Regioselectivity of the Reactions of Heteroatom-Stabilized Allyl Anions with Electrophiles

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Michaela Piffl was born in 1971. After having studied at Friedrich-Schiller-University Jena, Germany, the University of Strathclyde Glasgow, U.K., and King's College London, U.K., she received her Diploma in 1995 in Jena. She investigated heterogeneous catalysts for the dimerization of acrylonitrile. Her work was supported by the Studienstiftung des Deutschen Volkes. Currently, she is in the third year of her Ph.D. with Professor Anders. Her research interest is regioselective electrophilic attack at heterosubstituted allyl anions.

I. Introduction, Synthetic Importance, and Theoretical Significance

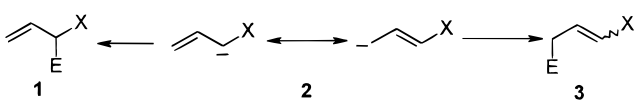
Allyl anions are stabilized by resonance, and are considerably more stable than alkane anions: allyllithium has a stabilization energy of −15.7 kcal/mol, whereas that for *n*-propyllithium has been calculated to be 4.0 kcal/mol.[1] Furthermore, propene has a pK_a of 47.1−48.0[2a] (or = 43[2b]), whereas the pK_a of alkanes are between 50 and 60.[3] Considerable further stabilization can arise when an allylic anion contains a heterosubstituent. An unsymmetrically substituted allyl anion **2** is an ambident anion, which can react with electrophiles at two sites (cf. Scheme 1). The site selectivity of such reactions is both of considerable synthetic importance and of theoretical interest, and the discussion of such site selectivity to give **1** vs **3** is a major objective of this review.

Hengyuan Lang was born in China in 1962. He received his Ph.D. from Beijing Institute of Technology in 1989. Following five years of postdoctoral studies in Professor Katritzky's group at the University of Florida, he is now a research scientist at Trega Biosciences, Inc., San Diego, working on the design and synthesis of small molecular and heterocyclic combinatorial libraries. He has authored or co-authored more than 40 scientific papers and patents.

Professor Ernst Anders was born in 1942 in Germany. He studied chemistry at the Free University of Berlin and received his Ph.D. in theoretical and organic chemistry working with Professor Ernst Ruch at the Institute of Quantum Chemistry. He then moved to the Friedrich-Alexander-University of Erlangen-Nürnberg (Bavaria) to work on heterocyclic chemistry with Professor Hans-Jürgen Bestmann. After receiving his Doctor habilitus and the position of a Professor of Organic Chemistry at the University of Erlangen-Nürnberg, he was Visiting Professor in Göttingen, Germany, and Gainesville, FL. In 1993 he took his present position as a Full Professor at the Institute of Organic Chemistry and Macromolecular Chemistry (IOMC, Friedrich-Schiller-University of Jena). From 1995 to 1997, he was the Director of the IOMC. Presently he is the Vice Dean of the Faculty of Chemistry and Earth Sciences and chairman of the Collaborative Research Center (SFB No. 436) "Synthetic Analogues of Naturally Occurring Metal-Assisted Reactions". His present research fields focus on stereoelectronically stabilized cations, heterocyclic chemistry, organo–metal complexes, and computational chemistry.

An important role of heterosubstituted allyl anions is in the umpolung of carbonyl groups. The carbonyl function plays a central role in organic synthesis, consequently numerous transformations of this group have been developed. The carbonyl carbon usually serves as the electrophilic partner in polar condensation processes. However, a great deal of effort has

Scheme 1



1 2 3

also been devoted to find synthetic transformations in which the normal chemical reactivity of functional groups is reversed. Reversed polarity synthons of carbonyl compounds function as acyl anions or "masked" acyl anions. In *gem*-diheterostabilized allyl anions (sections III and IV), α-attack provides acyl anion equivalents whereas γ-attack can lead to homoenolate equivalents, synthons which are capable of transforming aldehydes and ketones into γ-lactols and γ-lactones.

If an allylic anion reacts with an aldehyde or unsymmetrical ketone, the question of the stereochemistry of the stereogenic center thus formed is raised. Additionally, if a γ-product **3** is obtained, the stereochemistry can be either *E* or *Z*. Utilization of chiral substrates or reagents further requires consideration of enantiomer and diastereomer separation. Initially, interest was focused on the regioselectivity of the reactions of unsymmetrical allylic anions to form carbon−carbon bonds; with the production of chiral homoallylic alcohols, the stereoselectivity of carbon−carbon bond formations has received increasing attention.

The scope of the present review is limited to heteroatom-stabilized allyl anions, i.e., to those where one (as in Scheme 1) or more heteroatoms are directly attached to the three-carbon systems of the anion. Such heterosubstitution generally considerably stabilizes the allyl anion. We discuss first allyl anions stabilized by a single heterosubstituent, considering successively halogen substitution, followed by O-, S-, Se-, N-, P-, Si-, and B-linked allylic anions. Second, allylic anions stabilized by two heteroatoms are considered, subdivided into those substituted by two identical geminal heteroatoms, two different geminal heteroatoms and two heteroatoms at the 1,2- or 1,3-position. Next, examples of three heteroatom-stabilized allylic anions are presented. Structures of the various classes of allylic anions are described in the light of NMR and crystallographic data. While the review is mainly concerned with lithium as the counterion; transmetalation with other metal ions is briefly discussed if appropriate, and summarized in the final section. No previous review has dealt with this subject matter in the manner described here, but many reviews have provided valuable overviews of much of this information: some important works are found in ref 4a−d.

II. Allylic Anions Stabilized by One Heteroatom (C═C–C–X)

Extensive work has been carried out on monoheterosubstituted allyl anions, covering a variety of O-, S-, N-, P-, and Si-linked derivatives in various oxidation states. Selenium- and boron-substituted allyl anions are less explored. From the synthetic point of view, sulfur- and phosphorus-stabilized allyl anions are probably the most important, but many other anions of this class are also of significant synthetic interest.

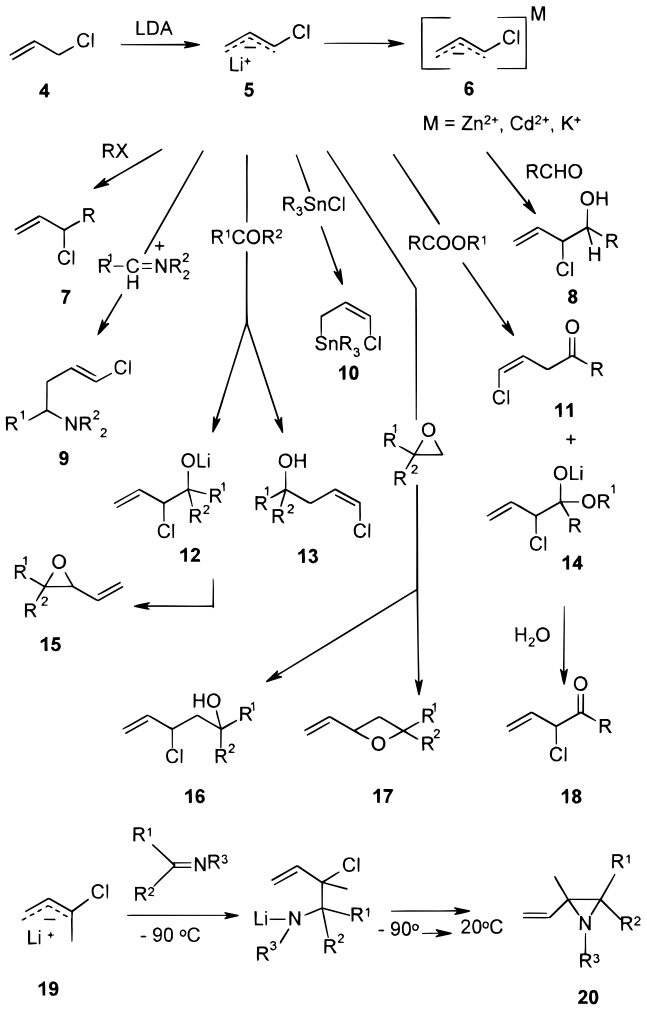
A. Halogen

Among the monohalogen-substituted allyl anions, most of the work has been carried out on the chloro derivatives together with some on bromine-stabilized anions. Fluoroallyllithium, while as yet unreported due to its structural instability, has been treated theoretically.[5]

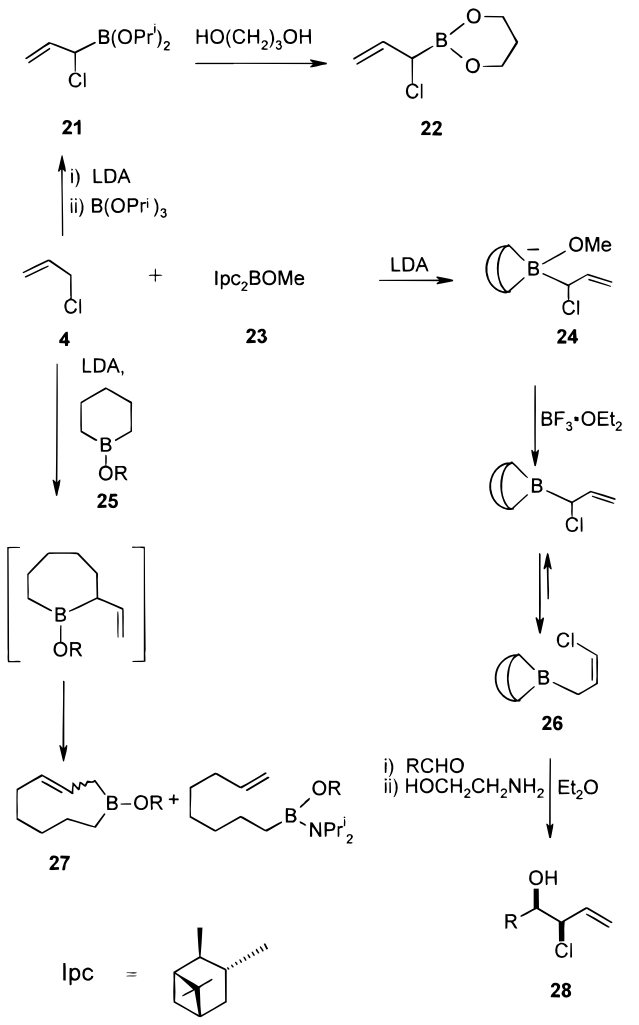
1. Allyl Chlorides (C═C–C–Cl)

Kharasch's examination of halogen-substituted allyl anions in 1939 provided the first examples of heterosubstituted allylic species to be studied.[6] Analogous to the corresponding bromides, allyl chlorides **4** undergo α-alkylation to **7** with aliphatic halides[7] and TMSCl (Scheme 2).[7,8] Such sequences were, for example, used for the preparation of lavanduol[9] and pheromones.[10] Similarly, 1-chloro-1-methylallyllithium **19** reacts with aldimines and ketimines via attack at the α-carbon to produce N-substituted ethylenic aziridines **20**.[11] However, mainly γ-attack to give **9** occurs with iminium salts (Scheme 2)[12] and upon stannylation to give **10**.[7,13] γ-Attack also occurs with aromatic and mixed ketones, aliphatic aldehydes and aromatic aldehydes with or without electron-donating substituents to produce γ-chlorinated β-ethylenic alcohols **13**.[7,14] Cyclic ketones cause formation of α-adducts while for aliphatic ketones and for aromatic aldehydes bearing an electron-attracting substituent, α- **12** and γ-products **13** are both observed.[14] In general, with aliphatic and aromatic esters α-attack is observed to give α-chlorinated β-ethylenic ketones **18** while the analogous products

Scheme 2



Scheme 3

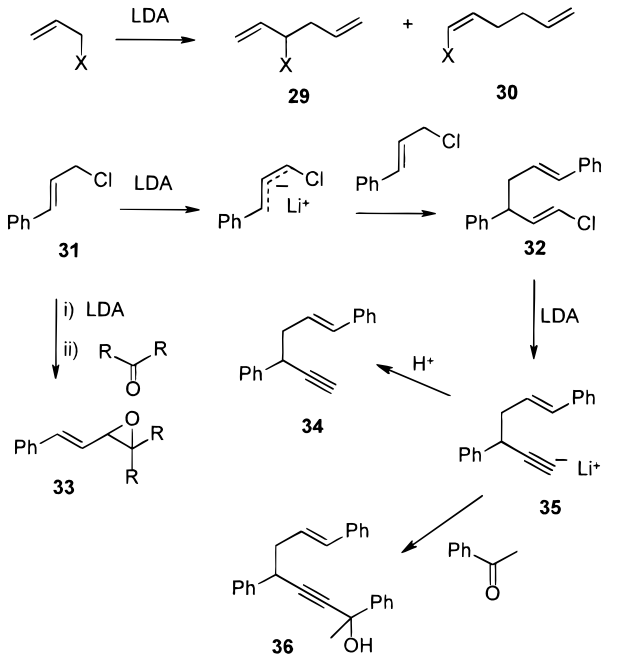


of γ-attack **11** are obtained if the ester contains a bulky group, e.g., with pivalic acid ethyl ester.[15] Depending on the conditions used, regioselective reaction of chloroallyl anions with epoxides can give either γ-ethylenic β-chloro alcohols **16** or 2-vinyloxetanes **17** (Scheme 2).[16] If lithium is replaced by zinc, potassium, titanium or magnesium as the counterion, α-attack to give **8** is achieved with aldehydes (Scheme 2).[13,17]

Similarly, α-adducts (α-chloroallylboronate) **21**, produced by reaction of lithiated allyl chloride from **4** with triisopropyl borate, furnish upon reaction with trimethylene glycol the cyclic α-haloallylboronate ester **22** (Scheme 3).[18] α-Addition of (−)-*B*-methoxydiisopinocapheylborane (Ipc$_2$BOMe) **23** to allyl chloride results in the formation of an "ate" complex **24** which is further treated with BF_3 furnishing the less sterically hindered γ-chloroallylborane **26** and reacts with carbonyl compounds to give *syn*-α-chlorohydrins **28** (Scheme 3).[19] Furthermore, reactions with cyclic borinates **25** can yield ring-expanded allylic boracycles **27**.[20,21]

α-Halogenoallyl carbanions have found only limited synthetic application, due to facile self-coupling: α **29** and γ **30** for X = Cl and α **29** for X = Br (Scheme 4).[13] Thus, *trans*-cinnamyl chloride **31** reacts in a γ-regioselective way to give the homocoupling product

Scheme 4

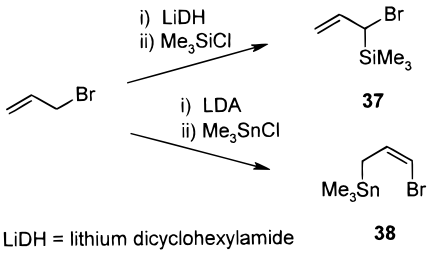


32 which upon HCl elimination and deprotonation furnishes the acetylide ion **35** and then the *trans*-enyne **34**. When the lithiation of *trans*-cinnamyl chloride was followed by addition of carbonyl compounds, e.g., cyclohexanone, acetophenone, γ-adducts (propargylic alcohols) **36** were obtained. However, deprotonation in the presence of an electrophile (Barbier technique) indicates that such allylic carbanions can react faster with an electrophile than with the starting halides. Hence in contrast unenolizable carbonyl compounds such as adamantanone, benzophenone, or fluorenone give complete α-regioselection in very high yield of trans styryl epoxides **33** (Scheme 4).[22]

2. Allyl Bromides (C═C–C–Br)

The addition of lithium dicyclohexylamide to a mixture of allyl bromide and chlorotrimethylsilane at −78 °C, results in the exclusive formation of α-product **37** of *Z* stereochemistry (Scheme 5).[8] In a further report, reactions with trialkylsilyl chlorides likewise produce α-products while mainly γ-products **38** are formed with chloroalkyltins.[13]

Scheme 5



B. Oxygen

Among O-linked substituents, we consider successively in separate sections alkyloxy, silyloxy, and carbonyloxy substituents. A separate section is al-

located to cases where extra stabilization of the anion is provided by the formation of a pentadienyl anion.

1. 1-Alkoxy-2-propenes (C═C–C–OR)

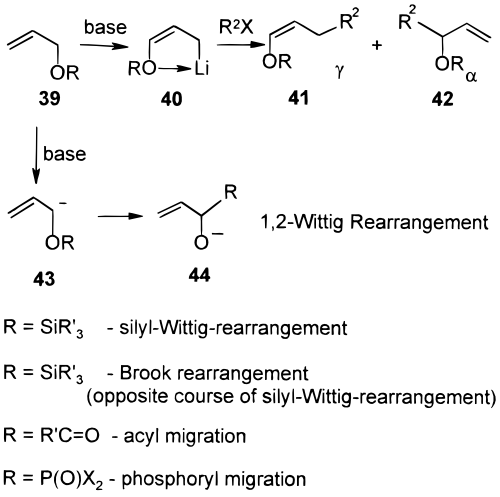
1-Alkoxy-2-propenes **39** can easily be metalated with *sec*-butyllithium at −65 °C in THF. At higher temperatures they tend to undergo 1,2-Wittig rearrangement **43** → **44** (Scheme 6).[23−33] Various types of 1,2-Wittig rearrangements are classified according to the substituent on the oxygen as shown in Scheme 6.

Lithiated 1-alkoxy-2-propenes **40** react with alkyl halides to give a mixture of enol ethers **41** (γ-attack) and allyl ethers **42** (α-attack) (Scheme 6). The regioselectivity is rather insensitive to change in solvent or temperature, but is influenced by the oxygen ligand R (steric effects). For example, the *tert*-butyl allyl ether favors the γ-product with *Z* stereochemistry determined by five-membered ring chelation.[34,35]

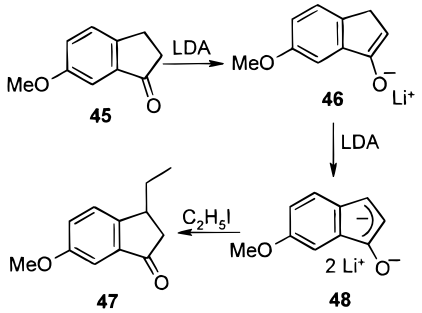
The dianion **48** of 1-indanone **45** undergoes almost exclusive γ-attack to give **47** upon addition of 1 equiv of alkyl halide (Scheme 7), which can be explained in terms of the electronic repulsion of the charged oxygen which is reinforced by the aspiration to maintain maximum charge stabilization by delocalization.[36]

Reactions of heterosubstituted allylic anions with carbonyl compounds as electrophiles frequently show the opposite regioselectivity to that found for alkylation reactions. Thus, lithiated trimethylsilyl allyl ether (**40**, R = SiR_3) and *tert*-butyl allyl ether (**40**, R = ^{t}Bu) give predominantly α-products **49** with cyclo-

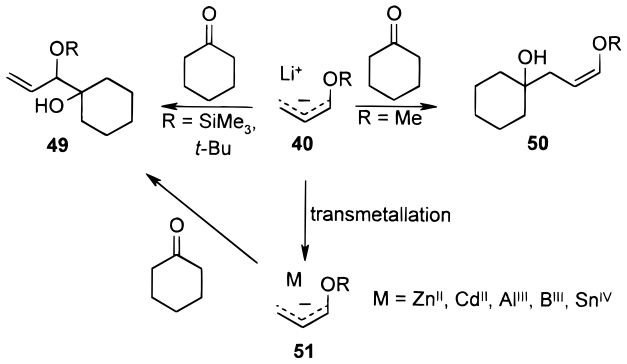
Scheme 6



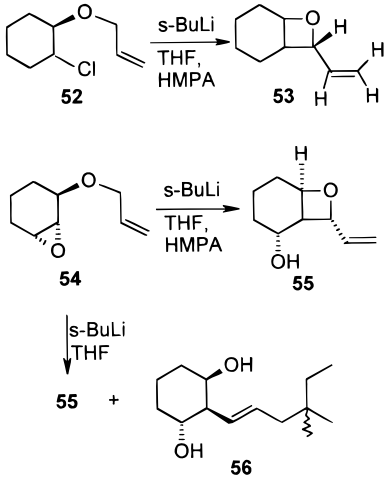
Scheme 7



Scheme 8



Scheme 9



hexanone. However, the yield of the γ-product **50** is increased by using a smaller group in the ether, although even with methyl allyl ether some α-product **49** is observed beside γ-attack.[37]

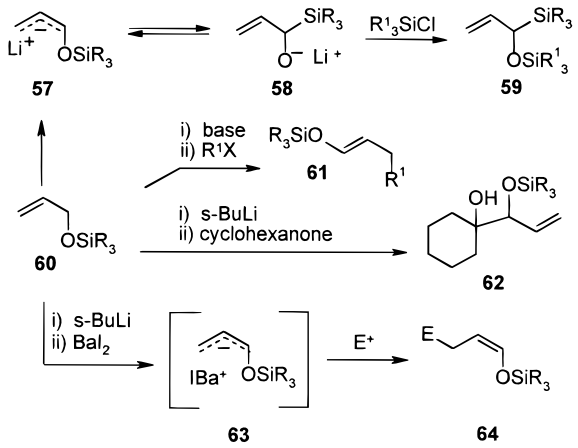
Replacement of the lithium counterion in **40** by treatment with zinc chloride[34] to give **51** as does $CdCl_2$[38,39] results in exclusive formation of α-adducts **49** in subsequent reactions with aldehydes and ketones. Similar α-direction is achieved upon replacement of the lithium counterion with triethylaluminum[40,41] or via boron "ate" complexes[42] (Scheme 8). Another way to achieve α-attack is to use (α-ethoxybutenyl)tributyltin.[43] Furthermore, highly regioselective conjugate 1,2-α-carbonyl additions of allylzinc[34,35] and allylcadmium reagents[44] to enones is observed.

To obtain predominantly γ-products, Mukaiyama[45] treated cinnamyl ether with *s*-BuLi, Weiss' base, Schlosser's base or KDA (Seebach's base) followed by the reaction with the electrophile. This method has been used in asymmetric synthesis. The yield and the optical purity strongly vary with the solvent and the type of base applied. An intramolecular example is the cyclization of allyloxycarbanions of **52** and **54** to vinyl oxetanes **53** and **55** (Scheme 9).[46]

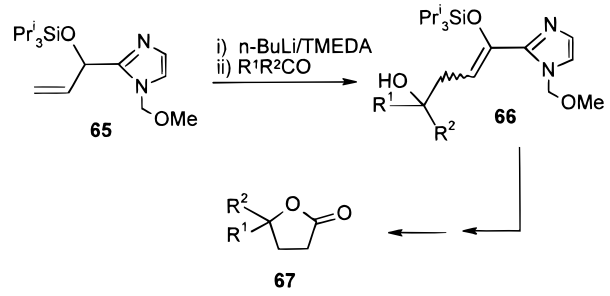
2. Silyl Allyl Ethers (C═C–C–OSiR$_3$)

Allyloxy carbanions **57** of silyl allyl ethers **60** are in rapid equilibrium with the corresponding silyl alkoxides **58** (silyl-Wittig-rearrangement) (Scheme 10).[47−49] Hard electrophiles (TMSCl, chloroformates, diphenyl carbonate, and protons) react exclusively or

Scheme 10



Scheme 11



predominantly at the oxygen to give, for example, **59** (Scheme 10).[50−52] However, Still and Macdonald[35] suggest that the alkoxy silane is the major anionic species in solution at low temperatures where alkylation results in the formation of only C-alkylated products furnishing predominantly γ-attack **61** with primary halides.[35] In general, the analogous reaction with aldehydes or ketones gives predominantly α-products for example **62**[53] (Scheme 10). Siloxyallylbarium compounds **63**, obtained by reaction of the corresponding lithium derivatives with BaI_2, react with carbonyl compounds and alkyl halides to give exclusively the (*Z*)-γ-products **64**[54] (Scheme 10)

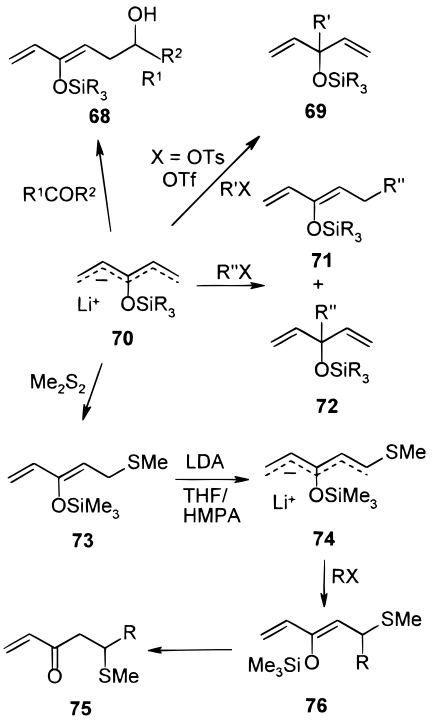
The reaction of deprotonated 2-[1-(triisopropylsiloxy)allyl]-*N*-methoxymethylimidazole **65** with ketones and aldehydes yields regioselectively the γ-product **66** (enoyl silyl ethers of 2-acylimidazoles) which eventually furnish γ-lactones **67** (Scheme 11).[55]

3. 3-[(Trialkylsilyl)oxy]-1,4-pentadiene

Lithiated 3-(trialkylsilyloxy)-1,4-pentadiene **70** shows a γ-selective reaction to **68** with carbonyl compounds, whereas a mixture of α- **72** (minor) and γ-adduct **71** is obtained upon alkylation (Scheme 12).[56] Products of γ-reaction **71** are often preferred with primary and alkenyl halides, but the nature of the leaving group is important. Thus, dominant α-substitution to **69** is observed with tosyl and triflate as leaving groups, whereas additives such as HMPA or TMEDA and transmetalation by zinc or potassium do not significantly change the γ/α ratio in the alkylation of the anion.[57]

γ-Selective sulfenylation to give **73** followed by further deprotonation to **74** and alkylation, which now is directed by the methylthio substituent, gives

Scheme 12



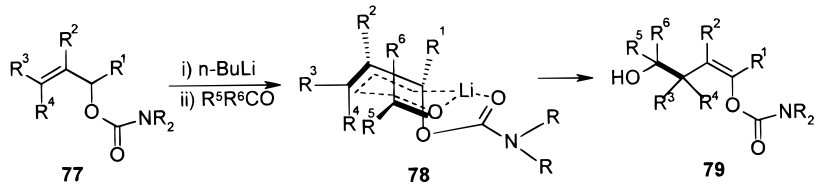
entirely γ-product **76** with respect to the silyloxy group (see also section V.B.3).[58]

4. 2-Alkenyl Carbamates (C═C–C–O–CO–NR$_2$)

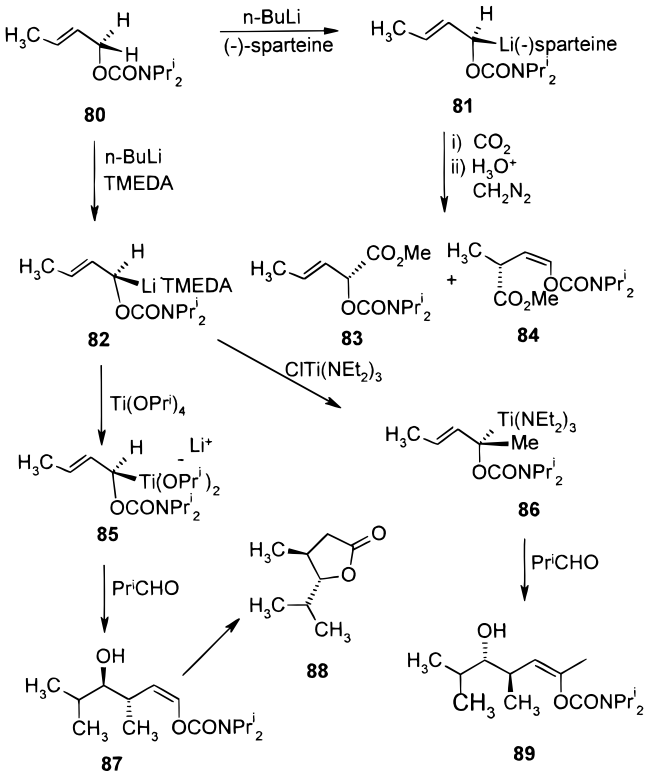
Anions of 2-alkenyl carbamates **77** undergo regioselective γ-reactions with carbonyl compounds to afford γ-hydroxyenol carbamates **79** (Scheme 13) which can be converted into lactols and oxidized on to lactones.[59,60] The γ-selectivity is enhanced with increasing γ-substitution, decreasing α-substitution, or decreasing reactivity of the carbonyl compounds. At the same time the number of alkyl groups should not exceed three, as the kinetic acidity of the 1,3,3-trimethyl derivative is already too low to be lithiated.[61] The regiochemistry of alkylation and silylation is dependent on the position of the alkyl groups in the allylic system. A six-membered transition structure **78** is postulated,[59] in which the lithium cation is held at the α-carbon atom by the oxygen of the carbamate. Crotyl carbamates are also used for diastereoselective homoaldol reactions. The anti diastereoselectivity is improved by application of organotitanium or organoaluminum reagents.[62,63]

(−)-Sparteine complexes **81** of lithiated primary *O*-2-alkenyl carbamates **80** undergo carboxylation with inversion of configuration to produce 39% α- **83** and 30% γ-adduct **84** (Scheme 14). Transmetalation of 1-lithio-2-butenyl-*N*,*N*-diisopropylcarbamate **82** with $(TiO^iPr)_4$ to **85**, followed by carboxylation, proceeds via inversion and the addition of the aldehydes occurs in an anti S_E' process;[64,65] homoaldol adducts **87** and the corresponding γ-lactones **88** are synthesized. Asymmetric synthesis is carried out using chiral starting materials which are stannylated and undergo enantioselective homoaldol addition under the influence of $TiCl_4$.[66] There are other examples for asymmetric synthesis leading to ho-

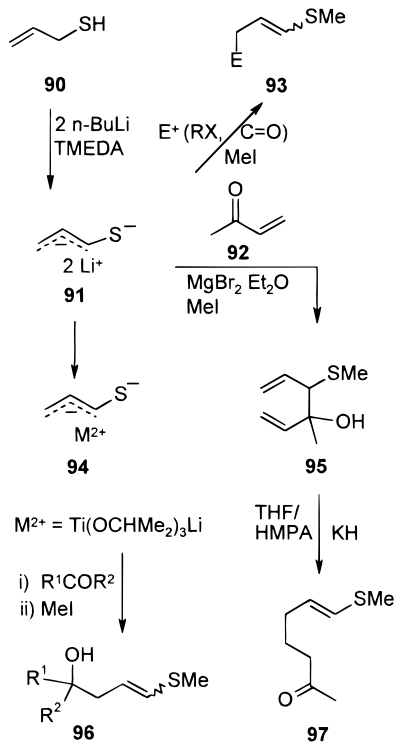
Scheme 13



Scheme 14



Scheme 15



moaldol products under the influence of titanium compounds.[59,60,67−69] As already mentioned lithium−titanium exchange of lithiated 2-alkenyl carbamate by $Ti(O^iPr)_4$ proceeds via retention while for $ClTi(NEt_2)_3$ inversion of the configuration is achieved to give for example **89** upon reaction of **86** with aldehydes. For $ClTi(O^iPr)_3$, no stereoselectivity is observed.[70,71]

C. Sulfur

Much of the synthetic utility of sulfur functionality arises from the ability to stabilize negative charge on an adjacent carbon atom. The stabilizing group can be either a sulfide, a sulfoxide, or sulfone group, whereby allylic sulfoxides play an important role in asymmetric synthesis due to the ease of introducing chiral sulfoxide. Dithiocarbamates, sulfinamides, and sulfoximines are also discussed.

1. Allyl Mercaptans (CH_2═CH–CH_2–SH)

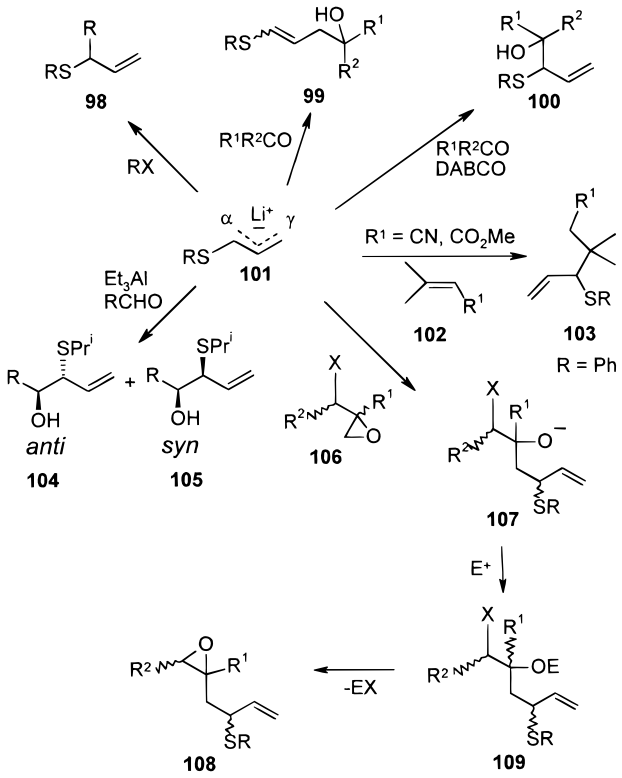
Allyl mercaptan dianions **91** are preferentially attacked at the γ-carbon to form **93** (60/40 to 90/10 γ/α ratio) by alkyl halides, epoxides, and carbonyl compounds (Scheme 15).[72] The γ-selectivity is improved by addition of HMPA and/or KO^{t}Bu. Upon addition of $MgBr_2$, the reaction with α,β-unsaturated aldehydes and ketones, cf. **92**, is highly 1,2-α-regioselective to give **95**. However, a subsequent oxy-Cope rearrangement eventually leads to the 1,4-γ-adduct **97**.[73] The dianion of allyl mercaptan after titanation to **94** affords almost exclusively the γ-product **96** with aldehydes and ketones (Scheme 15). The 2-methyl analogue of the mercaptan shows a similar regioselectivity but gives a somewhat lower yield.[73,74]

2. Allyl Sulfides (C═C–C–SR)

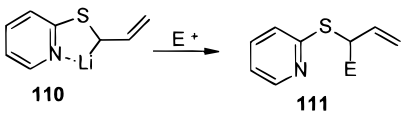
Thioethers show an opposite behavior with respect to the oxygen-substituted allylic anions in that allyl thioether anions **101** are α-alkylated to **98** and react at the γ-terminus with carbonyl compounds to form **99** (Scheme 16). High α-selectivity is achieved upon alkylation in the presence of 1,4-diazabicyclo[2.2.2]-octane (DABCO) due to the formation of dissociated ion pairs (in the absence of DABCO: intimate ion pairs).[40,75] α-Regioselectivity (**110** → **111**) is also enhanced by intramolecular chelation of lithium to the heteroaromatic ring (Scheme 17).[76]

In the course of the synthesis of a chrysanthemic acid precursor, 1,4-α-additions of lithium allyl phenyl sulfides **101** to 3,3-dimethylacrylonitrile and to methyl 3,3-dimethylacrylate **102** were observed to give **103** (Scheme 16).[77] Lithiated allyl phenyl **101** sulfide reacts with oxiranes containing an adjacent leaving group predominantly at the allylic anion α-carbon (cf.

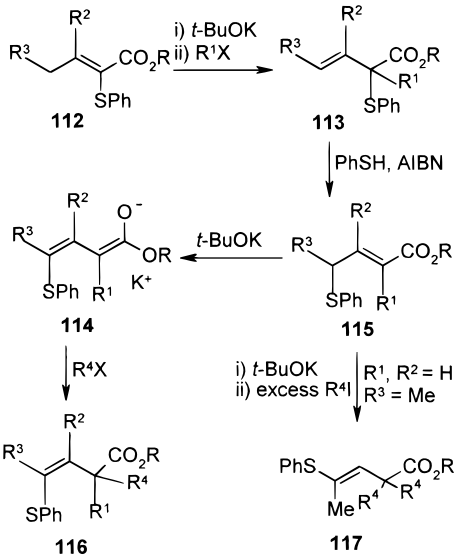
Scheme 16



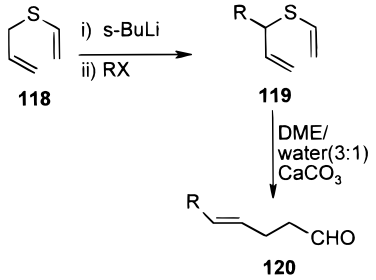
Scheme 17



Scheme 18



Scheme 19



106) (Scheme 16) (trans opening of epoxides). The fate of the primary open-chain product **107** depends on the leaving group X. Hence, epichlorhydrin **106** ($R^1 = R^2 = H$, X = Cl) allows isolation of the alcohol **109** while with tosylate in situ ring closure to a new oxirane **108** is observed.[78,79]

Exclusive α-attack is observed on converting **101** into triethylaluminum or trialkylboron "ate" complexes for both carbonyl compounds[80] and reactive halides,[42] although "ate" complexes produce with aldehydes a mixture of the syn- **104** and anti-isomers **105**.[81] In general, "ate" complexes should facilitate the coupling reaction, because of the more ionic nature of the C−Al bond and the longer bond imposes less steric hindrance (Scheme 16).

"Titanation" of the lithioallyl sulfides causes high regioselectivity, and also excellent chemical selectivity of the resulting nucleophilic reagents. Such titanium reagents give α-products with carbonyl compounds in a stereocontrolled manner with high diastereoselectivity,[82] save for γ-substituted allyl sulfides where γ-selectivity is observed.[83]

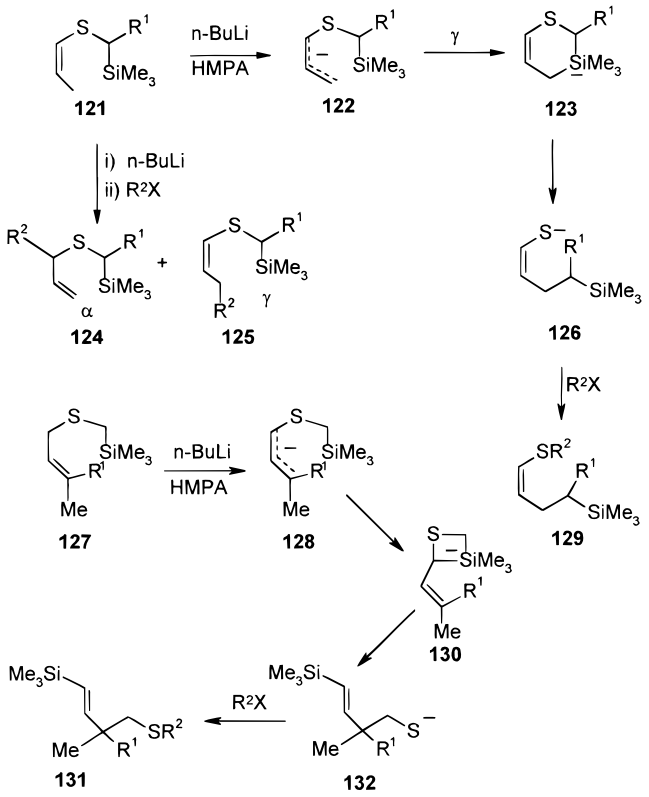
Lithio-γ-(methylthio)crotonate esters[84] and γ-(phenylthio)crotonate **115** esters when deprotonated with potassium *tert*-butoxide undergo γ-alkylation to **116** and to **117** when excess of alkylating agent is applied. By contrast, **112** having both groups CO_2R and RS at the same end of the allyl moiety, undergoes exclusive α-alkylation to **113** as both groups increase the coefficient of the HOMO at their point of attachment on the allyl anion (Scheme 18).[85]

1-(Vinylthio)allyllithium from **118** reacts with halides RX to give α-products **119** from which subsequent thio-Claisen rearrangements produce γ,δ-unsaturated aldehydes **120** highly stereoselectively (Scheme 19).[86]

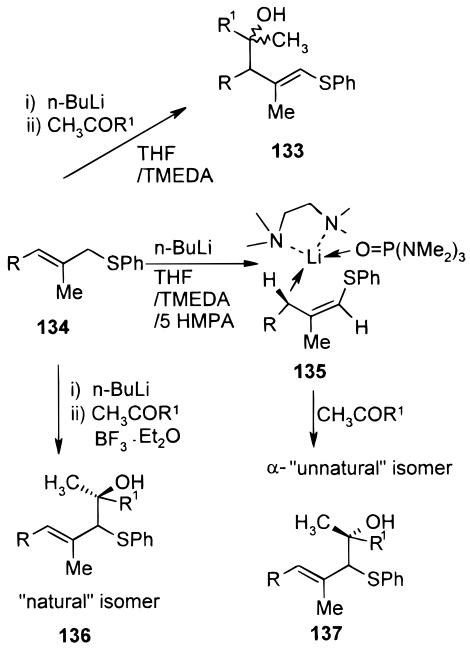
In the absence of HMPA, 3-[[(trimethylsilyl)methyl]thio]allyllithium from **121** reacts with allyl halides to give a mixture of α- **124** and γ-products **125** (Scheme 20). The presence of HMPA enhances the nucleophilicity of the allylic anion and facilitates the rearrangement of the initially formed α- or γ-adducts. An intramolecular attack at the α- and γ-positions, respectively, on Si takes place. After deprotonation to **122** the mechanism is thought to involve a pentacoordinated silicate intermediate **123**, giving the lithium alkenyl sulfide **126** which is then trapped by alkyl halides to form **129**. On the other hand, the rearrangement from **127** to **131** is assumed to proceed upon deprotonation to **128** via a four-membered five-coordinated silicate intermediate **130** to give **132** which is then alkylated to **131** (Scheme 20).[87]

The coupling of an allyl sulfide anion from **134** with a ketone represents the key step in a synthesis of erythronolide B.[88] The use of THF/TMEDA gives the γ-adduct **133**, while the system THF/TMEDA/5HMPA produces the α-adduct **137** ("unnatural stereoisomer") (Scheme 21). This reaction is thought to proceed via a η^1-complex **135** due to the presence of HMPA while under the former conditions (^{n}BuLi/THF/TMEDA) a η^3-complex is assumed. In contrast,

Scheme 20



Scheme 21

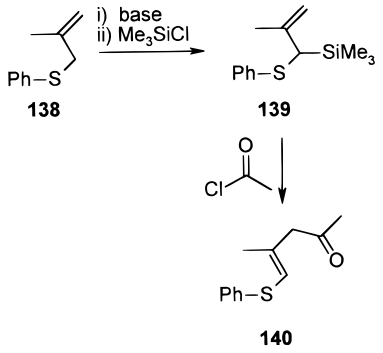


the "natural stereoisomer" **136** is obtained in the presence of $BF_3{\cdot}Et_2O$. The reaction proceeds via a chelate-controlled mechanism whereby the ketone is precomplexed or preactivated by $BF_3{\cdot}Et_2O$ followed by addition to the allyl sulfide anion to give α-adduct **136**.

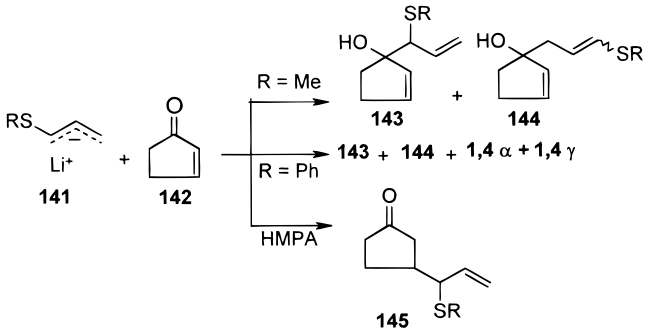
To achieve regioselective γ-acylation of $CH_2{=}C(Me)$-$CH_2{-}SPh$, the 2-methyl-substituted allylic sulfide **138** needs to be first converted to the α-silylallylic sulfide **139** and hence to **140** (Scheme 22).[89]

(Methylthio)- and (*tert*-butylthio)allyllithium (cf. **141**) give, with cyclopentenone **142**, the α-1,2-adduct

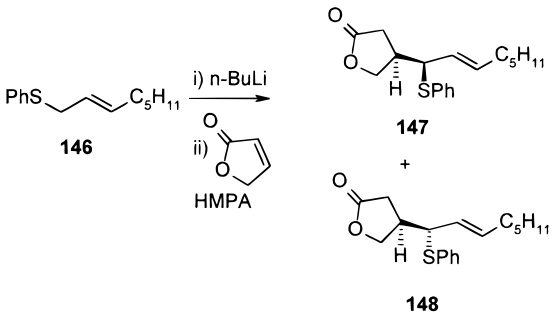
Scheme 22



Scheme 23



Scheme 24



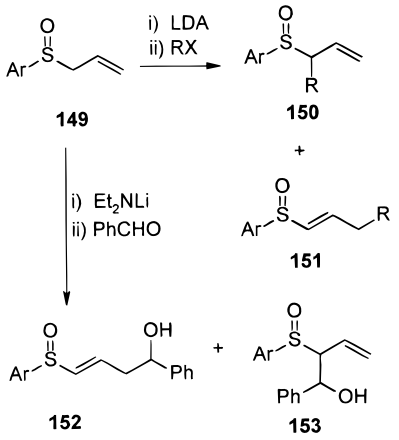
143 and the γ-1,2-adduct **144**, while the phenyl analogue of **141** in addition gives small amounts of 1,4-α- and γ-addition products. The formation of the 1,4-α-addition product **145** with hardly any 1,4-γ-attack, can be enhanced by the presence of 1 equiv of HMPA (Scheme 23).[90,91]

Conjugate addition to allyl phenyl sulfides,[92] e.g., **146** also gave α-products **147** and **148** (Scheme 24). This route can eventually furnish a prostaglandin, whereby the key step involves the reaction of the lithium enolates of **147** and **148**, produced in the initial conjugate addition step, with triphenyltin followed by alkylation[93−95] or a stereoselective steroid synthesis by subsequent trapping of the enolates with benzyl bromide.[96]

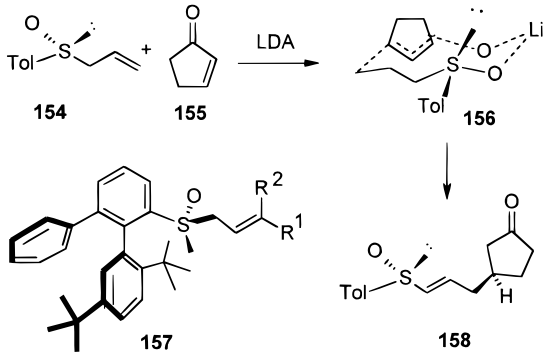
3. Allyl Sulfoxides (C=C–C–SOR)

Chiral sulfoxides can easily be introduced into a molecule and this is an important strategy for asymmetric synthesis. Allylic sulfoxides **149** were reported to form α- **150** (major) and γ-products **151** (minor) upon alkylation[76] (Scheme 25). The ratio of the mixture depends on both the type of allyl sulfoxide and the electrophile.[97,98] Solladié[99] reported mainly

Scheme 25



Scheme 26



γ-attack in the reaction with benzaldehyde to give **152** alongside a minor amount of **153** from α-attack. Carbonyl attack is possibly thermodynamically controlled while the alkylation is under kinetic control.

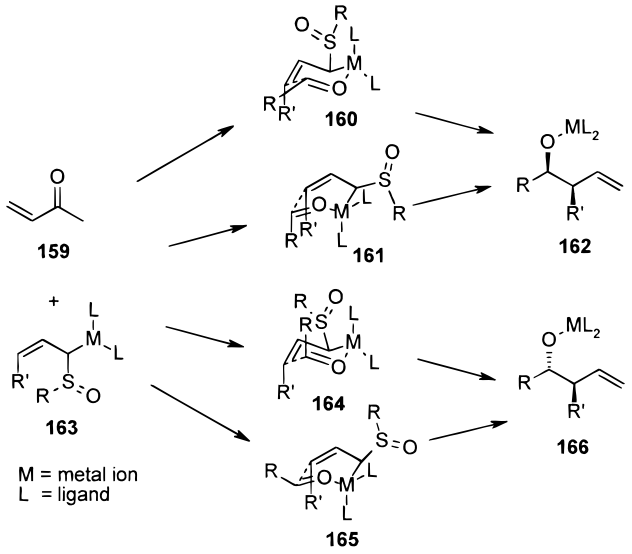
Chiral allylic sulfoxide **154** gives regiospecific asymmetric conjugate addition to various cyclic enones (cf. **155**) with high diastereomeric excess[100] via a 10-membered "*trans*-decalyl" or "trans-fused chair−chair" transition structure **156** furnishing 1,4-γ-adducts **158** (Scheme 26).[92,101−106] Better regio- and diastereoselective addition is achieved by the utilization of sterically demanding auxiliary-modified allylic sulfoxides **157**[107] for which the relative configuration depends on whether the product is formed under kinetic or thermodynamic control.[108]

In comparison to cyclic enones, sulfoxides add to acyclic enones via a six-membered transition intermediate **160**, **161**, **164**, and **165** which is characteristic for the reaction of unsaturated carbonyl derivatives **159** with allyl compounds **163** (M = B, Ti, Li, etc.) to give **162** and **166** (Scheme 27).[109] If large substituents on the acyclic enone increase its steric rigidity the reaction is predicted to proceed via the extended *trans*-decalyl transition structure (see Scheme 26).[110]

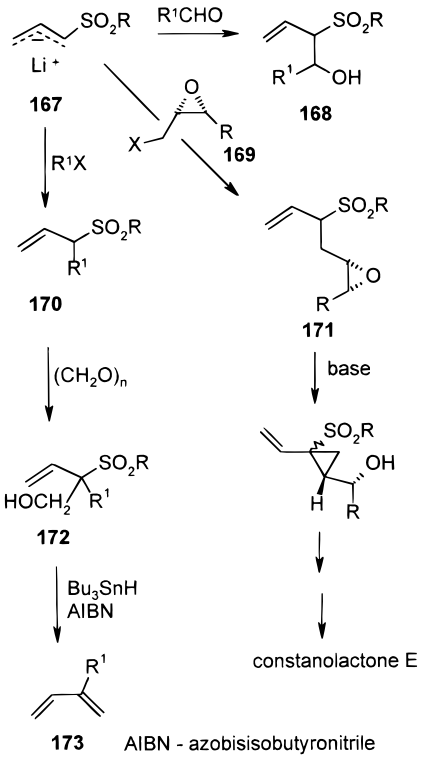
4. Allyl Sulfones (C═C–C–SO₂R)

Allyl sulfone anions **167** are obtained by treatment of the corresponding sulfur compound with ^{n}BuLi in THF, or RMgX, or in a two-phase system of concentrated aqueous NaOH and a quaternary ammonium catalyst. Lithiated allyl sulfone reacts α with alkyl halides or Me_3SiCH_2Cl give **170**[111−113] and with

Scheme 27



Scheme 28



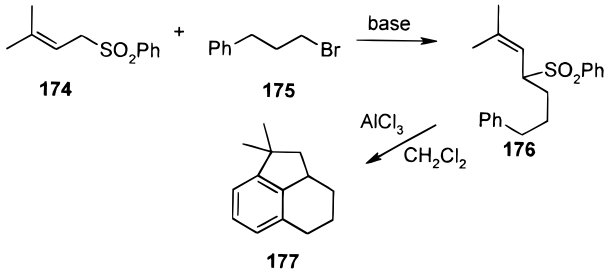
aldehydes to give α-adducts **168** regio- and diastereoselectively (Scheme 28).[114]

α-(Hydroxymethyl)allyl sulfones **172** are obtained upon hydroxymethylation with paraformaldehyde (α-attack) and the products can be converted into 2-substituted 1,3-butadienes **173** (Scheme 28).[115] The reaction of allyl phenyl sulfone with a chiral epoxide (cf. **169**) is used in the synthesis of constanolactone E (Scheme 28).[116]

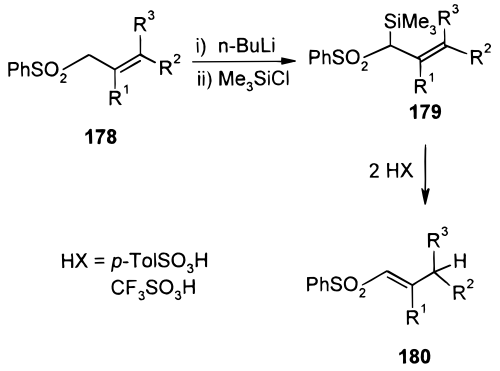
Similarly, the α-product **176** is obtained from the alkylation of prenyl sulfone **174**.[117] This is used for the synthesis of cyclized products (cf. **177**) by addition of $AlCl_3$ (Scheme 29).

Furthermore, allyl sulfones **178** can be converted to vinyl sulfones **180** via silylation at the α-carbon

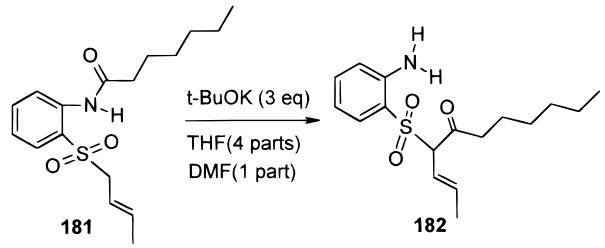
Scheme 29



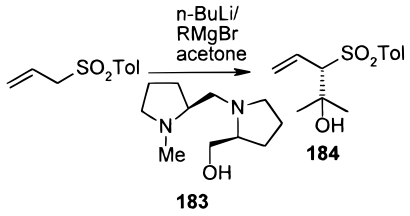
Scheme 30



Scheme 31



Scheme 32



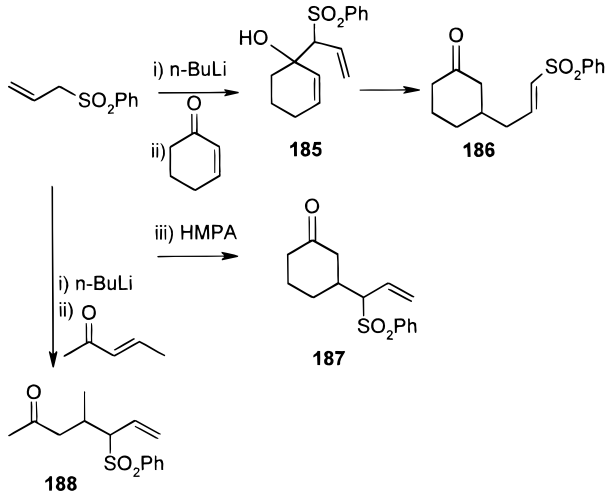
to give **179** followed by protodesilylation (Scheme 30).[118]

Allyl sulfone **181** can form α-product **182** via an intramolecular transfer of an acyl group (Scheme 31).[119]

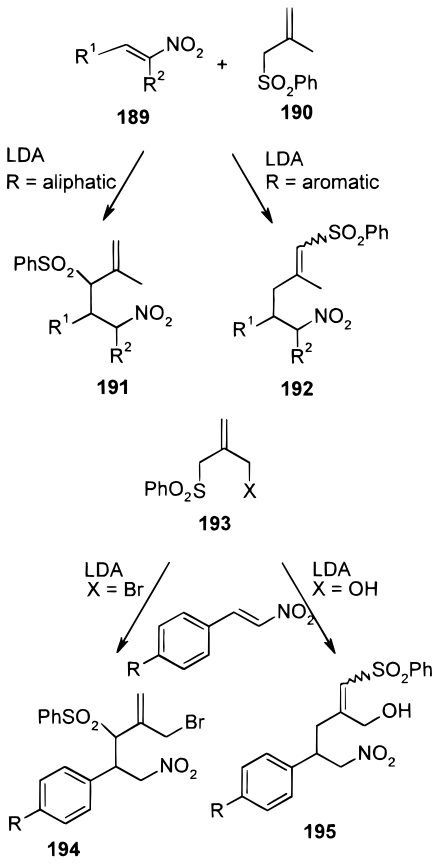
The reaction of lithium and magnesium salts with acetone in the presence of a chiral diamine **183** gives α-substituted chiral sulfones **184**. The enantioselectivity is improved up to a value of 50% ee by transmetalation from lithium to magnesium derivatives (Scheme 32).[120]

In the presence of HMPA the conjugate addition to cyclic and acyclic enones proceeds exclusively via 1,4-α-attack to give **187**. Without HMPA present, with cyclic enones the 1,2-α-addition product **185** is formed followed by a rearrangement to the 1,4-γ-adduct **186** (Scheme 33).[121] The α-regioselectivity for acyclic enones (cf. **188**) is not changed in the absence

Scheme 33



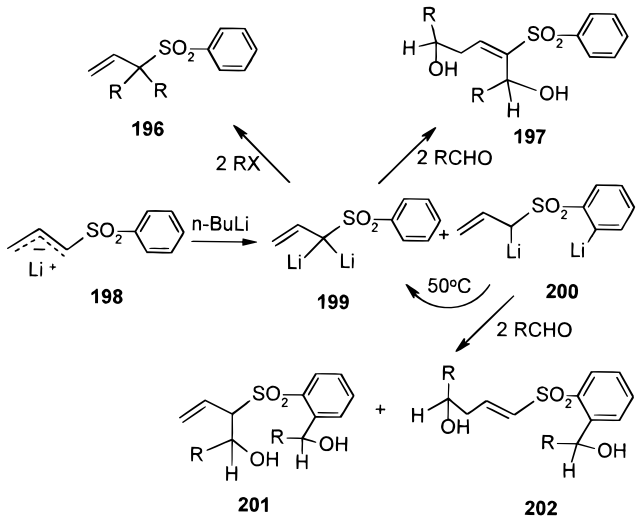
Scheme 34



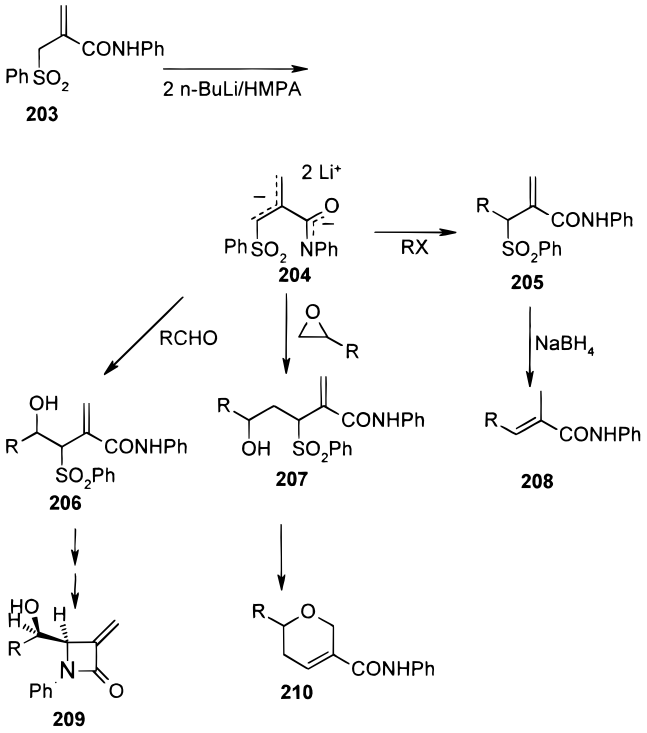
of HMPA.[122] More details about the influence of HMPA on the conjugate addition of γ-crotonolactone to allyl sulfones, allyl sulfides, and allyl thiocarbamates are given by Haynes.[122]

The Michael addition of allyl sulfone **190** to aromatic nitroolefins (cf. **189**) yields predominantly γ-(*E*)-adducts **192**, whereas aliphatic nitroolefins (cf. **189**) form exclusively the α-products **191**, in which the syn-isomer is mainly found. The presence of an OH substituent in the sulfone (cf. **193**) causes formation of only (*Z*)-γ-adducts **195**, whereas the presence of a bromine substituent in the methyl group of methylallyl sulfone **193** reverses the regiochemistry to give **194** (Scheme 34).[123]

Scheme 35



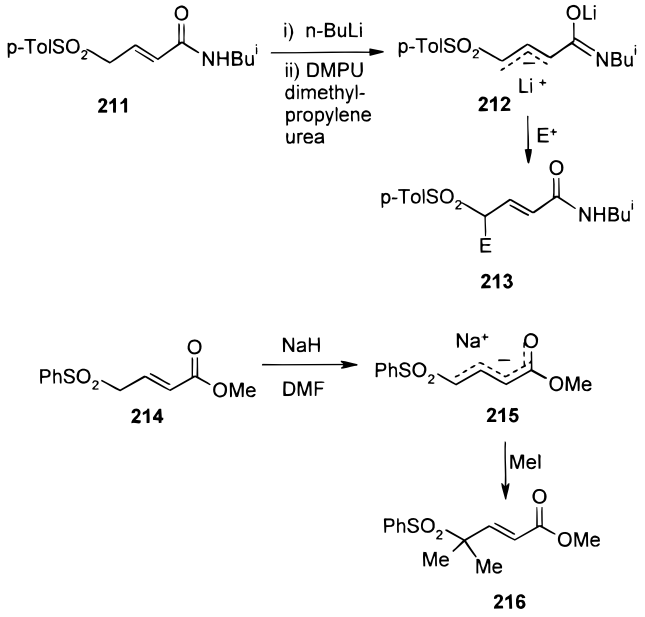
Scheme 36



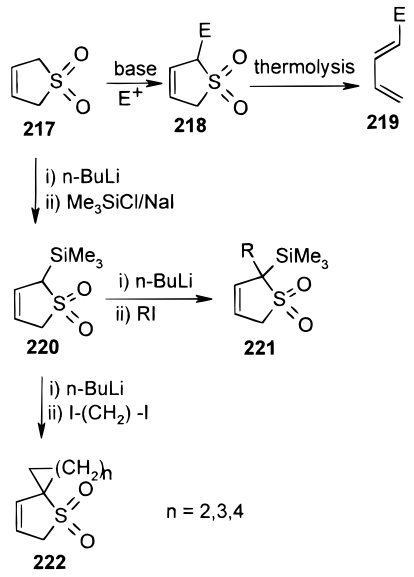
Treatment of monolithioallyl phenyl sulfone **198** with an excess of ^{n}BuLi affords a mixture of 1,1-dilithiated allyl phenyl sulfone **199** and 1,*o*-dilithiated **200**[124] as shown by quenching with an excess of benzaldehyde to give the 1,*o*-**201** and 3,*o*-(*E*)-diadducts **202** and the 1,3-(*E*)-diadduct **197** (Scheme 35).[125] With alkyl halides, double alkylation of the dianion mixture occurs selectively at the α-position to form **196**[126] and this is used in the synthesis of pheromone analogues. At 50 °C, the α,*o*-dianion **200** is converted into the thermodymically more stable α,α-dilithio intermediate **199**.[124]

Predominantly α-products are also found for the electrophilic reactions of the dianion of *N*-phenyl-2-[(phenylsulfonyl)methyl]propenamide **204**, which is used for the preparation of α-methylene-*β*-lactams **209**,[127] the synthesis of α,*β*-unsaturated amides **208** and 5,6-dihydro-2*H*-pyrans **210** (Scheme 36).[128]

Scheme 37



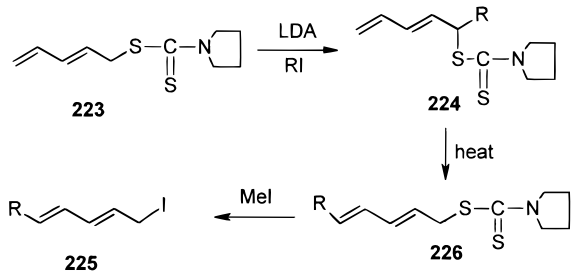
Scheme 38



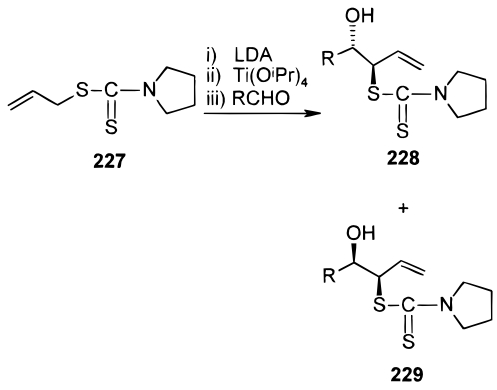
The allyl sulfone dianion **212** gives regiospecific and stereoselective reactions with alkyl bromides, aldehydes and electrophilic olefins at the α-position to the sulfone group to form **213** (Scheme 37).[129] Furthermore, for the dienolate anion **215**, derived from the *γ*-(phenylsulfonyl)crotonate **214**, α-alkylation is predominantly observed to give **216** (Scheme 37).[130] The complementary conjugative effects of the sulfonyl and the carbonyl substituents result in preferential formation of **216**. Catura and Najera reported that the treatment of methyl (*E*)-4-tosyl-2-butenoate of type **214** with 2 equiv of sodium hydride and different mono- and dihalides gives mixtures of *γ*,*γ*- and α,α- or α,*γ*- and *γ*,*γ*-dialkylated products.[131]

Similarly to allyl sulfones, deprotonated 2,5-dihydrothiophene 1,1-dioxide **217** reacts with alkyl halides, aldehydes to give exclusively α-products **218**. Subsequent desulfonylation (thermolysis) leads to substituted buta-1,3-dienes **219**.[132−134] Tso et al. have prepared 2,2-dialkylated or spiro analogues **221** or

Scheme 39



Scheme 40



222 through 2-(trimethylsilyl)-2,5-dihydrothiophene 1,1-dioxide **220** which is obtained by lithiation and reaction with $Me_3SiCl{\cdot}NaI$.[135]

5. Allyl Dithiocarbamates (C═C–C–S–CSNR$_2$)

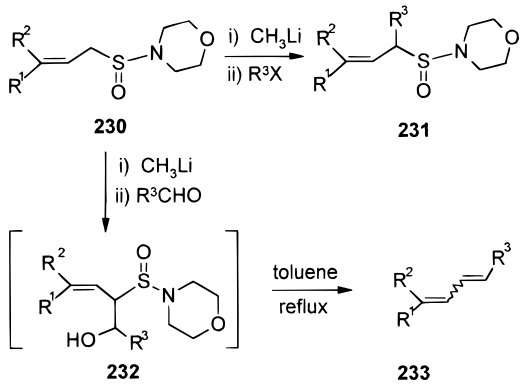
Pentadienyl dithiocarbamate **223** is alkylated in the α-position (Scheme 39).[136] Product **224** undergoes presumably a double [3,3]-sigmatropic rearrangement to form **226**.[137] Treatment of the latter with MeI gives 1-iodo-2,4-(*E*,*E*)-dienes **225** (or tetraenes depending on R).[138] Pheromone synthesis has proceeded via these steps.[139,140]

α-Products **228** and **229** are usually obtained in the reaction of allyl dithiocarbamate anions from **227** with aldehydes via titanium reagents (Scheme 40).[141] In the absence of $Ti(O^iPr)_4$, both the α- and γ-products are observed.[142−144]

6. Allylsulfinamides (C═C–C–SONR$_2$)

Prepared from allyl alcohols and 4-(chlorosulfenyl)-morpholine in the presence of triethylamine, allylsulfinamides **230** undergo α-alkylation apparently with high regioselectivity to **231** (Scheme 41),[145] although Julia reported a low diastereoselectivity except for $R^1 = p$-Me-C_6H_4, $R^2 = H$.[146] No isomerization of the double bond in **231** was detected after the alkylation. Reaction of **230** with aldehydes gives the α-anti-adducts (β-hydroxysulfinamides) **232** which are unstable and can be converted into the corresponding polyene **233** (mainly *E* product) by heating under reflux in toluene (Scheme 41).[145] The yield of the alkyl sulfide anion is improved by using methyllithium as the metalating agent since butyllithium can lead to side reactions.

Scheme 41



7. Allyl Sulfoximines (C═C–C–SONR)

The thermal rearrangement of allylic sulfoximines **234** to allylic sulfinamides **236** can occur thermally but only in a few cases.[147a,b] However under palladium(0) catalysis this rearrangement is a general and facile process.[147c,d] The rearranged products **236** can be converted to N-protected allylic amines by mild base hydrolysis. The alkylation of allylic sulfoximines **234** (R^1 = Ph, CH_2Ph, R^2 = Tol) gives α-alkylated products **235** as mixtures of diastereoisomers.[148] An optically active allylic sulfoximine gave an α-alkylated product as a single diastereoisomer.[147c]

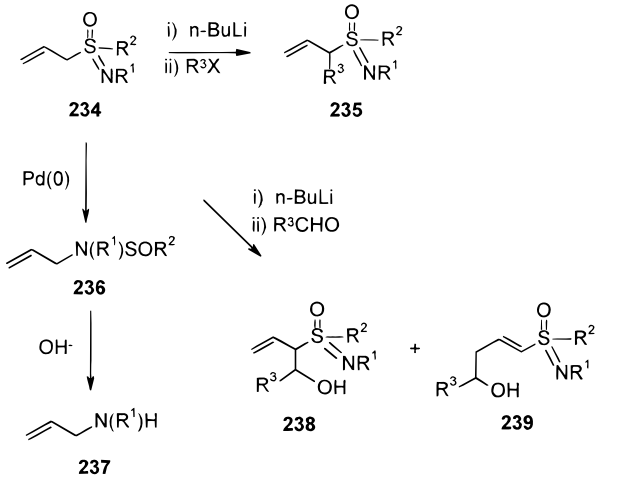
Reaction of lithiated **234** (R^1 = Ph; R^2 = Tol) with benzaldehyde gave a 5.3:1 mixture of the α-adduct **238** and the γ-product **239**, while a similar reaction with pivaldehyde yielded only the α-product **238**.[148] In related examples, α-products were exclusively formed from the reaction of lithiated *N*-*tert*-butyldiphenylsilyl[149a] and *N*-methyl[149b] allylic sulfoximines with aldehydes. Lithiation of racemic *N*-tosyl allylic sulfoximine **234** (R^1 = Ts; R^2 = Ph) followed by quenching with benzaldehyde or isobutyraldehyde gave exclusively the α-product **238** as mixtures of diastereoisomers.[149c]

The reaction of lithiated sulfoximines **234** with cyclic enones gave mixtures of regio- and diastereoisomers. The regioselectivity is dependent on the nature of the N-substituent.[148,149a,150,151] *N*-Tosyl derivatives give exclusively α-1,4-products **240**, while this orientation of adduct is only slightly favored in the case of the *N*-phenyl derivatives. *N*-*tert*-Butyldiphenylsilyl derivatives, by contrast, favor γ-1,4-adducts (**241**).

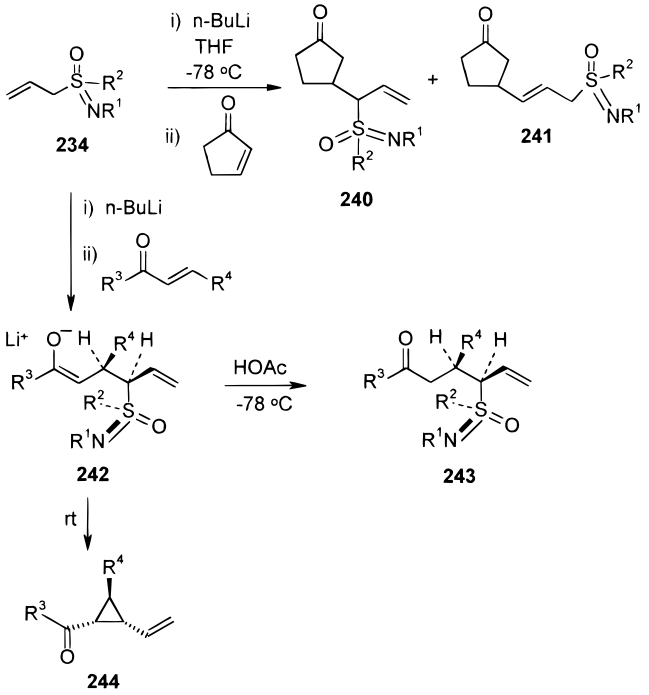
For acyclic enone cases, the regioselectivity is also influenced by the nature of the R^1 and R^2 on **234** and the reaction conditions, while the diastereoselectivity can be achieved.[149a,150,151a] In one case, the addition of acyclic enones to the lithiated *N*-tosyl-*S*-allyl-*S*-phenylsulfoximines in THF at ∼78 °C followed by quenching with acetic acid at same temperature produced exclusively the 1,4-α-adducts **243** with high diastereoselectivity (Scheme 43).[150] Warming a solution of the anionic adducts **242** to room temperature gave the racemic vinylcyclopropanes **244**.

Diastereomerically pure γ-hydroxyvinyl sulfoximide is obtained with titanium reagents (Scheme 44).[152,153]

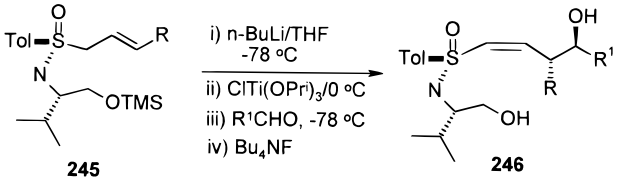
Scheme 42



Scheme 43



Scheme 44

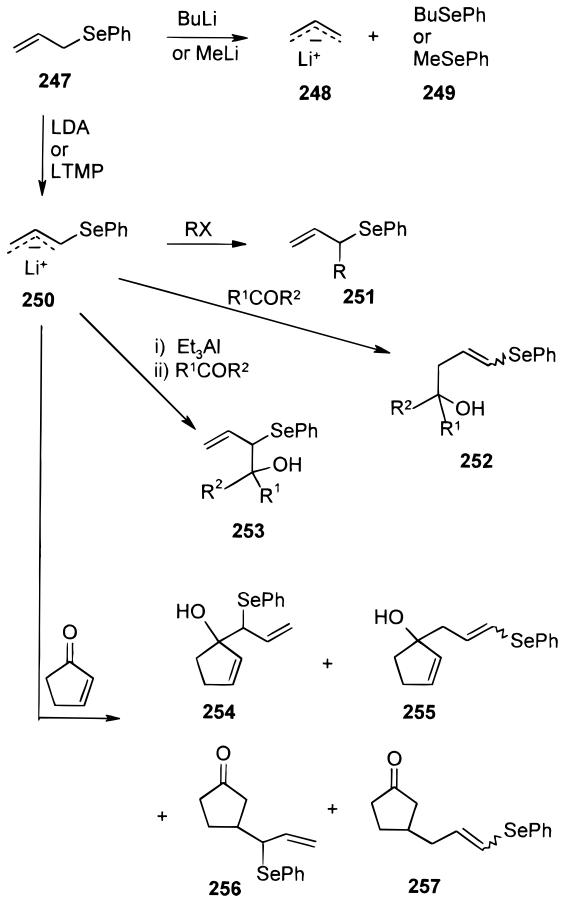


D. Selenium

Allyl phenyl selenides are valuable precursors of allyllithiums and of metalated allyl phenyl selenides. Similar to sulfur-stabilized analogues, anions of allyl selenides undergo reversible 1,3-shifts. Allyl selenoxides also show [2,3]-sigmatropic rearrangements. In general the chemical behavior of these compounds is similar to their sulfur analogues.

Thus, allyl phenyl selenide anion **250** reacts with alkyl halides at the α-position to give **251**, whereas it is attacked at the γ-terminus by carbonyl compounds forming **252**.[154] However, a reversed regioselectivity is observed with triethylaluminum "ate" complexes, i.e., α-adducts **253** (predominantly anti) are produced with carbonyl compounds (Scheme 45).[42] Upon transmetalation of **250** with magnesium compounds the regioselectivity is also converted to α.[41] The regioselectivity also depends on the nature of the electrophile. While TMSCl gives predominantly (82:18) α-attack on allyl selenide anions, $PhSiMe_2Cl$ forms a mixture of regioisomers α:γ = 41:59.[155] Increased α-selectivity is achieved with substituents at the γ-position.

Scheme 45



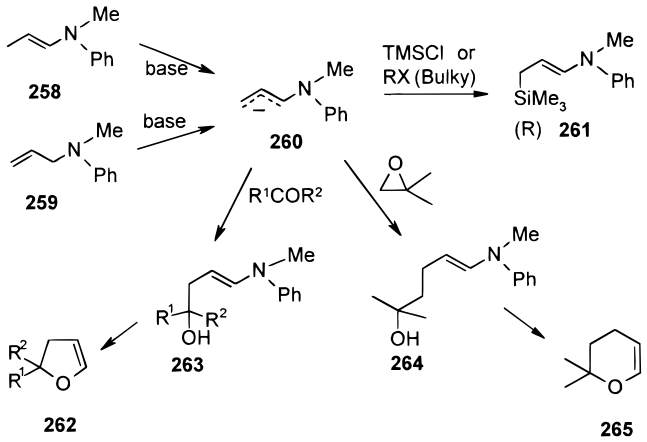
Similar to allyl sulfides, (phenylseleno)allyllithium **250** undergoes a HMPA mediated conjugate 1,4-α-addition to 2-cyclopentenone. Without HMPA present, α- **254** and γ-1,2-addition **255** are observed together with a little α- **256** and γ-1,4-addition **257** (Scheme 45).[90]

As treatment of **247** with ^{n}BuLi or methyllithium leads to rapid transmetalation furnishing the allyllithium **248** and alkyl phenyl selenides **249**, allyl selenides (cf. **247**) are metalated with LDA or lithium 2,2,6,6-tetramethylpiperidide (LTMP) (Scheme 45).[156]

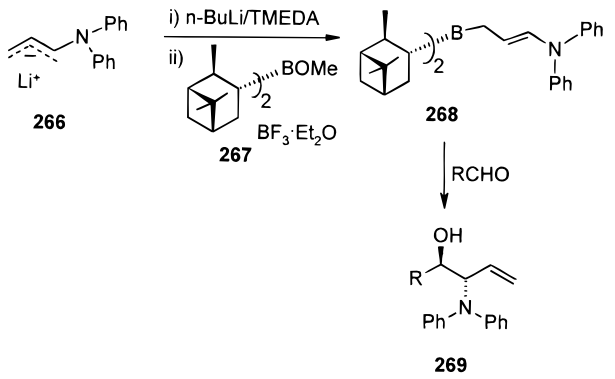
E. Nitrogen

We discuss here acylic allylamines, their functionalized derivatives (including phosphoramides, *N*-nitrosoallylamines, nitropropenes, allylimines, allylamides, and ureas) and analogous cyclic amines (e.g., pyrrolidine) together with allyl derivatives of heterocycles (e.g., benzotriazole, carbazole).

Scheme 46



Scheme 47



1. Allylamines (C═C–C–NR$_2$)

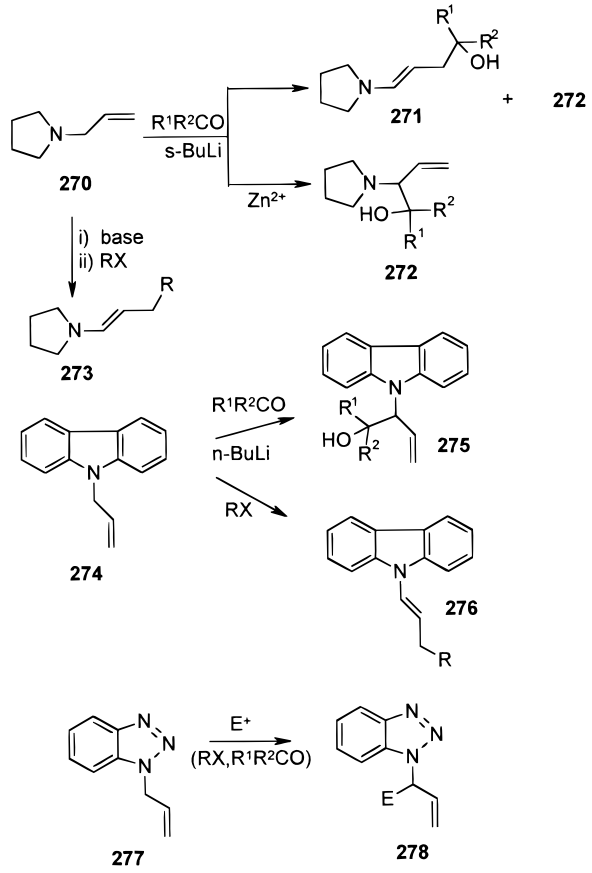
Lithiated allylamines **260** are prepared by deprotonation of enamines **258** or allylamines **259**.[157] γ-Products **261**, **263**, and **264** result exclusively or predominantly for reactions with TMSCl,[157] bulky alkyl halides, carbonyl compounds, and epoxides (Scheme 46).[158] The hydroxy derivatives produced from the carbonyl compounds and epoxides give upon heating dihydrofurans **262** and dihydropyrans **265**, respectively.[159] The resulting silylated enamines can be lithiated again and react with RX to give α-products with respect to the trimethylsilyl group.[157] However, in some cases additional substituted products are found as in the reactions of [C═C−C−N(Me)-Ph] with Me_3SiCl, RX, RCHO, and RCOR.[160−162] For example a mixture of the α- and γ-products was obtained with methyl iodide.[163]

Lithiated allyldiphenylamine **266** gives the γ-adducts **268** [(*E*)-allylboranes] with (−)- and (+)-*B*-(methoxydiisopino)campheylborane **267** and boron trifluoride−diethyl etherate. Upon treatment with aldehydes, **268** provides anti β-diphenylamino alcohols **269** which are γ-adducts with respect to boron and α-adducts to the nitrogen. The reaction proceeds with excellent anti-relative stereochemical control (Scheme 47).[164]

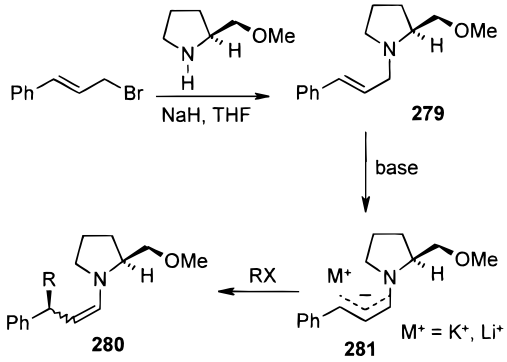
2. 1-Allylpyrrolidines (C═C–C–N(CH$_2$)$_4$), 9-Allylcarbazoles (C═C–C–Cb), and N-Allylbenzotriazoles (C═C–C–Bt)

The anions from 1-allylpyrrolidine **270** and 9-allylcarbazole **274**[165] are both alkylated at the γ-terminus in high yields to give (*E*)-**273** and (*Z*)-**276**,

Scheme 48



Scheme 49



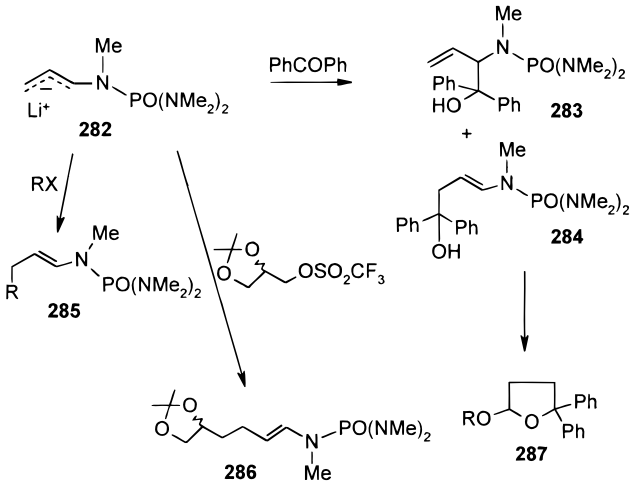
respectively. In contrast, reactions of 1-allylpyrrolidine anion with carbonyl compounds exhibit low regioselectivity to form equal amounts of α- **272** and γ-products **271**.[166] Application of Zn^{2+} as the counterion favors the formation of the α-adduct **272**.[167] 9-Allylcarbazole reacts with ketones mostly at the α-position to form **275**,[168] while 1-allylbenzotriazole **277** generally gives the α-products **278** with alkylating agents and carbonyl derivatives (Scheme 48).[169]

Enantiomerically pure 1-allyl-2-(*S*)-methoxymethylpyrrolidine **279** is γ-alkylated with high diastereoselectivity to yield enamine **280** (Scheme 49).[170] The diastereoselectivity varies with the nature of the counterion, the solvent and the reaction temperature. The better solvated lithium salt (cf. **281**) gives a lower d.e. in THF than the potassium salt while changing to less complexing petrol ether causes a significant increase of the diasereoselectivity.

3. Allylphosphoramides (C═C–C–N(Me)PO(NMe$_2$)$_2$)

Phosphoramide anion **282** undergoes γ-alkylation to give **285** with various alkylating agents,[171,172] whereas a mixture of the α- **283** and γ-products **284** is obtained upon treatment with benzophenone. Intramolecular cyclization of **284** results in the formation of γ-lactols **287** (Scheme 50). The presence of the bulky groups on phosphorus in **282** is one possible reason for the γ-attack by electrophiles.[173] A reaction of this type has been employed in the synthesis of a key chiral synthon **286** (δ-valerolactone derivative which is a Mosquito oviposition attracting pheromone) (Scheme 50).[174] Replacement of lithium in **282** by magnesium leads almost exclusively to γ-substitution to give (*Z*)-enamides.[172,175]

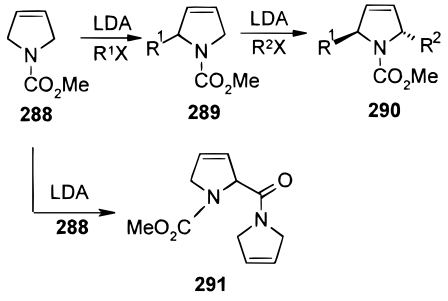
Scheme 50



4. 3-Pyrrolines

Lithiated 1-(methoxycarbonyl)-3-pyrroline **288** affords the α-alkylated product **289** with high regioselectivity;[176] in addition, bisalkylation of **288** yields a single diastereoisomer **290** with a trans configuration (Scheme 51).[177] The intermediate anion of **288** is very reactive and, unless alkylation is carried out immediately after the anion is formed, it reacts with another molecule of the starting material to form the amide **291**.[178]

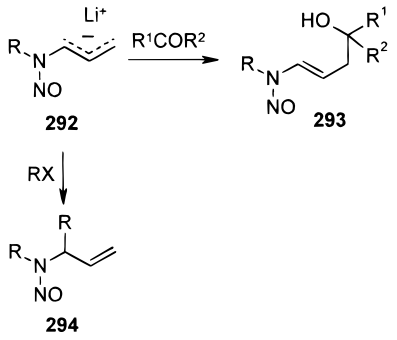
Scheme 51



5. N-Nitrosoallylamines (C═C–C–N(NO)R)

The deprotonation of *N*-nitrosoallylamines, followed by reaction of **292** with allyl halides, yields kinetically favored α-adducts **294**. Reactions with carbonyl compounds are reversible thus giving the γ-*E*-adducts **293** under thermodynamic control (Scheme 52).[179]

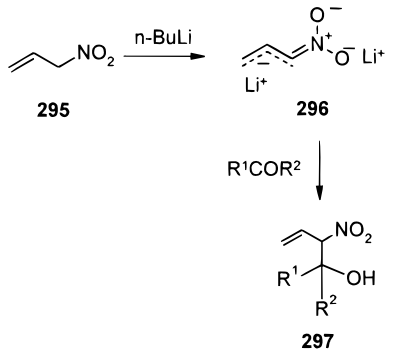
Scheme 52



6. 3-Nitroprop-1-enes (C═C–C–NO$_2$)

Nitropropene **295** undergoes double-deprotonation to give the dianion **296**, which upon treatment with carbonyl compounds, forms α-nitroallyl alcohols **297** (Scheme 53).[180]

Scheme 53



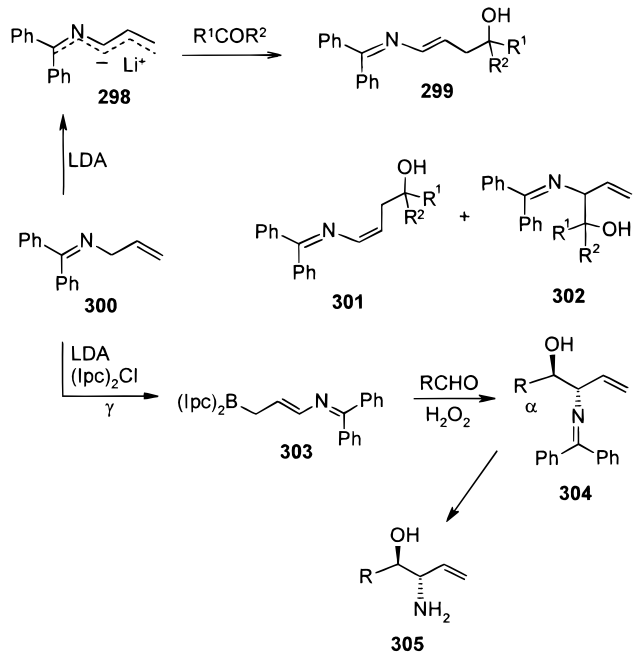
7. N-Allylimines (C═C–C–N═C)

N-Allylimine anions **298** are prepared by deprotonation of **300**. Generally, the reaction of **298** with less reactive ketones affords regiospecifically the *E*-γ-isomer **299**, while with more reactive ketones, small amounts of *Z*-isomer **301** are also observed together with the α-adduct **302** (Scheme 54). The reactions of **298** with aldehydes yields mixtures of the α- **302** (R^1 = H) and γ-adducts **299**, **301** (R^1 = H); addition of HMPA and a low reaction temperature (−78 °C) favors γ-attack (100% with benzaldehyde). Simply applying low temperature and apolar solvents (e.g., hexane) improves the yield of the α-product.[181] Conversion of **300** to the boron reagent **303**, via γ-attack, followed by reactions with aldehydes yields the α-adducts **304** with respect to nitrogen and then the amine **305** (Scheme 54).[182]

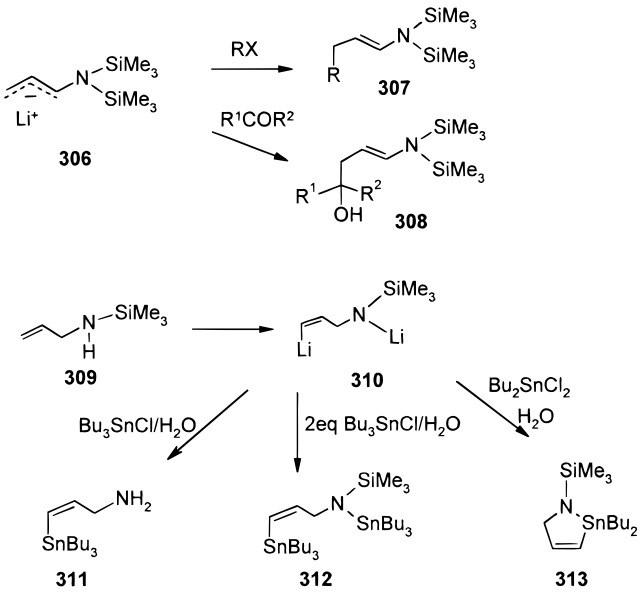
8. Bis(trimethylsilyl)allylamines (C═C–C–N(SiMe$_3$)$_2$) and (Trimethylsilyl)allylamines (C═C–C–NH(SiMe$_3$))

Lithiated bis(trimethylsilyl)allylamine **306** gives (*E*) γ-adducts **307** and **308** in reactions with alkyl halides, TMSCl, and carbonyl compounds (Scheme

Scheme 54



Scheme 55

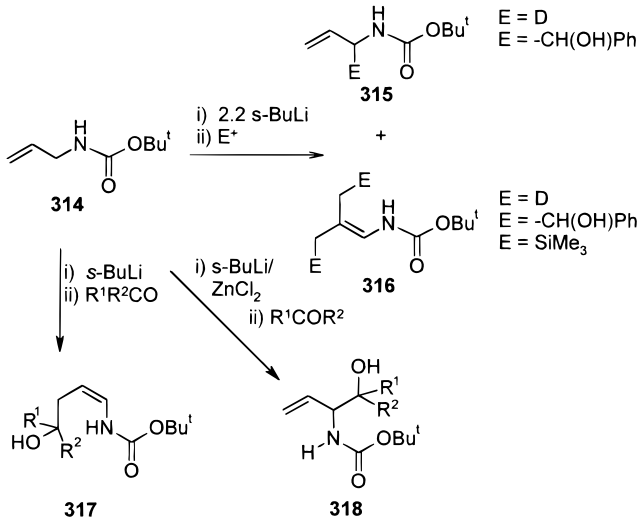


55).[183] (Trimethylsilyl)allylamine **309** can be dilithiated to give **310** which yields various γ-products, e.g., *N*,*C*-bis(tributylstannyl) compound **312** (or **311**), (*Z*)-3-(tributylstannyl)allylamine **313** with electrophiles Bu_3SnCl and Bu_2SnCl_2, respectively (Scheme 55).[184]

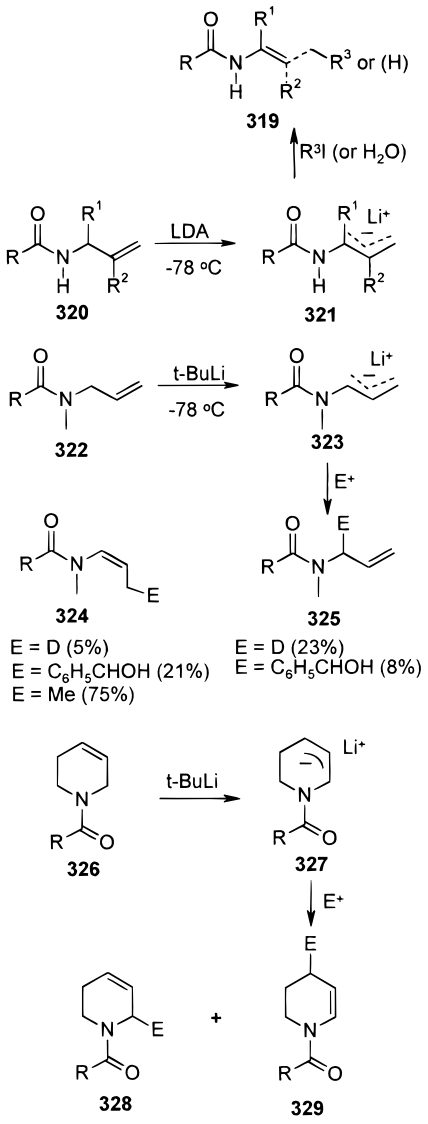
9. N-Allylcarbamates (C═C–C–NC(O)OR), Allylureas (C═C–C–NC(O)N), and N-Allylamides (C═C–C–NC(O)R)

The *N*-allylcarbamate **314** forms the dianion on treatment with 2.2 equiv of *s*-BuLi/TMEDA. The reactions of this dianion with electrophiles favor predominantly γ-attack to produce **316** (*Z*-isomer) (Scheme 56) save for benzaldehyde which gives a 1:1 mixture of α/γ-adducts (**315**, **316**). The γ-product **316** is formed exclusively with TMSCl. The γ-regioselectivity of the reaction of the lithium dianion with

Scheme 56

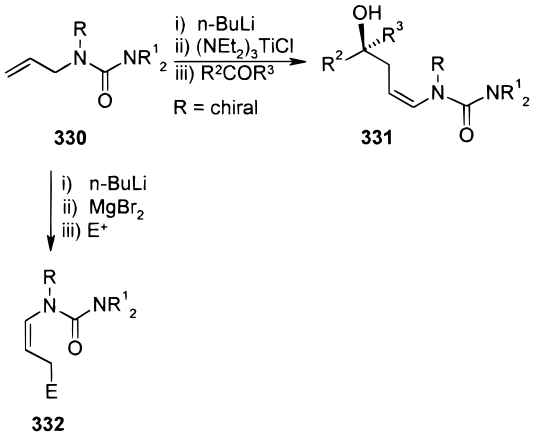


Scheme 57



carbonyl compounds to give **317** is altered by changing the counterion to Zn^{2+}. Thus, α-adducts **318** are obtained with aldehydes and ketones, whereas the diastereoselectivity is enhanced with increasing the

Scheme 58



steric bulk of the carbonyl compound (highest for benzaldehyde).[185]

Secondary allyl amides **320** undergo dilithiation to form *N*-lithio-α′-lithioallyl amides **321** which react with alkyl iodides and H_2O to give enamides **319** (γ-product, Scheme 57).[186]

Lithiated *N*-alkyl-*N*-allyl amides **323** react with electrophiles (RX, RCHO, Me_3SiCl, etc.) to give mainly γ-products along with minor amounts of α-products **325** (Scheme 57).[187] In the Δ^3-piperidinyl amide **326** case, both α- **328** and γ-products **329** are obtained, in ratios which depend on the electrophile.

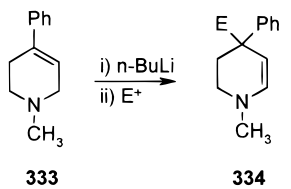
A highly diastereoselective homoaldol reaction is carried out with chiral *N*-allylureas **330** by lithiation and then transmetalation with a Ti derivative and reaction with carbonyl compounds resulting in γ-products **331**.[188] With Li^+ as the counterion, α- and γ-products are afforded with alkyl halides, aldehydes, and ketones. Replacement of Li^+ by Mg^{2+}, Zn^{2+}, or Cd^{2+} normally leads to α-attack; however, on transmetalation with Mg^{2+} the γ-products are obtained to give (*Z*)-enamides **332** (Scheme 58).[175]

10. Pyrroline and Piperidine (Tetrahydropyridine) Formamidines

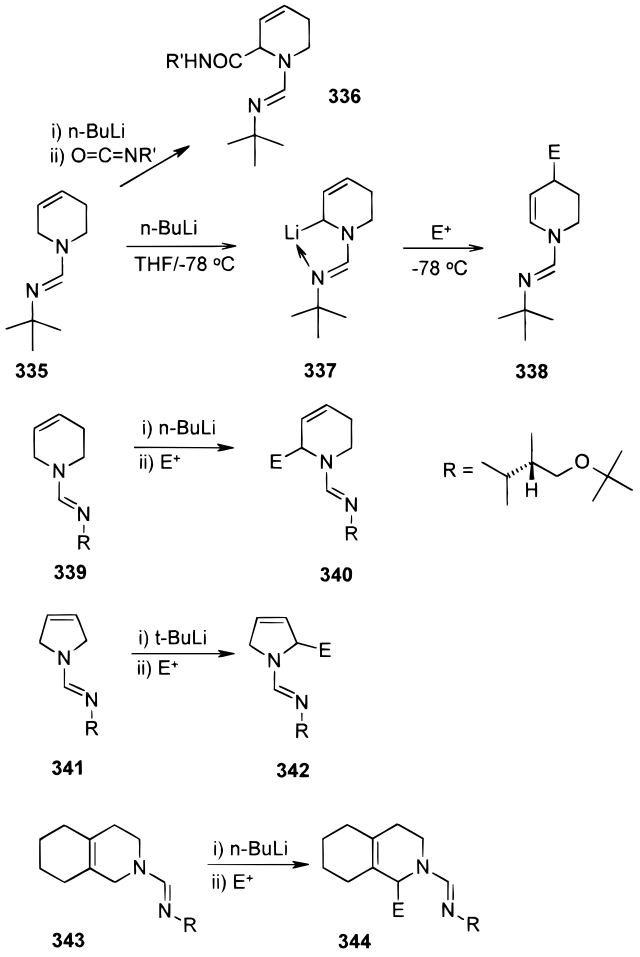
The anion from tetrahydropyridine **333** is attacked at the γ-carbon by electrophiles to give **334** (Scheme 59).[189,192,193] Similarly, the anion **337** of the tetrahydropyridine amidine **335** forms predominantly γ-adducts **338** (Scheme 60).[189−191]

However, α-products, e.g., **336** are synthesized in the reaction of tetrahydropyridine formamidine **335** with 2,6-dimethylphenyl isocyanate (Scheme 60).[189,190] Similarly, Meyers[194] reported that the valine-based chiral formamidine **339** gave upon alkylation predominantly the α-product **340**, in contrast to the formation of **338** upon reaction with the *tert*-butylformamidine of tetrahydropyridine. Pyrroline formamidines **341**[195] and those derived from octahydroisoquinoline (cf. **343**)[196] also give predominantly the α-attack products **342** and **344**, respectively (Scheme 60).

Scheme 59



Scheme 60



F. Phosphorus

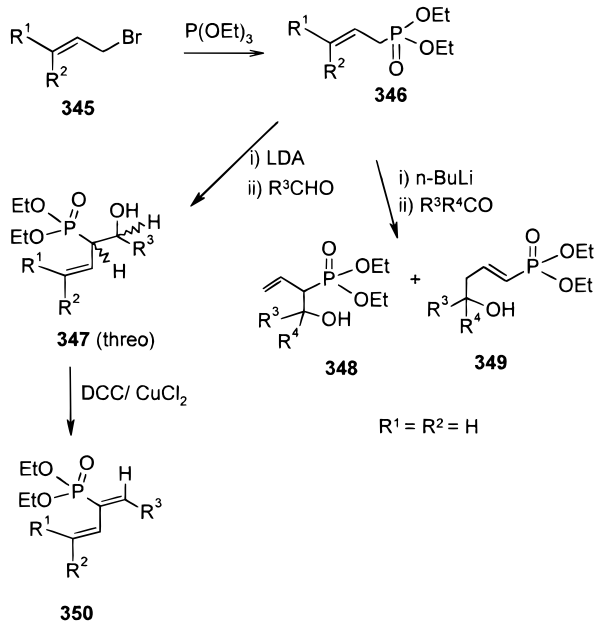
Reflecting their different oxidation states, phosphonates and phosphine oxides are discussed separately. A further section deals with phosphonamides which could alternatively have been considered with the phosphinoxides. One study of allylic phosphines is covered.

1. Allylphosphonates (C=C–C–PO(OR)$_2$)

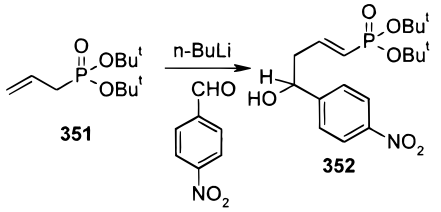
Allylphosphonates are used for the preparation of dienes[197] and polyenes[198] via olefination with carbonyl compounds. Most of the allylic phosphonates described are stabilized by additional functionality in the γ-position (see sections III and IV).

Allylphosphonates **346** are prepared by Arbuzov phosphorylation from the corresponding allyl bromides **345**. The reactions of lithiated **346** with aromatic and aliphatic aldehydes[199] result predominantly in α-threo-products **347** except for a few examples in which mixtures of α- and γ-adducts (e.g., R^3 = 4-Cl-C_6H_4; $R^1 = R^2$ = H) or γ-adducts (R^3 = 2-Cl-C_6H_4, 4-NO_2-C_6H_4; $R^1 = R^2$ = H) are obtained. The products **347** can be converted stereospecifically into dienes **350** using DCC (dicyclohexylcarbodiimide) activated by copper(II) as dehydrating agent (Scheme

Scheme 61



Scheme 62

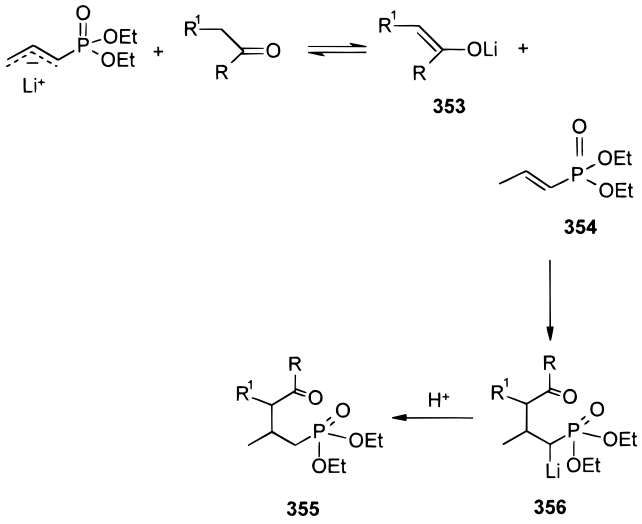


61).[197] However, the 2-hydroxyalkylphosphonates **347** are not always effective precursors for the dienes **350** if other functional groups stabilizing the diene are missing.[200] The reaction of the anion of **346** with ketones usually gives α-products **348**,[201] but with benzophenone the γ-product **349** is formed exclusively and acetophenone yields a mixture of both α- and γ-isomers under conditions of kinetic control at −78 °C (Scheme 61).

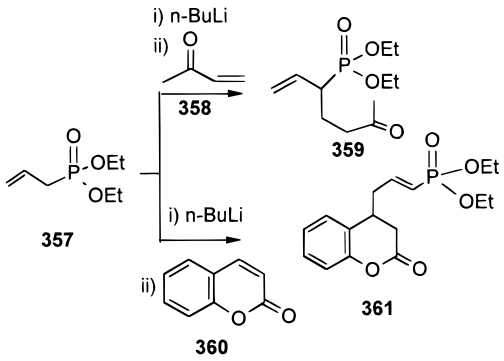
Furthermore, the extent of the formation of α-products **348** vs γ-products **349** depends critically on the substrate's structure and is influenced by steric interactions.[202] The latter plays a role in the reaction with benzaldehyde, in which the γ-selectivity is increased with the increase of steric hindrance of the phosphoryl group.[203] Thus, γ-selectivity is observed for the *O*,*O*-di-*tert*-butylphosphoryl group where **351** gives **352** (Scheme 62). Treatment of allylic phosphonates with various para-substituted benzaldehydes shows the further dependence of the regioselectivity on the nature of the electrophile: while in general α-product **348** is observed, γ-attack **349** occurs in the reaction with *p*-nitrobenzaldehyde.[204]

In addition, increasing the reaction temperature to favor thermodynamic control can have a dramatic effect on the composition of the reaction products. Beside the α- **348** and γ-products **349**, δ-ketoalkylphosphonate **355** (Scheme 63) is now formed as the main product resulting from the reaction of the lithium enolate **353** with the isomerized vinylic phosphonate **354**. However, in case of benzophenone

Scheme 63



Scheme 64



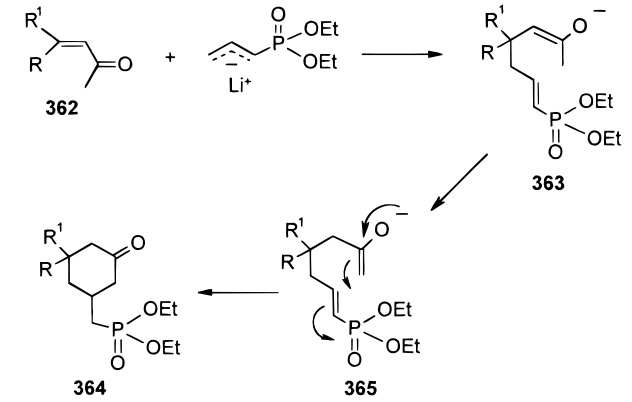
the "thermodynamic" product was identical to the "kinetic" γ-product **349**.[205]

Allylphosphonates **357** react smoothly with α,β-unsaturated ketones, but the reaction course depends on the structure of the carbonyl substrate. Thus, the configurationally constrained (*Z*)-unsaturated ketone coumarin **360**, adds at the γ-carbon to give **361** (*E*-isomer), whereas but-3-en-2-one **358** affords the α-adduct **359** (Scheme 64).[206]

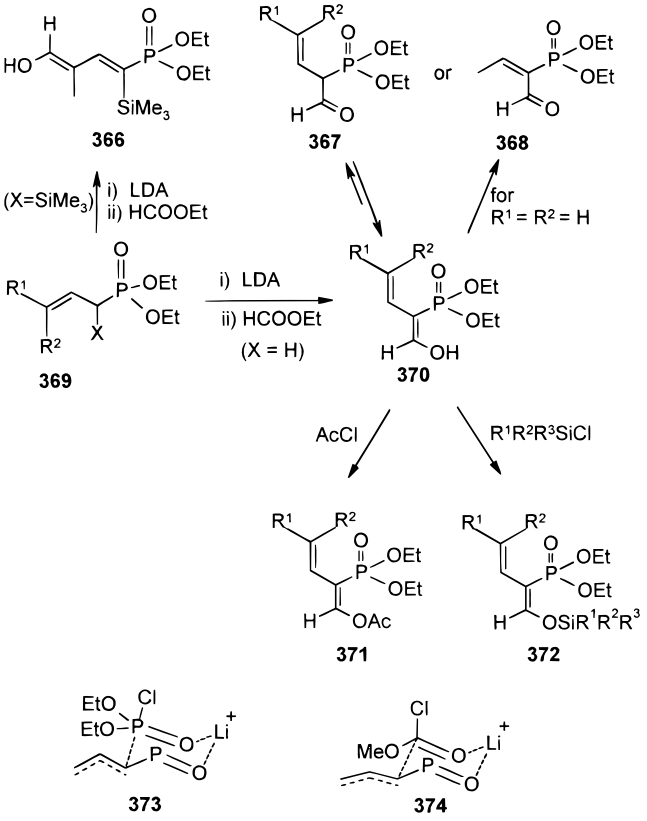
The reaction of β-substituted cyclic and acyclic α,β-unsaturated ketones, e.g., **362** which bear an enolizable α′-hydrogen and no leaving group in position β involves an annulation to afford a cyclohexanone derivative **364** via **363** and **365** (Scheme 65).[206] Similar to sulfoxides (section II.C.3) and phosphine oxides (section II.F.2), reaction with enones occurs by 1,4-γ-addition products to give intermediates **363**.[104,105]

Strict α-regioselectivity is observed in the reaction of lithiated **369** with ethyl formate (Scheme 66) or ethyl chloroformate to give **370**, or a mixture of **370** with its tautomeric aldehyde **367**, or the conjugated aldehyde **368** due to prototropy of the enol **370** ($R^1 = R^2 = H$). The product **370** can be transformed into the corresponding stable O-acetylated **371** and O-silylated **372** derivatives which are stabilized by the silicon substituent.[207] Steric hindrance due to the trimethylsilyl group at the α-position of **369** ($X = SiMe_3$) results in strict γ-regioselectivity, giving the 1-(*E*)-2-phosphonodienol **366** in high yield with excel-

Scheme 65



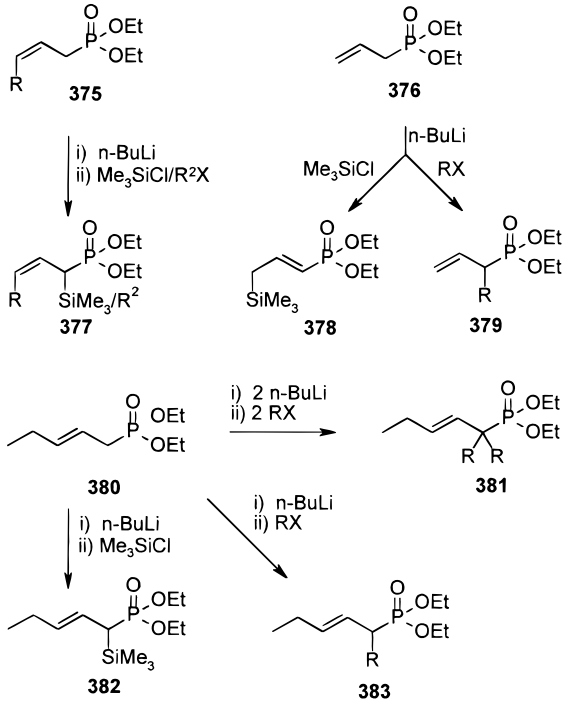
Scheme 66



lent stereoselectivity. α-Regioselectivity is also observed in phosphorylation and carboxymethylation reactions of **369** (X = H) involving a chair conformational transition state, e.g., **373** and **374** (Scheme 66).[208]

In general, γ-substituted allyl phosphonates **375** are silylated[209] exclusively at the α-position and also α-alkylated[198] by a variety of alkyl halides to give **377**. In contrast to that, strict γ-trimethylsilylation (cf. **378**) of unsubstituted lithiated diethyl allylphosphonate **376**[210] was observed although alkylation occurred again at the α-position (cf. **379**).[211] However, diethyl 2-pentenylphosphonate **380** showed α-regioselectivity under the same conditions to give **382** and **383**, respectively,[211] in agreement with earlier reports.[198] Excess of base and halide results exclusively in formation of α,α-dialkylated product **381** (Scheme 67).

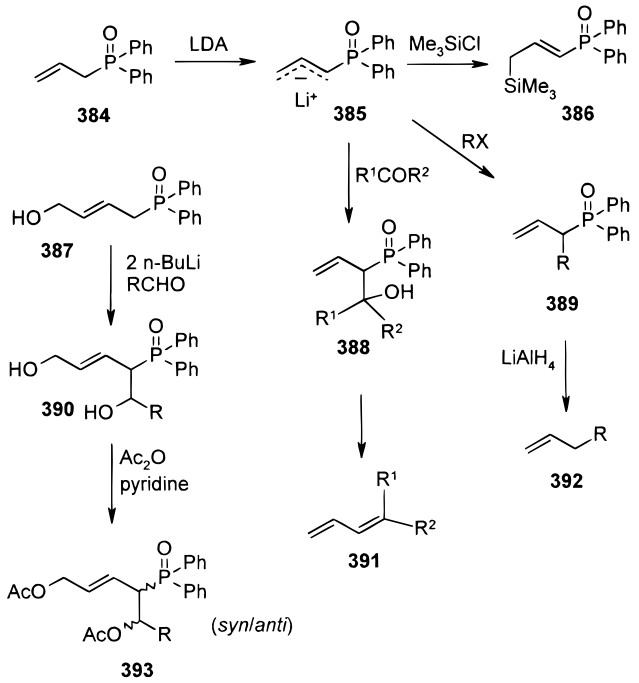
Scheme 67



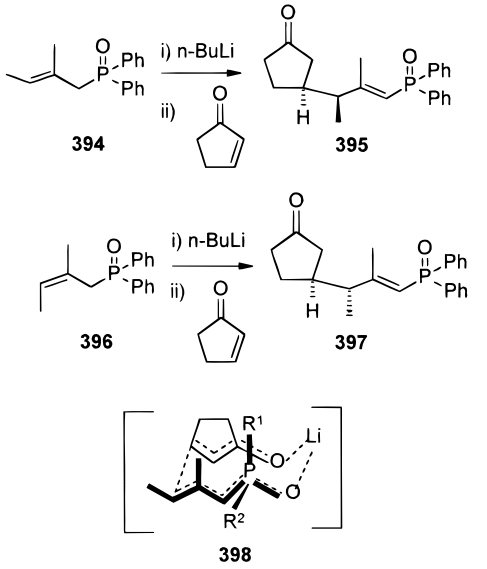
2. Allylphosphine Oxides (C═C–C–P(O)R_2)

Allyl phosphine oxides **384** form anions **385** which react with TMSCl at the γ-terminus to form (*E*)-**386**[212] while numerous alkyl halides give exclusively α-adducts **389** which can then be transformed into olefins **392** with $LiAlH_4$ (Scheme 68).[198] In general, electrophilic reaction of **385** with carbonyl compounds takes place exclusively at the α-position to give **388** and thus stereospecifically the corresponding (*E*)-1,3-diene **391**. δ-Hydroxyallylic phosphine oxides **387** afford α-adducts **390** upon treatment with aldehydes.[213] Peracetylation of **390** results in two easily separated diastereomeric diacetates **393** (Scheme 68).[214]

Scheme 68



Scheme 69

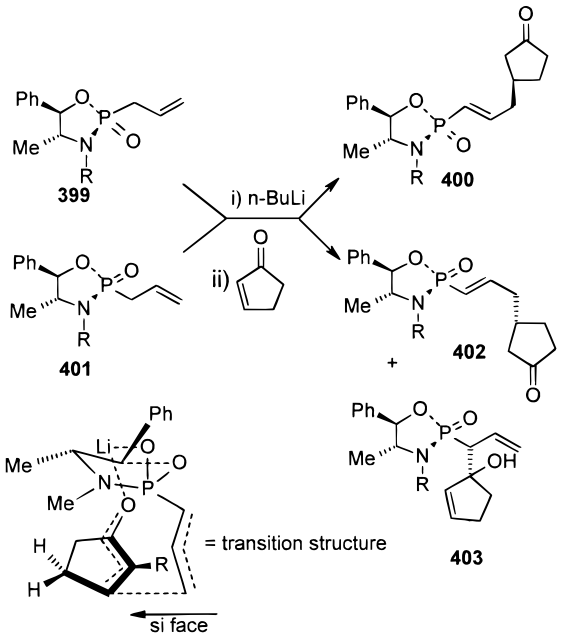


Lithiated (*E*)- **394** and (*Z*)-allylphosphine oxides **396** and phosphonates yield, in a highly diastereoselective manner, the corresponding 1,4-γ-syn-product, e.g., (*E*)-tiglyl phosphinoxides **395** and the 1,4-γ-anti-adduct, e.g., (*E*)-angelyl phosphinoxides **397** upon reaction with 2-cyclopentenone (Scheme 69).[104,105,215] A *trans*-decalyl or trans-fused chair−chair transition state **398** is postulated. There is a destabilizing influence of the methyl groups on the normal "trans-fused chair−chair"-like extended transition state resulting in access to "cis-fused boat−boat"-like, "cis-fused chair−chair"-like, and "trans-fused boat−chair"-like transition states involving planar lithiated reagents. The configuration at the phosphorus atom determines the face selectivity of the reaction of the lithiated carbanion with an enantiofacial enone according to the transition state model.[215] To obtain exclusive face selectivity, the substituents (R^1 and R^2, **398**) additional to the allyl group and attached to the stereogenic phosphorus must have quite different steric requirements; the small substituent, e.g., a phenyl group (R^1 = Ph, **398**), exclusively adopts a pseudoaxial and the large substituent, e.g., a *tert*-butyl group (R^2 = ^{t}Bu, **398**), a pseudoequatorial disposition in the transition state.[216]

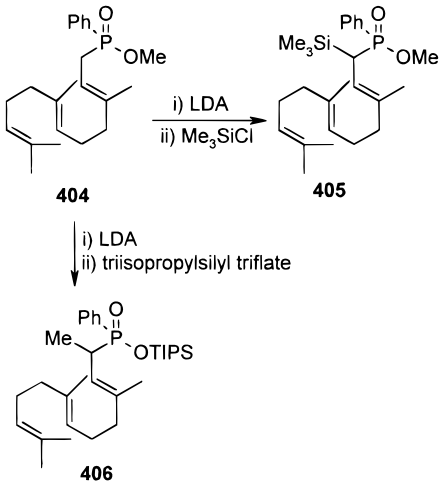
Reaction of the chiral allylphospholidines **399** (R = Me, ^{i}Pr) with α,β-unsaturated cyclic ketones gives the 1,4-γ-addition to provide **400**; replacing the methyl group at the nitrogen with the isopropyl group (R = ^{i}Pr, **399**) remarkably enhances the enantioselectivity.[217] In contrast, the diastereomeric phospholidines **401** gives poor diastereofacial selectivity and form 1,4-γ-adducts **402** and 1,2-α-adducts **403** (Scheme 70).[217]

Lithiated allylidenoxyphosphorane **404** is alkylated and silylated at the α-position to give **405** and **406** (Scheme 71), whereby the reaction could involve a direct C-silylation or a more likely O-silylation followed by C−O rearrangement.[218a] Thus, deprotonation of **404** followed by addition of triisopropylsilyl triflate (TIPS) yields an ester **406** as a mixture of two P/C_α-diastereomers due to migration of the methyl group. This rearrangement has been applied to the

Scheme 70



Scheme 71



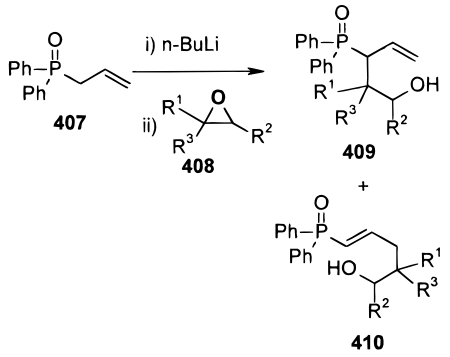
syntheses of a squalene from farnesol. However, application of chlorotrimethylsilane instead of TIPS results in exclusive C-silylation (cf. **405**).

Epoxides **408** are attacked by the lithiated anion of allyldiphenylphosphine oxide **407** in 1,2-dimethoxyethane. A boron trifluoride−diethyl ether complex promoted ring-opening reaction and affords a mixture of both α- **409** and γ- **410** products (Scheme 72). When toluene is used as solvent, a pronounced preference for γ-attack of the anion is observed.[218b]

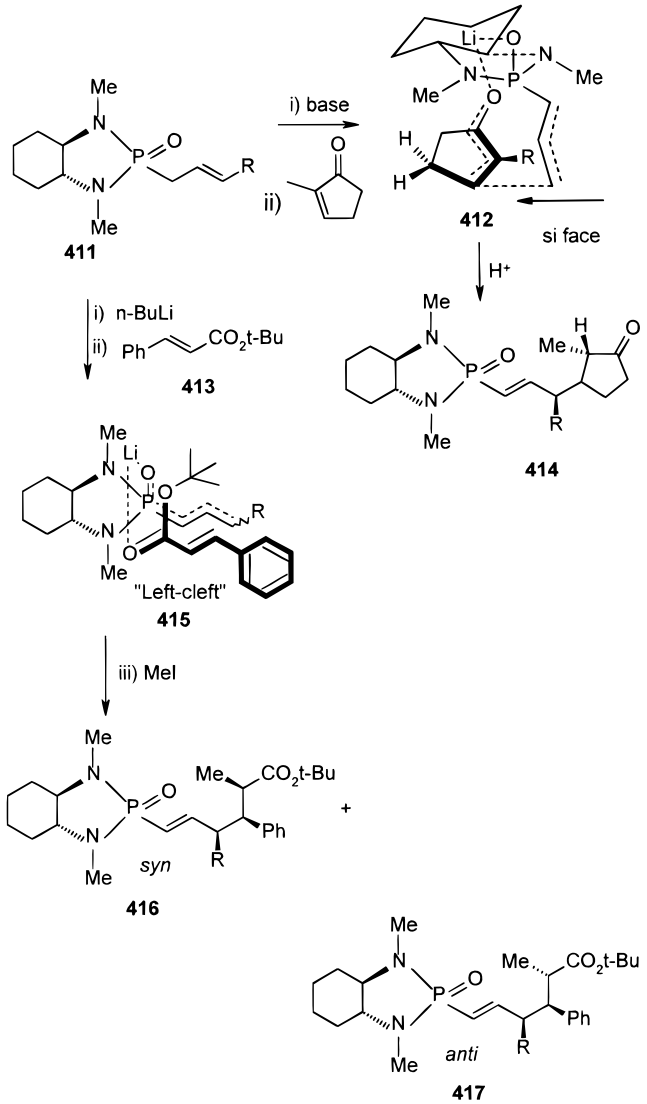
3. Chiral Phosphonamides (C═C–C–P(O)(NR)$_2$)

Chiral phosphonamides are important precursors for asymmetric synthesis and are therefore dealt with in this separate section. The addition of *tert*-butyl cinnamate **413** to crotylphosphonamide derivative **411** yields *syn*-**416** and *anti*-**417** γ-adducts in excellent yield and high diastereoselectivity (ratio 92:8) (Scheme 73). Similar behavior is shown by allyl-3,4-dihydro-4-oxo-(2*H*)-pyridine-1-carboxylate.[219,220] Consecutive asymmetric Michael additions with cinnama-

Scheme 72



Scheme 73

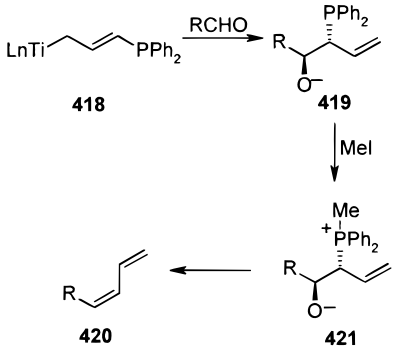


te ester can be carried out with excellent diastereoselectivity. The course of the reaction can be explained by the initial attack of the allyl reagent on the si face of *tert*-butylcinnamate coordinated to phosphorus and "anchoration" in the left-cleft, whereas lithium is chelated by the enolate (cf. **415**).[220] In general, chiral nonracemic allyl phosphonamides **411** result in diastereomerically pure or highly enriched γ-products (cf. **414**, **416**, and **417**) upon reaction with α,β-unsaturated cyclic ketones, esters, lactones, and lactams. In the case of 3-methylcyclohexanone the inclusion of HMPA enhances the amount of 1,4-γ-addition with high stereoselectiviy. The *trans*-decalinoid transition state **412** (Scheme 73) is assumed to be similar to the one proposed by Haynes for allylic sulfoxide and phosphine oxides.[221]

4. Allyl Phosphines (C═C–C–PR$_2$)

A lot of attention has been paid to lithiated phosphonates and phosphinoxides, but much less to phosphines. The (diphenylphosphino)allyltitanium reagent **418** also provides via **419** and **421** a stereoselective route to conjugated polyenes **420** (Scheme 74).[222] To our knowledge, so far no investigation has been carried out on the regioselectivity of the lithiated species.

Scheme 74



G. Silicon

In the early 1970s Corriu et al. reported the first α-silylallyl anion.[223] Since then, numerous such carbanions[224] have been used as synthetic intermediates.[225−231]

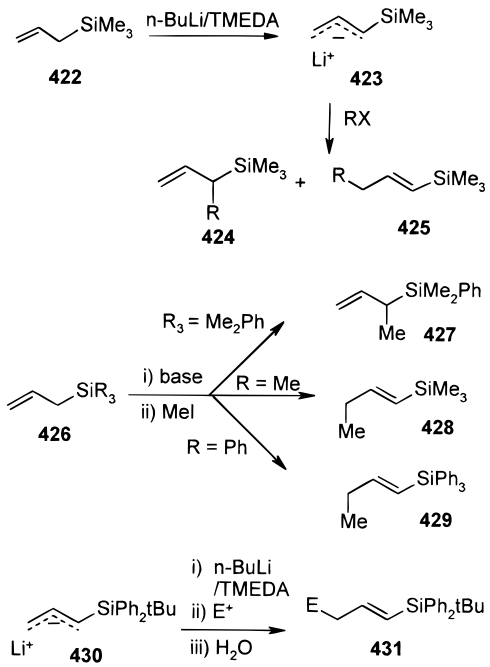
We first deal with the allyltrialkylsilanes in some detail, followed by a separate section for their functionalized derivatives. Cyclic silanes are treated briefly and, because of its interesting behavior, silylated methylenecyclopropene is discussed in a separated subsection. Finally bissilylated olefins which do not belong in one of these sections are considered.

1. Allyltrialkylsilanes (C═C–C–SiR$_3$)

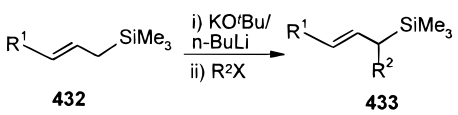
Allyltrialkylsilanes such as **422** give anions **423** which react with primary halides to give a mixture of α- **424** and γ-(*E*)-adducts **425**.[232] In contrast to allyltrimethylsilane **422**[223,233,234] and allyltriphenylsilane (**426**, R = Ph),[223] which are γ-methylated to form **428** and **429** respectively, allylic dimethylphenylsilane (**426**, R$_3$ = Me$_2$Ph)[235] undergoes preferential α-attack with methyl iodide to give **427** (Scheme 75).

No significant changes in the ratio **424**:**425** is caused by the addition of 1,4-diazabicyclo[2.2.2]-octane (DABCO), crown ethers or various metal salts. An appreciable change in orientation of the reaction of allyltrimethylsilane with alkyl halides is caused by use of the Lochmann−Schlosser base, KO^{t}Bu/^{n}-BuLi, which gives predominantly γ-alkylation **425**.[232] Bulkier substituents on silicon also result in increasing γ-regioselectivity reflecting greater steric hindrance to α-alkylation.[229,236] For example, allyl(*tert*-butyl)diphenylsilane anion **430** affords regioselectively

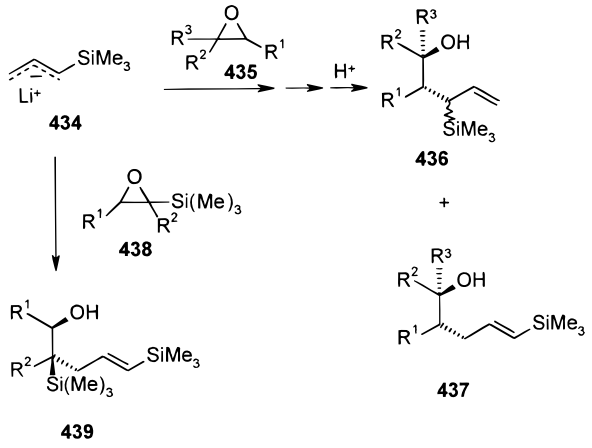
Scheme 75



Scheme 76



Scheme 77

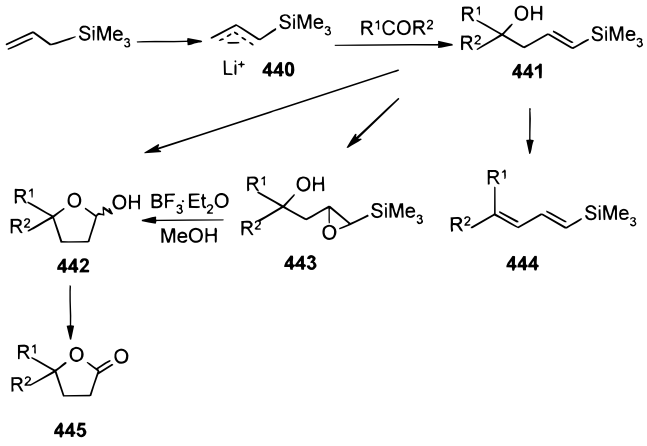


the γ-adduct **431** upon treatment with electrophiles (Scheme 75).[237] In the absence of internal chelation a substituent in the γ-position of γ-substituted allylsilyl anion from **432** tends to favor α-alkylation to form **433** (Scheme 76).

Reaction of **434** with epoxides **435** produces a mixture of the α- **436** and (*E*)-γ-isomers **437**; ethylene oxide (**435**, $R^1 = R^2 = R^3 = H$) and monosubstituted derivatives (**435**, R^1 or R^2 or $R^3 \neq H$) afford mainly α-adducts **436** while 1,2-di- (**435**, R^1 and $R^2 \neq H$, $R^3 = H$) and 1,1,1-trisubstituted derivatives (**435**, R^1, R^2, $R^3 \neq H$) yield γ-adducts **437**.[238] The reaction of epoxysilanes **438** with lithiated allylsilane **434** gives predominantly the (*E*)-γ-product **439** (Scheme 77).[239]

Reactions of allyltrialkylsilane anions **440** with carbonyl compounds furnish preferentially (*E*)-γ-

Scheme 78



addition products **441**[227,240−242] which can lead upon further transformations to the corresponding epoxides **443**, γ-lactols **442**, γ-lactones **445**, and 1-silyl-1,3-dienes **444** (Scheme 78).[243,244]

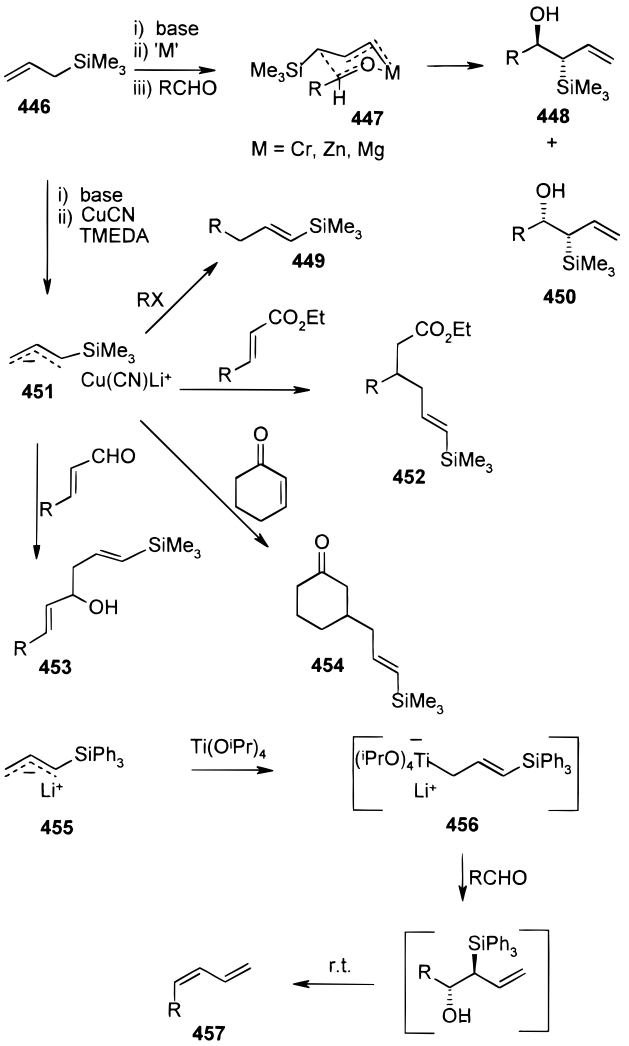
In general, metalation with organoaluminum,[41,42,245] organoboron,[246] organotitanium,[247−249] or organozinc[250,251] compounds directs the reaction of allyltrialkylsilanes **446** with aldehydes to the α-position to give **448** and **450** (see also section IX.D). The reaction of the analogous allylgermanes −C═C−CH_2−$GePh_3$− which usually show behavior similar to allylsilanes− proceeds less regioselectively.[250] Furthermore, addition of magnesium bromide is effective in directing α-regioselectivity by complexation with the carbonyl compound and thus rendering it a more reactive electrophile.[233] These reactions proceed via a chair transition states **447**. Similarly, the (trimethylsilyl)-allylchromium reagent affords with carbonyl compounds anti-configurated α-products via the chair transition state **447** (in Mg, Zn, or Cr cases).[252,253] The titanium reagent **456**, obtained by transmetalation of the lithiated allyltriphenylsilane **455**, undergoes a regioselective and steroselective reaction to give 1,3-dienes **457**,[254] whereas the copper reagent **451** obtained from allyltrimethylsilane **446** gives mainly or exclusively the γ-products **449** with carbonyl compounds as well as with alkyl and acyl halides. Reaction of α,β-unsaturated esters and ketones produces 1,4-γ-adducts **452** and **454**, while with α,β-unsaturated aldehydes 1,2-γ-adducts **453** are afforded (Scheme 79).[255]

2. Functionalized Allyltrialkylsilanes (C═C−C−SiR_3)

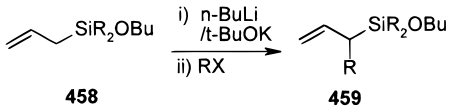
The substituents on silicon exert considerable influence on the regioselectivity and also the stereoselectivity of these reactions.[256]

a. Alkoxysilyl-Substituted Allylanions. The α-regioselectivity of alkylation reactions with the anions of alkoxysilyl-substituted allyl derivatives **458** is improved compared with that of simple alkyl-substituted anions due to the chelation of the lithium counterion by the alkoxy group in proximity to silicon (Scheme 80),[230] an effect which is also observed for alkoxy-substituted 1-silyl-2-methylallyl carbanions generated with the Lochmann−Schlosser's base.

Scheme 79



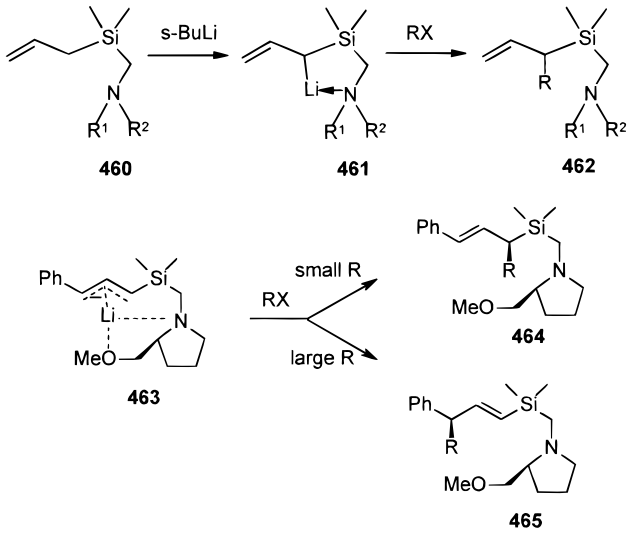
Scheme 80



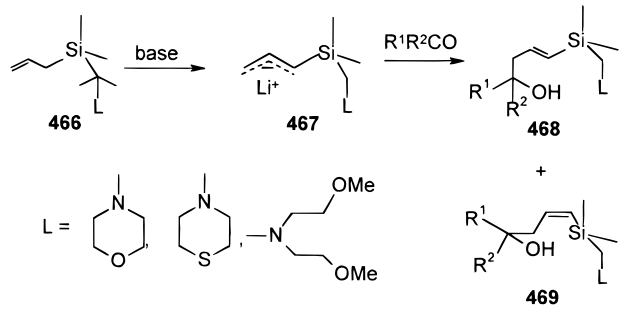
b. Aminosilyl-Substituted Allylanions. While a dialkylamino group on silicon favors γ-alkylation,[257] aminomethyl substituents on the silicon atom as in **460** are effective ligands for the lithium ion for direction α-orientation. For example, 100% regioselectivity is achieved for the methylation of **461** (R = CH_2CH_2OEt) to give **462** (Scheme 81).[230] The course of the reaction is dependent on the solvent; for example, the regioselectivity in ether is much higher compared with that in THF and dependent on the size of the alkylating agent.[231] Silylallyl carbanions **463** bearing a chiral lithium complexing substituent remote from silicon are similarly α-alkylated by small electrophiles in nonpolar solvents to give **464** and γ-attacked by secondary halides to form **465**. Both types of reaction proceed stereoselectively (Scheme 81).[258]

The reactions of aminomethyl-substituted silylallyl anions with carbonyl compounds give a mixture of the α- and γ-products whereby the γ-selectivity is increased with the decrease of the steric bulkiness

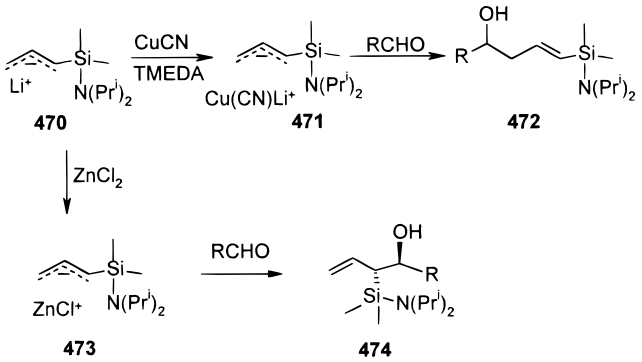
Scheme 81



Scheme 82



Scheme 83



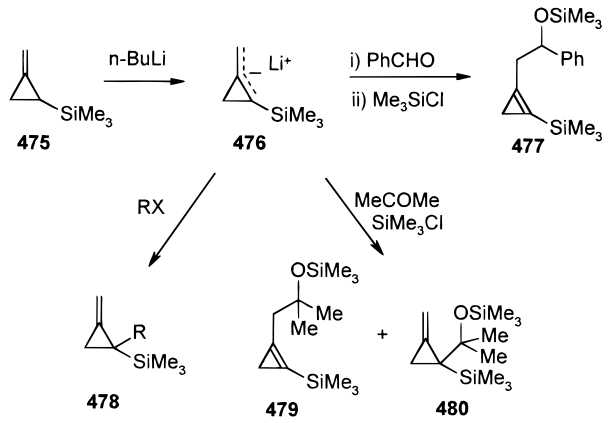
of the amino group. If the silyl moiety in **466** contains a group L which is capable of internal chelation (**467**), the reactions with carbonyl compounds give preferentially γ-addition products such as **468** and **469** (Scheme 82) analogous to allyltrialkylsilanes.[259]

The addition of copper cyanide to form **471** also improves the γ-selectivity to give **472**, similar to that of allyltrialkylsilanes (see also Scheme 79), while after transmetalation of aminosilyl-substituted allyl anion **470** with zinc the α-adduct **474** is obtained (Scheme 83).[260] The use of magnesium bromide in reactions with carbonyl compounds also causes the formation of α-product.

3. Silylated Methylenecyclopropanes

The reaction of silylated methylenecyclopropane anions **476** with benzaldehyde followed by quenching

Scheme 84

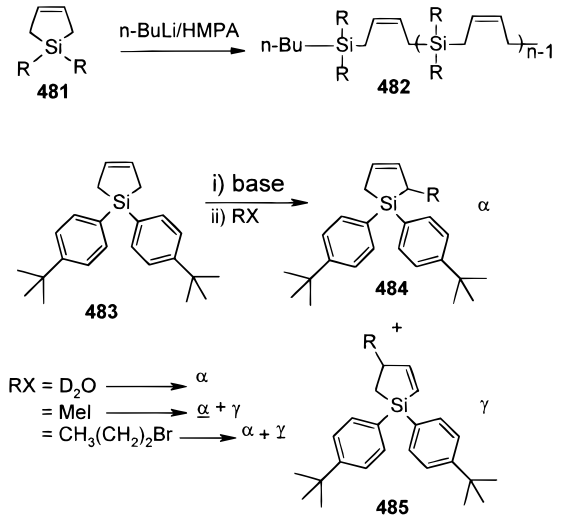


with TMSCl yields the γ-adduct **477** despite the formation of a highly strained cyclopropene ring, while in the reaction with acetone a mixture of cyclopropene **479** and methylenecyclopropane **480** is obtained. Alkylation occurs at the α-position to give **478** (Scheme 84).[261]

4. Cyclic Silanes

Cyclic silanes as **481** necessarily possess cisoid stereochemistry. Polymerization to **482** occurs if a methyl or phenyl group is the substituent on silicon. This process could be suppressed by introducing an electron-donating substituent on the phenyl ring attached to silicon;[262] the regioselectivity of the attack is now controlled by the steric demand of the electrophile. Thus D_2O yields exclusively α-adducts **484** while smaller electrophiles such as halomethanes give predominantly α-products **484** beside minor γ-attack to form **485**. Larger molecules, e.g., propyl bromide, yield a mixture of α- **484** and γ-adducts **485** favoring the latter **485** (Scheme 85).[263]

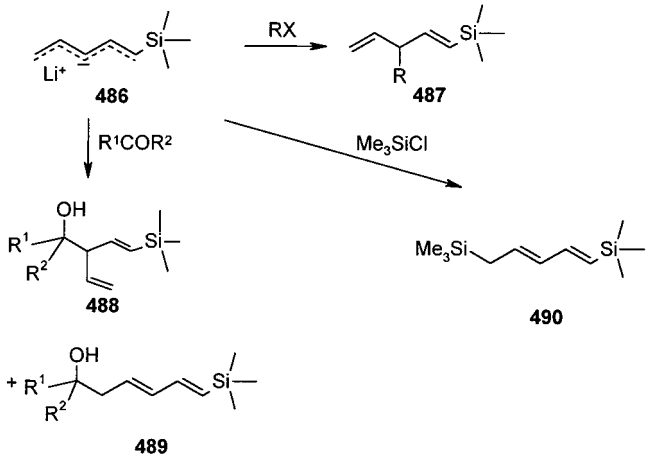
Scheme 85



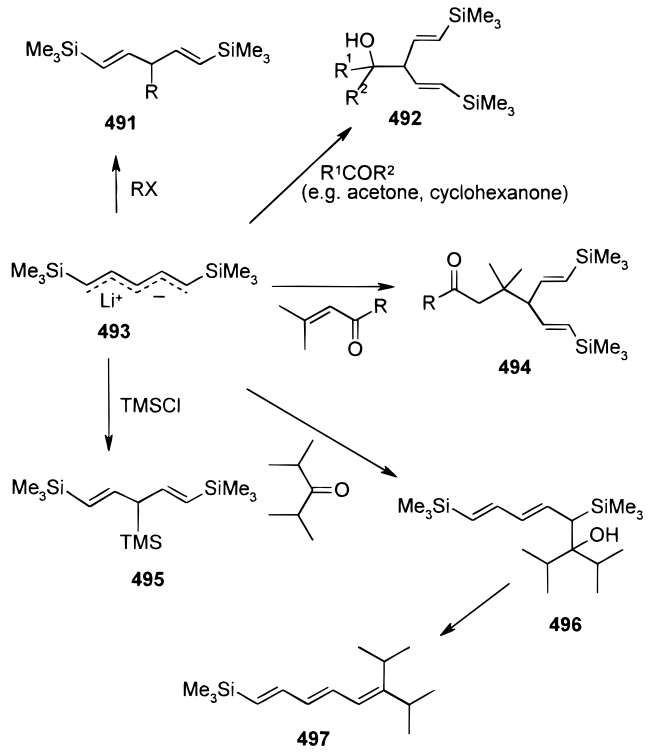
5. Pentadienylsilanes (C═C–C═C–C–SiR$_3$)

ϵ-Product **490** is exclusively formed in reactions of anion **486** with TMSCl, while upon alkylation the γ-product **487** is produced.[264] Reactions of **486** with carbonyl compounds produce a mixture of ϵ- **489** and γ-adducts **488** (Scheme 86). The γ-selectivity is

Scheme 86



Scheme 87



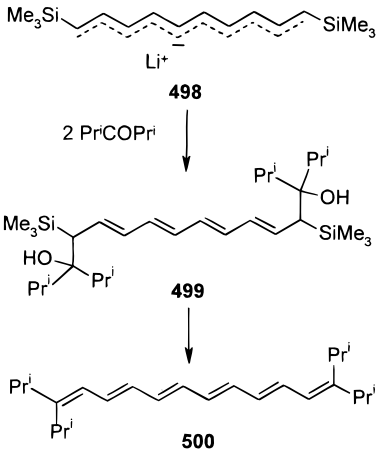
enhanced with magnesium, boron, or copper reagents[265] and similar behavior is observed with sterically less bulky carbonyl compounds and silanes with substituents on silicon favoring the γ-product.

In the reaction of 1,5-disilyated pentadienyllithium **493** with carbonyl compounds, like acetone or cyclohexanone, γ-addition occurs to give **492** while the reaction with bulky ketones, e.g., 2,4-dimethyl-3-pentanone, yields products of terminal attack **496** which are immediately transformed into the conjugated trienes **497** by Peterson elimination (Scheme 87). Conjugated addition to α,β-unsaturated enones yields predominantly products of central γ-attack **494**.[265] Furthermore, trimethylsilylation exclusively takes place at the central carbon, a reaction which is also observed in the alkylation with *tert*-butyl bromide to give **495** and **491** respectively (Scheme 87). However, with *sec*-butyl, isobutyl, and *n*-butyl bromides, a mixture of α- and γ-products is obtained.

Protonation with *tert*-butyl alcohol proceeds at the terminal carbon.[264]

1,10-Bis(trimethylsilyl) tetraene anion **498** shows α-selective addition of carbonyl compounds to give **499** followed by double-Peterson elimination furnishing the polyene **500** (Scheme 88).[265]

Scheme 88



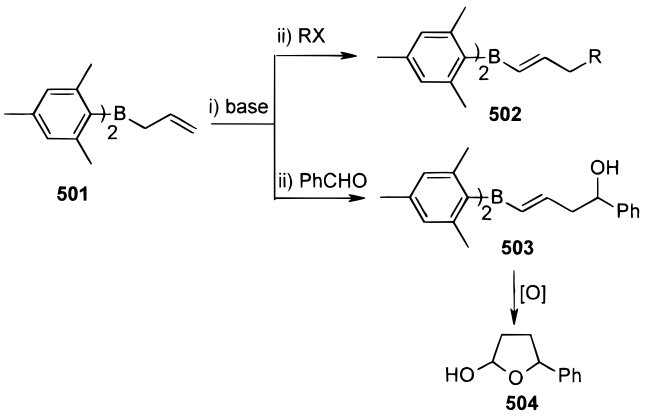
H. Boron

A review of allylboron chemistry up to 1972 is given by Mikhailov.[266] Boron compounds usually serve as auxiliaries due to the formation of "ate" complexes with anions stabilized by another heteroatom (see Scheme 3). The extent of the present section is limited to a discussion of allyldimesitylboranes and disiamyloct-1-enylborane.

1. Allyldimesitylboranes (C═C–C–B(Mes)$_2$)

Allyldimesitylboranes **501**, after deprotonation, are γ-alkylated producing (*E*)-vinylboranes **502** which can be oxidized to aldehydes. Treatment of **501** with benzaldehyde also yields the γ-product **503**, giving on oxidation a γ-lactol **504** (Scheme 89).[267]

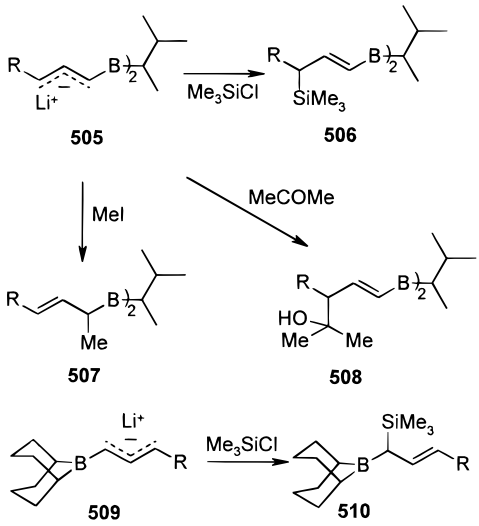
Scheme 89



2. Disiamyloct-1-enylborane (C═C–C–B(Siam)$_2$)

The regioselectivity of disiamyloct-1-enylborane anion **505** reactions is electrophile dependent. While with MeI and H_2O the α-carbon is attacked to give **507**,[268] upon deprotonation with lithium 2,2,6,6-tetramethylpiperidide followed by trimethylsilylation, γ-product **506** is obtained, owing to the steric repulsion between the bulkier siamyl substituent and the trimethylsilyl group (Scheme 90). Similarly, treatment of **505** with acetone yields γ-adduct **508**. By replacing the siamyl substituent with the less bulky 9-borabicyclo[3.3.1]nonan (9-BBN) group as in **509** α-attack is observed upon trimethylsilylation to give **510** (Scheme 90).[269]

Scheme 90



I. General Discussion

The orientation of reactions with electrophiles of allyl anions stabilized by a heteroatom (cf. Scheme 91) can be generalized as follows (however, for silicon species, there are numerous exceptions depending on substituents or for steric causes):

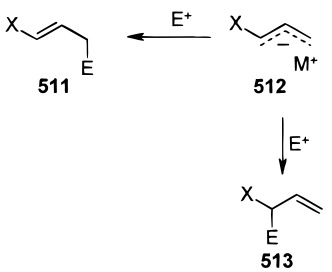
Whether the reaction of an allyl anion **512** with an electrophile gives an α-product **513**, a γ-product **511**, or a mixture of **511** and **513** depends on the following factors: (i) nature of heterosubstituent(s) X; (ii) nature of electrophile; (iii) nature of gegen cation M^+; (iv) reaction conditions including solvent and temperature; and (v) other substitution in starting allyl anion.

Of these factors i−iii are the most important. On the basis of factors i−iii, the heterosubstituents groups X can be divided into various classes:

a. One group of heterosubstituents causes exclusive α-substitution, regardless of the other factors: sulfone (SO_2R), benzotriazole (Bt), carbamoyl (NRCOR), and sulfinamide ($SONR_2$).

b. Another group of heterosubstituents generally shows α-substitution, but with these the amount of γ-substitution can be increased by increasing bulk attached to the heteroatom or increasing bulk of the

Scheme 91



incoming electrophile (e.g., R_3SiCl). This second group includes the phosphonates ($PO(OR)_2$), and phosphine oxides ($P(O)R_2$).

c. A third group of substituents tends to give mainly α-substitution with alkyl halides, but (at least for lithium gegenions) mainly γ-substitution with carbonyl electrophiles. This group comprises sulfoxides (S(O)R), sulfides (SR), dithiocarbamides ($SCSNR_2$), selenides (SeR), nitrosamines (N(NO)R), and chloride. Within these groups, changing the gegenion to another metal (Al, B, Ti, Mg, Zn) often changes the orientation of attack for carbonyl electrophiles from γ to α.

d. A fourth type of behavior is displayed by electron-rich negatively charged heterosubstituents, which tend to give predominately γ-products. This group includes alkoxides (O^-), mercaptides (S^-), and primary carbamoyl compounds (effectively N^-COR). Changing over the gegenion to another metal can sometimes give α-substitution products with these groups. Tertiary amines (NR_2) and trialkylsilicon substituents show behavior intermediate between groups c and d.

e. The alkoxide group (OR) occupies an intermediate place generally giving mixture of α- and γ-products but being capable of regioselective α-product using gegenions other than lithium.

f. The trimethylsilyloxy substituent ($X = Me_3SiO$) is unusual in that it forms mainly γ-products with alkyl halides, whereas with carbonyl electrophiles α-products are formed with a lithium gegenion, but γ-products after metal exchange.

The reasons for this behavior pattern will be discussed in section IX of this review.

III. Allylic Anions Stabilized by Two Identical Gem-Heteroatoms ($C{=}C{-}CX_2$)

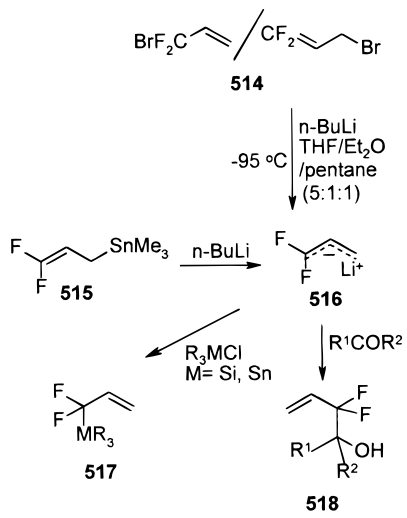
This section is divided in three major parts discussing the dihalogen-, dioxo-, and dithiosubstituted allylic anions. Each is of synthetic interest.

A. Two Halogen Substituents

1. gem-Difluoroallyllithium ($C{=}C{-}C{-}F_2$)

As mentioned in section II.A, the corresponding monofluorinated allylic anion species has not yet been synthesized. However, *gem*-difluoroallyllithium **516** was prepared using trimethyltin-substituted allyl reagent **515** which is transmetalated at low temperatures by reaction with ^{n}BuLi (Scheme 92).[270,271] Fluorinated anion **516** is not stable in solution and needed to be trapped in situ. All experiments to prepare a solution of reagent **516** from **515** failed even at −130 °C. Preparation in situ in the presence (base and electrophile added at the same time) of trimethylchlorosilane or trimethyltin chloride gave the α-product **517**, but this method cannot be applied successfully to carbonyl compounds since the rate of attack of ^{n}BuLi at carbonyls appears to be greater than its rate of attack at tin. However, the lithium−bromine exchange between ^{n}BuLi and 3-bromo-3,3-difluoropropene **514** at −95 °C in THF/Et_2O/pentene generating *gem*-difluoroallyllithium **516** and subsequent treatment with chlorosilanes, aldehydes, ketones, and esters resulted in the α-regioselective formation of products such as **518**, often in good yields (Scheme 92).[272] These authors assume that the difluoroallyllithium **516** exists in ether as a tight ion pair with significant covalent bonding and thus the lithium ion should coordinate at the site of greatest negative charge, i.e., at the CH_2 terminus. Hence it serves to block the CH_2 terminus (γ-carbon) from attack by an electrophile and to "free" relatively the CF_2 terminus where the electrophilic reaction takes place to give **517** and **518**.[273]

Scheme 92

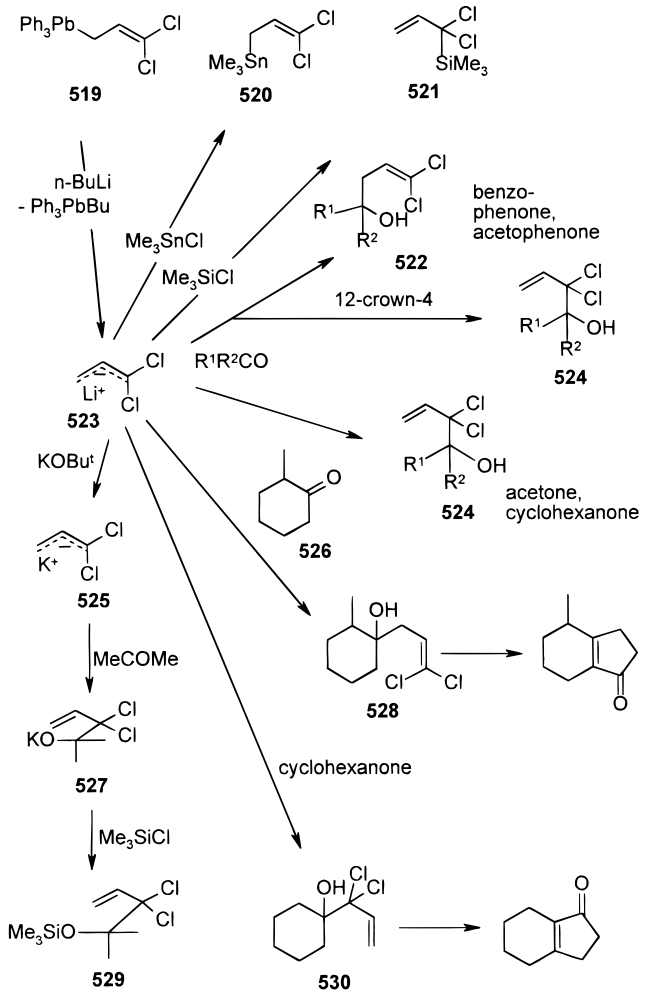


2. gem-Dichloroallyllithium ($C{=}C{-}CCl_2$)

gem-Dichloroallyllithium **523** was first obtained by reaction of ^{n}BuLi with 3,3-dichlorotriphenyllead **519** at −95 °C (cf. *gem*-chloro(trimethylsilyl)allyllithium). The reactions of **523** with carbonyl compounds lead predominantly to α-products **524** if R^1 (R^2) is an electron-releasing substituent,[274] whereas the amount of γ-product **522** increases if R^1 (R^2) is an electron-attracting substituent (Scheme 93).[275] This was rationalized in Pearson's hard/soft acid/base approach;[276,277] the CCl_2 terminus being the "soft" end and the CH_2 terminus the "hard" end. The double-bond character of the carbonyl group determines at which terminus the reaction takes place, e.g., with alkyl substituents the carbonyl function would be softer and hence more polarizable, and with electronegative substituents harder.[274] The α-regioselectivity is significantly increased in the presence of 12-crown-4 to give **524** (Scheme 93).[278] The reaction of *gem*-difluoroallyllithium with both trimethylchlorosilane and trimethlyltin chloride occurs at the α-position (cf. Scheme 92). *gem*-Dichloroallyllithium is also found to react with trimethylchlorosilane at the α-carbon to give **521** in contrast to the attack at the terminal γ-carbon by trimethlyltin chloride producing **520**.[279,280]

gem-Dichloroallyllithium **523** produced upon treatment of 3,3-dichloropropene with lithium diisopropylamide shows γ-regioselectivity with substrates with more reactive C=O bonds to give **522**. In contrast, *gem*-dichloroallylpotassium **525** which gave **527** (α) in the reaction with substituted benzalde-

Scheme 93



hydes (Scheme 93). It is known that the nature of the metal cation influences the equilibrium between tight ion pairs and loose (solvent-separated) ion pairs. Thus, Venturello et al. assume that in THF the lithium ion is more strongly solvated, due to the formation of solvent separated ion pairs, than the potassium counterion which is more tightly bound to the CCl_2 moiety.[281,282]

The reaction of 1,1-dichloroallyllithium with cyclic ketones to give α- or γ-products also depends on steric effects as well as on the ring size, etc. Thus, the addition of 2-methylcyclohexanone to the Li reagent gives only the γ-product **528** in contrast to cyclohexanone or 2-methylcycloheptanone which furnishes α-adducts **530** (Scheme 93).[283−286]

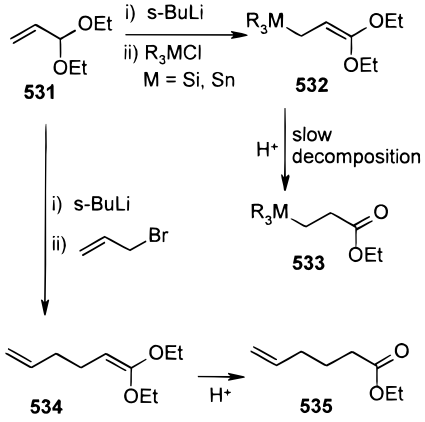
B. Two Oxygen Substituents

1. Allylic Ketals (C–C=C(OR)$_2$)

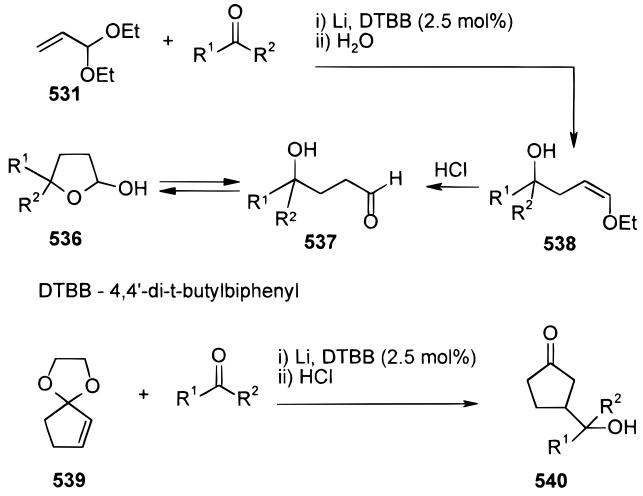
Formation of the anion is difficult and the anion once formed is highly unstable. γ-Regioselectivity is found to occur with organosilicon and organotin reagents as well as with allyl halides to give the corresponding ketone acetals **532** and **534**, respectively, which are converted into β-substituted propionic esters **533** and **535** respectively by acid hydrolysis[280] (Scheme 94).

The arene-catalyzed lithiation of acrolein diethyl acetal **531** in the presence of a carbonyl compound

Scheme 94



Scheme 95



leads after hydrolysis to the corresponding γ-products **538**—mainly the *Z*-isomer. The γ-hydroxyaldehyde **537** obtained upon acidic hydrolysis of **538** is in equilibrium with the cyclic hydroxyfuran **536** (Scheme 95).[287] The ethylene ketal **539** derived from 2-cyclopentenone gives after deprotonation and reaction with carbonyl compounds in the presence of DTBB and acidic hydrolysis the γ-adduct **540** (γ-hydroxyketone), similar to the reaction of acrolein diethyl acetal (Scheme 95).[287]

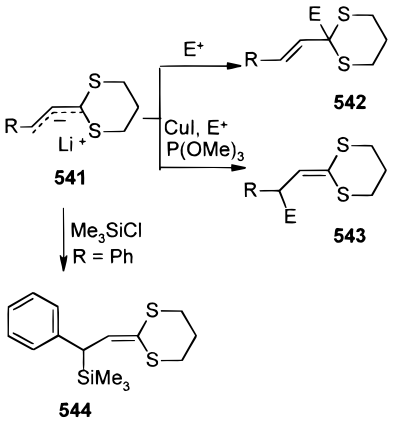
C. Two Sulfur Substituents

1. 2-(2-Propenyl)-1,3-dithianes (C=C–C(SR)$_2$)

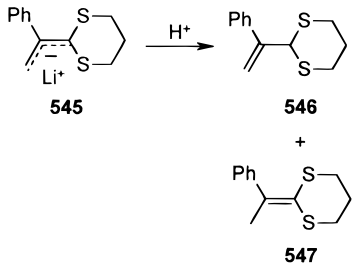
Bis(alkylthio)allyllithiums such as those obtained from cyclic dithianes **541** undergo α-attack upon alkylation to give **542**,[288,289] exhibiting greater regioselectivity than their acyclic analogues.[290] By contrast, treatment of the lithium salt of 2-(2-propenyl)-1,3-dithianes with cuprous iodide and trimethyl phosphite followed by addition of the electrophile leads exclusively to γ-product **543** (Scheme 96).[290]

The lithium salt of vinyl-1,3-dithiane **541** (R = H, Me) was exclusively α-alkylated, while α- and γ-products were both noticed with R = Ph. The HSAB principle has been used to explain this behavior, the α-carbon being harder than the γ-carbon. Exclusive γ-regioselectivity was achieved in the reaction with trimethylchlorosilane to give **544**.[291,292]

Scheme 96



Scheme 97



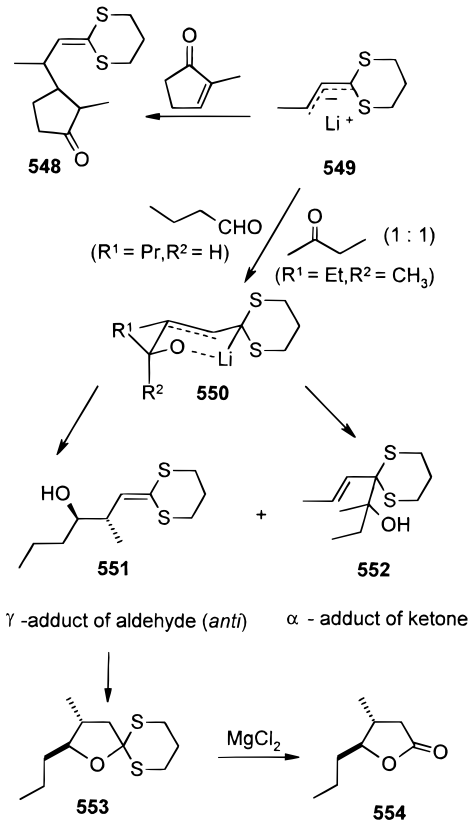
Lüning et al.[293] found that the regioselectivity of the protonation of **545** by water is highly dependent on the age of the allyllithium solution with α/γ- (**546**/**547**) ratios varying from 2.7:1 to 1:3.5 (Scheme 97).

Reactions of dithio-substituted crotyllithium **549** with aldehydes proceed at the γ-position to give **551** in a highly regio- and stereoselective manner.[294,295] A chairlike transition state **550** is proposed to account for the γ- and threo-selectivities (Scheme 98).[296] The regioselectivity of the reaction with ketones depends on the nature of the ketone. Hence, ketones with small substituents yield α-adducts **552**, while with bulky and unsaturated ketones, except 2-cyclopentenones, γ-products **548** are generated.[295] For example, the γ-1,4-product **548** is obtained with 2-methyl-2-cyclopentenone.[297] Fang[295] explained the regioselectivity of the reaction with ketones in terms of the HSAB principle.[276,277] Comparison of aldehydes and ketones following the rules of the HSAB principle reveals that, e.g., the α-addition of 3-pentanone to give **552** is much faster than the γ-addition of propanal producing **551**. The γ-adducts **551** are prone to cyclization, giving the corresponding spirodithianes **553** which can be converted into the γ-lactones **554** (Scheme 98).[298] In the reaction of cinnamyllithium with carbonyl compounds without the mediation of $BF_3 \cdot Et_2O$ (furnishing α-product **552**), no regio- and stereoselectivity was found with various carbonyl compounds except for benzophenone.[299]

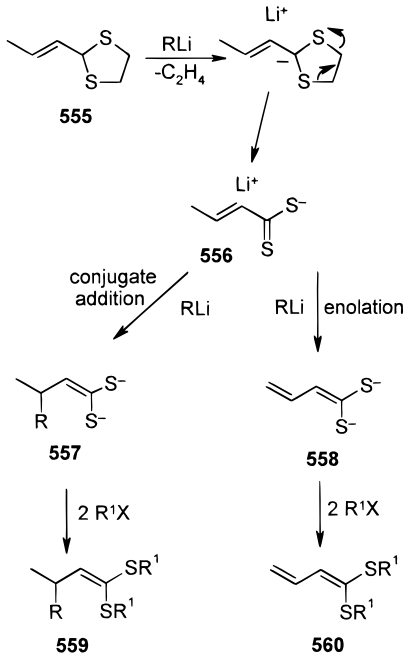
A side reaction of the deprotonation of 2-alkenyl- **555** and 2-benzyl-1,3-dithiolanes is the cycloelimination of ethylene which furnishes unsaturated dithiocarboxylate anions.[300] Thus, base-induced ring fragmentation produces the dithiocrotonate anion **556** which, depending on the nucleophilicity of the lithium reagent, gives conjugate addition to **557** (with moderately nucleophilic ^{n}BuLi, phenyllithium) or enolation to **558** (with less nucleophilic ^{t}BuLi, LDA, LTMP, LHDS). Subsequent alkylation resulted in formation of 1,1-bis(alkylthio)alk-1-enes **559** and 1,1-bis(alkylthio)alka-1,3-dienes **560**, respectively (Scheme 99).

The dithiosubstituted crotyllithium **561** reacts at the γ-terminus to give **564** with aliphatic aldimines **562**. In the presence of BF_3 the reaction occurs predominantly at the α-site and forms **563** (Scheme 100). This was also interpreted on the basis of the HSAB concept.[301]

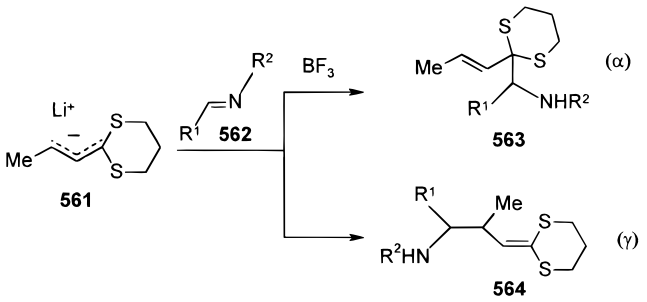
Scheme 98



Scheme 99

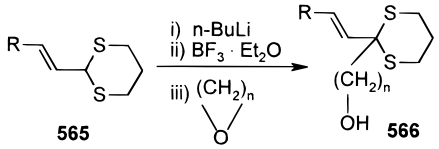


Scheme 100



In reactions of the allyl anion of **565** with three- to six-membered cyclic ethers the α-products **566** are formed in the presence of BF_3 (Scheme 101).[302]

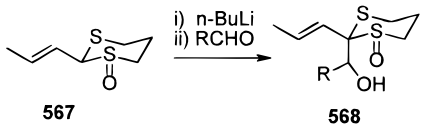
Scheme 101



2. 2-(2-Propenyl)-1,3-dithiane 1-Oxide (C═C–C(SR)(SOR))

The anion of 2-(2-propenyl)-1,3-dithiane 1-oxide **567** reacts with aldehydes at the α-site and predominantly on the face syn to the sulfinyl group affording **568** (Scheme 102)[298] in contrast to the dithiosubstituted crotyllithium (see section III.C.1).[294,295]

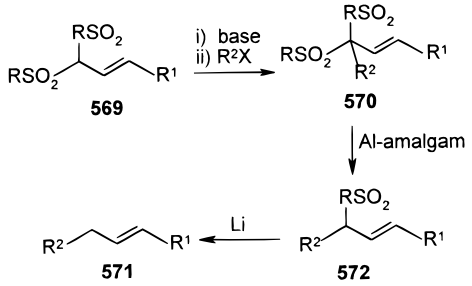
Scheme 102



3. 2-Alkenyl-1,1-disulfones (C═C–C(SO$_2$R)$_2$)

Allylic 1,1-disulfones **569** undergo α-alkylation to **570**. Upon reduction of **570** allylic sulfones **572** are produced which can be converted into olefins **571** by lithium in ethylamine (Scheme 103).[303]

Scheme 103



D. General Discussion

The bissulfone [C═C−C(SO$_2$R)$_2$] undergoes exclusive α-substitution, as does the monosulfide−monosulfoxide [C═C−C(SOR)SR].

For dithioketals [C═C−C(SR)$_2$], and for dichloro compounds [C═C−CCl$_2$, reactions often take place preferentially at the α-position, but more bulky electrophiles such as Me_3SnCl and carbonyl compounds react at least in part at the γ-postion.

The unstable ketal [C═C−C(OR)$_2$] reacts exclusively at the α-position.

An attempted rationalization of these results is presented in section IX.

IV. Allylic Anions Stabilized by Two Different Gem Heteroatoms (C═C–CXY)

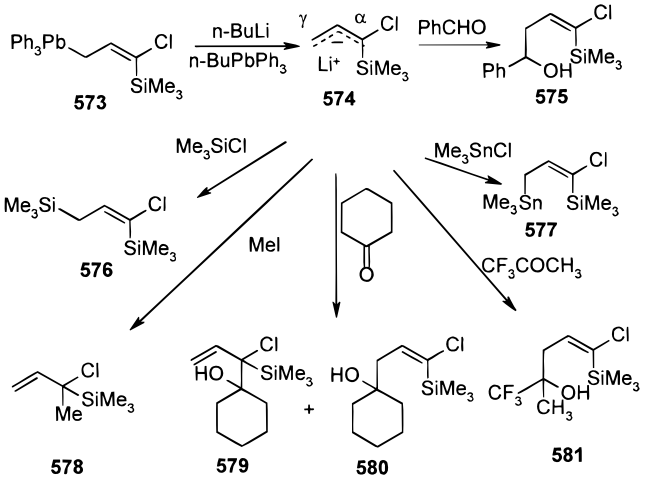
Various examples of allylic anions substituted by two geminal heteroatoms are considered. Besides those substituted by silicon and halogen, especially oxygen- and/or nitrogen-containing reagents are reviewed. Furthermore, the cyano function is treated here as a heterogroup and therefore cyanonitriles are also discussed.

A. Silicon with Halogen, Oxygen, Nitrogen, Sulfur, or Phosphorus

1. 1-Chloro-1-(trimethylsilyl)-2-propenes (C═C–C(Cl)(SiR$_3$))

Lithiated 1-chloro-1-(trimethylsilyl)-2-propenes **574** are prepared by the transmetalation reaction of ^{n}BuLi with the corresponding lead compound **573** (Scheme 104).[304] The coupling reaction of **574** with trimethylchlorosilane and trimethyltin chloride yields the γ-products **576** and **577**, respectively, while the alkylation with MeI gives α-products **578**. Seyferth and Mammarella explain the attack by carbonyl compounds in terms of the HSAB approach: the carbon atom substituted with chlorine and trimethylsilyl substituents should have greater negative charge delocalization hence be the "soft" terminus, while CH_2 represents the "hard" terminus. Thus, the reaction with benzaldehyde or 1,1,1-trifluoroacetone results in the formation of γ-adduct **575** and **581**, respectively, while the reaction with "softer" dialkyl ketones including cyclohexanone which is not sufficiently selective gives a mixture of α- and γ-adducts **579** and **580** (Scheme 104) in contrast to the formation of α-product **526** (Scheme 93) with *gem*-dichloroallyllithium. Since the trimethylsilyl group is not expected to be as efficient an electron-withdrawing group as the electronegative chlorine substituent the

Scheme 104

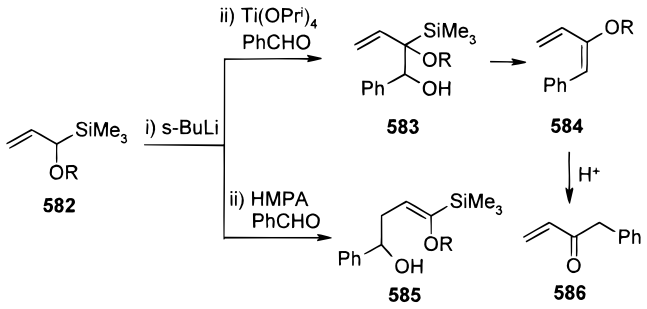


difference between "hard" and "soft" termini of **574** is probably less than that between "hard" and "soft" ends of *gem*-dichloroallyllithium and hence, **574** is expected to be less regioselective than the dichloro analogue. Furthermore, steric effects have also an influence on the course of the reaction since the trimethylsilyl group is sterically demanding (see *gem*-dichloroallyllithium section III.B for comparison).[304]

2. α-Alkoxyallylsilanes (C═C–C(OR)(SiR$_3$))

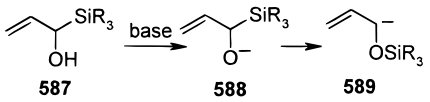
1-Lithio-1-(alkoxy)allyltrimethylsilane from **582** reacts with aldehydes to give both the α- **583** and γ-products **585**. However, transformation into the titanium reagent leads to exclusive generation of α-products **583** followed by Peterson elimination to form the dienyl ether **584** while in the presence of HMPA exclusively γ-attack to form **585** is observed. The dienyl ether **584** can be easily hydrolyzed to form the vinyl ketone **586** (Scheme 105).[305]

Scheme 105



α-Silyl alcohols **587** undergo Brook rearrangement,[306] whereas the alkoxy anion in **588** attacks the silyl group to form an α-alkoxy anion **589** (Scheme 106)[307,308] (see also section II.B).

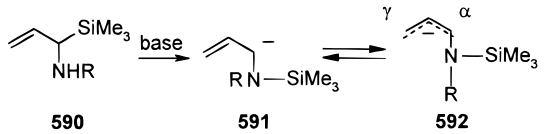
Scheme 106



3. α-Silylallylamines (C═C–C(NR$_2$)(SiR$_3$))

α-Silylallylamines **590** furnish aza-Brook rearrangement to products **591** and **592** upon treatment with bases (Scheme 107).[307]

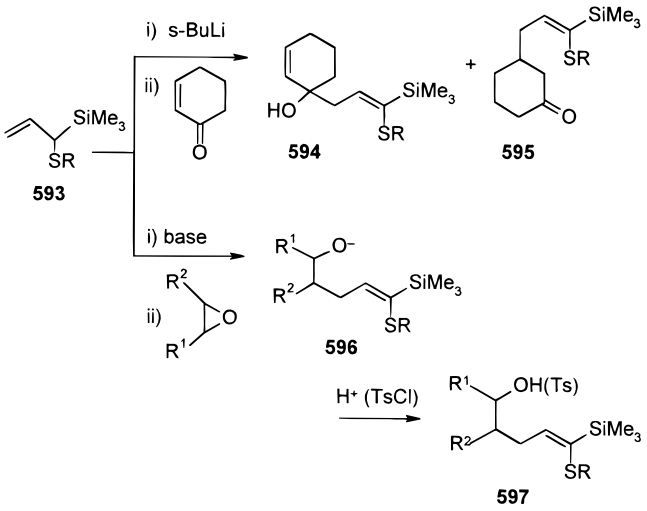
Scheme 107



4. α-(Trimethylsilyl)allyl Sulfides (C═C–C(SiMe$_3$)(SR))

The anion of (trimethylsilyl)alkylallyl or (trimethylsilyl)arylallyl sulfide **593** undergoes regioselective γ-addition with enones yielding predominantly the 1,4-adduct **595** even in the absence of HMPA (Scheme 108).[234] Furthermore, reaction with carbonyl compounds takes place preferentially at the γ-carbon (cf. **594**).[309] The reaction of lithiated **593** with epoxides also proceeds with γ-attack giving alkoxides **596**

Scheme 108

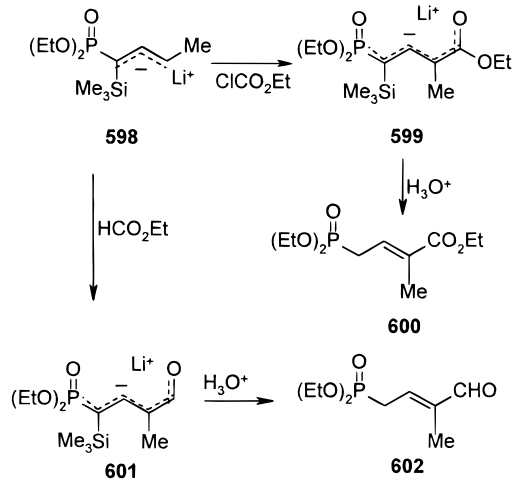


which can be converted into the corresponding alcohols or tosylates **597** (Scheme 108).[78]

5. Diethyl (Trimethylsilyl)crotylphosphonate (C═C–C(SiMe$_3$)(PO(OEt)$_2$)

Lithiated diethyl (trimethylsilyl)crotylphosphonate **598** is generated in situ from diethyl crotylphosphonate and reacts with ethyl chloroformate and ethyl formate at the γ-carbon to both heterogroups to give **599** and **601**, respectively, and upon hydrolysis the corresponding phosphonates **600** and **602** (Scheme 109).[209]

Scheme 109

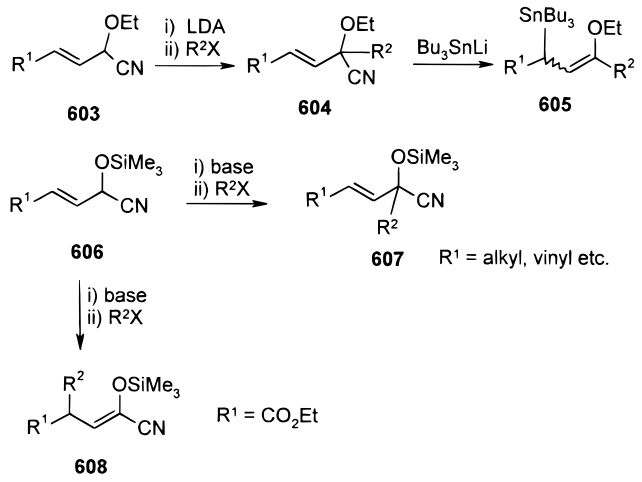


B. Protected Cyanohydrins

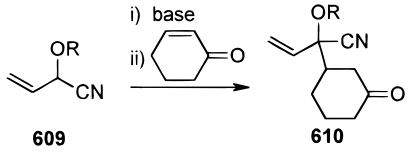
1. Alkoxy Cyanohydrins (C═C–C(CN)(OR))

Protected cyanohydrins are valuable synthetic intermediates[310,311] and act as acyl anion synthons. Treatment of the allyl anions of 2-ethoxy-3-alkenenitriles **603** with alkyl halides[312] produces α-products **604** and displacement of the CN group by tributylstannyllithium furnishes the γ-ethoxyallylstannanes **605** (Scheme 110).[313] α-Alkylation to give **607** is also reported for trimethylsilyl cyanhydrins **606** (Scheme 110),[314,315] although more electron-attracting substit-

Scheme 110



Scheme 111



uents in the γ-position, such as CO_2Et, favor γ-alkylation to give **608**.[316]

Reaction of the metalated cyanohydrins of **609** with α,β-unsaturated ketones gives conjugated α-1,4-addition products **610** (Scheme 111).[317−321]

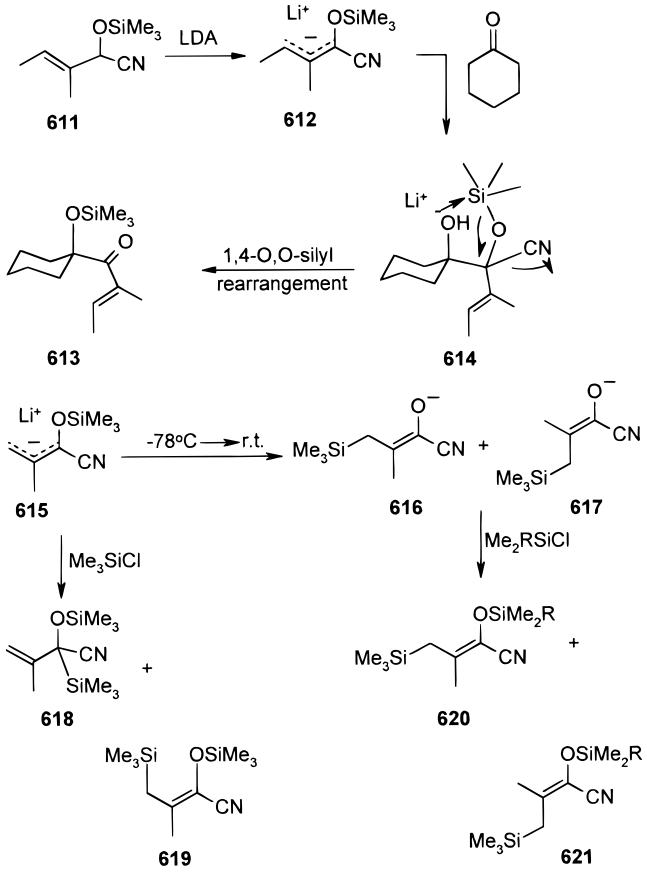
The anion **612** of oxytrimethylsilyl cyanohydrin **611** gives exclusively the α-products **614** in reactions with ketones or aldehydes at −78 °C accompanied[322] by 1,4-O,O-silyl rearrangement producing **613** (Scheme 112).[323] On warming to room temperature, the anion species **615** undergoes 1,4-O,C-silyl rearrangement to form the new O-anions **616** and **617** which again can be trapped by silylation to give **620** and **621**, respectively (Scheme 112). In contrast to the reaction of **615** with alkyl halides and carbonyl compounds, treatment with trimethylchlorosilane does not proceed regioselectively. A mixture of α- **618** and γ-adduct **619** is obtained (Scheme 112).[324]

The ethoxyethylsilyl cyanhydrin anion **623** also shows exclusive α-reactvity to give **622** at −78 °C. However, upon treatment with aldehydes and ketones γ-reactivity to form exclusively **624** is observed if the reaction is carried out at 0 °C.[325,326] Metalation of the α-product **622** at −78 °C followed by warming to 0 °C yields exclusively γ-product **624** (Scheme 113).

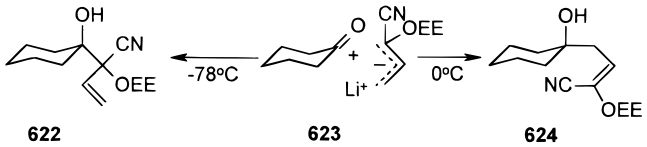
2. α-Cyanoallylamines (C═C–C(CN)(NR$_2$)

α-Cyanoallylamines **625** generally react at the γ-carbon with alkylating agents to give **627**[327,328] and with α-enones to give predominantly 1,4-addition (cf. **626**). An improvement of the yield of 1,4-adduct **626** is achieved by allowing the kinetically controlled product mixture to equilibrate.[329] Furthermore, asymmetrical alkylation at the γ-position was carried out.[330] If NR_2 in **625** is a morpholino group the alkylation takes places either exclusively or predominantly at the α-position producing **629** (Scheme 114).[331]

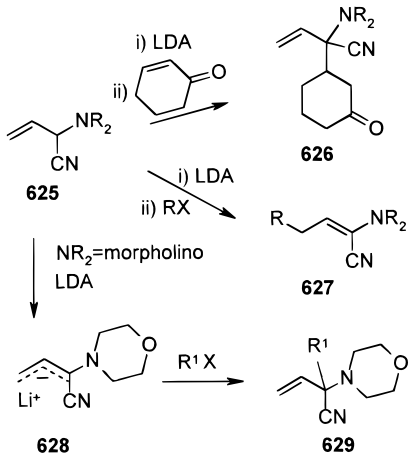
Scheme 112



Scheme 113

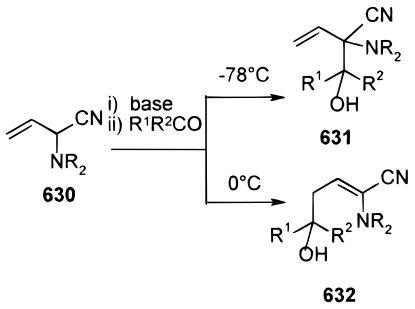


Scheme 114



Treatment of allylic aminonitriles **630** with ketones for 90 s at −78 °C in THF yielded α-condensation products **631**. When the same sequence is carried out at 0 °C or at −78 °C and allowed to warm to 0 °C only the γ-product **632** is observed (Scheme 115)[326] (cf. section IV.C.1). The overall yield of γ-adduct **632** can be improved by addition of anhydrous $ZnCl_2$ (cf.

Scheme 115



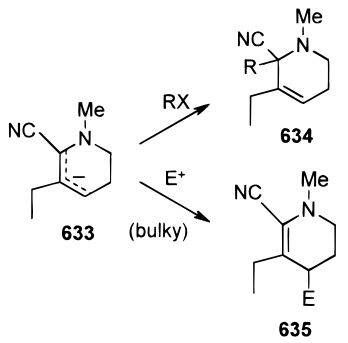
usual improvement of yield of α-product with $ZnCl_2$).

Lithiated $H_2C{=}CH{-}CH(CN)(NMePh)$ yields γ-products when reacted with RX, RCHO, and RCOR while both α- and γ-adducts are obtained with $Ph{-}CH{=}CH{-}CLi(CN)(NR_2)$.[332] The regioselectivity of the reaction of the former is remarkably high considering the exclusive α-attack for the oxygen analogues ($Ph{-}CH{=}CHLi(CN)(OSiMe_3)$, $Ph{-}CH{=}CH{-}CH_2{-}CLi(CN)$/(OEE).

3. 2-Cyano-Δ³-piperideines (C═C–C(CN)(NR₂))

Carbanions **633** produced by deprotonation of 2-cyano-Δ^3-piperideines give regioselective α-products **634**[333] with D_2O, methyl iodide, benzyl, and isopropyl bromide and the highly hindered *tert*-butyl chloride. However, with bulkier molecules, e.g., pivaloyl chloride, C_4-substituted product **635** is afforded (Scheme 116).[334] The acyclic aminonitriles of Ahlbrecht undergo γ-alkylation to give **627** (Scheme 114).[332] However **633** cannot form a metallocycle with Li situated at the C_4-position, a situation which is possible for acylic analogues.

Scheme 116

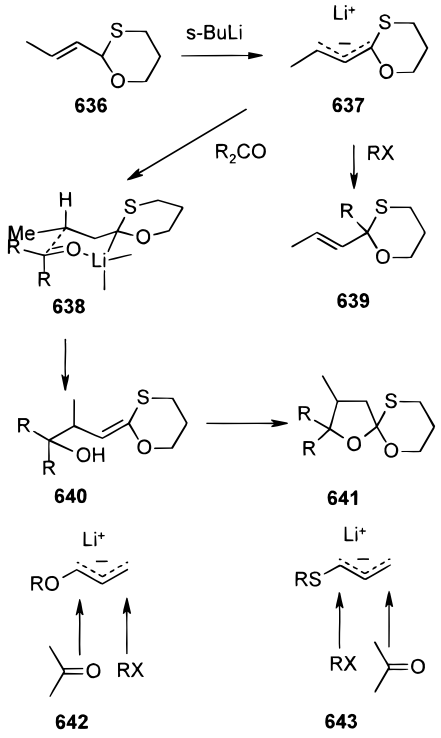


C. Oxygen with Sulfur or Nitrogen

1. 1-Alkoxy-1-(alkylthio)-2-propenes (C═C–C(OR)(SR))

α-Products are generated in the alkylation reaction of 1-methoxy-1-(alkylthio)allyl sulfide anions.[335,336] Hence, oxathio-substituted crotyllithium **637** reacts with alkyl halides predominantly at the α-site to give **639**, whereas aldehydes and ketones undergo non-diastereoselective reaction at the γ-terminus, giving **641** via a six-membered transition state **638** where lithium at the α-site coordinates the carbonyl oxygen leading to the γ-product **640** which readily cyclizes to spiro compound **641** (Scheme 117).[337] The comparison of the orientation of electrophilic attack of

Scheme 117

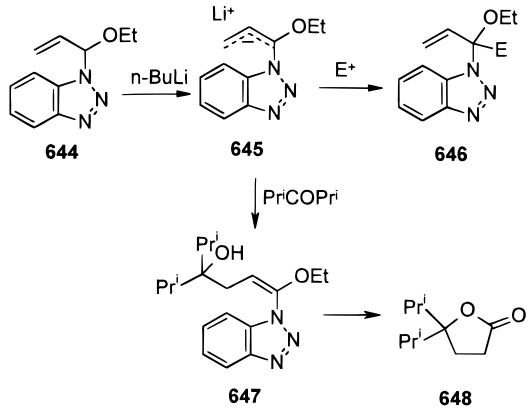


the oxythio-substituted reagents with those at the analogous monosubstituent derivatives (alkoxy allyl anion **642**—see also section II.B and lithiumallyl sulfide **643**—see also section II.C) (Scheme 117) shows a similarity to the latter (S) and suggests that stabilization by sulfur is more important for the prediction of the site of electrophilic attack than the oxygen.

2. N-(α-Ethoxyallyl)-1-benzotriazole and -1-triazole (C═C–C(OR)(NR₂))

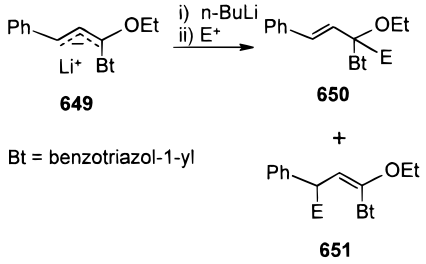
The oxygen- and nitrogen-substituted allyl anion **645** obtained upon deprotonation of *N*-(α-ethoxyallyl)benzotriazole **644** undergoes exclusive α-product **646** formation with alkyl halides, aldehydes, most ketones, and α,β-unsaturated esters while exclusive γ-attack to form **647** is observed with sterically hindered electrophiles, e.g., bulky ketones such as 2,4-dimethyl-3-pentanone. **647** was hydrolyzed to give γ-lactone **648** (Scheme 118).[338−343] This work has recently been reviewed in detail.[344]

Scheme 118



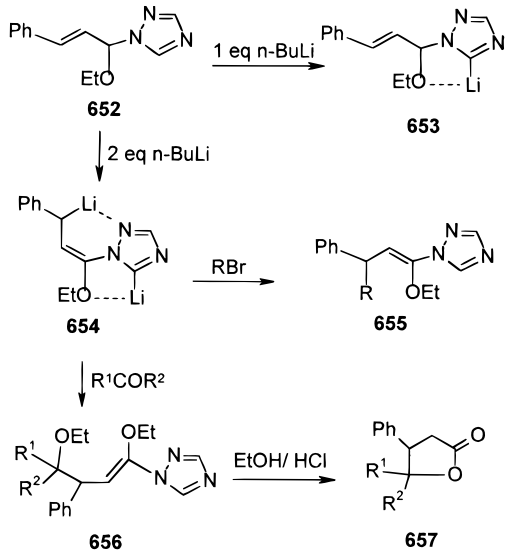
The γ-alkyl-substituted allylic anion of type **645** behave similarly.[345] However, the γ-phenyl-substituted allylic anion **649** reacts with alkyl halides giving mainly α-products **650** and some γ-products; for benzyl bromide predominantly γ-product **651** is obtained as it is softer than other alkyl bromides and the γ-position appears to prefer soft electrophiles while the α-position is favored by hard electrophiles. Aldehydes and ketones afford α,β-unsaturated ketones (α-adduct) besides γ-isomer **651** (Scheme 119).[345]

Scheme 119



The first deprotonation of 1,2,4-triazole-substituted alkoxyallyl compounds such as **652** with 1 equiv of ^{n}BuLi occurs at the ring forming **653**, because of the acidic proton on the triazole ring. The second lithiation is carried out at the chain. The dilithio derivative **654** yields the γ-alkylated product **655** upon treatment with 1 equiv of ethyl bromide. No α-product is observed. The same product **655** is obtained with 2 equiv of the alkyl halide. No ring alkylation takes place. The reaction of aldehydes and ketones with the dilithiated species **654** followed by hydrolysis affords the expected γ-lactones **657** via γ-adduct **656** (mixture of *E*- and *Z*-isomers) (Scheme 120).[345]

Scheme 120

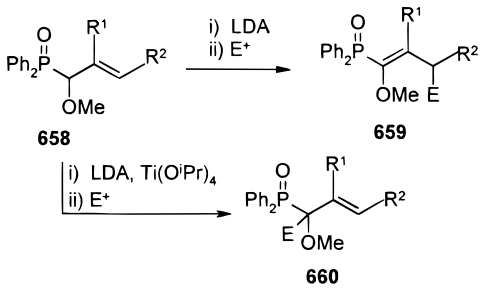


D. Oxygen and Phosphorus

1. α-Alkoxyallylphosphine Oxides (C═C–C(OR)(POPh$_2$))

α-Methoxyallylphosphine oxides **658** yield predominantly γ-adducts **659** with carbonyl compounds. The α-proportion of **660** can be increased by transmetalation with titanium (Scheme 121).[346] Maleki and Miller[347] observed a regioselectivity dependent on the

Scheme 121

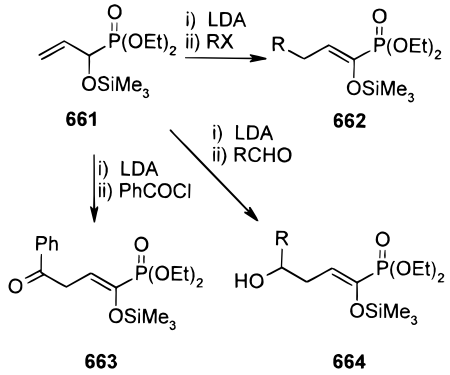


substitution pattern of the starting material and the nature of the electrophile. The α-alkoxyallylphosphine oxide anion reacts with silicon,[212] sulfur, and phosphorus electrophiles to give γ-attack products **659** (Scheme 121).[348]

2. α-(Trimethylsiloxy)allylphosphonates (C═C–C(OSiR$_3$)(PO(OEt)$_2$))

α-(Trimethylsiloxy)allylphosphonate **661** is γ-alkylated exclusively with RX.[349] Similarly, γ-attack is observed in the reaction with RCOCl and RCHO to give **663** and **664** respectively (Scheme 122).[350]

Scheme 122

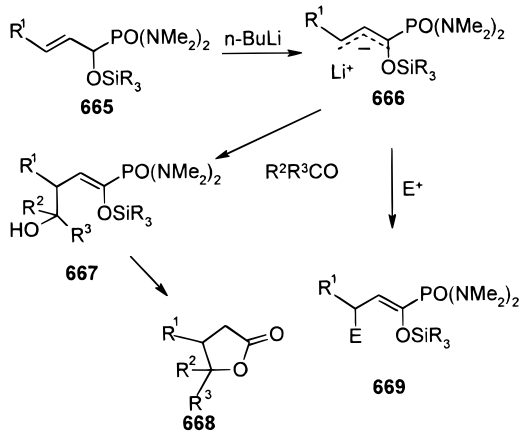


3. α-(Trimethylsiloxy)allylphosphonamides (C═C–C(OSiR$_3$)(PO(NMe$_2$)$_2$))

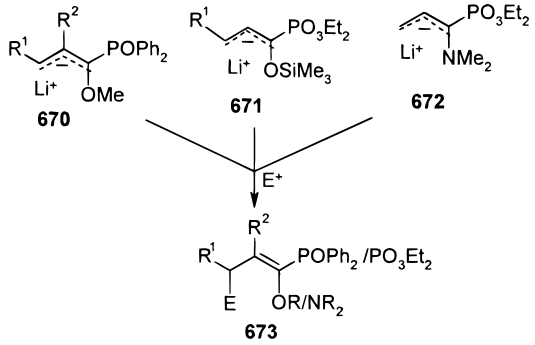
The anions **666** of α-(trimethylsiloxy)allylphosphonamide **665** are alkylated at the γ-position to give **669** as well as with aldehydes and ketones which form γ-adducts **667** followed by cyclization to γ-lactones **668** (Scheme 123). Similarly, δ-lactones are produced with epoxides.[351] Halides which impose greater steric constraints improve significantly the γ-regioselectivity as do noncoordinating solvents such as diethyl ether or hexane. A comparison of phosphorus activating groups with each other revealed that phosphonamides (e.g., **665**, Scheme 123) are less regioselective in the reaction with electrophiles than phosphonates (e.g., **661**, Scheme 122) with an otherwise identical set of substituents on the allylic carbanion.[352]

The allyl anions **670**,[347] **671**,[350] and **672**[353] (Scheme 124) exhibit a similar γ-regioselectivity toward electrophiles to give **673** due to the steric hindrance of the neighboring phosphoryl group and for **672** also caused by the amino group.

Scheme 123



Scheme 124

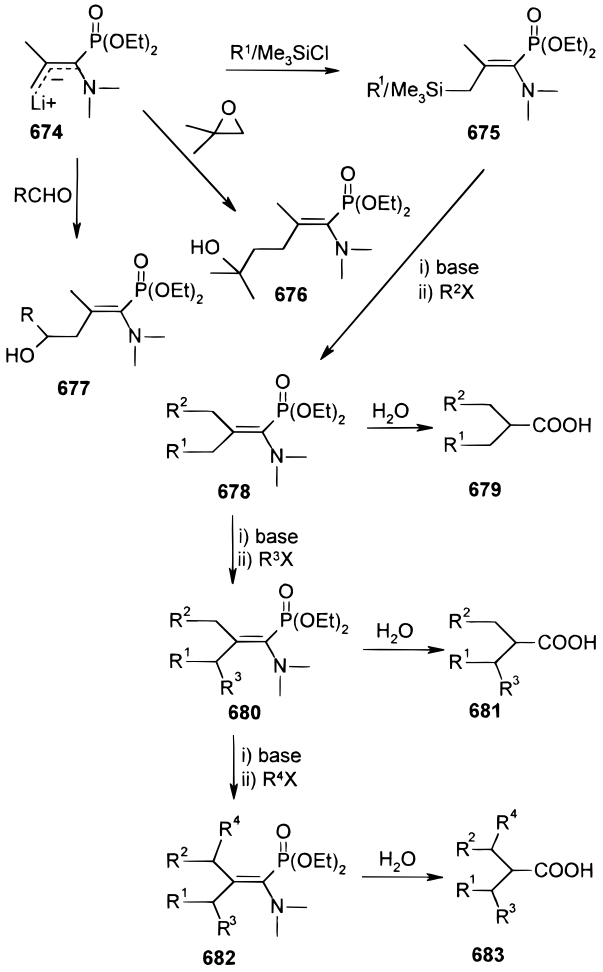


E. Nitrogen and Phosphorus

1. 1-(Diethoxyphosphoryl)-1-(dimethylamino)-1-propenes (C–C═C(NMe$_2$)(PO(OEt)$_2$)

1-(Diethoxyphosphoryl)-1-(dimethylamino)allyl anion **674** undergoes γ-alkylation and silylation to give **675** which can be alkylated again to give **678**, **680**, and **682** and yield upon hydrolysis the corresponding carboxylic acid **679**, **681**, and **683** alkylated at C-3. Reaction with benzaldehyde gives low yields of the δ-hydroxyallyl compound **677**, similar to the reaction with isobutenoxide producing **676** (Scheme 125).[354]

Scheme 125



F. General Discussion

The orientation of reactions with electrophiles of allyl anions stabilized by two different *gem*-heteroatoms are summarized in Scheme 126.

Geminal benzotriazole/alkoxy substituents (Bt−C−OR) direct substitution exclusively to the α-position for all electrophiles studied except very sterically crowed carbonyl groups where the regioselectivity favors γ-substitution. A rather similar pattern is shown for cyano/alkoxy (NC−C−OR) except that here reactions with carbonyl electrophiles are probably reversible and kinetically favor α-substition at low temperature but thermodynamically favor γ-substitution at high temperature. For cyano/diallylamino (NC−C−NR$_2$), conjugate addition occurs α but allylation gives α/γ mixtures.

Another set of geminal substituents shows essentially exclusive reaction at the γ-position. This includes P(O)R$_2$ or PO(OEt)$_2$ paired with OMe, OSiMe$_3$, NR$_2$, and SiMe$_3$. The SiMe$_3$/SR pair also belongs this class as does the ionized *N*-triazolyl/ethoxy derivative.

The SiR$_3$/Cl and SiR$_3$/OR pairs fall into an intermediate position showing a mixture of α- and γ-substitution.

V. Allyl Anions Stabilized by Two Non-Gem-Heteroatoms (XC═C–CY and C═CX–C–Y)

In addition to allyl anions stabilized by two identical heteroatoms, allylic systems bearing two different heteroatoms have been studied particularly those containing oxygen or sulfur.

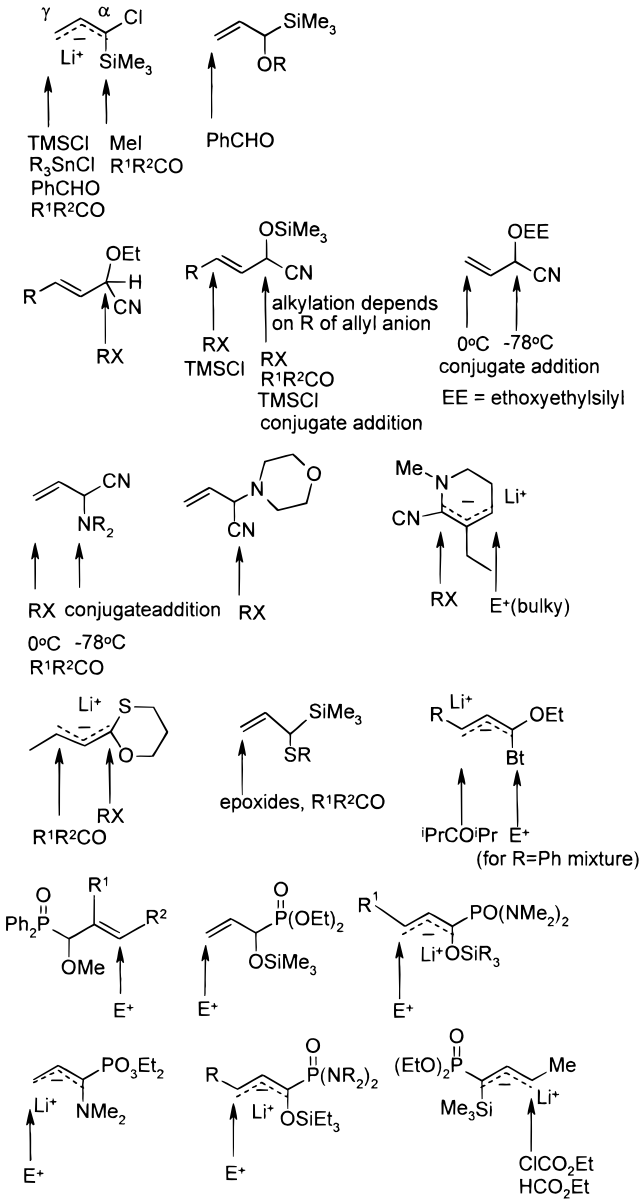
A. Two Identical Heteroatoms

Symmetrical allylic systems substituted in the 1- and 3-position by two identical heteroatom-linked substituents are a unique class of compounds, since attachment of an electrophile to either terminal carbon yields the same product. We also discuss compounds 1,3-disubstituted by two different functional groups linked by the same heteroatom.

1. 1,3-Bis(alkylthio)-1-propenes (RS–C═C–C–SR)

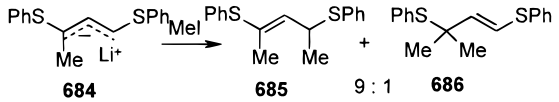
The 1,3-bis(methylthio)allyl anion is readily synthesized in a three-step sequence from epichlorhydrin. Although probably intrinsically unstable, it undergoes a clean reaction with electrophiles to give a protected form of the conjugated aldehyde RCH═

Scheme 126. Two Different *Gem*-Heteroatoms



CHCHO.[355,356] In the case of unsymmetrically substituted anions **684** with different steric requirements at the 1- and 3-allylic carbon atoms, the least hindered of these will be the most readily alkylated to give predominantly **685** (Scheme 127).[357] Oshima et al.[358] carried out the same reactions but used transmetalation with CuI.

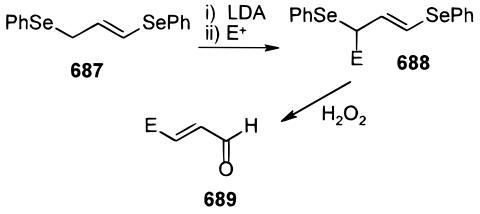
Scheme 127



2. 1,3-(Diphenylseleno)-1-propene (PhSe–C═C–C–SePh)

1,3-(Diphenylseleno)propene **687** after metalation reacts smoothly with alkyl halides, TMSCl, epoxides, and carbonyl compounds. The products **688** can be converted as shown into 3-substituted propenal derivatives **689** (Scheme 128).[359]

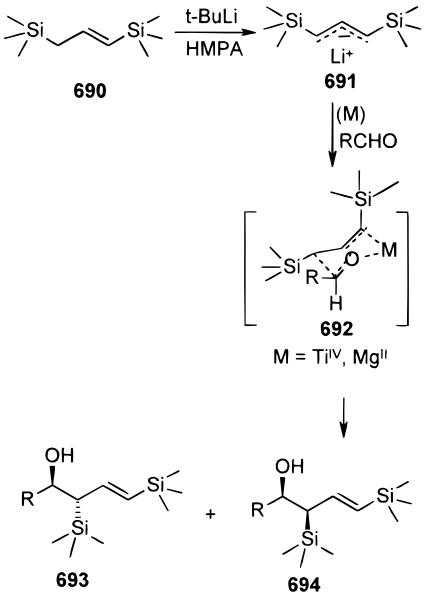
Scheme 128



3. 1,3-Bis(trimethylsilyl)propene (Me3Si–C–C═C–SiMe3)

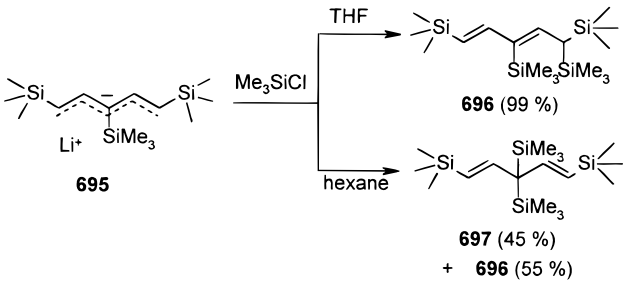
1,3-Bis(trimethylsilyl)propene **690** gives anion **691** which is attacked by carbonyl compounds producing **693** and **694** but with low yields and variable stereoselectivity.[360,361] This can be improved by addition of $MgBr_2$, trimethyl borate, or Cp_2TiCl (Scheme 129).[362] The reaction proceeds via a six-membered transition state exhibiting a chair conformation **692** (analogous to **447**, Scheme 79, section II.G.1).

Scheme 129



The reaction of 1,3,5-tris(trimethylsilyl)pentadiene anion **695** with trimethylchlorosilane leads to 1,1,3,5-tetrakis(trimethylsilyl)-1,3-pentadiene **696** with 99% regioselectivity in THF while in hexane a mixture of **696** (55%) and 1,3,3,5-tetrakis(trimethylsilyl)-1,4-pentadiene **697** (45%) is observed (Scheme 130).[264]

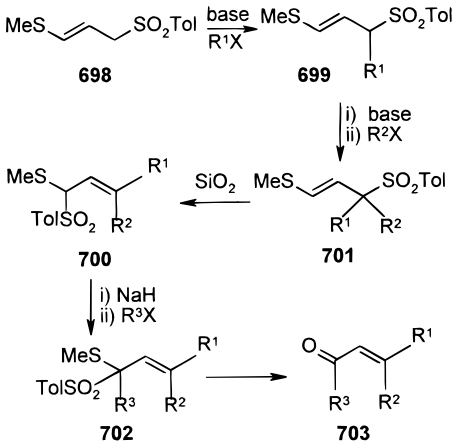
Scheme 130



4. 3-(Methylthio)-2-propenyl p-Tolyl Sulfones (MeS–C═C–C–SO2R)

3-(Methylthio)-2-propenyl *p*-tolyl sulfone **698** can undergo either mono- (cf. **699**) or double alkylation

Scheme 131

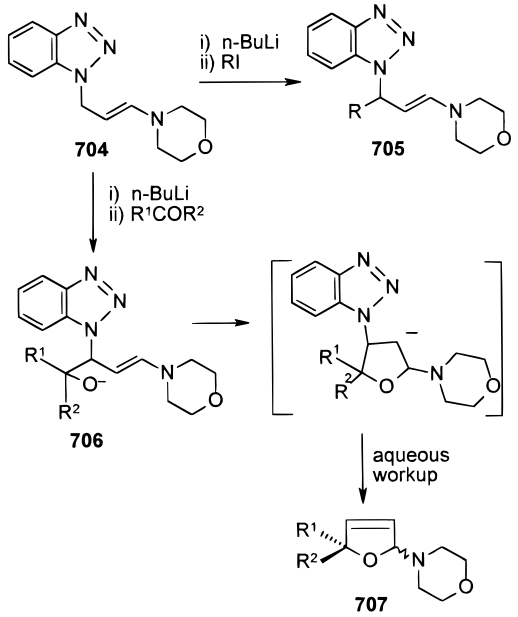


(cf. **701**, Scheme 131) at the α-position to the sulfonyl group.[356] SiO_2-catalyzed 1,3-rearrangement of **701** gives 1-(methylthio)-1-(*p*-tolylsulfonyl)-2-propene derivatives **700**, which using NaH in DMF are then alkylated at the α-position to produce **702**. Subsequent hydrolysis of **702** affords the α,*β*-unsaturated ketones **703** (Scheme 131).[363]

5. 1-(Benzotriazolyl)-3-(dialkylamino)-2-propenes (Bt–C–C═C–NR$_2$)

1-(3-Morpholinoprop-2-enyl)benzotriazole **704** gives α-substitution with respect to benzotriazole upon alkylation to give **705** and upon reaction with carbonyl compounds to form products **706**. The latter product cyclizes to furan derivatives **707** (Scheme 132).[364,365]

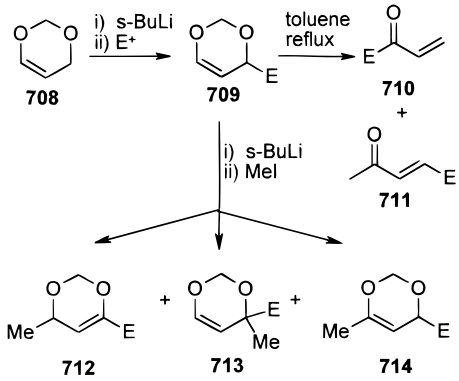
Scheme 132



6. 4H-1,3-Dioxins

Clean reactions of 4*H*-1,3-dioxin anion **708** with various alkyl halides, carbonyl compounds and ethylene epoxide takes place to give **709** which furnishes upon thermolysis a mixture of the enone **710** and the enal **711**. The 4*H*-alkyl-1,3-dioxin (**709**, E = alkyl) can be deprotonated again and treated with methyl iodide to give a mixture of three disubstituted dioxins **712**, **713**, and **714** (Scheme 133).[366,367]

Scheme 133

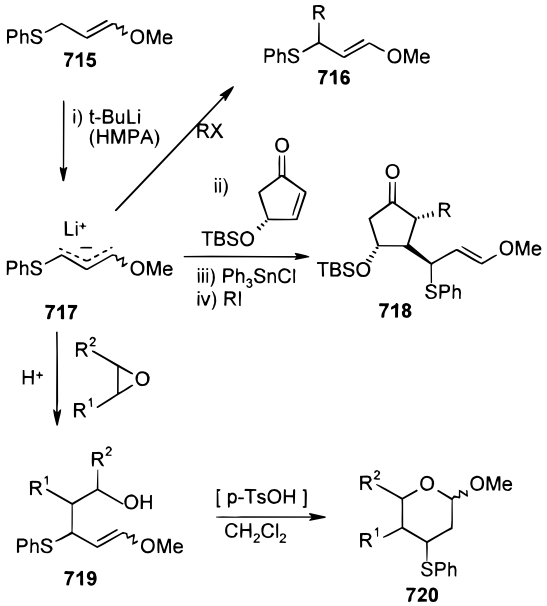


B. Sulfur with Oxygen, Silicon, or Halogen

1. γ-Alkoxyallyl Sulfides (RO–C–C═C–SR)

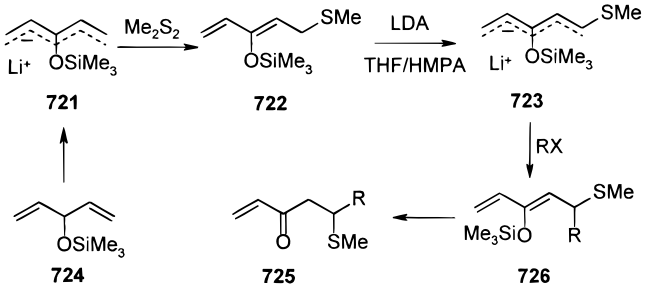
The *γ*-alkoxyallyl sulfide anion **717** is alkylated at the carbon α to the sulfur and *γ* to the alkoxy group to give **716**.[336,368−370] Such alkylation even occurs α to the sulfur atom when this is the more hindered carbon.[371] Furthermore, anion **717** reacts in the presence of HMPA α to the sulfur with carbonyl compounds forming **718**; enolate trapping with Ph_3SnCl was found crucial for effective α-attack in a synthesis of prostaglandins.[372] Similarly, an α-selective attack at the position adjacent to sulfur is observed in the reaction of **717** with epoxides to give bishomoallyl alcohols **719** which generate tetrahydropyrans **720** by acid-catalyzed cyclization (Scheme 134).[373]

Scheme 134



γ-Selective sulfenylation of **721** gives **722**. Subsequent alkylation of **723** is directed by the methylthio substituent in anion **723** to give entirely the *γ*-product **726** with respect to the silyloxy group. Compound **726** was then converted into the enone **725** (Scheme 135).[58]

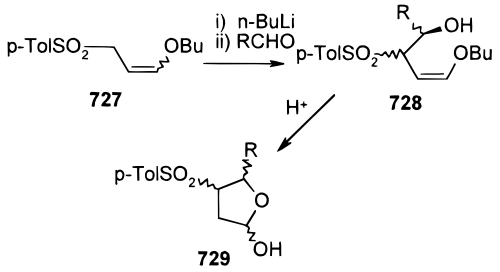
Scheme 135



2. γ-Alkoxyallyl Sulfones ((RO–C═C–C–SO_2Ar)

The γ-alkoxyallyl sulfone **727** on deprotonation and reaction with RCHO gives products **728** by substitution α to the sulfonyl group. Upon acidic hydrolysis, **728** can be converted into lactols **729** (Scheme 136).[374]

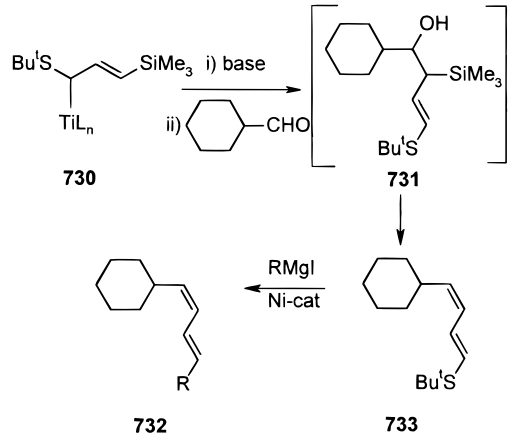
Scheme 136



3. 1-(Alkylthio)-3-(trimethylsilyl)-2-propenes (RS–C–C═C–$SiMe_3$)

The titanium reagent **730** derived from 1-(alkylthio)-3-(trimethylsilyl)-1-propene reacts with aldehydes α to the silicon producing **731** which furnishes the diene **733**. Subsequent displacement of the alkylthio group affords 1,4-disubstituted 1,3-dienes **732** stereoselectively (Scheme 137).[375]

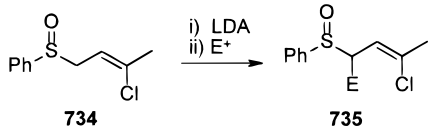
Scheme 137



4. γ-Chlorallyl Phenyl Sulfoxide (PhSO–C–C═C–Cl)

γ-Chloroallyl sulfoxides **734** exhibit α-regioselectivity to the sulfoxide site upon both alkylation and reaction with carbonyl compounds to give products of type **735** (Scheme 138).[376]

Scheme 138

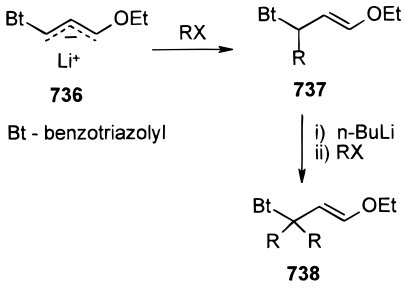


C. Oxygen with Nitrogen and Silicon

1. 1-Ethoxy-3-(benzotriazol-1-yl)-1-propenes (EtO–C═C–C–Bt)

Alkylation and reaction with carbonyl compounds of anion **736** occur at the α-position to the benzotriazole to give **737** which can be alkylated a second time producing **738** (Scheme 139).[377]

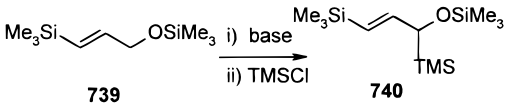
Scheme 139



2. 1-(Trimethylsilyl)-3-[(trimethylsilyl)oxy]-1-propenes (Me_3Si–C═C–C–$OSiMe_3$)

1-(Trimethylsilyl)-3-[(trimethylsilyl)oxy]-1-propene **739** is trimethylsilylated next to the (trimethylsilyl)oxy function yielding **740** (Scheme 140).[378,379]

Scheme 140



3. 1-(Trimethylsilyl)-1-propenyl N,N-Diisopropylcarbamate (Me_3Si–C═C–C–O–CO–NPr^i_2)

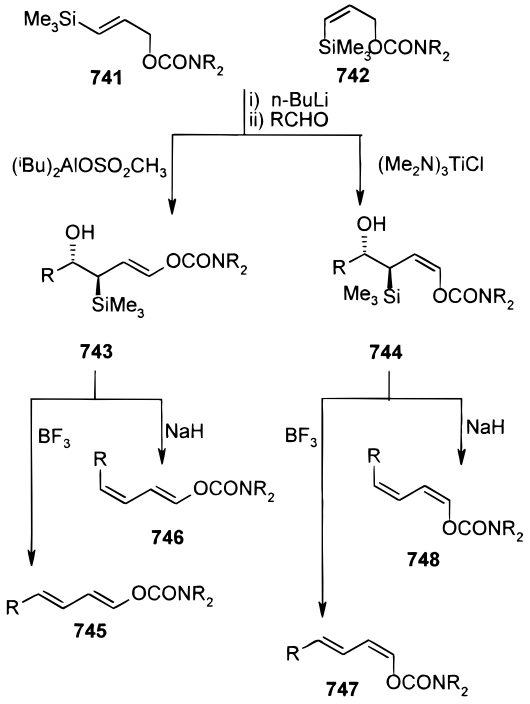
Stereoselective synthesis of all four steroisomeric 1-carbamoyloxy-1,3-alkadienes **745**, **746**, **747**, and **748** is carried out by an anti-diasteroselective homoaldol reaction of 3-(trimethylsilyl)-2-propenyl *N*,*N*-diisopropylcarbamates **741** and **742** with aldehydes via the alcohols **743** and **744** (Scheme 141).[62]

D. Nitrogen with Sulfur or Silicon

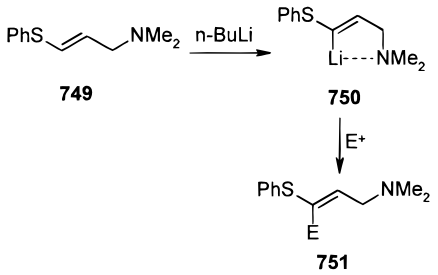
1. N,N-Dimethyl-3-(phenylthio)-2-propenylamine (PhS–C═C–C–NMe_2)

In this section an exception is discussed. *N*,*N*-Dimethyl-2-lithio-3-(phenylthio)-2-propenylamine **749** after deprotonation (cf. **750**) reacts at the carbon next to sulfur to give **751** (Scheme 142).[380] Obviously, *N*,*N*-dimethyl-2-lithio-3-(phenylthio)-2-propenylamine is metalated at the sp^2 carbon as found for vinyl sulfides in contrast to its sulfur (RS−C═C−C−SR) (cf. section V.A.1) and oxygen analogues (RS−C═C−C−OR) (cf.

Scheme 141



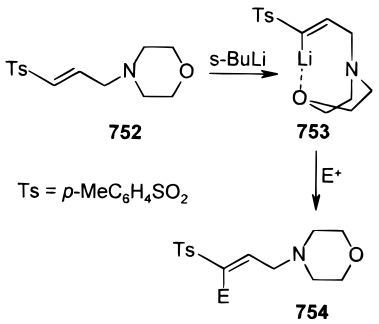
Scheme 142



section V.B.1) which are lithiated exclusively at the sp^3 carbon and form allylic anions.

Lithiation of (*E*)-*N*-(3-tosyl-2-propenyl)morpholine **752** with *s*-BuLi takes place in the vinylic position to give the corresponding γ-functionalized organolithium intermediate **753**. The further reaction of this anion with D_2O, alkyl halides, aldehydes, or ketones affords regio- and stereoselectively tosylated γ-functionalized allylmorpholines **754** (Scheme 143).[381a]

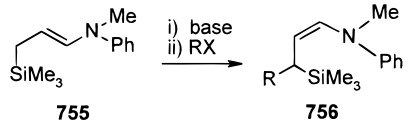
Scheme 143



2. γ-Silyl Enamines (R_2N–C═C–C–$SiMe_3$)

γ-Silylated enamines **755** are alkylated at the carbon adjacent to silicon forming **756** (Scheme 144).[157]

Scheme 144



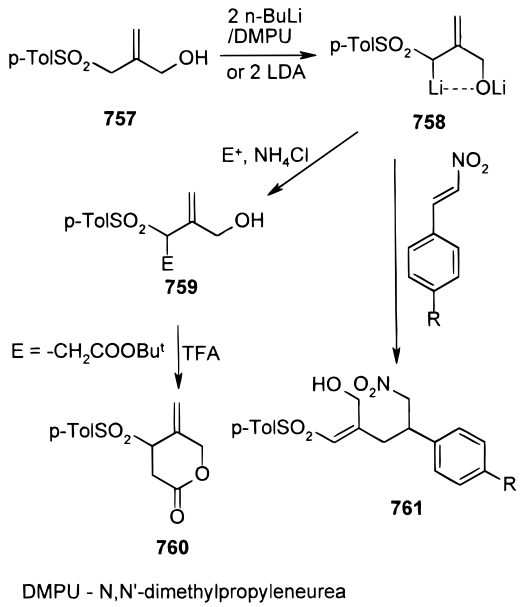
E. Others

This section deals with two classes of compounds which cannot readily be allocated to one of the previously mentioned subdivisions: each contains two heteroatoms, in the first class (sections E.1 to E.3) while one heteroatom is part of the allylic system, the other heteroatom is linked to the β-allyl carbon via a methylene group. Deprotonation could give alternative allylic anions stabilized by either heteroatom. The second class (section E.4) combines 1,2-heterosubstituted allyl anions.

1. 2-(Tosylmethyl)-2-propen-1-ol (See Also Scheme 34)

2-(Tosylmethyl)-2-propen-1-ol **757** on treatment with BuLi forms dilithiated dianion **758** which gives α-adducts **759** with alkyl halides and aldehydes. The product **759** obtained with *tert*-butyl bromoacetate as electrophile cyclizes to the corresponding δ-lactone **760** by treatment with 30% trifluoroacetic acid (TFA) (Scheme 145).[381b] By contrast, conjugate addition of **758** to nitroolefins occurs at the γ-position to tosyl, forming **761** (Scheme 145).[382]

Scheme 145

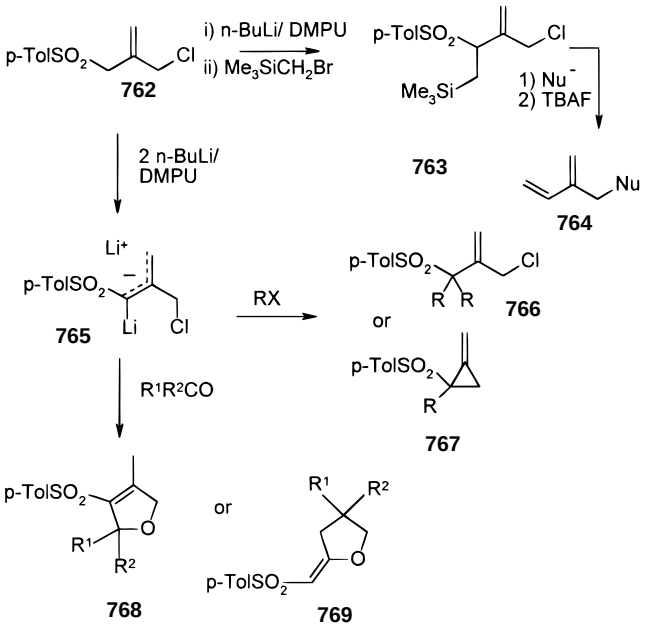


DMPU - N,N'-dimethylpropyleneurea

2. Sulfur and Halogen

a. 2-(Chloromethyl)-3-tosylpropene. The α-adduct **763** of the monolithiated derivative **762** can be transformed into a diene **764**.[383,384] 2-(Chloromethyl)-3-tosylpropene dianion **765** is alkylated exclusively at the α-position; reactive alkylating agents yield α,α-products **766** while less reactive agents afford products **767** obtained by γ-elimination. The reaction of **765** with aldehydes yields the corresponding tosylated dihydrofurans **768**.[385,386] Ketones reacted with the dianion at the less-hindered γ-position to give **769**

Scheme 146



(Scheme 146). The chlorine atom seems to play an important role in the structure of the anions by intramolecular complexation (CIPE effect).[385−387]

b. 1-(Phenylsulfonyl)-2-methylene-3-bromopropane (See Also Scheme 34). The monoanion of 1-(phenylsulfonyl)-2-methylene-3-bromopropane **770** yields α-products **771** and **773** upon reaction with a nitroolefin, the syn-isomer **771** being preferentially formed. The addition of a second molar equivalent of base to achieve a second deprotonation leads to increased *polymerization*. In contrast, reactions with unsaturated esters give the anti-adducts **772** (cyclization to **774**) as the major products.[388,389] In the presence of HMPA the diastereomeric ratio for the esters as acceptors changed to give mainly syn-product while there was no change with nitropropene. The influence of chelation evidently favors the formation of anti-diastereomer, since the chelation ability decreases for nitropropene. Whereas in case of α,*β*-unsaturated esters open chain products **772** could not be detected, only the *anti*-nitro derivative **773** cyclizes easily forming **775** (Scheme 147).[388,389]

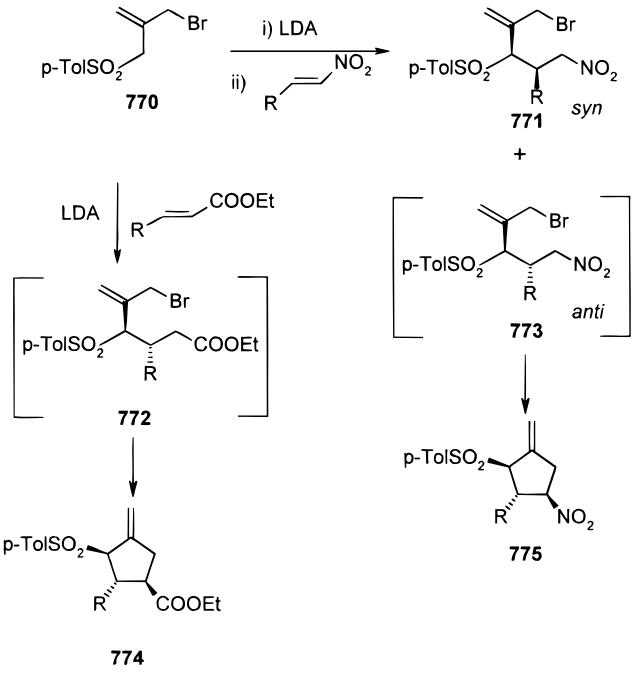
3. Sulfur and Nitrogen

Monolithiated benzyl[2-(tosylmethyl)-2-propenyl]-amine **777** reacts at the α-position to sulfur with D_2O, alkyl halides, propanal, etc. to give **779**. Dilithiation of **776** forming **778** takes place at the α-position and at the nitrogen to give **780** beside minor **779**. Upon treatment with dihalides as electrophiles, nitrogen-containing heterocycles **781** result via the adducts **779** and **780** (Scheme 148).[390]

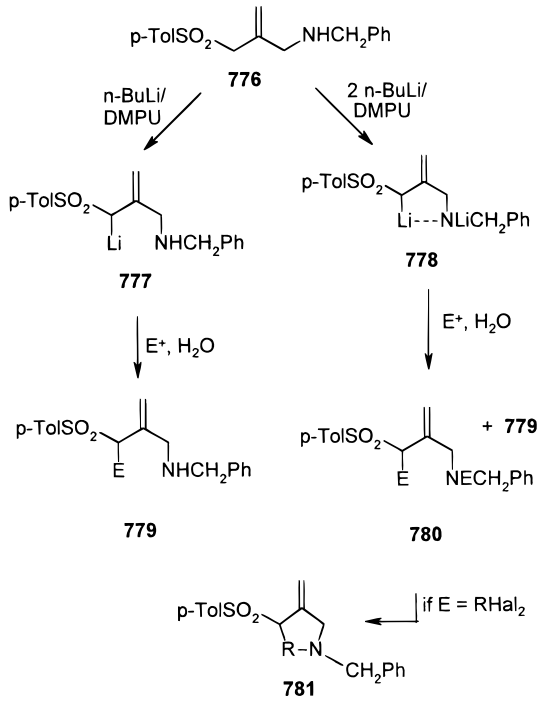
4. 2-(Alkylthio)allyl Sulfones and 2-Alkoxyallyl Sulfones

2-Alkylthioallyl sulfones **782** are α-alkylated with primary alkyl halides, forming **783**. A second alkylation affords α,α-dialkyl sulfones **784**. A 1,3-sigmatropic phenylsulfonyl shift converts **784** into **787**

Scheme 147



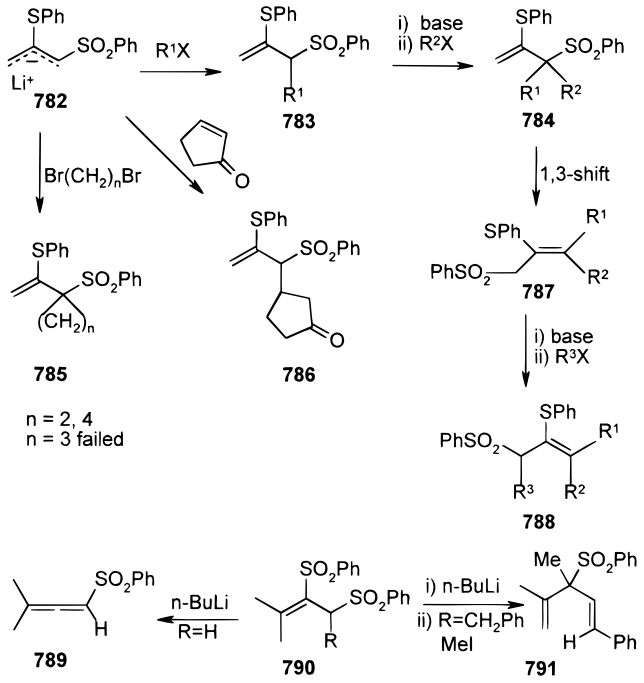
Scheme 148



which is again alkylated at the carbon next to the sulfonyl group producing **788**. 1,2-Dibromoethane and 1,4-dibromobutane cause dialkylation to give **785** while with 1,3-dibromopropane only the monoalkylated product is observed (Scheme 149).[391] α,*β*-Unsaturated carbonyl compounds react with **782** at the α-carbon, forming **786** (Scheme 149).[392]

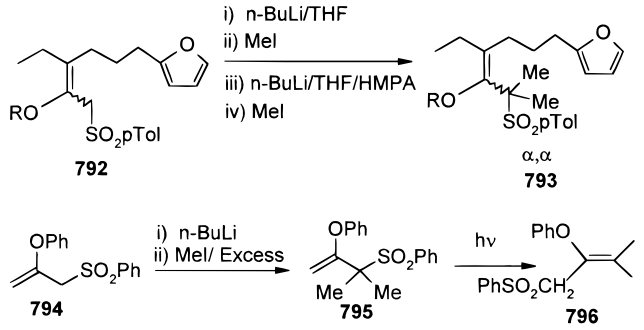
By contrast, treatment of disulfone **790** with ^{n}BuLi effects elimination of the sulfonyl group to give the allene **789**. In the presence of an electrophile, e.g., methyl iodide, the diene **791** is obtained (Scheme 149).[391]

Scheme 149



The alkoxyallylic sulfone **792** is deprotonated and α-alkylated twice with MeI to form **793**. To avoid the elimination of the ethoxy group, HMPA is required for the second alkylation (Scheme 150).[393] A similar reaction takes place with 2-oxo-substituted 1-sulfonylallyl anion **794**, whereby upon irradiation with 300-nm light in benzene the dialkylated sulfone **795** undergoes a quantitative 1,3-shift to give **796** (Scheme 150).[394]

Scheme 150



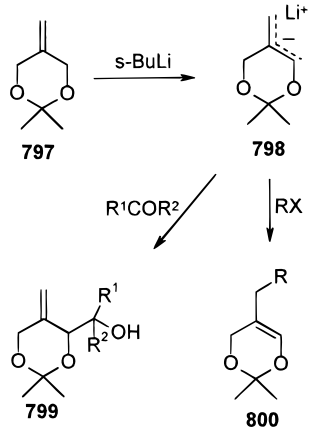
5. 5-Methylene-1,3-dioxanes

5-Methylene-1,3-dioxane **797** anions **798** form α-adducts **799** preferentially by reaction of these with carbonyl compounds.[395] In the presence of Zn^{2+} as the counterion, the α-product **799** is exclusively obtained, similar to the reaction of the oxyallyl anion. However, γ-adducts **800** are predominantly synthesized upon alkylation or trimethylsilylation (Scheme 151).[396]

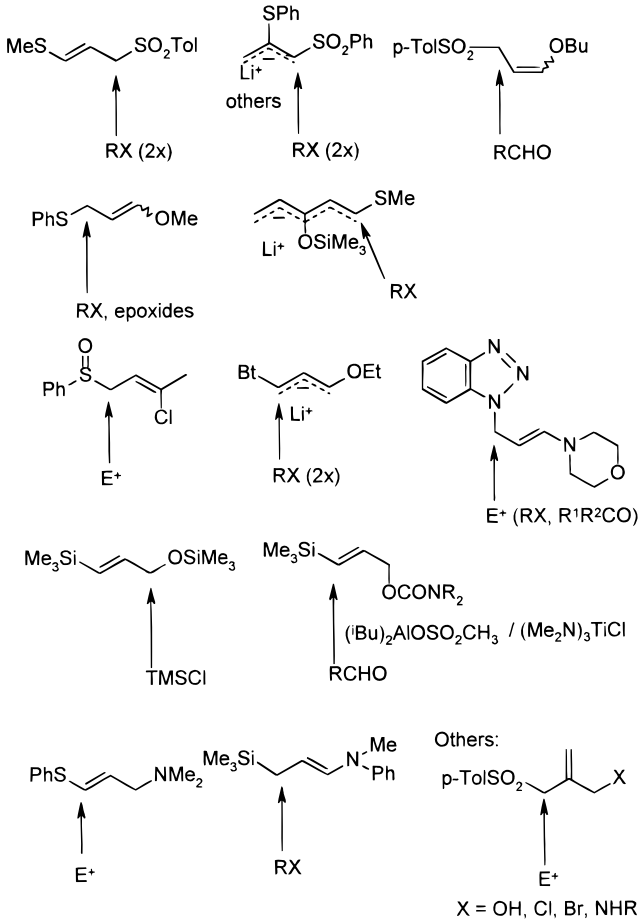
F. General Discussion

The orientation of reactions with electrophiles of allyl anions stabilized by two nonidentical and non-*gem*-heteroatoms is summarized in Scheme 152.

Scheme 151



Scheme 152. Two Non-*Gem*-Heteroatoms[a]



[a] Allyl anions with identical heterosubstituents are not in this scheme.

This general discussion deals with sections V.A through V.D. Obviously, when two identical heteroatom linked groups are in the 1- and 3-positions of an allyl anion, no regioisomers can arise. When the groups are different, then the most strongly α-directing group dominates. Thus, RSO_2 dominates over both OR and SR, and also over benzotriazolyl (unpublished work by A.R.K.). Group RSO dominates over Cl. Benzotriazolyl and SR each dominate over NR_2 and OR. As regards R_3Si, it dominates over NR_2 but is itself dominated by $OSiR_3$.

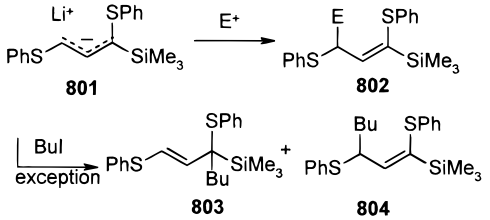
VI. Allyl Anions Stabilized by Three Heteroatoms (XYC═C–C–Z)

There have been only a few studies on allylic anions stabilized by three heteroatoms. Those discussed here contain either three different functional groups or two identical and another type of heteroatom-linked groups.

A. 1,3-Bis(phenylthio)-1-(trimethylsilyl)-1-propenes (PhS–C–C═C(SPh)(SiMe$_3$))

Predominant attack of epoxides at α to sulfur in allyl sulfide anions (cf. section II.C.1) and exclusive attack of epoxides γ to silicon at allyltrialkylsilyl anions is observed (cf. section II.G). In agreement with this, regioselective attack takes place for allyl derivatives substituted by both sulfur and silicon.[78] The silylbis(phenylthio)propene anion **801** gives one regioisomer **802** (attack at the carbon γ to silicon) upon reaction with aldehydes, methyl chloroformate, allyl bromide, and propenoxide, but there is one known exception: BuI produces a mixture of α- **803** and γ-regioisomers **804** (Scheme 153).[397]

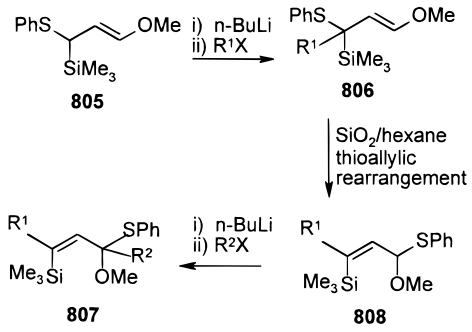
Scheme 153



B. 1-Methoxy-3-(phenylthio)-3-(trimethylsilyl)-1-propene (MeO–C═C–C(SPh)(SiMe$_3$))

Products **806** of alkylation α to sulfur are obtained from 1-methoxy-3-(phenylthio)-3-(trimethylsilyl)-1-propene **805** but this is followed by thioallylic rearrangement of **806** to 1-methoxy-1-(phenylthio)-3-(trimethylsilyl)-1-propene derivative **808**. A second alkylation also occurs at the α-position to sulfur producing **807** (Scheme 154).[398]

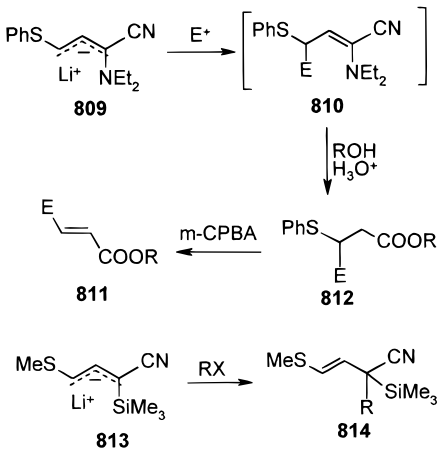
Scheme 154



C. 2-(Diethylamino)-4-(phenylthio)-2-butenonitrile (PhS–C–C═C(CN)(NEt$_2$))

Exclusive alkylation γ with respect to the cyano group of anion **809** to form **810** is observed. Similarly, carbonyl compounds attack at the γ-terminus with respect to the cyano substituent.[399] Alcoholysis of **810** gives ester **812** which upon S-oxidation and elimination furnishes the α,β-unsaturated ester **811**; hence anion **809** is a β-carbonyl vinyl anion equivalent (Scheme 155).[399] In contrast, the anion **813** of the corresponding ether 2-[(trimethylsilyl)oxy]-4-(methylthio)-2-butenonitrile undergoes allylation exclusively at the α-carbon to the cyano function to give **814** (Scheme 155).[316]

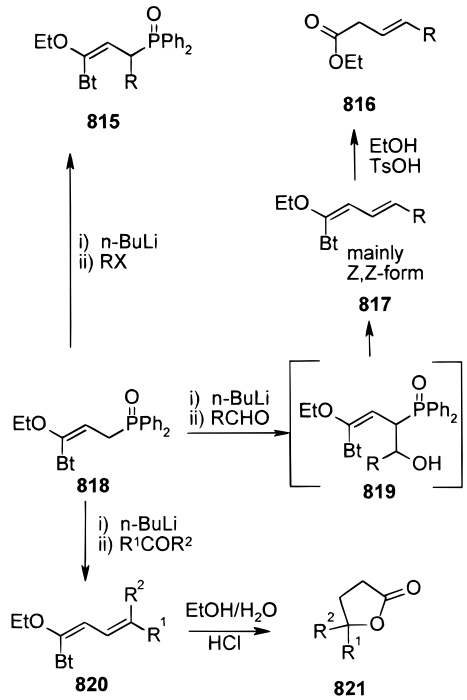
Scheme 155



D. 1-(Benzotriazol-1-yl)-3-(diphenylphosphoryl)-1-ethoxy-1-propene (Ph$_2$PO–C–C═C(Bt)(OEt))

Products **815** substituted α to phosphorus are obtained in the reaction of lithiated 1-(benzotriazol-1-yl)-3-(diphenylphosphoryl)-1-ethoxy-1-propene with electrophiles (RX, RCHO, RCOR). In the aldehyde and ketone cases, Horner reaction occurs to give substituted dienes **817** or **820**. Further acidic treatment of **817** under anhydrous conditions produces β,γ-unsaturated esters **816**, but hydrolysis under aqueous conditions affords γ-lactones **821** (Scheme 156).[400]

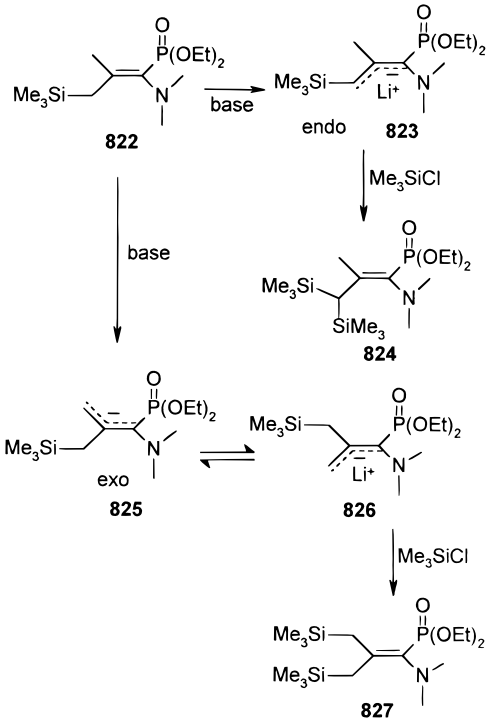
Scheme 156



E. 1-(Diethoxyphosphoryl)-1-(dimethylamino)-2-methyl-3-(trimethylsilyl)-1-propene ((EtO)$_2$) PO(NR$_2$)C═C–C–SiMe$_3$)

Deprotonation of **822** gives a mixture of the endo **823** and exo **824** anions. γ-Silylation with respect to phosphorus and nitrogen to yield **823** is observed for the endo-isomer. However, the exo-isomer **825** affords the 3,3′-bissilyl isomer **827** and not the expected analogous 3,3-bissilylated product (Scheme 157).[354]

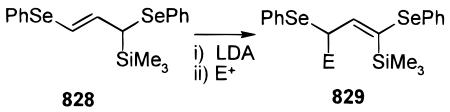
Scheme 157



F. 1,3-(Diphenylseleno)-1-(trimethylsilyl)-1-propene (PhSe–C–C═C–(SePh)SiMe$_3$)

After lithiation, 1,3-(diphenylseleno)-1-(trimethylsilyl)-1-propene **828** reacts with a range of electrophiles at the position γ to the trimethylsilyl function to give **829** (Scheme 158).[359]

Scheme 158

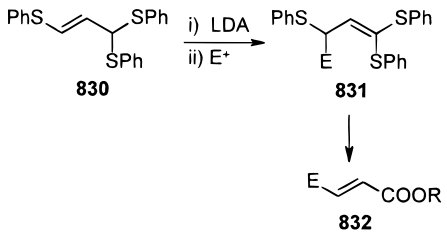


G. 1,1,3-Tris(phenylthio)-1-propene (PhS–C═C–C–(SPh)$_2$)

Both alkyl halides and carbonyl compounds attack the anion of dithio-substituted allylic system **830** exclusively at the carbon 3, forming **831**. Hydrolysis and elimination of 3 mol of thiophenol gives β-alkylated acrylate **832** (Scheme 159).[401]

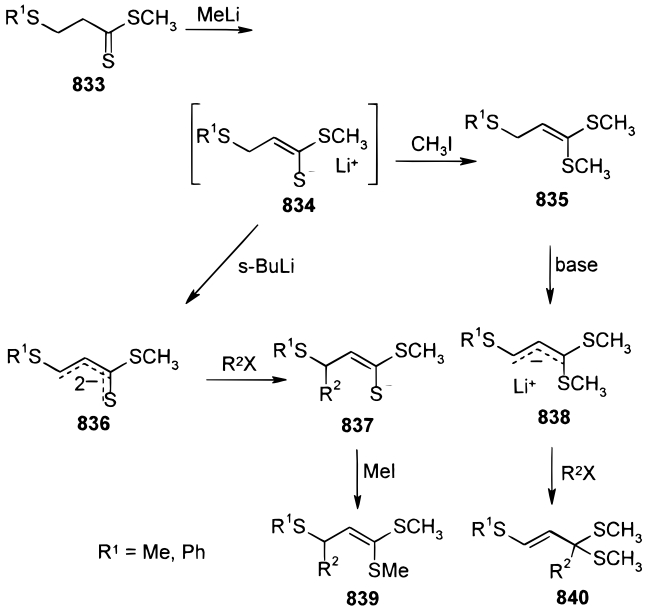
The dianions **836** of methyl 3-(methylthio)dithiopropanoate and methyl 3-(phenylthio)dithiopropanoate **833** with excess of methyl iodide form γ-methylated ketene acetal anions **837**; subsequent S-methylation yields **839**. However, if S-methylation of **834** occurs

Scheme 159



first to form **835**, α-attack at the monoanion **838** is observed to give **840** (Scheme 160).[402]

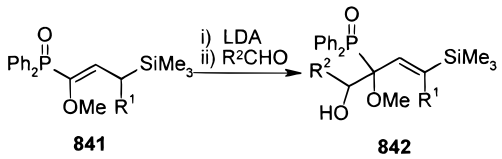
Scheme 160



H. α-Methoxy-γ-(trimethylsilyl)allyldiphenylphosphine Oxide ((MeO)(Ph$_2$PO)C═C–C–SiMe$_3$))

α-Methoxy-γ-(trimethylsilyl)allyldiphenylphosphine oxide **841** reacts after deprotonation with aldehydes at the γ-position to give **842** (Scheme 161).[212]

Scheme 161

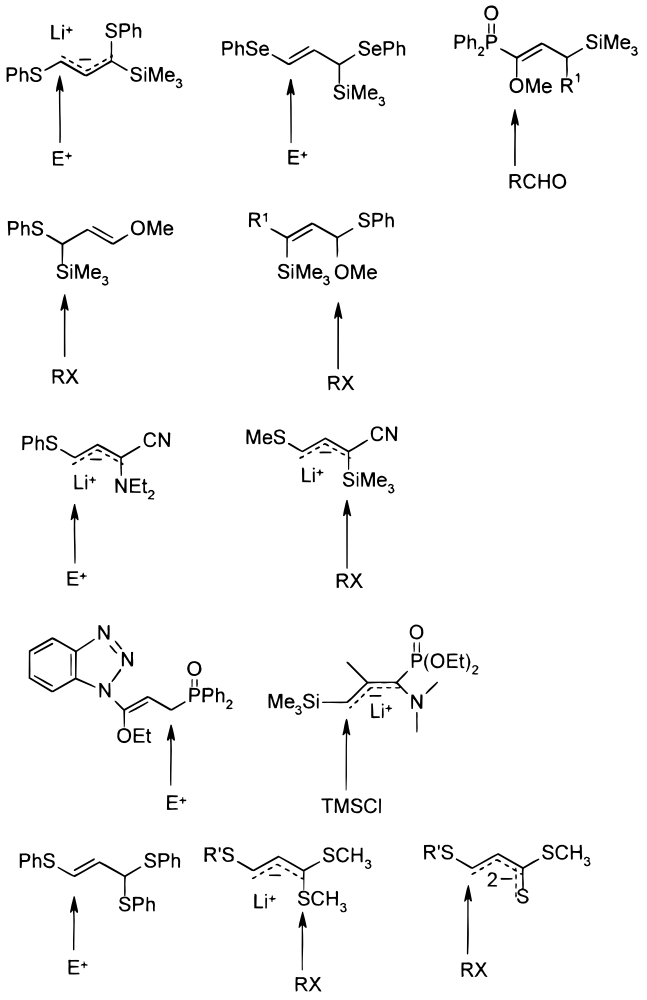


I. General Discussion

The more heteroatoms a molecule contains the more difficult it is to assess the regioselectivity of the attack (Scheme 162). The outcome of the reaction is usually consistent with the stabilizing or destabilizing effects of the substituents as assessed from the respective monoheterosubstituted anions, bearing in mind the extra steric hindrance from geminal substituent groups.

Lithiated 1,3-bis(phenylthio)-1-(trimethylsilyl)-1-propene **801** furnishes γ-products **802** at the carbon to silicon (Scheme 153). Upon treatment with electrophiles the reaction would proceed in a similar manner without the presence of the two sulfur-linked

Scheme 162. Allyl Anions Stabilized by Three Heteroatoms



groups. This outcome of the reaction is favored by the SPh group in the γ-position to silicon and also by the SPh α to the silicon because this impedes attack at the α-carbon in **801** (Scheme 153), since it is already substituted twice. However, if the SPh group in the γ-position to the silicon is replaced by a methoxy function, the α-carbon related to silicon and sulfur is attacked (Scheme 154). This is in agreement with the directing effects of oxygen and sulfur (see section V.14). 2-(Diethylamino)-4-(phenylthio)-2-butenonitrile **809** is alkylated at the carbon α to the thio group. This regioselectivity is enhanced by the cyano and the amino group in the γ-position (Scheme 155). Opposed directing effects contribute to the outcome of the reactions in the other cases discussed.

VII. Results Available on the Structure of Organometallic Intermediates and Their Non-metalated Precursors

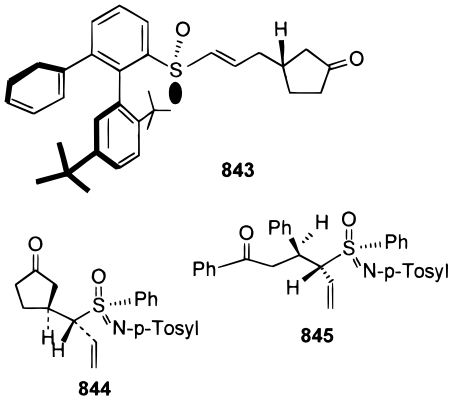
Though various crystal structures of non-metalated substituted allylic structures have been reported, there is still a dearth of information about the related allylmetals.

A. Crystallographic Data on Allyllithiums

1. Sulfur Derivatives

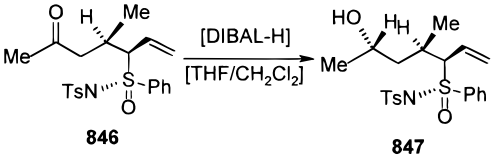
The X-ray structure of an allyl sulfoxide/cyclopentenone adduct **843** (Scheme 163) demonstrates the steric demand of modified biphenyl substituents at a sulfur atom[107] and the course of the highly regio- and diastereoselective reaction by which **843** is formed. Compound **843** results from the combination of the corresponding allyllithium with cyclopentenone in THF at −78 °C and presents an example for the utility of modified lithiated allyl sulfones.

Scheme 163



The crystal structures of several lithiated allylic sulfoximines have also been reported.[151a−c] Exclusive 1,4-α-addition of acyclic enones to lithiated *N*-*p*-tosyl-*S*-phenyl-*S*-prop-2-enyl sulfoximine proceeds in high yield and high diastereoselectivity to give the β-substituted γ-keto sulfoximine **846** (Scheme 164).[151a]

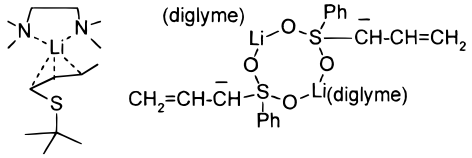
Scheme 164



Cyclic enones such as cyclopentenone and cyclohexenone add to give mixtures of the four possible diastereoisomers. The X-ray structure of one of the cyclopentenone adducts, **844** (Scheme 163), is shown. Benzylideneacetophenone reacted with the lithiated allyl sulfoximine to give predominantly one product, the 3*R**,4*R**,5*S** structure **845** (Scheme 163).[151a] The acyclic adducts **846** can easily be reduced with DIBAL-H to give the corresponding alcohols **847** with surprising diastereoselectivity. Scheme 164 shows significant characteristics of two relevant X-ray structures.[149c,151c] Solvent separated contact ion pairs of $[Li(12\text{-crown-}4)_2]^+$, and the sulfoximine anions showed the X-ray structure of a lithiated allylic sulfoximines/12-crown-4 complexes.[151c]

Stability problems of sulfur-substituted allyllithiums are apparent from investigations by Seebach et al.: the TMEDA complexed lithiated 2-butenyl *tert*-butyl sulfide **848** (X-ray structure: Scheme 165) was stable only up to −20 °C.[403] The Li^+ is coordinated at the TMEDA nitrogen atoms and the double bond, which acts as an additional ligand. These structural

Scheme 165



848 **849**

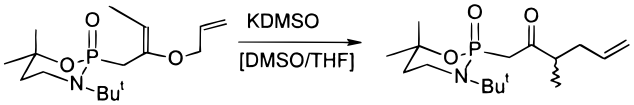
properties have been discussed in the light of ab initio model calculations.[403]

The structure of an allylic sulfone [$PhSO_2CH(CH{=}CH_2)Li{\cdot}diglyme]_2$ **849** (Scheme 165) was investigated in solution and in the crystal by Gais et al.[404] The crystalline material was obtained from the corresponding allyl phenyl sulfone by metalation with ^{n}BuLi in diglyme. The X-ray structure **849** shows a dimeric species in which the S−O−Li subunits form an eight membered ring. The Li^+ is coordinated by one sulfur oxygen atom and two diglyme oxygens, the anionic C(α) is not involved in the coordination system. ^{13}C and ^1H NMR data of **849** in THF-d_8 at 25 °C of this compound were interpreted in terms of a vinyl-substituted α-sulfonyl carbanion with a Li^+ gegenion.

2. Oxygen

The X-ray structure has been discussed of allyl vinyl ether **850** (Scheme 166). This species belongs to the interesting class of metalated allyl derivatives and undergoes the so-called "Carbanion Accelerated Claisen Rearrangement" to give **851** (Scheme 166).[405]

Scheme 166



850 **851**

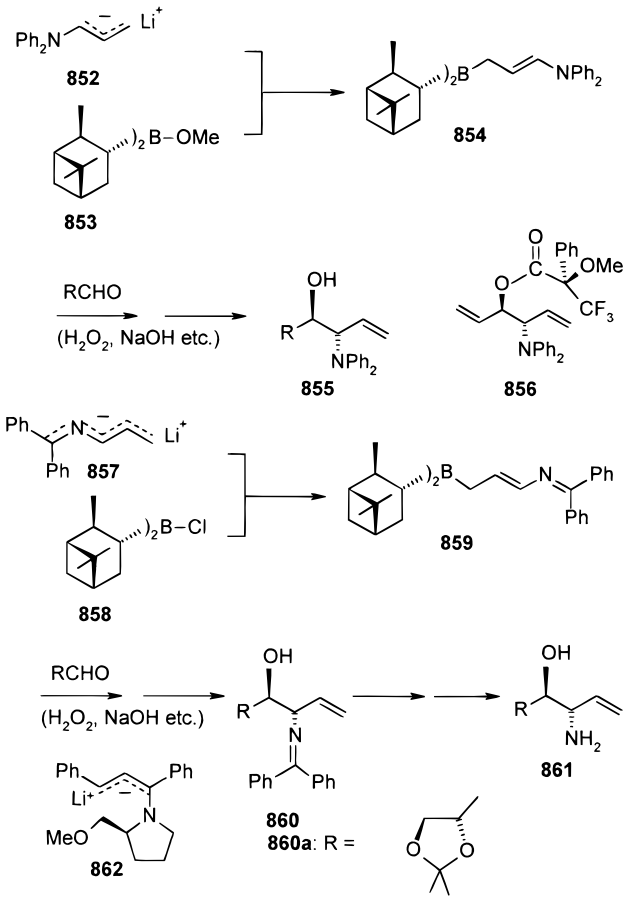
3. Nitrogen

The reactions of lithiated allyldiphenylamine **852** with (+)- or (−)-*B*-methoxydiisopinocamphylborane [$(Ipc)_2B(OMe)$, **853**] give the corresponding (*E*)-aminoallyl boranes (cf. **854** from (−)-*B*-**853**). Compounds **854** are useful reagents for the synthesis of 3-(diphenylamino)-4-hydroxyalkenes **855** (after reaction with a variety of aldehydes and conventional workup). Compounds **855** are chiral at the C4-center, the configuration of this carbon was determined by the X-ray structure of the corresponding Mosher ester **856** (Scheme 167).[164]

A comparable pathway leads to anti-β-hydroxy amines **861** via anti-β-diphenylimino alcohols (e.g., as the X-rayed example **860a**, Scheme 167).[182] In addition to diphenylamines, allyldiphenylimines have also been metalated and derivatives **857** reacted with $(Ipc)_2B-Cl$ (**858**) to give intermediates **859**. After reaction with aldehydes **859** were transformed to β-hydroxy(diphenylmethylene)amino alcohols **860** which finally gave, after conventional workup and deprotection, with high or complete stereocontrol, the anti-β-hydroxy amines target molecules **861**.

The crystal structure of a chiral 1-aminoallyllithium derivative, the dimeric (3*S*)-3-lithio-1-[(*S*)-2-

Scheme 167

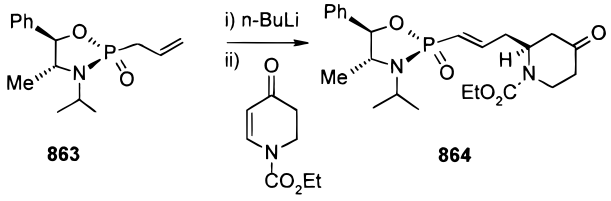


(methoxymethyl)pyrrolidino]-1,3-diphenylpropene **862** (Scheme 167),[406] obtained from its aminoallyl precursor and ^{n}BuLi/hexane in toluene at 0 °C, reveals interesting characteristics. The 1-aminoallyl group is nearly planar, the nitrogen atom is pyramidal with the lone pair directed toward the allyl moiety. The bond angles and interatomic distances indicate that the lithium is coordinated to the γ-center. The remaining coordination site of the metal cation is occupied by the benzyl group of the second monomeric moiety.

4. Phosphorus

The lithiated chiral 2-propenylphosphonamide species (cf. **863**, Scheme 168)[219] is an easily accessible reagent for the stereoselective 1,4-addition to ethyl 3,4,5,6-tetrahydro-4-oxo-pyridine-1-carboxylate. Scheme 168 shows the resulting product **864**, for which an X-ray structure is available.

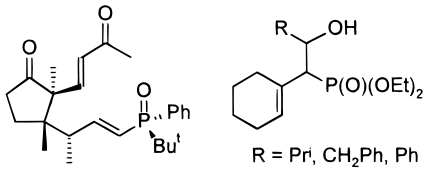
Scheme 168



863 **864**

The X-ray structure is also available of the vinyl phosphine oxide **865** (Scheme 169) which is a useful allylmetal precursor in a multistep synthesis of

Scheme 169



865 **866**

enantiomeric hydrindenones.[206] For these enantiospecific conversions the P(O)Ph(^{t}Bu) substituent of **865** plays an important role. Of comparable interest is the previously discussed X-ray structure of a novel type of an allyl vinyl ether **850** (Scheme 166).[405]

The X-ray structures of α-vinyl-β-hydroxyphosphonates **866**, accessible by reaction of lithiated diethyl-(1-cyclohexenyl)methylphosphonate with aldehydes, were recently reported (Scheme 169).[199,203]

5. Silicon

The X-ray structure of the TMEDA complexed [1,3-bis(trimethylsilyl)allyl]lithium **867** (see following section Scheme 170)[407] turns out to be fundamental for the ongoing discussion of the existence of delocalized allylic lithium cations, for which the actual answer is a "partial yes".[408] As discussed in subsequent sections, **867** was further investigated by NMR, semiempirical, and ab initio methods, which indicate that the isomerization barrier is very low (NMR and MO calculations) and that in the crystal the essentially symmetrical allyl anion moiety is perturbed by complexation with the TMEDA coligand (Li−C(α) 2.229(9) Å; Li−C(β) 2.269(10) Å).[407]

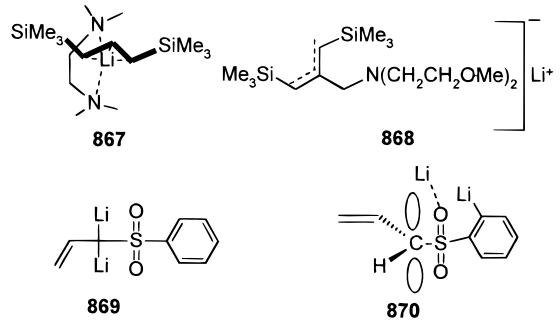
6. Unsubstituted Propene and 1,3-Diphenylpropene

An X-ray structure of the parent allyllithium compound, C_3H_5Li·TMEDA, was obtained by Weiss and Köster.[409] This structure crystallizes from a dispersion of allyllithium and TMEDA in hexane as a polymeric system in which the C(1) and C(3) atoms together with the Li^+ act as linking centers. The remaining coordination sites of the cation are saturated with the TMEDA ligand. The accuracy of the measurement of the structural parameters (e.g., bond lengths; Li−C(1) 2.2215(42); Li−C(3) 2.299(39) Å) do not allow very sophisticated interpretations. Nevertheless, these results initiated a variety of further research efforts. In 1987, the first X-ray structure of a crystalline monomeric allyllithium complex, C_3H_5-Li·(*N*,*N*,*N*′,*N*″,*N*″-pentamethyl-diethylene-triamine, PMDTA), was X-published by U. Schümann and E. Weiss.[410] Asymmetric bonding of the allyl group to the Li^+ is observed, with Li−C distances Li−C(1) 2.255(5) Å and Li−C(3) 2.720(4) Å. The central H(2) atom is bent slightly to the Li^+, the C_3H_5 unit is not planar. Interestingly, Boche's X-ray investigation of the [1,3-diphenyl-C_3H_3Li]·$(OEt_2)]_n$ revealed a crystalline material in which η^3-allyllithium units have been found which are aggregated to polymeric chains.[411] A conceivable benzyllithium structural element was not found in those crystals.

B. NMR Investigations

Various NMR studies have been carried out on allyllithium.[412,413] West and McKinley observed an

Scheme 170



867 **868**

869 **870**

$AB_4 \rightarrow AA'BB'C$ allyl transition for allyllithium by a temperature study in THF and diethyl ether. In solution the [AA′BB′C]Li^+ species is predominant at the temperatures studied.[414]

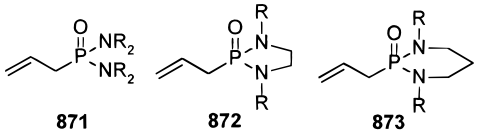
Thompson and Ford[415] used exchange rates of the terminal allyl protons to determine the rotational barriers about the carbon−carbon bonds of allylalkali metal compounds in THF. Allyllithium exists as an unsymmetrical dimer in THF in contrast to allyl sodium and allyl potassium which leads to a discrepancy between the experimentally determined and the calculated barriers of rotation. ^{13}C NMR investigations supported by cryoscopic measurements were accomplished on isotopically perturbed samples.[416] ^1H NMR temperature studies on several allyl boron derivatives showed that either permanent allylic rearrangement or cis−trans isomerization about the allylic bond occurs.[417]

1-(Trimethylsilyl)allyllithium is found in the exo form in various media. The complex with *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) probably exists as two monomeric tridentate-coordinated contact ion pairs. $^6Li\{^1H\}$-NOE experiments were carried out and rotational barriers determined.[418]

Fraenkel et al.[419] also described [1,3-bis(trimethylsilyl)allyl]lithium *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, a complex which is electronically symmetrical and exhibits an exo−exo configuration. The lithium cation is solvated dissymmetrically by one TMEDA and one diethyl ether molecule causing a small ^{13}C NMR shift between C1 and C3 and a large one between the two $(CH_3)_2N$ groups. In addition to ^1H and ^{13}C NMR, Saunders deuterium perturbation experiments were also described. Extensions of previous investigations[419] led Fraenkel and Qiu[408] to an interesting structure: The lithiated TMEDA complex **868** (Scheme 170), which is the internally solvated version of **867**, is an unusual example of an allyllithium in which nonequivalent terminal allyl ^{13}C signals as well as two different NMR shifts for the methylsilyl groups are observed. Boche et al.[407] explained the observations of Fraenkel et al.[419] on the [1,3-bis(trimethylsilyl)allyl]lithium·TMEDA by two dynamic processes: rotation of the Li^+-TMEDA moiety with respect to the allyl anion and inversion of the Li^+-TMEDA five-membered ring.

Glendenning et al.[420] investigated the structures of lithiated (*E*)-1-(*tert*-butylthio)but-2-ene and lithiated (*E*)-1-(phenylthio)but-2-ene in solution. The former can be described as a transoid carbanion

Scheme 171



871 872 873

where the heteroatom and nonallylic substituent do not play a significant role. The latter is stabilized by the phenylthio group and has cis geometry. An NMR study on 1-(dimethylamino)allyllithium is currently being carried out in the group of Ahlbrecht (private communication).

The three adducts **866** (Scheme 169), formed from diethyl (1-cyclohexenyl)methylphosphonate and the corresponding aldehydes, possess erythro configurations as demonstrated by NMR. Attractive intramolecular hydrogen bonding between the hydroxy and phosphoryl groups, as well as less steric repulsion if the large substituents are gauche to the vicinal hydrogen, is considered to be responsible for this configuration.[199]

Gais et al.[124] described α,α-dilithioallyl phenyl sulfone **869** to be more thermodynamically stable than the isomeric α,*O*-dilithioallyl phenyl sulfone **870** (Scheme 170). One equivalent of ^{n}BuLi lithiates phenyl 2-propenyl sulfone in THF to give the α-monolithiated compound. Under kinetic control, the second equivalent metalates the ortho position of the ring relative to the sulfonyl group. Upon heating to 50 °C, the more stable α,α-dilithiated product **868** is formed. Both steps have been monitored by ^{1}H NMR spectroscopy.

NOESY experiments on *β*-substituted *γ*-keto sulfoximines **845** (Scheme 163) show characteristic cross-peaks. Hence, the *N*-tosyl group is near the protons α to the keto group. A "hairpin structure" is preferred, which allows the anti configuration of the sterically demanding S-phenyl group and the rest of the side chain.[150]

The anions of the allylphosphonic diamides **871**−**873** (Scheme 171, R = Me, ^{i}Pr)[421] were found to exist in both *E*- and *Z*-forms in solution except for one species **872** (R = ^{i}Pr). In toluene a greater portion of the *Z*-isomer than in THF was identified. Toluene coordinates to a lesser extent to lithium than THF does; therefore, different anion conformations are observed in solution in agreement with theoretical calculations (see section VIII).

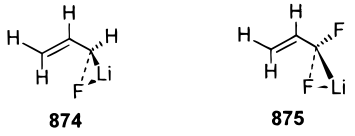
VIII. Summary of MO Calculations

A. α- and *γ*-Substituted Allylmetals: Substituent Effects on Reactivity and Structure

Tonachini et al. investigated halogen-substituted allyllithiums on various levels of ab initio theory.[5,282,422−424] With 3-21+G geometry optimizations and MP2/6-31+G single point energy calculations they estimated the structures **874** (monofluoroallyllithium) and **875** (difluoroallyllithium) to be most stable[5] (Scheme 172).

Slightly different structures were found as energy minima for the corresponding chloro- and dichloroallyllithium compounds. The most stable [CH_2═CH−CCl_2]Li structure, the Li^+ prefers a C(α)/C(*γ*) bridging position.[282] In both cases the regioselectivity predictions agree with the experimental findings, although the interpretation is more or less based on the HSAB principle and on the effect of the polarization of HOMO of the allylic unit: These interpretations show that monofluoroallyllithium should have a less pronounced tendency to α-attack. For both 1-fluoropropenide and 1,1-difluoropropenide the HOMO is polarized toward the α-carbon. Furthermore, double fluorine substitution causes a substantial flow of charge toward the halogen groups. Hence, a hard electrophile sensitive to charge distribution and a soft electrophile which is mainly sensitive to the HOMO polarization would both favor an attack at the α-carbon. For a similar discussion compare a paper by Venturello et al.[278] in which the importance of lithium complexation with 12-crown-4 in the reaction of (1,1-dichloroallyl)lithium with carbonyl compounds is discussed along the same lines.

Scheme 172

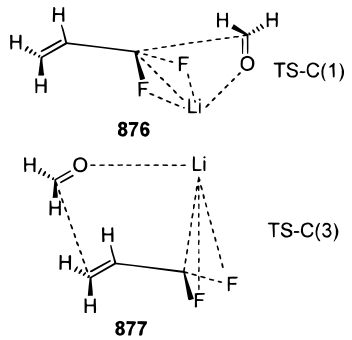


874 875

Unfortunately, transition structures for the alternative α- or *γ*-attack of carbonyl or other electrophiles are not included in these investigations. The same authors also investigated the monomer−dimer equilibrium in lithium *gem*-difluoroallyl and methyl systems.[422,423] Their ab initio methods show the equilibrium shifted in favor of the dimeric species, even after taking into account the oxygen−cation interactions of the solvent (water molecules were used to simulate ether), the equilibrium still seems to be on the side of the dimeric species.

The calculation of transition structures is included in a recent paper[424] in which the addition reaction of formaldehyde with (1,1-difluoroallyl)lithium and (1,1-dichloroallyl)lithium was investigated at the HF and the MP2 level, together with selected CAS-MCSF calculations. In general, MP2/3-21G(*) geometries were used for recomputing the energy barriers at the MP2/6-31G* level. Tonachini and Canepa found that for difluoroallyllithium, dichloroallylpotassium, and for both the free anions, α-attack is significantly preferred. Dichloroallyllithium can show a dichotomy of behavior as the energy difference between the two transition structures turns out to be much smaller and to favor the *γ*-pathway. Scheme 173 shows the

Scheme 173



876 877

transition structures **876** of the C(1) and **877** of the C(3) attack for the reaction of [CH_2=CH-CF_2]Li with formaldehyde. TS−C(3) is 17 kcal/mol higher in energy than TS−C(1).[424]

Other heteroatom-stabilized allylic anions have been investigated. The steric contribution of ester alkyl group of the dialkyl allylphosphonate carbanions on the regioselectivity of their reaction with benzaldehyde was determined by means of molecular mechanics calculations.[425]

Schleyer et al. carried out ab initio calculations on allylborane and its isomers. They estimated the energetic barrier of the [1,3]-sigmatropic boron migration, and discussed the IGLO calculated NMR chemical shifts.[426] The C_s symmetrically bridged structure of $CH_2CHCH_2BH_2$ is the most stable form of the parent allylborane, but the unsymmetrical open (C_1) conformation is only 0.1 kcal/mol higher in energy. In larger molecules, especially the alkyl groups on boron have an important influence on the barrier of the [1,3] sigmatropic shift.

MNDO calculations of the (3*S*)-3-lithio-1-[(*S*)-2-(methoxymethyl)pyrrolidino]-1,3-diphenylpropene by Ahlbrecht et al. are in acceptable agreement with the corresponding X-ray structure. Nevertheless, the well-known overestimation of the Li−C interaction is obvious.[406] This deficiency was overcome by determining an optimized set of parameters for lithium for Stewart's PM3 method.[427] The new parameters have been widely applied to a variety of lithiated compounds, in most cases the Li/PM3 method appears to be superior to Li/MNDO.[428] Orientating comparative calculations, including allyllithium, have been performed by Pratt et al.[429] Further calculations on allyllithium are in progress in our laboratories.

An X-ray/ab initio study of the thermally unstable lithiated 2-butenyl *tert*-butyl sulfide **848** (Scheme 165) was performed by Seebach et al.: They compared the X-ray data of that compound with those of a significantly simplified model compound (HS instead of ^{t}BuS, CH_2 instead of $CHCH_3$), using 3-21G//3-21G calculations. The overall structural data were reproduced surprisingly well despite the low level of theory.[403]

Denmark and Cramer employed ab initio methods at the HF/3-21G*//HF/3-21G* level to describe *p*-allylphosphinic diamide, its free anion and the lithiated species.[421] The former is supposed to show hyperconjugative interactions between the amide nitrogens and the C−P−O moiety. The free anion was determined to exist in both *E*- and *Z*-forms with a planar allylic π-system aligned with the P−O bond and favoring the *E*-isomer. For the lithiated species the *Z*-isomer is preferred with the lithium exhibiting both oxygen and carbon contacts. NMR spectroscopic data support the theoretical estimated charge distribution in the anion. Currently ab initio studies on [1-(dimethylamino)allyl]lithium are in progress in the group of Ahlbrecht.

On the basis of the X-ray structure (vide supra) of the *exo,exo*-[1,3-bis(trimethylsilyl)allyl]lithium·TMEDA·DEE,[407] Boche, Schleyer, and co-workers investigated two dynamical processes within the Li·TMEDA moiety. Both ab initio and MNDO calculations agree with the conclusion drawn from NMR investigations: the rotation of the Li·TMEDA and the inversion of the Li·TMEDA five-membered ring possess nearly the same activation energy.

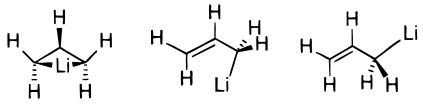
B. The Allyl Anion and Corresponding Allylmetals

There have been various theoretical calculations on allyllithium itself.[430]

In 1976 Palmieri et al.[430c] estimated the energy difference between the most stable bridged and the syn structure of allyllithium to be about 8 kcal/mol by means of RHF/STO-3G ab initio calculations, obviously not performing full geometry optimization. Clark, Jemmis, and Schleyer[430d] confirmed these qualitative results by choosing better basis sets (RHF/STO-3G for the geometry optimizations, RHF/4-31G and RHF/6-31G*, single point calculations to estimate relative energies). The syn- **879** and anti-isomers **880** were calculated within the constraints of C_s symmetry. Without that restriction, both would collapse to the bridged structure **878**. The latter turned out to be the most stable by about 16 kcal/mol (syn) and 19 kcal/mol (anti form) (Scheme 174). Furthermore, the allyl skeleton is significantly distorted from planarity, whereby the bonding between the HOMO of the allyl anion on C1 and C3 and the lithium p orbital with the axis parallel to C1−C3 is enhanced.

Similarly, Thompson and Ford[415] reported that the most stable structure of allyllithium is symmetrical and delocalized with the lithium centered above the plane of the allyl anion. The rotational barrier for the allyl anion[431,433] was predicted to be larger than the 10.7 kcal/mol observed for allyllithium. Additional studies of the positions of the hydrogen atoms in allyllithium have been reported.[430f] A comparative ab initio study by Clark, Rhode, and Schleyer reveals that allyllithium and -sodium prefer symmetrically bridged structures. Allylmagnesium hydride should exist with an asymmetric geometry, the barrier of the 1,3 MgH shift should be quite low.[434] More recently, these investigations have been continued for the allyl alkali metals (Li to Cs).[430j] With respect to the ^{13}C NMR spectra, the CCC angle widening in the metalated structures compared with free anion was recognized to be the main cause of the low J(C−H) coupling constants. Rotational barriers tend to decrease along the series Cs > Rb > K > Na in agreement with experimental findings, with that of allylcesium close to that of the "free" allylanion (∼28 kcal/mol). The largest deviation between the calculated barriers of such monomers was found for allyllithium and was attributed to the influence of solvation and aggregation (see below). Electron donation from the filled nonbonding allyl π orbital into the appropriate empty Li-2p-orbital is considered to

Scheme 174



878 **879** **880**

be responsible for the "bonding" between the anion and the lithium. In this context it should be taken into account that the "nature of the carbon lithium bond" is dominantly electrostatic.[435]

In agreement with MNDO calculations, cryoscopic measurements and ^{13}C NMR studies indicate that allyllithium exists in THF as an asymmetrical dimer. Under similar conditions, allylsodium and allylpotassium seem to prefer symmetrical structures. The discrepancy between the calculated barrier for isolated allyllithium (17.7 kcal/mol, ab initio) and the experimental value in THF (10.7 kcal/mol) is again attributed to the dimerization since MNDO calculations show that there should be little change in the rotational barrier due to solvation.[416]

Alkyl groups at C1 increase the C1−C2 bond order and decrease the C2−C3 bond order. The (*Z*)-alkyl-substituted allyl compounds are thermodynamically favored which can be explained in terms of anionic hyperconjugation of the alkyl group.[436,437] Other reports[430f] are analogous to that by Schleyer[430d] and also suggest that the allyl group is distorted out of plane (MNDO calculations on allyllithium and solvated species). The inner hydrogens H1 and H3 are further bent out of the plane of the carbon atoms away from lithium than H2 which is bent slightly toward the lithium. This is in agreement with X-ray data[438] for related molecules, but in contrast to conclusions from NMR investigations in THF.

Wiberg et al.[439] determined energies and charge distributions via ab initio methods at the MP4/6-311++G**//6-31G* level. The rotational barrier for the allyl anion was estimated to be about 19 kcal/mol. Due to delocalization, relatively little stabilization was found for the anion compared with the cation. Allylic anions are characterized by internal Coulombic stabilization due to an alternating (− + −) charge distribution for the allylic atoms which is caused by electronegative atoms at the terminal positions. Wiberg extended his investigations to heterosubstituted allyl radicals under application of the UMP2/6-311+G**, Becke3LYP/6-311+G**, and QCISD/6-311G** levels of theory.[440] In the course of this study the rotational barrier was estimated to be 20.3 kcal/mol. This value decreases to a minor extent with increasing solvent polarity. More significantly this barrier depends on the degree of methyl substitution.

The application of the IGAIM method by Keith and Bader[441] for the ^{13}C and ^{1}H chemical shift calculations at the 6-31+G* level of theory are summarized by Westiuk and Ma.[430k] The authors conclude that IGAIM will generally be useful to calculate shifts of unsaturated organolithium compounds.

IX. Conclusions and Outlook

A. Substituent Influences

Alongside the heteroatoms, steric effects of other substituents influence the orientation of electrophilic attack. Thus, bulky substituents on phosphorus in allylphosphoramides favor γ-attack by electrophiles[173] (cf. section II.E.3). Furthermore, the regioselectivity in alkoxy-2-propene anions is controlled by the nature of the alkoxy group, thus the *tert*-butyl allyl ether favors γ-alkylation[34,35] (cf. section II.B).

While sterically demanding groups on the heteroatom in allyltrialkylsilanes are γ-directing by hindering to α-attack (cf. above),[233,236] the presence of lithium complexing substituents on silicon favors α-regioselectivity, e.g., for silylalkoxyallyllithium (cf. **458**, Scheme 80) or (aminomethyl)silyl-substituted allylanions (cf. **460**, Scheme 81).[230]

B. Influence of the Nature of Electrophiles Used

The main electrophiles which have been studied are carbonyl compounds, alkyl halides, epoxides, α,β-unsaturated compounds (Michael acceptors), and trimethylsilyl chloride. Carbonyl compounds often show a reversed regiochemistry compared with alkyl halides.

Knowing the type of electrophile is not always sufficient to predict the site of attack. The HSAB approach is often very helpful differentiating between hard and soft electrophiles (cf. 1-chloro-1-(trimethylsilyl)-2-propene **573**) (section IV.A) (Scheme 104)[304] or lithiated 1-phenyl-3-ethoxy-3-(benzotriazol-1-yl)-1-propene **649** (section IV.C) (Scheme 119).[345]

In addition to its electronic character, the steric properties of an electrophile can also influence the regioselectivity. Thus, bulky electrophiles favor attack on allyl anions at the less hindered carbon, e.g., the benzotriazole derivative **644** (Scheme 118) is exclusively attacked at the γ-site with bulky ketones while alkyl halides, aldehydes, normal ketones, and α,β-unsaturated esters form exclusively α-product **646** (section IV.C).[338−343]

C. Influence of Reaction Conditions

1. Temperature

For some compounds the site of electrophilic attack has been demonstrated to depend on the reaction temperature, this is a result of kinetic versus thermodynamic control. A few examples are given.

Above −65 °C 1-alkoxy-2-propenes tend to undergo Wittig rearrangement[23−33] (cf. section II.B).

The reactions of allylphosphonate **346** with ketones afford α-products **350** except for benzophenone (**348**) and acetophenone (**348** and **349**) (Scheme 61). Raising of the reaction temperature substantially changes the composition of the reaction mixture (except for benzophenone) favoring formation of δ-ketoallylphosphonate **355** (Scheme 63) alongside the α- and γ-products **348** and **349**[205] (cf. section II.F).

Reactions of oxy trimethylsilyl cyanohydrin **611** with ketones or aldehydes at −78 °C give exclusively α-products **614** accompanied by subsequent 1,4-O,O-silyl rearrangement to form **613**.[323] On warming to room temperature, anions **615** undergo 1,4-O,C-silyl group rearrangement to produce new O-anions **616** and **617**. These species **616** and **617** can be trapped by silylation[327] (Scheme 112). Exclusive α-reactivity at −78 °C is also observed for lithiated ethoxyethylsilyl cyanhydrin **623** (Scheme 113); however, exclusive γ-reactivity results on treatment with aldehydes

and ketones if the reaction is carried out at 0 °C[322,325,326] (cf. section IV.B).

2. Additives

Changes in the regioselectivity mediated by DABCO and 12-crown-4 and also the effects of the addition of HMPA are discussed in this section.

The addition of DABCO to alkyl sulfide anion **99** (Scheme 16) favors the formation of dissociated ion pairs and therefore α-selective alkylation to give **100**.[40,75]

gem-Dichloroallylithium **523** is preferentially attacked at the γ-terminus **522** by substituted benzaldehydes, acetophenone, and benzophenone, while treatment with acetone and cyclohexanone gives α-product. The α-regioselectivity **524** is significantly increased in the presence of 12-crown-4 which deaggregates the oligomers in the presence of THF (Scheme 93)[278] (cf. section III.A).

[3-[[(Trimethylsilyl)methyl]thio]allyl]lithium **121** normally yields a mixture of α- **124** and γ-products **125**; however, in the presence of HMPA, rearrangement of the intermediate intramolecular α- **130** or γ-adducts **123** with the silicon group is facilitated (Scheme 20).[87]

The key step of an erythronolide B synthesis is the coupling of an allyl sulfide anion with a ketone; this reaction generates the γ-adduct **133** in THF/TMEDA while in THF/TMEDA/5 HMPA the α-adduct **137** is afforded (Scheme 21).[88]

A 2-alkoxyallyl sulfone **792** can be alkylated twice with methyl iodide to give **793**, but the second alkylation requires the presence of HMPA to avoid the elimination of the ethoxy group (Scheme 150).[393]

HMPA also reverses the regioselectivity of the addition of Michael acceptors to sterically hindered allyl sulfoximines **237** (Scheme 43), except for benzophenone. Predominantly the 1,4-γ-adducts **238** are produced for cyclic enones and mainly 1,4-α-adducts **240** for acyclic ones. In the presence of THF/HMPA these regioselectivities are reversed; cyclic enones now form 1,4-α-products **239** and acyclic enones give mainly 1,4-γ-products **241**. α-Adducts **242** are produced in THF with benzaldehyde while addition of HMPA results in a mixture of α- **242** and γ-adducts **243** (R = H). Exclusive formation of γ-product **243** (R = Ph) is observed for the reaction with benzophenone.[148]

The reactions of *N*-allylimine anions **298** with aldehydes produce mixtures of the regioisomers **299**, **301**, and **302** (Scheme 54). Addition of HMPA improves the γ-selectivity to give **299** and **301** (100% for benzaldehyde) while nonpolar solvents, such as hexane, favor the formation of α-products **302**[181] (cf. section II.E).

1-(Phenylsulfonyl)-2-methylene-3-bromopropene **770** reacts with unsaturated esters with predominant formation of anti-α-products **772** (Scheme 147). In the presence of HMPA the diastereomeric ratio changed to give mainly the syn-product **771**[412] (cf. section V.E).

3. Solvents

Examples of solvent-dependent reactivity include the following. The regioselectivity of the α-alkylation of aminomethyl-substituted allyltrialkylsilane anions **460** (Scheme 81) is higher in ether than in THF.[230] In a similar case, the regioselectivity of the α-alkylation of α-silylcinnamyl anion depends on the solvent and also the size of the alkylating agent[231] (see also section II.G).

The reaction of 1,3,5-tris(trimethylsilyl)pentadiene anion **695** with trimethylchlorosilane in THF leads to 1,1,3,5-tetrakis(trimethylsilyl)-1,3-pentadiene **696** with 99% regioselectivity. However, hexane as solvent affords a mixture of **696** (55%) and 1,3,3,5-tetrakis(trimethylsilyl)-1,4-pentadiene **697** (45%) (Scheme 130).[264]

D. Transmetalation

The nature of the counterion is another of the factors that affects the regioselectivity of heteroatom-stabilized allylic anions (cf. sections IX.A to IX.C). As already defined, the scope of this review is limited to lithium as counterion, but transmetalation with potassium, magnesium, aluminum, boron, zinc, copper, titanium ions, etc. is now briefly discussed. A comprehensive review entitled "Selective Reactions Using Allylic Metals" covers much of this field.[442]

The following section is organized according to the type of counterion, whereby in each subdivision various heteroatom-stabilized anions are discussed.

1. Aluminum and Boron

Transmetalation of lithium cations with aluminum or boron reagents leads to the formation of "ate" complexes and these generally react with electrophiles to furnish α-products. For example, reaction of allyl chloride **4** with triisopropyl borate gives α-haloallylboronate **21** (Scheme 3)[18] (cf. section II.A). The "ate" complex **24** (generated by addition of Ipc_2-BOMe **23** to allyl chloride **4**) on treatment with BF_3·Et_2O furnishes γ-chloroallylborane **25** which is trapped with carbonyl compounds to form *syn*-α-chlorohydrins **26** (Scheme 3)[19] (cf. section II.A).

Similar to the behavior of allyl chloride anions, the regiochemistry of dithio-substituted crotyllithiums **561** and **565** can also be reversed. In the presence of BF_3, reactions occur predominantly at the α-site, whereas the simple lithiated species reacts with aliphatic aldimines (Scheme 100)[301] and three- to six-membered cyclic ethers (Scheme 101)[302] at the γ-terminus (cf. section III.C).

Reaction of allyldiphenylamines **266** with boron compounds leads in the first instance to (*E*)-γ-adducts **268**. Further treatment with aldehydes yields adducts **269** which are γ with respect to boron but adjacent (α) to nitrogen (Scheme 47)[164] (section II.E). An analogous reaction is observed for *N*-allylimines **300** (Scheme 54).[182]

Allyl alkyl sulfide anions **101** after formation of triethylaluminum[40] and trialkylboron[80] "ate" complexes (Scheme 16) give α-products **104** and **105** in their reactions both with reactive halides[42] and with carbonyl compounds.[80] The regioselectivity is improved for halides and reversed for carbonyl compounds compared to the reaction with lithium as counterion (cf. section II.C).

Similarly, the γ-selective reaction of carbonyl compounds with allyl selenide anions **250** (Scheme 45)[42] (cf. section II.D) and silane anions[41,42,245] (cf. section II.G) (analogous to Scheme 79) is also reversed by the formation of "ate" complexes with triethylaluminum.

Carbonyl compounds and reactive halides are both directed to the α-position of alkoxyallyl anion **40** upon transmetalation with an aluminum reagent (Scheme 8)[40] (cf. section II.B).

2. Zinc and Cadmium

The presence of zinc reagents normally favors the formation of α-products, but an exception is lithiated allyl aminonitrile of **630** (Scheme 115) where the addition of anhydrous zinc chloride improves the yield of γ-addition product with ketones.[326]

Lithiated allyl chlorides **5** give mixtures of α- **10** and γ-adducts **12** with aldehydes: in the presence of zinc, potassium, titanium, or magnesium as counterion the regioselectivity is directed toward α-attack forming **8** (Scheme 2).[13,17]

Alkoxyallyllithium **40**, after transmetalation with zinc[34] or cadmium[39] reagents, also gives α-products **49** with enones and chiral aldehydes (Scheme 8) (cf. section II.B.1). Similarly, the predominant α-attack on **798** by carbonyl compounds to give **799**, and the γ-alkylation **800** of 1,3-dioxane derivatives **798** to form **800** (Scheme 151), can be changed by addition of a zinc compound to exclusive α-reaction[396] (cf. section V.E).

The attack of carbonyl compounds at allylpyrrolidine anion **270** proceeds with low regioselectivity to give a mixture of α- and γ-products by applying Zn^{2+} as counterion, the reaction is directed to the α-site to give **272** (Scheme 48).[167] Similarly, in the presence of Zn^{2+}, α-regioselectivity (**318)** of *N*-allylamides **314** is observed in reactions with aldehydes and ketones[185] (Scheme 56); by contrast, the lithiated species favors γ-attack by carbonyl compounds **317**[186] (cf. section II.E). Dithio-substituted crotyllithium **549** is affected in the same way[298] (cf. section III.C).

3. Magnesium

In analogy to zinc, magnesium as countercation usually affords α-products. An exception is the replacement in *N*-allylureas of lithium by magnesium,[175] zinc or cadmium counterions which favors the γ-product **332** similar to that given by the titanium derivative **331** (Scheme 58).[188] Another example of almost exclusive γ-substitution (cf. **284**) is the replacement in metalated *N*-allylphosphoramides **282** of lithium by magnesium (Scheme 50).[172] The presence of the bulky groups on phosphorus is one reason for the γ-orientated attack at the lithiated species.[173]

By contrast, addition of magnesium bromide directs the carbonyl compound attack on allyltrialkylsilane anions **449** (Scheme 79) to the α-position to give **451** and **453**,[233] an orientation change which also takes place with chromium and zinc reagents[253] (cf. section II.G.1).

Together with the yield the stereoselectivity of the reaction with carbonyl compounds is also improved by the addition of magnesium bromide, trimethyl borate, or Cp_2TiCl to allyl-1,3-bistrimethylsilane **690** (Scheme 129)[362] (cf. section V.A.3).

Magnesium reverses the γ-selective reaction of carbonyl compounds **252** with allyl selenides **247** to α **253** (Scheme 45)[41] (cf. section II.D).

As with lithium, magnesium salts influence the reaction with allyl sulfone in the presence of chiral diamines **183** to give α-substituted chiral sulfones **184** (Scheme 32). The enantioselectivity is improved up to 50% ee by transmetalation from lithium to magnesium[120] (cf. section II.C.4).

4. Titanium

α-Products are normally obtained if lithiated sulfides are transmetalated with titanium and subsequently reacted with carbonyl compounds.[82] However, γ-substituted allyl sulfides form an exception.[83] The titanium reagent **94** from the dianion **91** of allyl mercaptan **90**, and its 2-methyl analogue, yield almost exclusively γ-adduct **96** in their reactions with carbonyl compounds (Scheme 15)[74] (cf. section II.C).

In general, titanation favors α-attack, as exampli-fied by transmetalated lithiated [1-alkoxy-1-(trimethylsilyl)allyl]silane **582** (Scheme 105)[305] (cf. section IV.A), α-methoxyallylphosphinoxide **658** (Scheme 121)[346] (cf. section IV.D), and 1-(alkylthio)-3-(trimethylsilyl)-1-propene **730** (Scheme 137)[375] (cf. section V.B).

Transmetalation to give organotitanium and organoaluminum reagents enhances the anti-diastereoselectivity of γ-hydroxyenol carbamates produced from crotyl carbamates (section II.B.4).[62] Other examples of asymmetric synthesis leading to homoaldol products under the influence of titanium compounds are given in Scheme 14 (section II.B.4).[59,60,64−71,152,153] Lithium−titanium exchange of lithiated 2-alkenyl carbamate by $Ti(O^iPr)_4$ proceeds with retention to give **85**, whereas $Ti(NEt_2)_3$ causes inversion of the configuration forming **86** (Scheme 14)[70,71] (see also section II.B.4).

α- and γ-product mixtures are observed for dithiocarbamate **227** in the absence of $Ti(O^iPr)_4$,[141] while the titanium reagent undergoes α-attack to give **228** and **229** (Scheme 40)[142−144] (cf. section II.C).

The addition of $Ti(O^iPr)_4$ to lithiated allyldiphenylphosphine followed by condensation with aldehydes gives exclusively α-erythro-adducts **419** (Scheme 74)[222] (cf. section II.F).

5. Copper

While titanium reagents favor α-selectivity of the attack by carbonyl compounds on allyltrialkylsilanes **449**, copper reagents give mainly the γ-adduct **456** (Scheme 79)[255] (cf. section II.G). Such a reaction course is typical for copper-mediated transformations. Thus, while bis(alkylthio)allyllithium **541** yields α-products **542** upon reaction with electrophiles, after prior treatment with cuprous iodide and trimethyl phosphite the γ-products **543** are obtained (Scheme 96)[290] (cf. section III.C). The regioselectivity of [1-(alkylthio)allyl]lithium **101** is reversed by copper to afford γ-alkylation and α-attack by carbonyl compounds[358] (cf. section II.C.1). The γ-selectivity of pentadienyl-

silane anions **486** is increased with copper, magnesium, and boron reagents[265] (cf. section II.G.5).

6. Potassium

gem-Dichloroallylpotassium **525** exhibits α-selectivity in its reactions with carbonyl compounds to give **527** (Scheme 93), a behavior which contrasts to that of its lithium analogue **523**[281,282] (cf. section III.A). In the alkylation of allyltrialkylsilane anions **422**, application of Schlosser's base KO^{t}Bu/BuLi enhances the γ-regioselectivity to give **425** (Scheme 75)[232] (cf. section II.G).

7. General Discussion

Regioselectivity of the reaction of carbonyl compounds is enhanced by use of less electropositive metals such as Zn^{2+} and Ti^{4+} as counterions.[37] In general, transmetalations to the organoaluminum,[41,42,245] organoboron,[246] organotitanium,[247−249] and organozinc[250,251] compounds direct the reactions of allyltrialkylsilane anions with aldehydes into the α-position. (cf. section II.G).

A similar directing effect is achieved upon addition of triethylaluminum[40,41] to the allyl system or via boron "ate" complexes[42] with X = OR, SR, Se, and Si (Scheme 8).

E. Utility in Synthesis and Asymmetric Synthesis

Numerous reactions of allyl anions with electrophiles proceed not only with high regioselectivity, but also stereoselectivity. The allyl carbamates and sulfur-, nitrogen-, and phosphorus-stabilized allyl anions play important roles in asymmetric synthesis. A few examples are mentioned to give an impression about the type of reaction occurring.

Asymmetric induction can emanate from any of the following: the allylic part of the reagent or its substituents, the counterion M or its ligand, the carbonyl compound.[61]

1. Oxygen

Transmetalation of 1-lithio-2-butenyl-*N*,*N*-diisopropylcarbamate **82** with $(TiO^iPr)_4$, followed by carboxylation provides homoaldol adducts **87** and **89** and the corresponding γ-lactones **88**. The transmetalation proceeds with inversion and the aldehydes add in an anti S_E' process (Scheme 14).[64,65] Lithium−titanium exchange of lithiated 2-alkenyl carbamate by $Ti(O^iPr)_4$ proceeds with retention to give **85**, whereas $Ti(NEt_2)_3$ causes inversion of the configuration forming **86** (Scheme 14)[70,71] (section II.B.4). Quite a few other examples of asymmetric synthesis in the presence of titanium reagents are given in the literature.[59,60,66−69]

2. Sulfur

While triethylalumium/trialkylboron "ate" complexes produce a mixture of the erythro- and threo-isomers with aldehydes, aluminum compounds give only erythro-products with very high stereoselectivity.[40] To improve the stereoselectivity of the reaction with chiral aldehydes Bu_3SnCl/BF_3 could be used which gives either predominantly or exclusively to the α-syn-product.[81]

Chiral α-substituted allyl sulfones **184** are obtained from the reactions of lithium and magnesium salts of allyl sulfone with acetone in the presence of a chiral diamine **183** (Scheme 32).[120] By transmetalation from lithium to magnesium derivatives the enantioselectivity is improved to 50% ee[120] (cf. section II.C.4).

Similar to the monoanion, the allyl sulfone dianion **223** reacts regiospecifically and stereoselectively with alkyl bromides, aldehydes, and electrophilic olefins at the α-position to the sulfone group (Scheme 39).[129]

To achieve better regio- and diastereoselective addition sterically demanding auxiliary-modified allyl sulfoxides **157** are applied (Scheme 26).[107]

Allyl sulfinamides **230** are α-alkylated to give **231** with high diastereoselectivity,[145] while Julia reported a low diastereoselectivity except for $R^1 = p$-Me-C_6H_4, R^2 = H).[146] The α-anti-adduct (β-hydroxysulfinamide) **232** is obtained in the reaction with aldehydes (Scheme 41).

Diastereomerically pure γ-hydroxyvinyl sulfoximide is obtained by transmetalation from lithium to titanium reagents[152,153] (cf. section II.C.7).

3. Nitrogen

Asymmetric synthesis is frequently required in the synthesis of natural products. For example, electrophilic reaction at an allylphosphoramide is used to synthesize δ-valerolactone derivatives which are key chiral synthons leading to a mosquito oviposition attractant pheromone (Scheme 50).[174]

Allylamine **300** is transmetalated with *B*-methoxydiisopinocampheylborane $(Ipc)_2Cl$ followed by asymmetric reaction with aldehydes which yields the α-adduct **305** with respect to nitrogen (Scheme 54).[182]

There are also examples of temperature dependence and counterion and the solvent influence on enantiomeric excess. For chiral allylamines, the alkylation reactions proceed with high diastereoselectivity but the enantiomeric excess varies with the counterion, the solvent (higher for petrol ether compared with THF) and the temperature[170,175] (cf. section II.E.2).

4. Phosphorus

Allylphosphonate **346** reacts with aromatic and aliphatic aldehydes[199] leading mainly to α-threo-product **347**. There are a few exceptions in which mixtures of α- and γ-adducts are observed (R^3 = 4-Cl-C_6H_4, 4-NO_2-C_6H_4; $R^1 = R^2$ = H) (Scheme 61). The adducts can be converted stereospecifically into dienes **350**.[197]

γ-Syn-products **397** (e.g., (*E*)-tiglyl phosphinoxides) and anti-adducts **395** (e.g., (*E*)-angelyl phosphinoxides) are obtained in a highly diastereoselective manner in the reactions of lithiated (*E*)- and (*Z*)-allylphosphine oxides **394**/**396** and allylphosphonates with 2-cyclopentenone (Scheme 69).[104,105,215]

Similar to phosphinoxides, consecutive asymmetric Michael additions of chiral phosphonamides with α,β-unsaturated ketones, esters, lactones, and lactams can be carried out with excellent diastereoselectivity.[220,221] The addition of *tert*-butyl cinnamate **413** to crotylphosphonamide derivative **411** yields syn **416**

and anti **417** γ-adducts in excellent yields and high diastereoselectivity (ratio 92:8) (Scheme 73). Similar behavior is shown by 3,4-dihydro-4-oxo-(2*H*)-pyridine-1-carboxylate[219] (cf. section II.F).

F. Rationalization of Results

There have been numerous investigations on the regioselectivity of heteroatom-stabilized allylic anions.[37,42,75,166,224,442−448] However, there is still no general concept to describe the regioselectivity of the reaction of electrophiles with these compounds.

The rule of thumb of Still and Macdonald[53] is quite useful for predicting the orientation of electrophilic attack. They state that allyl anions substituted by anion-destabilizing groups (OR, NR_2) have an increased electron density at the γ-carbon and hence favor γ-alkylation, whereas carbonyl compounds react at the α-terminus. Anion-stabilizing groups (SR, BR_2) should have a complementary charge distribution and therefore demonstrate α-alkylation and γ-attack by carbonyl compounds. However, this rule of thumb does not apply to allyl anions substituted by strong electron-withdrawing groups and to free allyl anions; the lithium cation and the allylic anion must be associated. This rule is also modified by various other factors, for instance by steric effects or ionizing cosolvents.

The "allopolarization principle"[449] of Gompper and Wagner was applied to kinetically controlled reactions. They rationalize that the change of the selectivity of a reaction is a function of a change in polarity of the ambident anion, whereby the "polarity index" is determined by the relative charge density at the potential reactive centers. Consequently, donor substituents favor attack at the γ-terminus, while α-regioselectivity is observed for acceptor substituents. However, this concept cannot be applied to reactions having π-complexes or ion pairs as intermediates, since the course of their following reactions can no longer be deduced from the properties of the starting materials.[449]

Pearsons HSAB[276,277] was also used to interpret the outcome of these reactions, but it does not differentiate between kinetic and thermodynamic control of a reaction and further it does not take into consideration that the "hardness" of the heteroatoms has an influence on the reaction of neutral compounds and their anions.

X. References

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