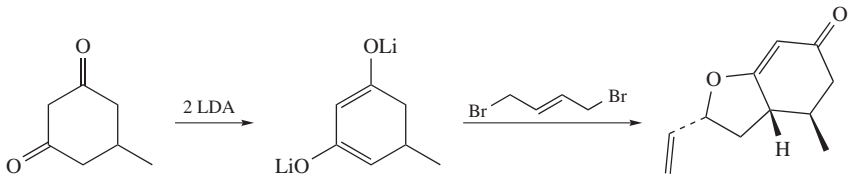
The dianions of β-enamino ketones react with a wide range of electrophiles such as alkyl halides, oxiranes, nitriles, esters, aldehydes and ketones[37]. Dalpozzo and coworkers reported the generation of the dianion derived from β-enamino ketones with lithium 2,2,6,6-tetramethylpiperidide and the reaction of the dianion with nitroalkene (Scheme 24)[38]. The dianion underwent exclusive alkylation at the γ-carbon atom to give the monoalkylated product in high yield. This reaction is useful for the introduction of a nitro group into a ketone side chain.



LTMP: lithium 2,2,6,6-tetramethylpiperidide 83%

SCHEME 24

Langer and coworkers reported on the [3 + 2]-type C,O-cyclodialkylation of cyclohexane-1,3-dione dianion with 1,4-dibromo-2-butene (Scheme 25)[39]. The formation of the tetrahydrofuran-fused cyclohexenone can be explained by a regioselective attack of the terminal carbon of the dianion on the 1,4-dibromo-2-butene and subsequent S_N2'-type cyclization. This reaction proceeded with a high degree of diastereoselectivity. An excellent review of this type of cyclization reaction is now available elsewhere[40].



37% (>98:2)

SCHEME 25

IV. REFERENCES

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