# Nucleophilic Dearomatizing ($D_NAr$) Reactions of Aromatic C,H-Systems. A Mature Paradigm in Organic Synthesis

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## 1. Introduction

Organic synthesis is a pivotal part of organic chemistry having as its main objectives the preparation of new

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F. López Ortiz was born in Avilés, Spain. He graduated from the University of Oviedo in 1980 and received a Ph.D. degree (1987) working on organic synthesis via α-lithiated phosphazenes under the supervision of J. Barluenga and F. Palacios. From 1987 to 1989 he was a postdoctoral Humboldt fellow (Germany), first (1987–1988) at the University of Siegen with H. Günther, undertaking research on NMR of organolithium compounds in solution, and second (1988–1989) at the Max Planck Institute für Kohlenforschung (Mülheim a.d. Ruhr) with R. Benn investigating $^{187}$Os NMR. In November 1989 he became Profesor Titular at the University of Oviedo, where he started his own research. He moved to the University of Almería (1996), where he is Professor of Organic Chemistry. His current research activities range from the application of phosphorus-stabilized carbanions in organic and organometallic chemistry to mechanistic studies of reactions involving organometallic species through multinuclear magnetic resonance.

M. J. Iglesias was born in Oviedo, Spain, and graduated from the University of Oviedo in 1981. She received her Ph.D. degree (1987) for work on heterocyclic chemistry with J. Barluenga and V. Gotor. She moved to the Instituto Nacional del Carbón (INCAR, CSIC) in Oviedo for a postdoctoral stay (1990–1992) with Dolores Guillén, carrying out research on coal tar pitches. She became Investigador Contratado for the period 1995–1999 at INCAR, where she continued investigating coal derivatives. In 2000 she joined Professor López Ortiz's group at the University of Almería, where she is now Profesor Contratado Doctor working on the development of synthetic methodology based on the use of lithiated phosphorus-containing compounds.

molecules and the development of methods aimed at the obtention of compounds of known interest. The retrosynthetic analysis of a target molecule allows the deconvolution of complex structures into fragments of smaller size.[1] Although these fragments are structurally simpler than the target, they must be adequately functionalized to achieve the designed transformations. Therefore, the availability of low-cost, easy to handle starting materials that may be readily transformed into the required synthons is a must for an efficient synthetic process.[2]

Ignacio Fernández was born in Spain in 1976 and obtained his Ph.D. from the University of Almería in 2003, under the direction of Fernando López Ortiz. He has been involved in several student exchange programs, which took him first to Bath with Matthew G. Davidson (2000), then to Würzburg with Dietmar Stalke (2001), and then to Zürich with Paul S. Pregosin (2003). In 2006, after two and a half years in the Swiss Federal Institute of Technology (ETHZ), he returned to the University of Almería as a Ramón y Cajal associate researcher. His current research interests are focused on the applications of multinuclear NMR studies to problems in organometallic chemistry and the development of new synthetic methodologies and metal-based catalysts.

C. M. Andújar Sánchez was born in Almería, Spain. She obtained her first degree in chemistry (Licenciatura) from the University of Almería in 1998 and received a Ph.D. degree in 2003 working on synthetic methodology using anions derived from phosphine–borane complexes and *N*-phosphorylphosphazenes with Professor López Ortiz. She then moved to the industrial sector, where she is currently working.

Aromatic hydrocarbons fit very well with these features, presenting the added value of the cyclic skeleton. The conjugated $\pi$ system of an aromatic ring can be considered a masked internal functionalization, which can be conveniently exploited once the chemical inertness imposed by the aromaticity is overcome through dearomatizing methods. The resulting alicyclic compounds still contain carbon−carbon double bonds, thus bringing the opportunity to attain the desired degree of functionalization.

Extensive work on dearomatization reactions has led to the development of a number of methods for the disruption of the aromatic system of arenes and its subsequent derivatization. The Birch reduction, a single electron-transfer process, is probably the best known in organic synthetic chemistry.[3] In addition, a variety of alternatives are available, such as chemical[4] and microbial oxidation,[5] hydrogenation,[3b,6] radical cyclization,[7] electrolysis,[4b,8] photo-[9] and thermocycloaddition reactions,[10] and electrophilic[11] or nucleophilic addition to the aromatic system.

G. Ruiz Gómez was born in Madrid, Spain. She studied chemistry at the University of Almería and completed her first degree (Licenciatura) in July 2000. She was awarded a Ph.D. in 2006 for work on dearomatizing reactions of phosphinamides and phosphonamides under the direction of Professor López Ortiz. She is currently a postdoctoral fellow in Professor López-Ortiz's group with interest in the synthesis of non-natural peptides and peptide analogues.

The last two processes generally require some type of activation. In this context, complexation to transition metals is a very useful method for generating either electron-rich or electron-deficient aromatic rings. Transition metal mediated dearomatizations have attracted great attention over the past decade, and the subject has been covered by several reviews. In the first case, the activation of the aromatic ring is achieved through $\eta^2$-coordination of the arenes by electron-rich and $\pi$-basic metal fragments containing osmium(II) and rhenium(I).[12] Back-donation from the metal to the aromatic ligand renders it susceptible to dearomatization by electrophilic attack. In contrast, electrophilic transition metal groups, usually tricarbonyl chromium, $Cr(CO)_3$, tricarbonyl manganese, $Mn(CO)_3^+$, and, to a lesser extent, $CpFe^+$ and $CpRu^+$, form hexahapto complexes with aromatic ligands, which are activated toward nucleophilic addition.[13]

Concerning carbon nucleophiles, organolithium reagents are the prototypal one in organic chemistry. Their reactions with aromatic hydrocarbons bearing an electron-withdrawing functional group may follow three different routes: (1) addition to the functional group, (2) ortho lithiation,[14−20] or (3) [1,4], [1,6], or [1,8] conjugate addition to the aromatic nucleus. For aromatic systems having an alkyl substituent ortho to the functional group, lateral metalation is an alternative pathway.[20,21] The intermediate carbanions are generally quenched with a suitable electrophile (Scheme 1).

This review encompasses dearomatization reactions promoted by nucleophilic addition to aromatic hydrocarbons excluding transition metal temporarily coordinated $\pi$-systems. Nucleophilic addition to fullerenes, spherical aromatic molecules,[22] will not be considered here. The aim is to present a general overview of the methods available to effect the dearomatization, emphasizing their scope and limitations. The following discussion will essentially cover those processes leading to isolable dearomatized products through the combined sequence of nucleophilic dearomatization−electrophilic trapping reactions. Scheme 1 shows the activating groups, nucleophiles, and type of reactions that will be treated in the review. It will also be shown that this synthetic methodology represents a powerful tool for the chemo-, regio-, and stereoselective creation of carbon−carbon and carbon−heteroatom bonds, converting simple aromatic compounds into more elaborated materials. Moreover, the dearomatized compounds formed contain a combination of functional groups in a cyclic framework, which can be further transformed to obtain products of potential biological activity. The presentation will follow a system based on the functional group linked to the aromatic ring. Although the reactivity of a system is often the result of a combination of factors, the activating group is probably the most important. Michael additions to electrophilic $\alpha,\beta$-unsaturated systems have been extensively reviewed.[23] In contrast, the literature related to nucleophilic conjugate additions to non-metal-complexed aromatic nuclei has been treated in rather old reviews covering only partial aspects of this chemistry. The papers by Gaertner[24] and Fuson[25] provide an assessment of the scope and limitations of the reaction of organometallic reagents with aryl ketones up to the beginning of 1958. Bartoli[26] reviewed the literature up to 1982 related to the addition of Grignard reagents to nitro compounds. Although these reviews represent the starting point for the present paper, we have attempted to cover all of the literature from 1955 to January 2005. Additionally, work not surveyed previously on nucleophilic additions to aryl nitriles will be included here. Some examples and studies may have been unintentionally overlooked if the subject has not been abstracted and is therefore unsearchable by keyword, substructure, or reaction. Furthermore, partial aspects of the subject have been previously reviewed in a different context,[27] for example, the chemistry of naphthyl oxazolines,[14,16,28,29] nucleophilic aromatic substitution reactions,[30−33] and dearomatizing cyclization reactions.[34,35] In these cases, the presentation of the new material will be preceded by a short summary of the fundamentals and main applications of the methodology, which will enable comparison among the procedures under discussion. Finally, dearomatizing reactions through [2,3]-sigmatropic rearrangements are outside the scope of the current review.[36,37]

## 2. Unsubstituted Aromatic Hydrocarbons

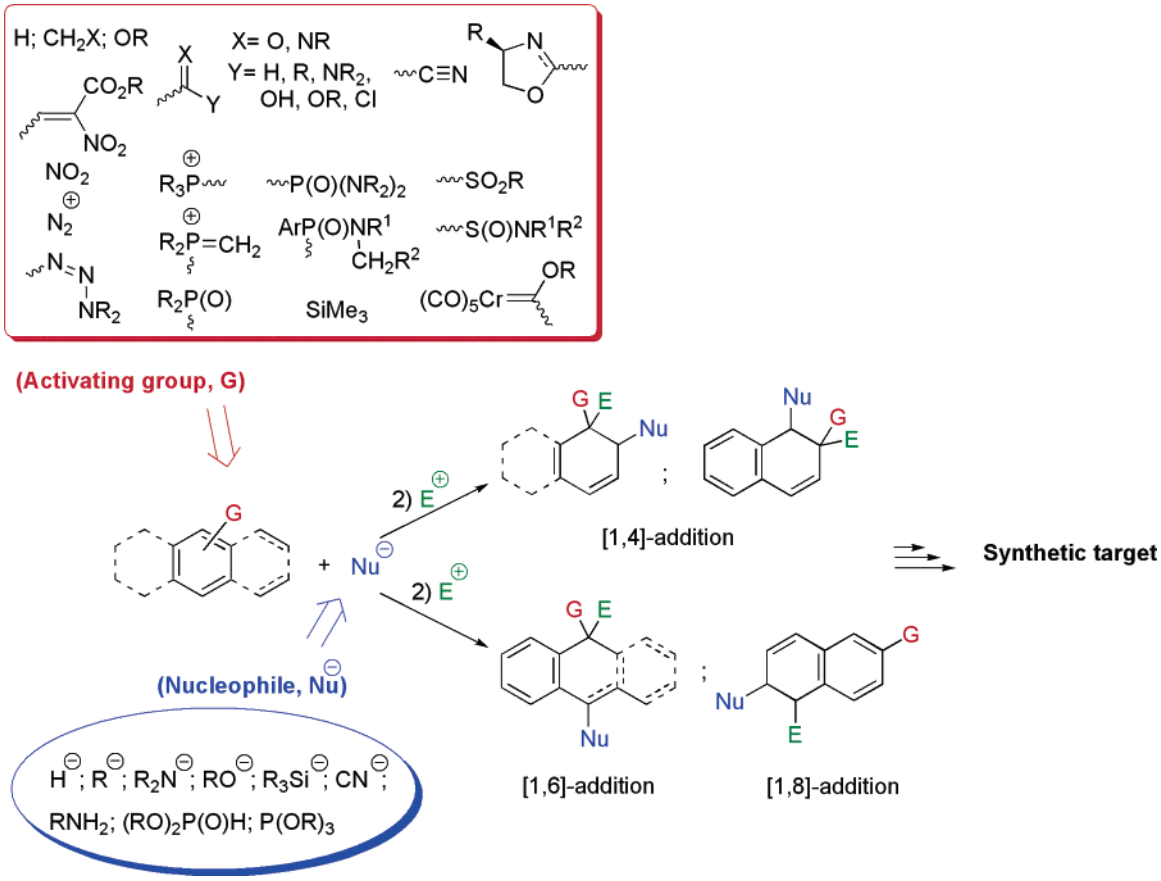
### 2.1. Naphthalene, Anthracene, and Phenanthrene

Contrary to what could be expected, the addition of negatively charged reagents to the electron-rich nucleus of unsubstituted aromatic hydrocarbons such as naphthalene **1**, anthracene **2**, and phenanthrene **3** has been successfully achieved in a number of cases. The interest of these processes lags, on the one hand, in the design of routes alternatives to Friedel−Craft reactions for the preparation of alkylated aromatic compounds that may have substituent patterns not available through electrophilic reactions. Obviously, in those cases when conjugate addition is followed by a chemical or photochemical oxidation step, the aromaticity of the system is recovered. Among other applications, the availability of alkylated polycyclic aromatic hydrocarbons is of some importance for biological testing as potential carcinogenic substances. On the other hand, the dearomatized adducts contain a cyclohexadiene system that might show peculiar conformational and stereochemical aspects.

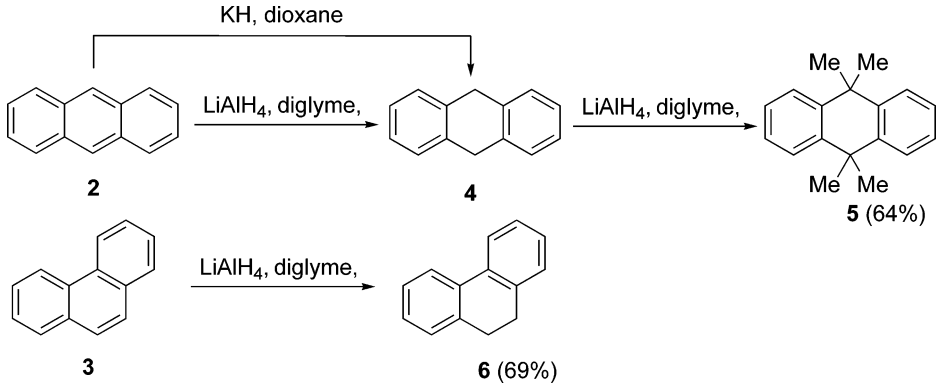
#### 2.1.1. Reactions with Hydride Transfer Agents

Hydride addition to nonfunctionalized aromatic compounds is a process of rather limited scope.[3a,38] Anthracene **2** and phenanthene **3** are reduced to the corresponding 9,10-dihydro derivatives **4** and **6** upon heating with $LiAlH_4$ in diglyme at 150 °C (Scheme 2).[39] However, in the case of **2** the reaction continues to give 9,9,10,10-tetramethyl-9,10-

**Scheme 1**




**Scheme 2**



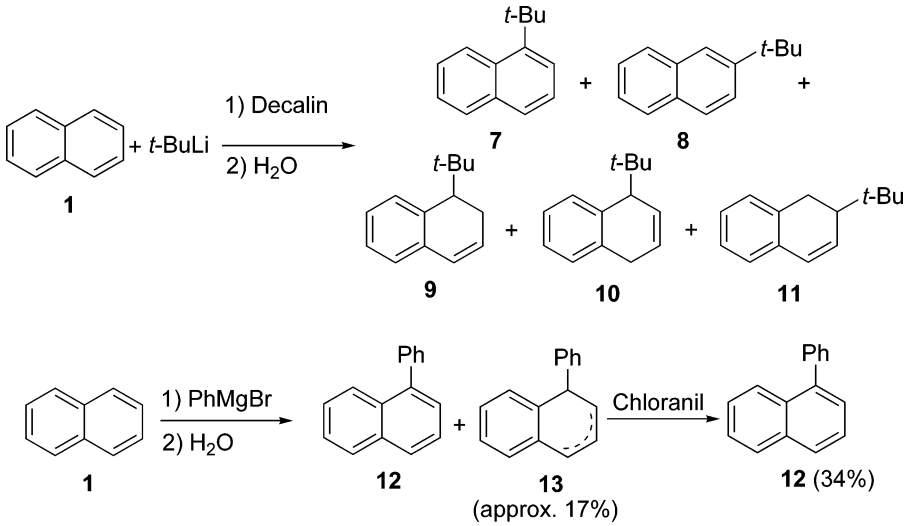

dihydroanthracene **5** as a result of partial demethylation of diglyme under the forcing conditions used. Intermediate **4** was identified as the major product of the reaction through NMR analysis at a reaction time of 30 min. The reduction of anthracene with potassium hydride can be performed in refluxing dioxane. The milder reaction conditions provided the dihydro compound **4** as part of a mixture (2:3) with unreacted starting material (Scheme 2).[40]

### *2.1.2. Reactions with Carbon Nucleophiles*

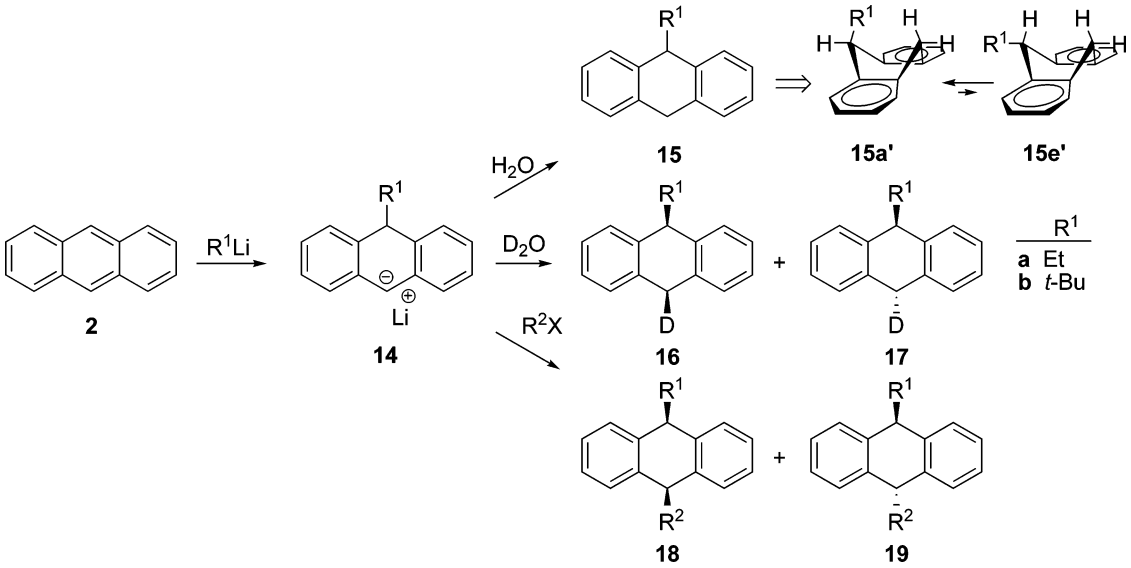
Strong nucleophiles such as alkyl-lithium, -sodium, and -potassium reagents generally react with aromatic compounds through metalation of the aromatic ring. However, Dixon et al. showed alkylation as a significant reaction when alkyl-lithiums (reactivity order of *t*-BuLi > *s*-BuLi > *n*-BuLi) were heated with benzene, naphthalene, or phenanthrene.[41] The harsh conditions used favor the aromatization of the initial adduct via elimination of lithium hydride. Methylation of anthracene and phenanthrene has been readily achieved with methylsulfinyl carbanion ($CH_3SOCH_2^-$),[42] whereas the methylation of phenanthrene with sulfonyl carbanion ($PhSO_2CH_2^-$) must be assisted by the strong co-ordinating agent HMPA.[43] In both cases, only rearomatized products were isolated. The addition of allylic lithium systems into anthracene and then hydrolysis to afford the dearomatized adduct has also been addressed by Fraenkel and co-workers.[44,45]

In the reaction of *tert*-butyl-lithium with naphthalene **1** at 60 °C in decalin, besides the α- and *β*-*tert*-butylnaphthalenes (**8** and **7**, respectively), a 17% yield of a mixture of *tert*-butyldihydronaphthalenes **9**−**11** was obtained (Scheme 3).[46] The kinetic study of the transformation indicated the quantitative formation of an intermediate complex of formula $[(RLi)_2(ArH)]$ prior to the rate-determining addition of *t*-BuLi to naphthalene.[47] Alkylation and arylation of naphthalene

**Scheme 3**




**Scheme 4**



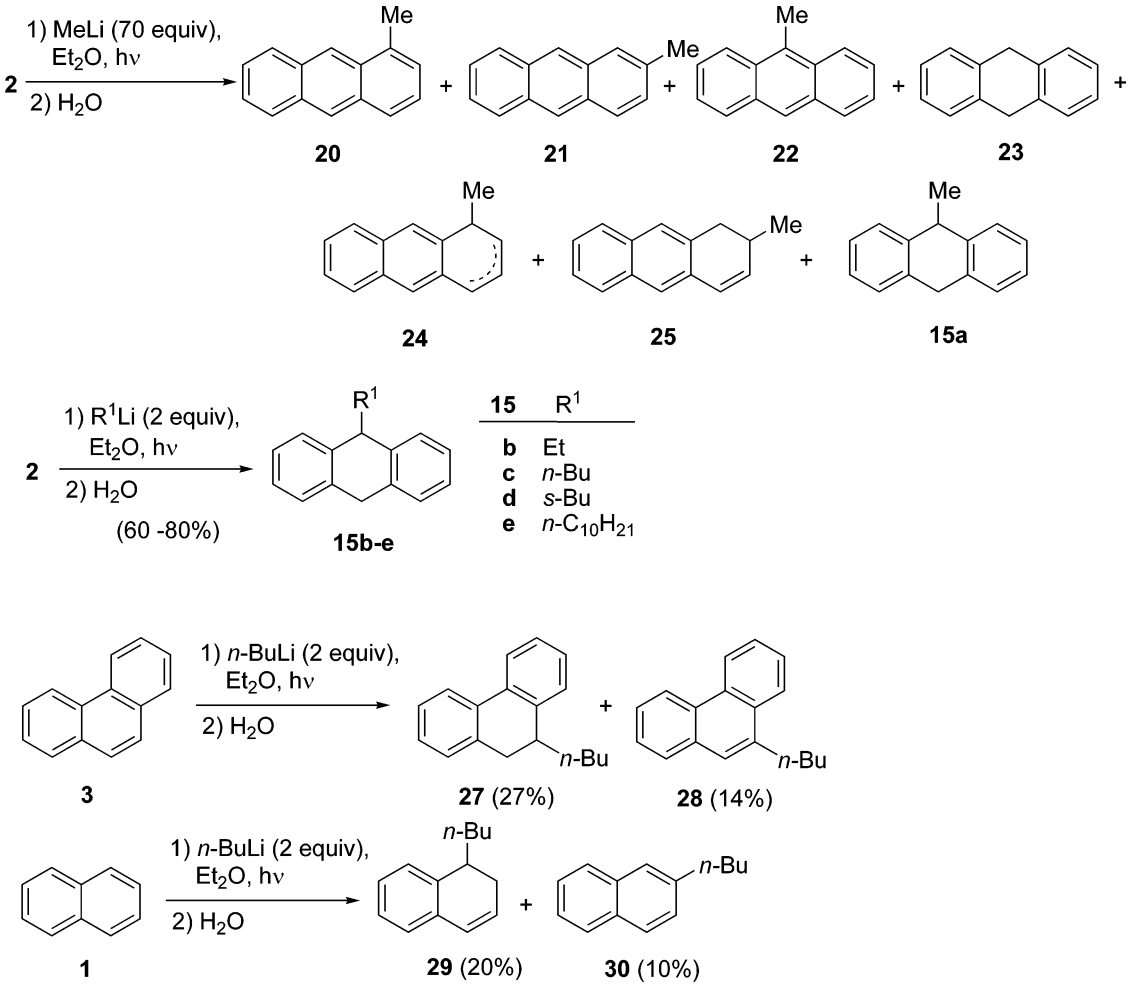

with Grignard reagents proved to be feasible as well. Thus, phenyl- and butylmagnesium bromide added to naphthalene and biphenyl when heated at 200 °C in such hydrocarbon solvents as decalin. In this way, 1-phenylnaphthalene (34%), 1-*n*-butylnaphthalene (9%), and terphenyl (6% yield, mixture of ortho and para regioisomers) were obtained.[48] The hydrolysis of the reaction of phenylmagnesium bromide and naphthalene at 200 °C afforded a mixture of 1-phenylnaphthalene **12** and 1-phenyldihydronaphthalenes **13** (in approximately 17% yield) (Scheme 3). The proportion of dihydro derivatives increased when the reaction was performed at 150 °C. The mixture was quantitatively dehydrogenated to **12** with chloranil.

Following the work of Dixon et al., the reaction of alkyllithium reagents with anthracene **2** and the subsequent electrophilic quench were studied extensively, presenting some inconsistent results. Thus, the stereoselectivity of the reaction, the identification of the configuration and conformation of the stereoisomers generated, and the reaction mechanism are aspects that raised considerable controversy. The addition takes place smoothly using ethereal or hydrocarbon solvents in the presence of co-ordinating additives. Intermediate 9-alkyl-10-lithio-9,10-dihydroanthracene **14** formed has been trapped with $H_2O$, $D_2O$, and alkyl halides, yielding 9,10-dihydroanthracenes **15**−**19** (Scheme 4).[49]

Anions such as **14** (Scheme 4) could be generated in two alternative ways: through lithiation of the parent 9-alkyl-9,10-DHA with *n*-BuLi or by sequential Birch reduction−alkylation of the anthracene substrate. Several 9-alkyl-9,10-DHA derivatives **15** have been prepared according to these methods.

Methylation of anthracene by reaction of a THF/$Et_2O$ (5:3) solution of **2** with MeLi (5.3 equiv) at 50−55 °C for 7 h and oxidation of the reaction mixture (20% conversion) with Pd/C in xylene gave a mixture of 1-, 2-, and 9-methylanthracenes **20**:**21**:**22** in a ratio of 7:1:92.[50] Photolysis (Pyrex filter, transparent to 300 nm) of an identical solution led to a new set of products that includes 9,10-DHA **23** (21%) besides the alkylated anthracenes **20** (4%), **21** (21%), and **22** (15%). When the methylation was carried out in diethyl ether under irradiation and using a very large excess of MeLi (70 equiv), the analysis of the hydrolyzed reaction mixture showed the presence of 9,10-DHA **23**, 1-, 2-, and 9-methyldihydroanthracenes **24**, **25**, and **15a** and their respective aromatized derivatives **20**−**22** (Scheme 5, top). The mixture was dehydrogenated with Pd/C, yielding **20** (3%), **21** (12%),

**Scheme 5**




**22** (19%), and 19% of recovered **2**. The ESR spectrum measured after irradiation is consistent with an electron-transfer/alkyl-transfer process. However, a mechanism involving partial alkylation via anionic addition cannot be discarded. The photochemical alkylation of anthracene with ethyl-, *n*-butyl-, *s*-butyl-, and *n*-decyl-lithium in diethyl ether proved to be much more efficient. In all cases, good yields of 9-alkyl-9,10-dihydroanthracenes **15b**−**e** were obtained using a 2:1 molar ratio of alkyl-lithium and hydrocarbon (Scheme 5; Table 1, entries 2−5).[51] In the particular case of *s*-butyl-lithium, the reagent instantaneously added to the aromatic hydrocarbon, giving **15d** in 80% yield even in the absence of irradiation. This is a remarkable solvent effect as compared with the reaction carried out in decalin, which required heating at 160 °C for 41 h.[41] The reaction in benzene, under conditions similar to those used with $Et_2O$, dropped the yield of **15d** to 13%, whereas, in hexane, 96% of anthracene was recovered. No alkylated products were observed for reactions with methyl- and vinyl-lithium. The study of the photolysis of *n*-butyl-lithium and anthracene **2**, phenanthrene **3**, naphthalene **1**, and biphenyl **26** revealed that the reactivity decreased in the series anthracene > phenanthrene > naphthalene ≫ biphenyl. Butylation of **3** gave low yields of 9-*n*-butyl-9,10-dihydrophenanthrene **27** (27%) together with a 30% yield of the aromatized derivative **28**. The analogous reaction with naphthalene afforded a mixture of 1-butyl-1,2-dihydronaphthalene **29** (20%) and 2-butyl-naphthalene **30** (10%) (Scheme 5; Table 1, entries 13 and 14). No alkylation was found for biphenyl **26**.

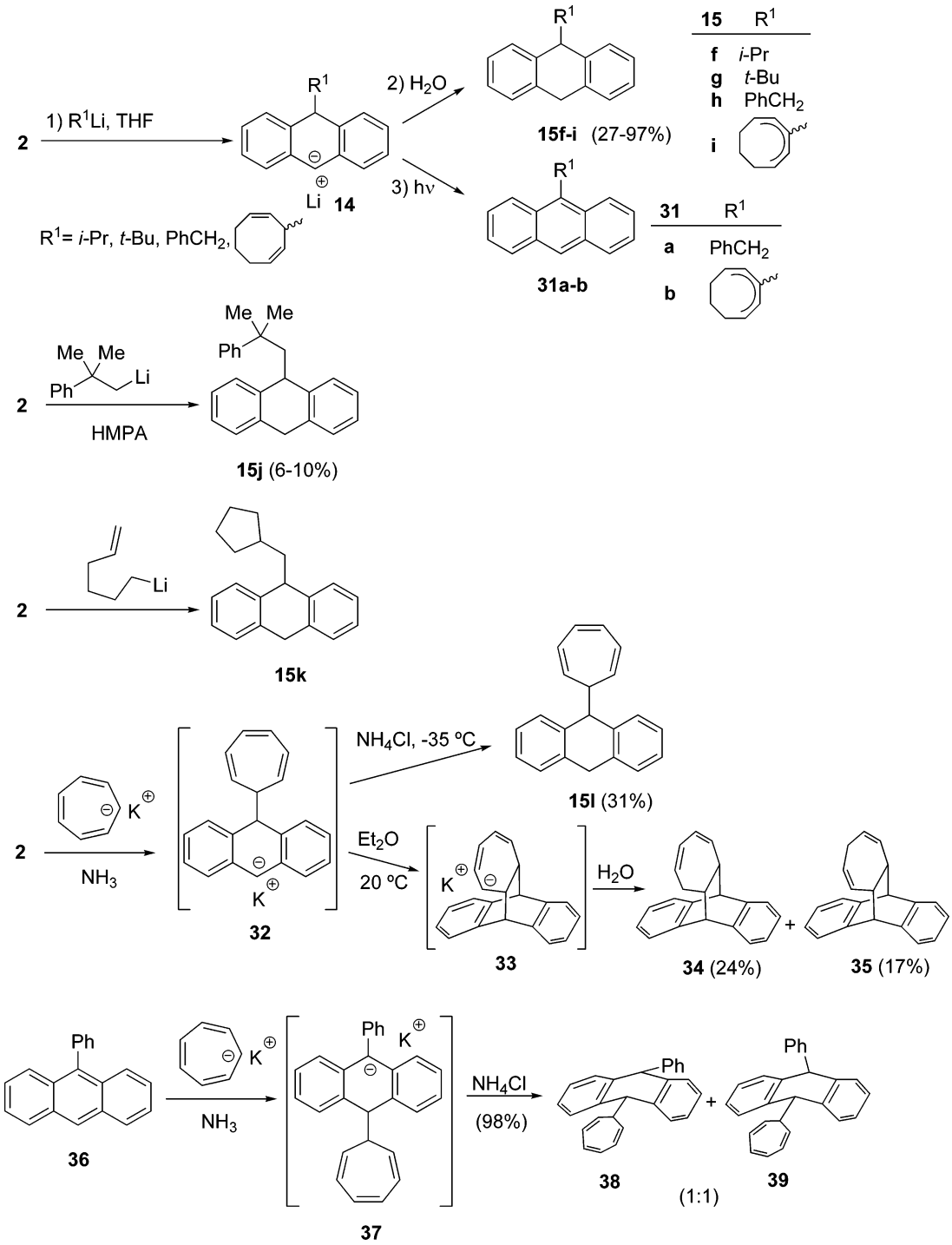
**Table 1. Dearomatized Compounds Obtained through Nucleophilic Addition−Hydrolysis of Aromatic Hydrocarbons 1−3**

| entry | SM | $R^1M$ | $R^1$ | yield (%) |
|---|---|---|---|---|
| 1 | **2** | MeLi | Me | **15a**, 19[a] |
| 2 | **2** | EtLi | Et | **15b**, 74[b,c] |
| 3 | **2** | *n*-BuLi | *n*-Bu | **15c**, 60[c,d] |
| 4 | **2** | *s*-BuLi | *s*-Bu | **15d**, 80[c] |
| 5 | **2** | $n$-$C_{10}H_{21}Li$ | $n$-$C_{10}H_{21}$ | **15e**[c,e] |
| 6 | **2** | *i*-PrLi | *i*-Pr | **15f**, >97[f] |
| 7 | **2** | *t*-BuLi | *t*-Bu | **15g**, 27[f,g] |
| 8 | **2** | $PhCH_2Li$ | $PhCH_2$ | **15h**, 80[h] |
| 9 | **2** | CODLi | COD[j] | **15i**, 89[h] |
| 10 | **2** | neophylLi | neophyl | **15j**, 10[i] |
| 11 | **2** | $CH_2{=}CH(CH_2)_4Li$ | $c$-$C_5H_9CH_2$ | **15k**, >97[j] |
| 12 | **2** | $C_7H_7K$ | $C_7H_7$ | **15l**, 31[k] |
| 13 | **3** | *n*-BuLi | *n*-Bu | **27**, 27[c] |
| 14 | **1** | *s*-BuLi | *s*-Bu | **29**, 20[c] |

[a] After dehydrogenation of the dearomatized product. Data taken from ref 50. [b] After dehydrogenation of the dearomatized product. [c] Data taken from ref 51. [d] Quenching the reaction with $D_2O$ afforded 9-butyl-10-deutero-9,10-dihydroanthracene in a yield of 50%. [e] Yield not given. [f] Data taken from ref 49e. [g] For an improved procedure giving **15g** in 45% yield see ref 66. [h] Data taken from ref 52. [i] Cyclooctadienyl. [j] Data taken from ref 53. [k] Data taken from ref 54.

*Iso*-propyl-,[49e] *tert*-butyl-,[49e] benzyl-[52] and cyclooctadienyl-lithium[52] added smoothly to **2** in THF without requiring photolysis. After acidic workup, the corresponding dihydro derivatives **15f**−**i** were isolated (Scheme 6; Table 1, entries 6−9). In the reaction with *t*-BuLi minor amounts of two additional dearomatized products were isolated. They were assigned as the 1,2-dihydro derivatives resulting from the

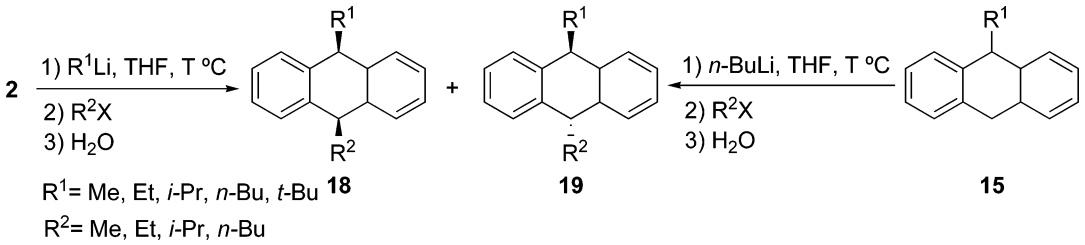
**Scheme 6**




nucleophilic attack at positions 1 and 2 of the anthracene ring. In the case of **15i**, a mixture of double-bond isomers of the cyclohexadiene moiety were formed. Interestingly, photolysis of the anionic adduct with visible or long-wavelength ultraviolet light at −80 °C resulted in the elimination of LiH, leading to the aromatized products **31**. The ESR spectrum of the reaction mixture of benzyllithium and **2** measured at −78 °C is identical to that of the anthracene radical anion, suggesting that single electron-transfer processes (SET) may compete with the nucleophilic addition in the alkylation of anthracene with these organolithium reagents.

In contrast, the bulky neophyl-lithium did not undergo reaction with anthracene in THF, $Et_2O$, and $Et_2O$-TMEDA at room temperature. 9-Neophyl-9,10-dihydroanthracene **15j** was formed only when the reaction was performed in hexamethylphosphorotriamide (HMPA), albeit in very low yield (6−10%) (Scheme 6; Table 1).[53] The isolation of the product with the alkyl substituent un-rearranged is consistent with a favored polar process in the alkylation of aromatic hydrocarbons, rather than a SET one. In fact, alkylation of anthracene with 5-hexenyl-lithium at room temperature gave exclusively 9-cyclopentylmethyl-9,10-DHA **15k** (Scheme 6).[53] Lithiocyclization of 5-hexenyl-lithium occurred rapidly in the temperature range from −10 to 20 °C. The formation of **15k** indicates that intramolecular cyclization is easier than intermolecular attack to the aromatic hydrocarbon.

**Scheme 7**




9-Alkyl-9,10-DHAs **15** exist preferentially in the **15a′** conformation (Scheme 4). For $R^1$ = Et, *i*-Pr, and *t*-Bu the alkyl group is almost entirely in the pseudoaxial orientation, whereas for $R^1$ = Me both conformers seem to exist at equilibrium. On the basis of the homoallylic coupling constants and chemical shifts observed for H9 and H10, a contribution of 75% in the pseudoxial orientation has been estimated.[49e]

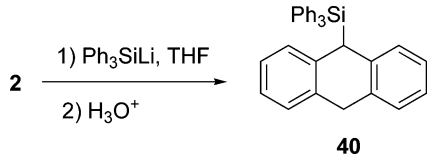
The 8-$\pi$ electron potassium cycloheptatrienide anion also adds to anthracene in liquid ammonia to give the dearomatized anion **32**, which, upon protonation with ammonium chloride, affords 9-(2,4,6-cycloheptatrien-1-yl)-9,10-DHA **15l** in 31% yield (Scheme 6; Table 1).[54] In diethyl ether at 20 °C, anion **32** undergoes an anionic cyclization leading to a new anionic species **33**. Aqueous work yields a mixture of cycloadducts **34** and **35**. The reaction has been extended to 9-phenylanthracene **36**, with which the addition occurs in a [1,4] manner giving rise, after treatment with $NH_4Cl$, to a 1:1 mixture of *cis*- and *trans*-9-cycloheptatrienyl-10-phenyl-9,10-dihydroanthracenes **38** and **39**, respectively, in 98% yield (Scheme 6). The higher yield of dearomatized products thus obtained may be due to the higher solubility of substrate **36** in liquid ammonia and/or the higher stability of the intermediate anion **37** compared to that of **32**.

Deuterolysis of **14** ($R^1$ = Et) was reported to give **16** with total stereoselectivity.[49c,55] However, later work showed that the reaction leads to mixtures of cis and trans isomers **16** and **17** (Scheme 4), respectively, in a different ratio depending on the reaction conditions used. The addition of ethyllithium to **2** in cyclohexane at room temperature for 3 h in the presence of *N*,*N*,*N*′,*N*′-tetramethyl-*o*-phenylenediamine (TMOPD) and subsequent quench with $D_2O$ lead to a mixture of **16a** and **17a** in a ratio of 39:61.[56] Performing the deuterolysis with deuteriotriphenylmethane gave 57:43 mixtures of **16a** and **17a**. In THF as solvent at room temperature and in the absence of chelating bisamine, equal proportions of both isomers were found, whereas the cis:trans ratio changed to 64:36 when the anion was quenched with a diluted solution of $D_2O$ in THF at −20 °C.

Similarly, mixtures of **16b** and **17b** (ratio of 70:30 to 52:48, depending on the temperature of the reaction) were obtained upon treatment of anthracene **2** with *tert*-butyllithium in THF followed by the addition of $D_2O$. Interestingly, in the presence of HMPA (THF/HMPA, 30:20 v/v) only the cis isomer **16b** was formed.[57−59]

The observed stereoselectivity in the alkylation of the dearomatized anions **14** (Scheme 4) caused also some controversy due to inconsistent results. It turns out that, although in some cases a single stereoisomer is formed,[56] the stereoselectivity of the reaction is a balance of several factors, the most important one being the size of the alkyl groups in the reactants[60] and the solvent.[61] Contrary to the total cis stereoselectivity claimed by Harvey and Davis[62] for the preparation of dialkylated dearomatized products via nucleophilic addition in THF, the process generally affords mixtures of cis and trans isomers **18** and **19**, respectively (Scheme 7).[63−65] As mentioned above, these anions may be generated either through addition of alkyl-lithiums to anthracene or through metalation of 9-alkyl-9,10-DHAs with *n*-BuLi. Both methods produced the same ratio of stereoisomers for the same anion/electrophile pair. The 9,10-dialkyl-9,10-DHAs isolated include combinations of ethyl-, *iso*-propyl-, *n*-butyl-, and *tert*-butyl-lithium with methyl, ethyl, *n*-butyl, and *iso*-propyl halides.[62] Under these conditions, methyl-lithium does not add to **2**. However, heating MeLi and anthracene at 50 °C, followed by subsequent quench with MeI, gives a mixture of *cis*- and *trans*-9,10-dimethyl-9,10-DHA in approximately equal amounts in 56% yield. This result contrasts with the much more complex mixture obtained in the analogous methylation−protonation previously mentioned[50] and might be due to differences between the reaction mechanisms of both processes. Evidence in favor of either a polar or a SET mechanism for the dialkylation of anthracene has been reported. These aspects will be discussed in section 2.1.4. The addition stage proceeds smoothly in THF and triethylamine but fails completely in petroleum ether or benzene. In the cis isomers, the substituents exist in a pseudoaxial orientation and the boat-shaped 9,10-dihydroanthracene system becomes more flattened with the size increase of the alkyl groups. In the trans stereoisomer the preferred conformation sets the largest substituent in the pseudoaxial orientation, thus minimizing the interactions with the peri hydrogens.[63,65,66]

**Scheme 8**



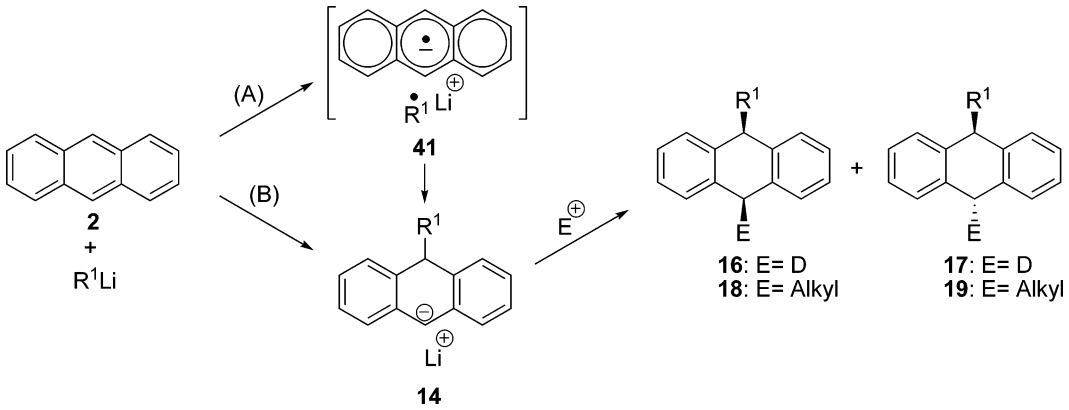

### *2.1.3. Reactions with Heteroatom Nucleophiles*

There are just a few examples of nucleophilic attack of negatively charged heteroatoms on an unactivated aromatic ring. Gilman and Marrs found that triphenylsilyl-lithium reacts with anthracene to give, after protonation of the intermediate anionic adduct with diluted sulfuric acid, 9,10-dihydro-9-(triphenylsilyl)anthracene **40** in 30% yield (Scheme 8).[67] The reason for the low yield probably was due to the participation of the dearomatized anion in alternative transformations (e.g., disproportionation, polymerization, and oxidation).

### *2.1.4. Mechanistic Studies of the Nucleophilic Dearomatizing Alkylation*

The elucidation of the mechanism of 9,10-disubstituted-9,10-DHAs has attracted great interest. On the basis of the reaction products' composition, either SET[52,60,64] (Scheme

**Scheme 9**



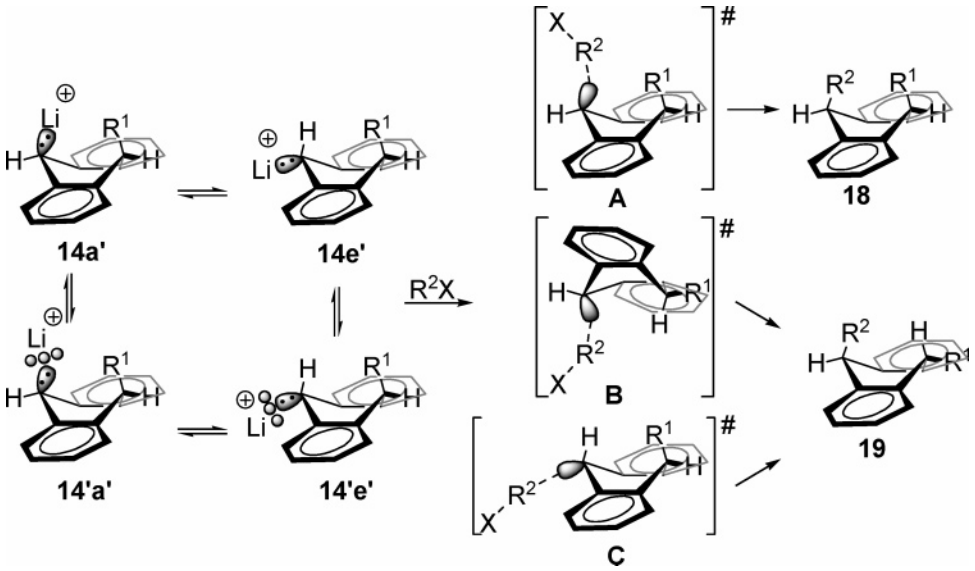

9, route A) or polar mechanisms[53,66] (Scheme 9, route B) have been proposed for the thermal addition of organolithiums to anthracene and subsequent reaction with electrophiles. ESR spectra of solutions of the nucleophile and the aromatic hydrocarbon provide evidence for the presence of radical anions, which supports the participation of SET processes in the pathway leading to the alkylated dearomatized compounds.[52] However, when the reaction is performed under photolytical conditions, it cannot be discarded that direct addition of the carbanion to anthracene takes place to some extent.[50] Whatever the mechanism, the addition stage ends with the formation of a dearomatized carbanion **14**, which can be trapped with several electrophiles. The reaction with alkyl halides is generally better described as a $S_N2$ displacement[66] than as an alternate sequence consisting of halogen−metal exchange.[65] In this interpretation, the resulting benzylic halide would undergo rapid coupling with the new alkyl-lithium formed to give the observed 9,10-dialkylated products.

To shed light on the mechanism of nucleophilic addition−electrophilic trapping in anthracene **2**, the structure of the intermediate species formed was investigated. In a pioneering work, Nicholls and Szwarc studied the UV[49c,55] and $^1$H NMR[49d] spectra of anions **14** generated through the reaction of $R^1$Li ($R^1$ = Me, Et, *n*-Bu) and **2** in THF. Ultraviolet spectra showed two absorption maxima of similar intensity at $\lambda_{max}$ = 400 and 450 nm. When the sample cools, the intensity of the peak at 450 nm increases at the expense of that at $\lambda_{max}$ = 400 nm, which disappears at temperatures below −55 °C. Interestingly, the UV spectrum of the lithium salt of 9,10-DHA, prepared by the reaction of *n*-butyl-lithium with the aromatic hydrocarbon, also showed two absorption bands at $\lambda_{max}$ = 400 and 450 nm at temperatures below −60 °C. The two species present in solution were identified as ion pairs differently coordinated by the solvent. The shortest wavelength absorption corresponds to contact ion pairs (CIP), whereas the peak at $\lambda_{max}$ = 450 nm is produced by solvent separated ion pairs (SSIP). Addition of glyme-3 favored the formation of SSIP. From the analysis of the $^1$H NMR spectra, it was concluded that the carbanionic center possesses a considerable $sp^2$ character and the anionic system exists in a preferred nonplanar conformation with the lithium cation and the alkyl group being located on the same side of the molecule. Although the conformation was erroneously assigned, subsequent studies carried out by other authors[59,66,68] supported the main conclusions of this work.

The existence of the carbanion structured in ion pairs represents the basic concept for understanding the stereoselectivity of the deuteration and alkylation of anions **14**. However, this concept has been interpreted in different ways. The reaction of alkyl halides with 9-alkyl-10-lithio-9,10-DHAs provides cis products for primary halides but trans products when both alkyl groups are large, the exception being the methylation of the 9-methyl derivative. In this case, the reaction proceeds with poor stereoselectivity. The stereochemical outcome of these reactions has been explained by assuming a model involving an equilibrium between the CIP isomers **14a′** and **14e′** and the corresponding SSIP species **14′a′** and **14′e′** (Scheme 10). Conformational preferences are determined by two factors. First, delocalization of the negative charge through the neighboring rings is maximized when the anion is in the pseudoaxial position. Second, steric interactions of the alkyl substituent $R^1$ with the peri hydrogens are minimized in the pseudoaxial orientation. Concerning the approach of the electrophile to the carbanionic center, access to the pseudoequatorial side of the p-orbital is hindered by the peri hydrogens, whereas transannular steric interactions between the electrophile and $R^1$ may be an important obstacle for a pseudoaxial attack. These arguments have been used to propose transition states A and B−C (Scheme 10) as responsible for the formation of, respectively, *cis*- and *trans*-9,10-dialkyl-9,10-DHAs.[60,66,69] A kinetic study of the alkylation of a series of anions **14** ($R^1$ = H, Et, *i*-Pr, *t*-Bu) with primary and secondary halides showed that for primary halides the preferred attack is on conformer **14a′**; that is, the reaction proceeds through transition state A.[70] With an increase in the size of $R^1$, the reaction rate decreases and, concomitantly, the amount of trans product **19** increases. However, for the reaction with secondary alkyl halides, attack by yielding transition states B and/or C could be operative.

In the protonation of a series of 9-alkyl-10-*tert*-butyl-9-lithium-9,10-DHAs, formed by metalation of either the cis or trans parent hydrocarbon with *n*-BuLi, Panek and Rodgers found that the cis compound was predominantly obtained. However, addition of 6.5 equiv of HMPA or performance of the reaction in HMPA as solvent led to the exclusive formation of the trans product.[68] The anions have no memory of the stereochemistry of their precursors. In agreement with previous studies,[49c,d,55] the UV and $^1$H NMR spectra of the lithium salts showed the existence of two types of ion pairs ($\lambda_{max}$ = 444 nm, CIP; $\lambda_{max}$ = 464 nm, SSIP). In THF and HMPA the only species observed were absorbing at 464 nm. The fact that the protonation of the anions in $Et_2O$ and THF solutions afforded mainly cis hydrocarbons implies that ion pairs of similar structure exist in these solvents. Moreover, the inversion of the stereoselectivity in the protonation of the anions with increase in the amount of HMPA was taken

**Scheme 10**




as an indication that a series of ion pairs with different environments are present in solution. They are spectroscopically indistinguishable in THF, HMPA, or $Et_2O$-HMPA. However, they can be chemically distinguished. On protonation, contact and tight ion pairs preferentially formed the cis hydrocarbon, whereas loosely associated ion pairs and free ions led to the preferred generation of trans products. The anion is considered to be essentially flat, and the cation can drive the protonation in $Et_2O$ and THF solutions by coordination to the proton donor. The same model was used to explain the reaction course of the protonation and deuteration of 10-alkyl-9-lithio-9,10-DHAs. Hence, boat-to-boat equilibrium is not a necessary condition to account for the stereochemistry of these reactions. Similar conclusions were obtained through $^{13}C$ NMR spectroscopy in the analysis of the alkylation of anions **14**.[71] As mentioned above, the possible role of an electron-transfer mechanism cannot be excluded. It is known that HMPA favors one-electron reduction of anthracene by alkyl-lithiums.[72]

## 2.2. Polycyclic Aromatic Hydrocarbons with More than Three Rings

Zieger and co-workers reported the butylation[73] and ethylation[74] of perylene **42** by treating it with *n*-BuLi and EtLi in THF and refluxing benzene, respectively. Low yields of 1-butyl- (13.2%) and 1-ethylperylene (2%) were obtained; these were the first examples of substitution of the perylene ring at a position other than C3. Under the reaction conditions used the intermediate adducts eliminated lithium hydride to give the aromatized products. By performing the methylation of **42** with MeLi in benzene at 80 °C for 24 h in the presence of a stoichiometric amount of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) it was possible to isolate the methyldihydroperylenes **43** in 33% yield.[75] Dehydrogenation of **43** over 5% palladium−carbon afforded 1-methylperylene **44** (Scheme 11, top). The use of neophyl-lithium failed under similar conditions.[53] Interestingly, phenanthrene **3** did not undergo reaction with methyl-lithium in boiling benzene.

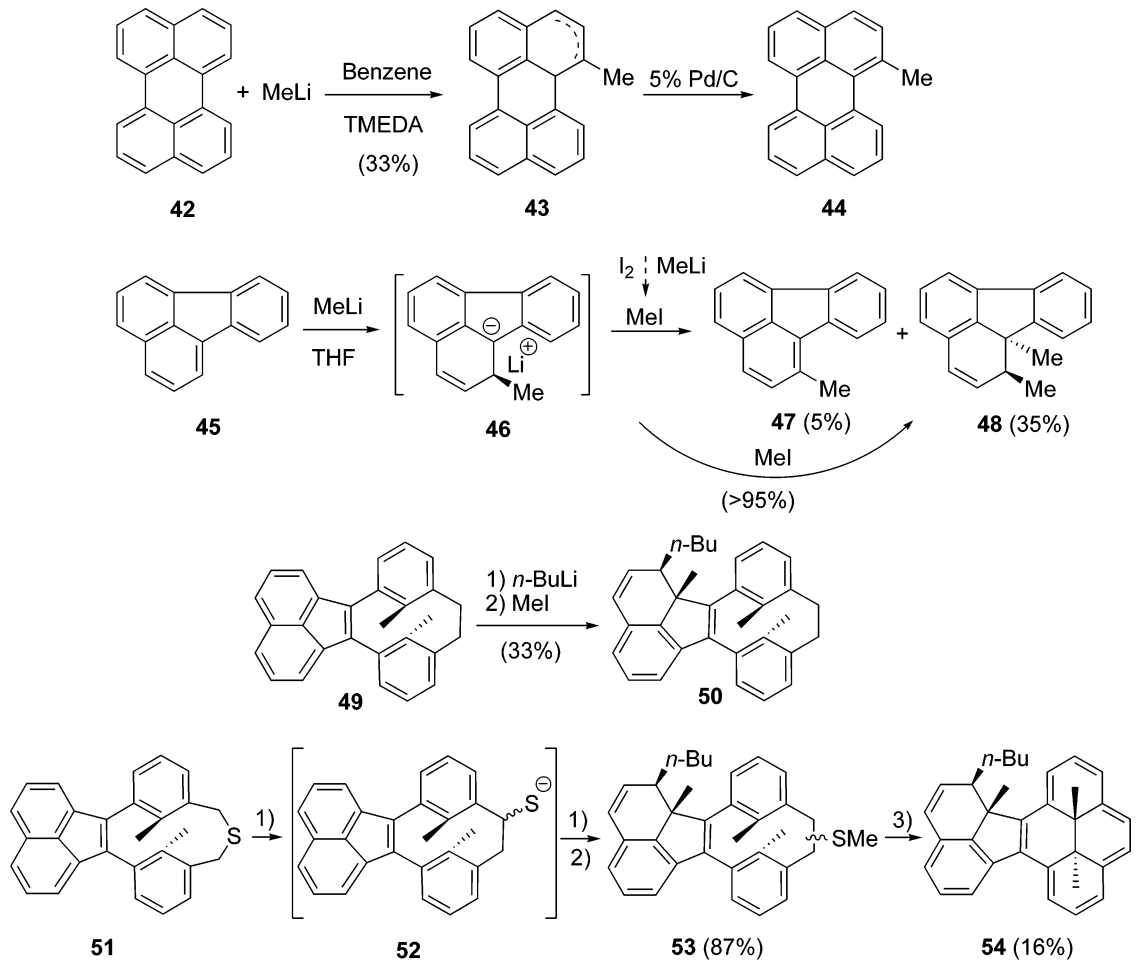
In later work, Carlson et al. described an improved method for the methylation of perylene in high yield.[76] Hydrocarbon **42** was treated with 2 equiv of MeLi in THF at −78 °C, and the reaction was allowed to reach room temperature overnight. Further oxidation with iodine in dichloromethane at 0 °C for 15 min led to 1-methylperylene **44** in 85% yield. The methylation of pyrene to give 1-methylpyrene proceeded also in good yields (60%). In this case, the reaction was carried out under UV irradiation at 254 nm. However, the application of this procedure to the methylation of fluoranthene **45** produced 1-methylfluoranthene **47** in only 5% yield, the major product being the dearomatized dimethyl derivative **48** (35%) (Scheme 11). The formation of **48** was explained by trans alkylation of the anion **46**, resulting from the addition of MeLi to **45** with methyl iodide arising from the decomposition of the excess of methyl-lithium employed. Compound **48** was obtained quantitatively when MeI was added instead of iodine. The synthesis of **48** represents the first example of a nucleophilic addition on a nonalternant aromatic hydrocarbon.

Recently, a new example of a conjugate addition to a nonalternant aromatic hydrocarbon has been reported. Treatment of cyclophanene **49** with *n*-butyl-lithium followed by quenching with methyl iodide afforded compound **50** (Scheme 11).[77] The driving force for the reaction was attributed to the relief of strain in the annelated acenaphthylene unit of **49** by addition of the organolithium reagent. *n*-Butyl-lithium underwent reaction with thiacyclophanene **51** in a similar manner, leading to the isolation of **53** as a mixture of isomers. In this case, prior to the nucleophilic addition step, the thioether moiety suffers a Wittig rearrangement, giving the intermediate **52**. Methylation of **53** with dimethoxycarbonium fluoroborate caused the elimination−valence isomerization to produce **54**, illustrating a further example of the classic 14 $\pi$-e annulene aromaticity.[78]

## *3. Benzylic Systems*

Nucleophilic dearomatizing reactions ($D_NAr$) of aromatic hydrocarbons bearing a benzylic fragment have been achieved mainly through $S_N'$ processes. As discussed below, the leaving group at the benzylic position is displaced in a conjugate manner generally through nucleophilic attack to the C10 position of an anthracene ring in a [1,5] manner, leading to the formation of an exocyclic carbon−carbon double bond and, consequently, to a dearomatized compound. Reactants and products have the same number of $\pi$ electrons, although with a different distribution (see Schemes 12−23). Extended conjugation of the unsaturated system provides the stabilization necessary to isolate the dearomatized derivatives.

**Scheme 11**




1) *n*-BuLi, THF. 2) MeI. 3) $(MeO)_2CH^+ BF_4^-$, $CH_2Cl_2$

## 3.1. Anthrylmethyl Halides and Alcohols

### *3.1.1. Reactions with Hydride Transfer Agents*

In a study of the mechanism of the hydride reduction of alkyl halides, Nojima et al. found that the treatment of (9-anthryl)arylmethyl chlorides and bromides **55a**−**i** with lithium aluminum hydride (LAH) in diethyl ether, THF, or diglyme afford mixtures of products **56** and **57**, both resulting from the reduction of the anthracene ring at $C_\alpha$−X and at C10, respectively (Scheme 12; Table 2).[79] In the reaction in $Et_2O$ solution, the decrease in the ratio **56**:**57** correlates with the increase of the electron-withdrawing ability of the $R^2$ group at the Ar substituent (Table 2). In the presence of 12-crown-4 ether, the reactivity of the chlorides **55a**−**e** toward the reduction decreased notably. These results were interpreted as evidence of lithium cation assistance to the cleavage of the carbon−halogen bond.

Lithium triethylborohydride in THF[79] and sodium borohydride in aqueous diglyme[80] also effected reduction of halides **55** to give mixtures of anthracenyl derivatives **56** and dearomatized compounds **57**. Electron-withdrawing substituents in Ar favored the formation of **57** with respect to the aromatized compound **56** (Table 3). The same trend is observed when the steric crowding at the $C_\alpha$−Cl increases (cf. entries 3, 10, and 11 in Table 3).[81] However, in trifluoroacetic acid, the reaction of **55a**−**e** with $NaBH_4$ gives almost exclusively anthracene hydrocarbons **56**.[81] The exception is **55g** (Ar = $C_6H_5$; $R^1$ = H; X = Br), which affords a mixture of **56** and **57** in 91% yield and in a ratio 78:22.[80] The reaction of **55c** (Ar = $C_6H_5$; $R^1$ = H; X = Cl) with cycloheptatriene as hydride donor in sulfur dioxide also gave a 1:1 mixture of **56** and **57** in 80% yield.[82]

Interestingly, the reduction of chlorides **55a**−**e** and bromides **55f**−**i** afforded similar product distribution. In the reduction of bromides **55f**−**i** small amounts of dimers **58** ($C_\alpha$−$C_\alpha$ coupling), **59** ($C_\alpha$−$C_{10}$ coupling), and **60** ($C_{10}$−$C_{10}$ coupling) were also obtained. Formation of **58**−**60** was inhibited by performing the reaction in the presence of tributyltin hydride, indicating that these dimers proceed from the coupling of (9-anthryl)arylmethyl radicals.[79]

The results of the reduction of **55** with different hydride transfer reagents under a variety of conditions suggest that in dry solvents compounds **56** and **57** are formed via $S_N$ and $S_N'$ displacement reactions, respectively. However, in protic media, the distribution of products and the rates of reaction are consistent with a reaction mechanism involving the participation of cationic intermediate species.

Under the conditions used for the reductions, the dearomatized products were stable, suggesting that they were formed under kinetic control. The quinoidal compounds were converted into the isomeric aromatized derivatives by treatment with either an acid ($H_2SO_4$) or a base (*t*-BuOK/*t*-BuOH or *n*-BuLi/$Et_2O$). However, the stability of 9,10-DHAs was raised when the bulkiness at the benzylic carbon was

**Scheme 12**

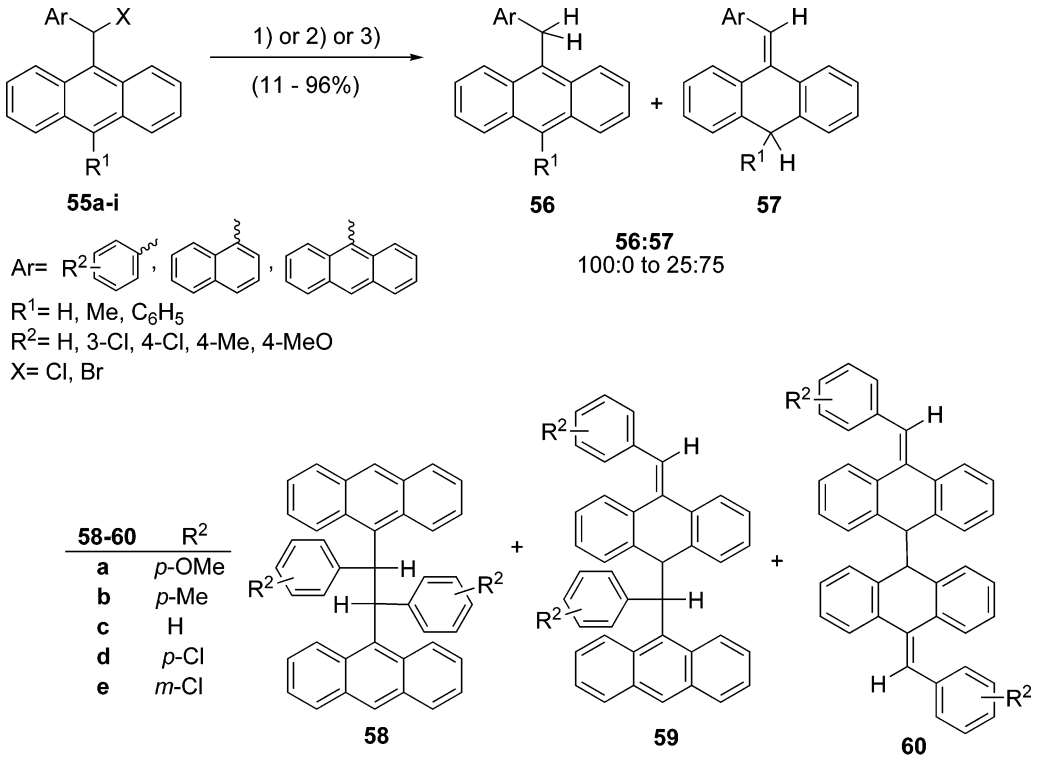



**Table 2. Distribution of Products in the Reduction of (9-Anthryl)arylmethyl Halides 55 with $LiAlH_4$ in $Et_2O$ and THF[a]**

| | | | | | | $LiAlH_4/Et_2O$[b] | | $LiAlH_4/Et_2O$[c] 12-crown-4 | | $LiAlH_4$/THF[b] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| entry | SM | Ar | $R^1$ | X | prod | yield (%) | ratio **56**:**57** | yield (%) | ratio **56**:**57** | yield (%) | ratio **56**:**57** |
| 1 | **55a** | 4-MeO-$C_6H_4$ | H | Cl | **a** | 95 | 100:0 | 30 | 85:15 | 95 | 68:32 |
| 2 | **55b** | 4-Me-$C_6H_4$ | H | Cl | **b** | 95 | 90:10 | 15 | 55:45 | 63 | 27:73 |
| 3 | **55c** | $C_6H_5$ | H | Cl | **c** | 49[d,e] | 79:21 | 7 | 45:55 | 26 | 26:74 |
| 4 | **55d** | 4-Cl-$C_6H_4$ | H | Cl | **d** | 33 | 74:26 | 7 | 66:36 | 19 | 46:54 |
| 5 | **55e** | 3-Cl-$C_6H_4$ | H | Cl | **e** | 11 | 71:29 | 7 | 96:4 | 16 | 69:31 |
| 6 | **55f** | 4-Me-$C_6H_4$ | H | Br | **b** | 93 | 79:21 | | | 87 | 31:69 |
| 7 | **55g** | $C_6H_5$ | H | Br | **c** | 92 | 68:32 | | | 87 | 29:71 |
| 8 | **55h** | 4-Cl-$C_6H_4$ | H | Br | **d** | 79 | 66:34 | | | 77 | 49:51 |
| 9 | **55i** | 3-Cl-$C_6H_4$ | H | Br | **e** | 76 | 61:39 | | | 55 | 72:28 |

[a] Data taken from ref 79. [b] Ten molar equivalents of $LiAlH_4$ at 20 °C for 10 min. [c] Reaction performed in the presence of 2 equiv of 12-crown-4 at 20 °C for 60 min. [d] At 38 °C and 120 min: yield of 72%, ratio **56**:**57** of 82:18.[82] [e] With cycloheptatriene in $SO_2$ at 20 °C for 10 min: yield of 80%, ratio **56**:**57** of 50:50.[82]

increased, as the stabilization achieved by aromatization is surpassed by the destabilizing effect of the steric interaction with the peri hydrogens in the corresponding anthracene isomers.[81]

Similar to chlorides **55a**−**e**, treatment of anthrylmethyl alcohols **61a**−**e** with sodium borohydride in trifluoroacetic acid gave products with a quinoidal structure for those derivatives bearing electron-withdrawing substituents (entries 18 and 19 of Table 3; Scheme 13).

In the search for a method of preparing 9,9′-dianthrylmethane **56k** (Scheme 14), Applequist and Swart found that the reduction of the 9,9′-dianthrylcarbinol **61f** with a 2:1 mixture of aluminum chloride and LAH in diethyl ether afforded **57k** in almost quantitative yield (Scheme 14).[83] Isomerization of **57k** to the target compound **56k** was achieved by treatment with potassium *tert*-butoxide in refluxing *tert*-butanol. The facile formation of the dearomatized system was demonstrated by synthesizing two additional examples. Thus, the reaction of **61f** with zinc chloride in ethanol and with thionyl chloride and pyridine in benzene gave **57l** and **57m**, respectively, in acceptable to good yields.

### *3.1.2. Reactions with Carbon Nucleophiles*

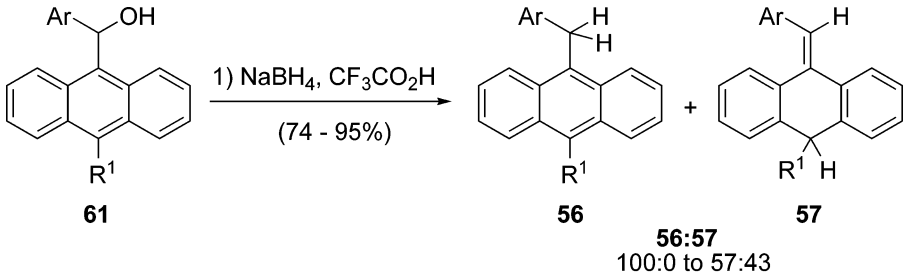
The reactivity of (9-anthryl)arylmethyl halides **55** toward Grignard and lithium reagents under a variety of conditions was also investigated to obtain insight into the reaction mechanism. The reaction of chlorides **55a**−**d** or bromides **55f**−**h** with a series of organomagnesium bromides in diethyl ether afforded a mixture of $C_\alpha$ (**62**), and C10 alkylation (**63**) products (Scheme 15; Tables 4 and 5), together with the three dimerization products **58**, **59**, and **60** already observed in the hydride reduction of bromides **55f**−**i** (Scheme 12), and two reduction products (**64** and **65**).[84] The product composition is insensitive to the halide **55** used. The alkylated derivatives **62** and **63** may be formed by direct nucleophilic substitution or through a SET mechanism, in which a radical from the Grignard couples to a radical from the halide within

**Table 3. Distribution of Products in the Reduction of (9-Anthryl)arylmethyl Halides 55 and Alcohols 61 with $LiAlH_4$ in Diglyme, $LiBEt_3H$ in THF, and $NaBH_4$ in Aqueous Diglyme[a]**

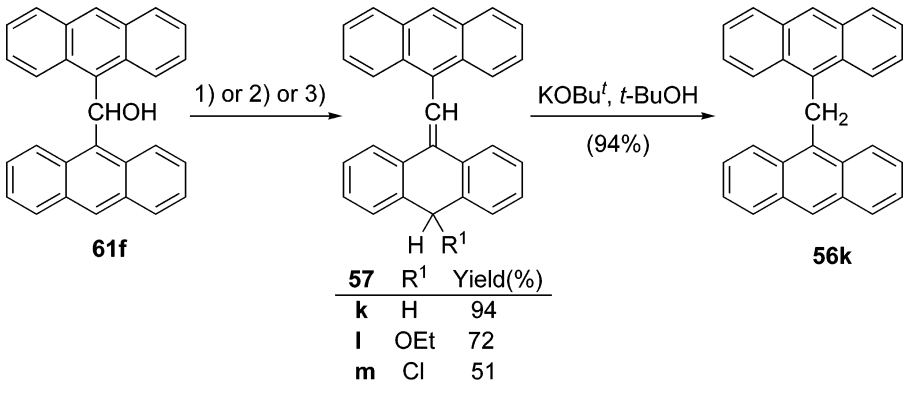
| | | | | | | $LiAlH_4$/diglyme[b] | | $LiBEt_3H$/THF[c] | | $NaBH_4$/80% diglyme[d] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| entry | SM | Ar | $R^1$ | X | prod | yield (%) | ratio **56**:**57** | yield (%) | ratio **56**:**57** | yield (%) | ratio **56**:**57** |
| 1 | **55a** | 4-MeO-$C_6H_4$ | H | Cl | **a** | 76 | 68:32 | 83 | 41:59 | 81 | 100:0[f] |
| 2 | **55b** | 4-Me-$C_6H_4$ | H | Cl | **b** | 44 | 50:50 | 68 | 18:82 | 81 | 45:55[f] |
| 3 | **55c** | $C_6H_5$ | H | Cl | **c** | 28 | 43:57 | 70 | 11:59 | 86[e] | 42:58[f] |
| 4 | **55d** | 4-Cl-$C_6H_4$ | H | Cl | **d** | 63 | 85:15 | 56 | 18:82 | 96 | 33:67[f] |
| 5 | **55e** | 3-Cl-$C_6H_4$ | H | Cl | **e** | 70 | 95:5 | 50 | 16:84 | 86[j] | 33:67[f,g] |
| 6 | **55f** | 4-Me-$C_6H_4$ | H | Br | **b** | 73 | 47:53 | | | 88 | 46:54[f] |
| 7 | **55g** | $C_6H_5$ | H | Br | **c** | 53 | 40:60 | | | 95 | 37:63[f] |
| 8 | **55h** | 4-Cl-$C_6H_4$ | H | Br | **d** | 68 | 73:27 | | | 94 | 32:68[f] |
| 9 | **55i** | 3-Cl-$C_6H_4$ | H | Br | **e** | 69 | 92:8 | | | | |
| 10 | **55j** | 1-naphthyl | H | Cl | **f** | | | | | 81 | 25:75[h] |
| 11 | **55k** | 9-phenanthryl | H | Cl | **g** | | | | | 86 | 33:67[h] |
| 12 | **55l** | $C_6H_5$ | Me | Cl | **h** | | | | | 80 | 45:55[i] |
| 13 | **55m** | $C_6H_5$ | $C_6H_5$ | Cl | **i** | | | | | 90 | 100:0[i] |
| 14 | **55n** | 1-naphthyl | $C_6H_5$ | Cl | **j** | | | | | 82 | 72:28[h] |
| 15 | **61a** | 4-MeO-$C_6H_4$ | H | OH | **a** | | | | | 74 | 100:0[j] |
| 16 | **61b** | 4-Me-$C_6H_4$ | H | OH | **b** | | | | | 78 | 100:0[j] |
| 17 | **61c** | $C_6H_5$ | H | OH | **c** | | | | | 95 | 100:0[j] |
| 18 | **61d** | 4-Cl-$C_6H_4$ | H | OH | **d** | | | | | 90 | 68:32[j] |
| 19 | **61e** | 3-Cl-$C_6H_4$ | H | OH | **e** | | | | | 91 | 57:43[j] |

[a] Data taken from ref 79. [b] Ten molar equivalents of $LiAlH_4$ at 20 °C for 10 min. [c] Five molar equivalents of $LiBEt_3H$ at 20 °C for 60 min. [d] Five molar equivalents of $NaBH_4$ at 20 °C for 30 min. [e] At 50 °C for 120 min: yield of 92%, ratio **56**:**57** of 43:57.[82] [f] Data taken from ref 80. [g] In trifluoroacetic acid at 0 °C for 5 min: yield of 91%, ratio **56**:**57** of 78:22.[80] [h] Data taken from ref 81. [i] Reaction time of 5 min.[80] [j] Reaction performed in trifluoroacetic acid at 0 °C for 5 min. Data taken from ref 80.

**Scheme 13**

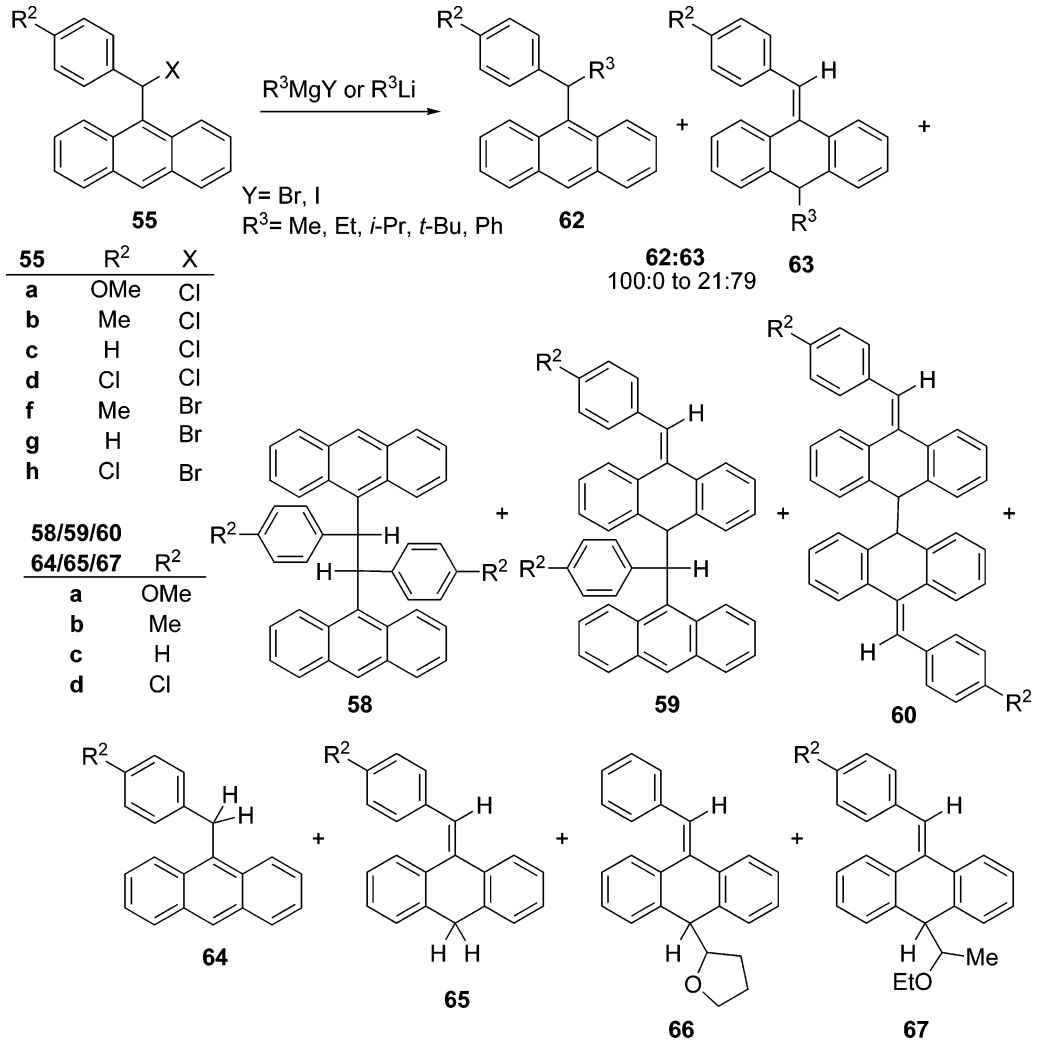



**Scheme 14**




a cage. (9-Anthryl)arylmethyl radicals that escape from the cage might dimerize to give **58**−**60**. The product compositions shown in Tables 4 and 5 are consistent with a rate-determining SET step for the reactions with *tert*-butyl-, isopropyl-, and ethylmagnesium bromides (i.e., absence of substantial para substituent effect on the **62**:**63** and **59**:**60** ratio) and a $S_N$ mechanism for the reactions of PhMgBr (i.e., large para substituent effect on the **62**:**63** ratio and very low yield of dimeric products). The reaction of methylmagnesium bromide represents the borderline between both mechanisms, with the alkylation products being formed via nucleophilic substitution and the dimers through a SET process. The yield

**Scheme 15**




of dimers **58**−**60** increases when the methylation is performed with MeMgI, as this Grignard reagent is expected to have a lower ionization potential than the corresponding bromide, favoring the SET mechanism. Additional support for these conclusions came from the reaction with MeMgBr carried out in the presence of *p*-dinitrobenzene (*p*DNB). The dinitro compound is a well-known trapping agent of organometallic reagents and radical anions. Its presence in the reaction medium led to a significant increase in the yield of alkylation products, and the ratio **62**:**63** increases with the increment of the electron-donating ability of the para substituent $R^2$, as expected for a nucleophilic substitution mechanism.

The use of THF as solvent in the reaction of Grignard reagents with chlorides **55a**−**d** produced a remarkable change in the product composition (Table 5). The para substituent effect on the ratios of **62**:**63** and alkylation/dimerization products suggests that alkylation takes place by a nucleophilic displacement. Addition of $FeCl_3$ to the reaction medium results in a notable acceleration of the reaction and promotes the almost exclusive formation of dimers **58**−**60**. This result implies that organoiron species participate in the process and favor a SET mechanism. In the reactions with MeMgBr, a new product **66** (Scheme 15) with a quinoidal structure was obtained in yields ranging from 5 to 35%. The formation of **66** was rationalized by a mechanism involving the coupling between the radical resulting from hydrogen abstraction of the solvent and the starting halide **55**.

Methyl- and ethyl-lithium undergo reaction with **55a**−**d** in diethyl ether to give a mixture of products similar to that found in the analogous reaction of ethylmagnesium bromide (Table 6). Once again, the virtually constant ratios of alkylated compounds **62**:**63** and dimers **59**:**60** indicate that a SET mechanism is operative for both organolithium reagents. In the case of MeLi, this behavior contrasts with that observed in the reaction with MeMgBr. Furthermore, a quinoidal product **67** (Scheme 15) involving the participation of the solvent was also formed in the reactions of MeLi.

Stabilized carbanions such as sodium diethyl malonate and sodium diacetylmethane also underwent reaction with 9-(α-chlorobenzyl)anthracene **55c** to give as major compound quinoidal products **63u**,**v** resulting from the preferred attack of the bulky nucleophile at the C10 position of the anthracene ring (Scheme 16; Table 6).[82] In the reaction with sodium diethyl malonate, the anthryl carbinol **61c** was also obtained in a yield of 22%.

### *3.1.3. Reactions with Heteroatomic Nucleophiles*

The nucleophilic displacement of halide from (9-anthryl)-arylmethyl chlorides and bromides **55** was extended to reagents bearing nucleophilic oxygen and nitrogen atoms. Sodium ethoxide in ethanol, sodium methoxide in methanol,

**Table 4. Distribution of Products in the Reaction of (9-Anthryl)arylmethyl Chlorides 55 with Grignard Reagents[a]**

| | | | | $R^3MgBr/Et_2O$[b] | | $R^3MgBr/p$DNB[c]/$Et_2O$[d] | |
|---|---|---|---|---|---|---|---|
| entry | SM | $R^2$ | $R^3$ | alkylation (%)[e] [ratio **62**:**63**] | dimerization (%)[e] [ratio **59**:**60**] | alkylation (%)[f] [ratio **62**:**63**] | dimerization (%)[f] [ratio **59**:**60**] |
| 1 | **55a** | MeO | *t*-Bu | **a**, 40 [35:65] | **a**, 42 [59:41][g,h] | | |
| 2 | **55b** | Me | *t*-Bu | **b**, 48 [30:70] | **b**, 36 [58:42][g,h] | | |
| 3 | **55c** | H | *t*-Bu | **c**, 42 [29:71] | **c**, 37 [50:50][h] | | |
| 4 | **55d** | Cl | *t*-Bu | **d**, 43 [27:73] | **d**, 39 [51:49][h] | | |
| 5 | **55a** | MeO | *i*-Pr | **e**, 66 [50:50] | **e**, 25 [50:50][g,h] | | |
| 6 | **55b** | Me | *i*-Pr | **f**, 68 [34:66] | **f**, 26 [53:47][g,h] | 54 [42:58] | 39 [68:32] |
| 7 | **55c** | H | *i*-Pr | **g**, 66 [33:67] | **g**, 26 [52:48][h] | | |
| 8 | **55d** | Cl | *i*-Pr | **h**, 64 [33:67] | **h**, 25 [50:50][h] | | |
| 9 | **55a** | MeO | Et | **i**, 88 [84:16] | **i**, 9 [61:39][g,h] | | |
| 10 | **55b** | Me | Et | **j**, 90 [54:46] | **j**, 6 [58:42][g,h] | 84 [51:49] | 10 [52:48] |
| 11 | **55c** | H | Et | **k**, 85 [49:51] | **k**, 12 [56:44][h] | | |
| 12 | **55d** | Cl | Et | **l**, 75 [44:56] | **l**, 18 [52:48][h] | 74 [40:60] | 21 [53:47] |
| 13 | **55a** | MeO | Ph | **m**, 96 [68:32] | **m**, 4 [60:40] | | |
| 14 | **55b** | Me | Ph | **n**, 100 [42:58] | | | |
| 15 | **55c** | H | Ph | **o**, 92 [23:77] | **n**, 8 [56:44] | | |
| 16 | **55d** | Cl | Ph | **p**, 96 [22:78] | **o**, 4 [60:40] | | |
| 17 | **55a** | MeO | Me | **q**, 100 [92:8] | | | |
| 18 | **55b** | Me | Me | **r**, 75 [62:38] | **p**, 25 [59:41][h] | 90 [62:38] | 10 [55:45] |
| 19 | **55c** | H | Me | **s**, 66 [41:59] | **q**, 34 [50:50] | 96 [43:57] | 4 [50:50] |
| 20 | **55d** | Cl | Me | **t**, 33 [46:54] | **r**, 67 [50:50] | 89 [38:62] | 6 [55:45] |

[a] Data taken from ref 84. [b] Five equivalents of Grignard reagent at 0 °C for 2 h. [c] *p*-Dinitrobenzene. [d] Nine equivalents of Grignard reagent and 1 equiv of *p*-DNB at 0 °C for 2 h. [e] Normalized, 100% = % alkylation + % dimerization + % reduction. [f] Normalized, 100% = % alkylation + % dimerization + % reduction + % unreacted chloride. [g] Dimer **58** was also obtained in yields of <3%. [h] Reduction products **64** and **65** were also formed in yields ranging from 2 to 21%.

**Table 5. Distribution of Products in the Reaction of (9-Anthryl)arylmethyl Chlorides 55 with Grignard Reagents[a]**

| | | | | $R^3MgBr/THF$[b] | |
|---|---|---|---|---|---|
| entry | SM | $R^2$ | $R^3$ | alkylation (%)[c] [ratio **62**:**63**] | dimerization (%)[c] [ratio **59**:**60**] |
| 1 | **55a** | MeO | *i*-Pr | **e**, 71 [39:61] | **e**, 27 [55:45][f] |
| 2 | **55b** | Me | *i*-Pr | **f**, 60 [21:79] | **f**, 35 [52:48][f] |
| 3 | **55c** | H | *i*-Pr | **g**, 60 [21:79] | **g**, 38 [50:50][f] |
| 4 | **55d** | Cl | *i*-Pr | **h**, 60 [22:78] | **h**, 37 [48:52][e,f] |
| 5 | **55a** | MeO | Et | **i**, 77 [69:31] | **i**, 23 [69:31][e] |
| 6 | **55b** | Me | Et | **j**, 30 [50:50] | **j**, 70 [48:52][e] |
| 7 | **55c** | H | Et | **k**, 13 [41:59] | **k**, 87 [47:53] |
| 8 | **55d** | Cl | Et | **l**, 23 [36:64] | **l**, 77 [54:46] |
| 9 | **55a** | MeO | Me | **q**, 79 [83:17] | **s**, 21 [63:37][e] |
| 10 | **55b** | Me | Me | **r**, 46 [52:48][d] | **p**, 37[50:50][e] |
| 11 | **55c** | H | Me | **s**, 19 [42:58] | **q**, 19 [50:50] |
| 12 | **55d** | Cl | Me | **t**, 14 [39:61][d] | **r**, 14 [50:50] |

[a] Data taken from ref 84. [b] Five equivalents of Grignard reagent at 0 °C for 1 h. [c] Normalized, 100% = % alkylation + % dimerization + % reduction + % unreacted chloride + % **66**. [d] Reaction time of 120 min. [e] Dimer **58** was also obtained in yields of <3%. [f] Reduction products **64** and **65** were also formed in yields ranging from 2 to 21%.

methanol and ethanol in the presence of triethylamine, and sodium azide in aqueous DMF underwent reaction with halides **55** to give mixtures of substituted anthracenes **68** and 9,10-dihydro derivatives **69** (Scheme 17; Tables 7 and 8).[80−82]

For halides **55** unsubstituted at C10, the yield of quinoidal products increased with the increasing electron-withdrawing ability of the substituent at the Ar moiety. Substituents at the C10 position produced two opposing effects. On the one hand, the increase of positive charge at that position is advantageous for a $S_N'$ reaction, whereas, on the other hand, crowding at that position might prevent the approach of the nucleophile, favoring the formation of products of nucleophilic substitution at the benzylic carbon. The product distribution obtained for **55c** ($R^1$ = H) and **55l** ($R^1$ = Me) indicates (cf. entries 3 and 11 in Tables 7 and 8) that steric effects are of minor importance for a methyl substituent. In contrast, the yield of anthracene derivatives increased when the access to the ring position is hindered by the presence of a phenyl substituent (cf. entries 3/12 and 9/13 in Table 7 and 2/14 and 4/15 in Table 8). As expected, the yield of anthracenes **68** increases as the substituent at the benzylic position becomes larger (cf. entries 3, 9, and 10 in Table 7).

The rearrangement of quinoidal compounds into the isomeric aromatized derivatives in the presence of an acid or a base or simply through column chromatography on silica gel or on alumina showed the same trends already mentioned for the 9,10-DHAs **57**.[80]

## 3.2 Anthrylmethyl Ammonium Salts

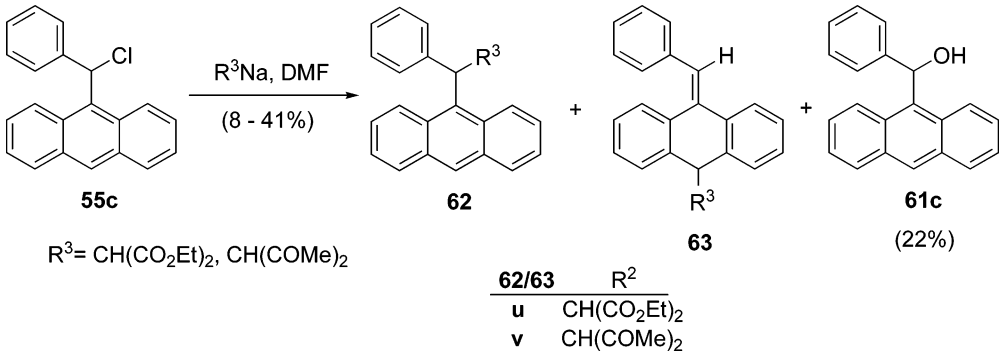
In contrast to the previously described dearomatizations involving anthrylmethyl chlorides, the reaction of **70** with sodium diethyl methylmalonate **71** as nucleophile gave exclusively the substitution product **72a** via a $S_N2$ displacement (Scheme 18). Apparently, quaternary ammonium salt **73a** behaves similarly when allowed to react with a stoichiometric amount of the same nucleophile. However, the use of a substoichimetric amount of **71** revealed that the transformation is actually a stepwise process. Under such conditions, the dearomatized derivative **74a** is isolated (Scheme 18).[85] This compound is transformed into the final product **72a** by reaction with **71**. α-Lithiated nitroparaffins **75a**−**c** also produce the $S_N'$ displacement of the ammonium group of **73**, affording high yields of compounds **74b**−**d**. The intermolecular nature of the process is further demonstrated by the formation of **74b** in 91% yield when **74a** is treated with 10 equiv of lithium 2-nitropropane **75a** at 25 °C. These results suggest that the mechanism of the reaction involves two stages. First, nucleophilic attack to the C10 position of **73** with conjugated displacement of the ammonium group affords dearomatized intermediates **74**. Second, addition of the nucleophile to the exocyclic carbon−carbon double bond of **74** is followed by rearomatization due to the elimination of the stabilized anions **71** or **75**.

**Table 6. Distribution of Products in the Reaction of (9-Anthryl)arylmethyl Chlorides 55a−d with Alkyl-lithium Reagents and Stabilized Carbanions[a]**

| | | | | $R^3Li/Et_2O$[b] | | $NaCH(CO_2Et)_2/DMF$[c] | $NaCH(COMe)_2/DMF$[d] |
|---|---|---|---|---|---|---|---|
| entry | SM | $R^2$ | $R^3$ | alkylation (%)[e] [ratio **62:63**] | dimerization (%)[e] [ratio **59:60**] | alkylation (%) [**63**] | alkylation (%) [ratio **62:63**] |
| 1 | **55a** | MeO | Me | **q**, 53 [54:46] | **s**, 31 [50:50] | | |
| 2 | **55b** | Me | Me | **r**, 32 [46:54] | **p**, 34 [61:39] | | |
| 3 | **55c** | H | Me | **s**, 29 [47:53] | **q**, 46 [51:49] | **u**, 36 | **v**, 49 [16:84] |
| 4 | **55d** | Cl | Me | **t**, 30 [51:49] | **r**, 51 [53:47] | | |
| 5 | **55a** | MeO | Et | **i**, 70 [46:54] | **i**, 29 [43:57] | | |
| 6 | **55b** | Me | Et | **j**, 68 [52:48] | **j**, 32 [51:49] | | |
| 7 | **55c** | H | Et | **k**, 67 [51:49] | **k**, 30 [54:46] | | |
| 8 | **55d** | Cl | Et | **l**, 66 [56:44] | **l**, 30 [54:46] | | |

[a] Data taken from ref 84. [b] Five equivalents of alkyl-lithium at 0 °C for 2 h. [c] One equivalent of sodium diethylmalonate at 50 °C for 2 h.[82] [d] Three equivalents of sodium diacetylmethane at 50 °C for 2 h.[82] [e] Normalized, 100% = % alkylation + % dimerization + % reduction + % **55**.

**Scheme 16**




**Scheme 17**

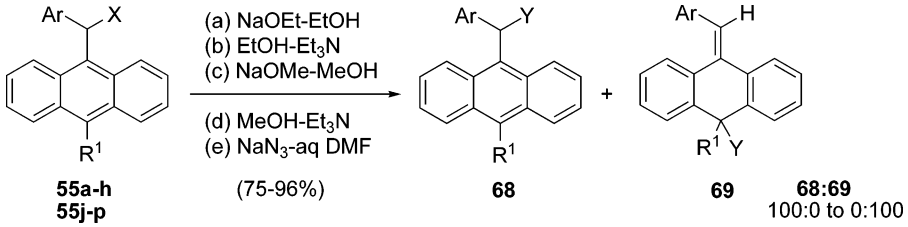



**Table 7. Distribution of Products in the Reaction of (9-Anthryl)arylmethyl Halides 55 with EtOH and NaOEt (Y = OEt)[a]**

| | | | | | | Nu = EtOH[b] | | Nu = NaOEt[c] | |
|---|---|---|---|---|---|---|---|---|---|
| entry | SM | Ar | $R^1$ | X | prod | yield (%) | ratio **68:69** | yield (%) | ratio **68:69** |
| 1 | **55a** | 4-MeO-$C_6H_4$ | H | Cl | **a** | 91 | 100:0 | 80 | 100:0 |
| 2 | **55b** | 4-Me-$C_6H_4$ | H | Cl | **b** | 95 | 49:51 | 82 | 54:46 |
| 3 | **55c** | $C_6H_5$ | H | Cl | **c** | 84 | 33:67 | 86 | 26:74 |
| 4 | **55d** | 4-Cl-$C_6H_4$ | H | Cl | **d** | 92 | 21:79 | 96 | 24:76 |
| 5 | **55e** | 3-Cl-$C_6H_4$ | H | Cl | **e** | 91 | 13:87 | 91 | 14:86 |
| 6 | **55f** | 4-Me-$C_6H_4$ | H | Br | **b** | 93 | 50:50 | 91 | 40:60 |
| 7 | **55g** | $C_6H_5$ | H | Br | **c** | | | 91 | 22:78 |
| 8 | **55h** | 4-Cl-$C_6H_4$ | H | Br | **d** | | | 94 | 22:78 |
| 9 | **55j** | 1-naphthyl | H | Cl | **f** | 86[d] | 12:82 | 92[d] | 9:91 |
| 10 | **55k** | 9-phenanthryl | H | Cl | **g** | 96[d] | 0:100 | 95[d] | 0:100 |
| 11 | **55l** | $C_6H_5$ | Me | Cl | **h** | 91 | 10:90 | 88 | 21:79 |
| 12 | **55m** | $C_6H_5$ | $C_6H_5$ | Cl | **i** | 93[d] | 100:0 | 90[d] | 100:0 |
| 13 | **55n** | 1-naphthyl | $C_6H_5$ | Cl | **j** | 89[d] | 100:0 | 91[d] | 100:0 |

[a] Data taken from ref 80. [b] Reaction performed in the presence of 3 equiv of triethylamine at 20 °C for 5−30 min. [c] Three equivalents of sodium ethoxide in ethanol at 20 °C for 5−30 min. [d] Data taken from ref 81.

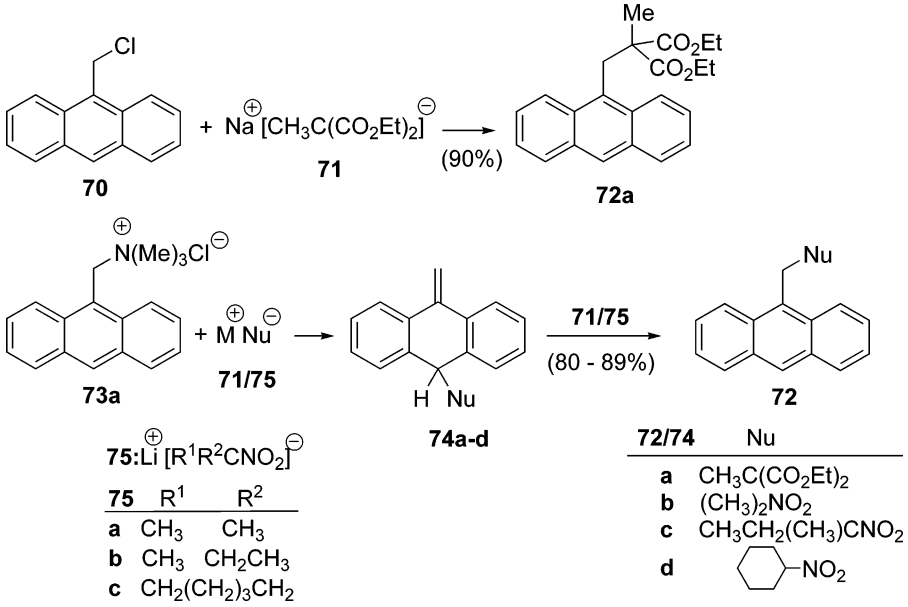
Nearly a decade later, Nojima et al. reported an additional application of substrates **73** for the preparation of 9,10-DHAs **74**. These type of compounds, unsubstituted at the methylene carbon, are generally unstable relative to the aromatized derivatives.[86] Considering that, compared to the benzylic substitution in **70**, the nucleophilic attack to the aromatic ring in **73** was a consequence of the bulkiness of the amino group and the poor leaving ability of triethylamine, the authors envisaged the synthesis of **74** through hydride reduction of salts **73**. The treatment of **73a−c** with LAH in diethyl ether gave predominantly 9-methylidene-9,10-dihydroanthracenes **74e−g** together with small amounts of 9-methylanthracenes **76** (Scheme 19).[87] In the reaction of salt **73c** ($R^1$ = *i*-Pr) with 3 equiv of LAH, two additional

**Table 8. Distribution of Products in the Reaction of (9-Anthryl)arylmethyl Halides 55 with MeOH, NaOMe, and $NaN_3$[a]**

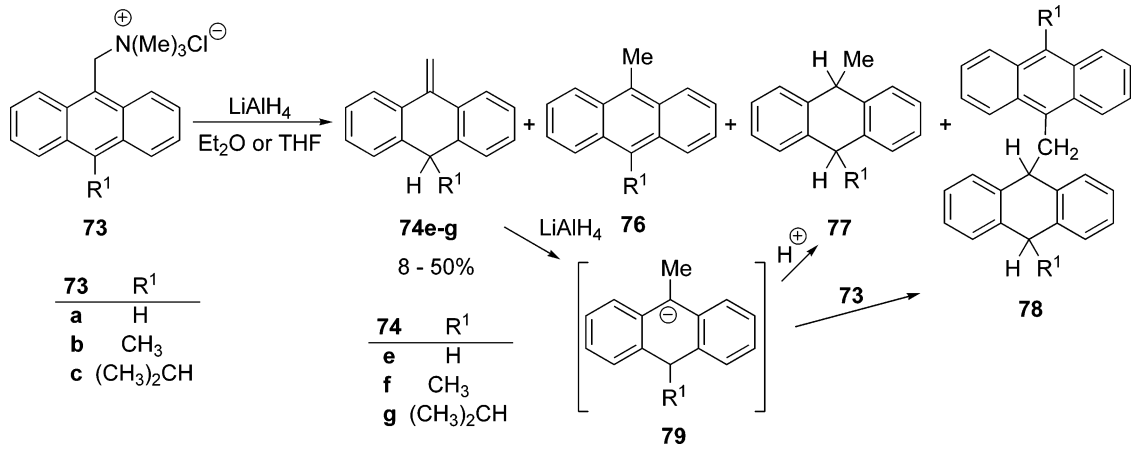
| | | | | | Nu = MeOH[b] (Y = OMe) | | Nu = NaOMe[c] (Y = OMe) | | Nu = $NaN_3$[d] (Y = $N_3$) | |
|---|---|---|---|---|---|---|---|---|---|---|
| entry | SM | Ar | $R^1$ | X | yield (%) | ratio **68**:**69** | yield (%) | ratio **68**:**69** | yield (%) | ratio **68**:**69** |
| 1 | **55a** | 4-MeO-$C_6H_4$ | H | Cl | | | | | 85[e] | **k**, 75:25 |
| 2 | **55b** | 4-Me-$C_6H_4$ | H | Cl | | | | | 75 | **l**, 37:63 |
| 3 | **55c** | $C_6H_5$ | H | Cl | | | | | 90 | **m**, 33:67 |
| 4 | **55d** | 4-Cl-$C_6H_4$ | H | Cl | | | | | 94 | **n**, 28:72 |
| 5 | **55e** | 3-Cl-$C_6H_4$ | H | Cl | | | | | 96 | **o**, 24:76 |
| 6 | **55f** | 4-Me-$C_6H_4$ | H | Br | | | | | 93[f] | **l**, 36:64 |
| 7 | **55g** | $C_6H_5$ | H | Br | | | 89 | **w**, 30:70 | 89 | **m**, 26:74 |
| 8 | **55h** | 4-Cl-$C_6H_4$ | H | Br | | | | | 91 | **n**, 26:74 |
| 9 | **55j** | 1-naphthyl | H | Cl | | | | | 85[g] | **p**, 28:72 |
| 10 | **55k** | 9-phenanthryl | H | Cl | | | | | 90[g] | **q**, 32:68 |
| 11 | **55l** | $C_6H_5$ | Me | Cl | 94 | 11:89 | 85 | **x**, 57:43 | 80 | **r**, 27:73 |
| 12 | **55m** | $C_6H_5$ | $C_6H_5$ | Cl | 95 | 100:0 | 95 | **y**, 100:0 | 85[g] | **s**, 65:35 |
| 13 | **55n** | 1-naphthyl | $C_6H_5$ | Cl | | | | | 89[g] | **t**, 54:46 |
| 14 | **55o** | 4-Me-$C_6H_4$ | $C_6H_5$ | Cl | | | | | 83 | **u**, 76:24 |
| 15 | **55p** | 4-Cl-$C_6H_4$ | $C_6H_5$ | Cl | | | | | 85 | **v**, 64:36 |

[a] Data taken from ref 80. [b] Reaction performed in the presence of 3 equiv of triethylamine at 20 °C for 5−30 min. [c] Ten equivalents of sodium methoxide in methanol at 20 °C for 5−30 min. [d] Three equivalents of sodium azide in aqueous DMF at 20 °C for 5−30 min. [e] In DMF: yield of 85%, ratio **68f**:**69f** of 68:32. [f] In DMF: yield of 94%, ratio **68g**:**69g** of 32:68. [g] Data taken from ref 81.

**Scheme 18**




**Scheme 19**




products, **77** and **78**, were obtained in yields of 17 and 14%, respectively (Table 9). When the reduction was performed in THF as solvent, the yield of these byproducts increased significantly. The formation of **77** and **78** was explained by assuming the participation of anionic species **79** resulting from the addition of hydride to **74** due to the increased

**Table 9. Distribution of Products in the Reaction of (9-Anthrylmethyl)trimethylammonium Chloride 73 with LAH[a,b]**

| entry | $R^1$ | prod | equiv of LAH | yield (%)[c] 74 | 76 | 77 | 78 |
|---|---|---|---|---|---|---|---|
| 1 | H | **a** | 1 | 48 (32) | 3 (6) | | 4 |
| 2 | H | **a** | 3 | (8) | 17 (5) | 38 | 25 |
| 3 | $CH_3$ | **b** | 1 | 48 (40) | 3 (7) | 8 | 14 |
| 4 | $CH_3$ | **b** | 3 | (44) | 8 (8) | 23 | 45 |
| 5 | *i*-Pr | **c** | 1 | 35 (33) | 2 (1) | 5 | 33 |
| 6 | *i*-Pr | **c** | 3 | (50) | 2 (10) | 12 (17) | 20 (14) |

[a] Reactions performed at 70 °C for 1 h. [b] Data taken from ref 87. [c] Yields given in parentheses correspond to reactions performed in diethyl ether at 35 °C for 5 h.

nucleophilicity of LAH in THF as compared with diethyl ether. Table 9 shows the distribution of products obtained in diethyl ether and THF as a function of the relative concentration of LAH.

## 3.3. Anthrylmethyl Hexachloroantimonates

The treatment of (9-anthryl)aryl hexacholoroantimonates **80** (Scheme 20) with a variety of nucleophiles afforded almost exclusively anthracene products derived from nucleophilic attack to the benzylic carbon. Only the reactions with hydride transfer agents ($LiAlH_4$, $NaBH_4$, and cycloheptatriene, CHT) and PhMgBr gave mixtures of anthracene derivatives **56**, **62**, and **68** and dearomatized products **57**, **63**, and **69** (Scheme 20; Tables 10 and 11).[80,82,88] Compound **80f** ($R^1$ = *i*-Pr; $R^2$ = H), having an isopropyl group at C10, was the exception (Table 11, entry 6). This chemical behavior is almost reversed in (9-anthryl)diphenylmethyl hexachloroantimonate **81**. In this case, crowding increase at the benzylic site prevents the approach of the nucleophiles, favoring the capture at the ring position. Depending on the nucleophile used, quinoidal products **84** are obtained exclusively or as a mixture with anthracenes **83** (Scheme 21; Table 10). However, the substitution of the hydrogen at the C10 position of **81** by a phenyl group, as in compound **82** (Scheme 22), inhibited the nucleophilic attack on that position. The reactions of **82** with $NaBH_4$, $LiAlH_4$, $NaN_3$, NaSPh, and KOH led to the selective formation of anthracene products **85** (Scheme 22; Table 10). Apparently, the reaction with NaOEt in ethanol was an exception. In this case only the quinoidal compound **86** was obtained (Table 10, entry 11).

The preference for nucleophilic attack in hexachloroantimonates strongly differs from that described for halides **55**. To explain such differences, it has been suggested that the former react through a tight ion pair, whereas the interaction with the salts, **80**−**82,** takes place on a free ion or a solvent-separated ion pair.

Additionally, the effect of the substituents at the C10 position is rationalized by the increase in the thermodynamic stability of the dearomatized products when the substituents at C10 become larger. Similar to the effect of crowding at the benzylic position, steric interactions of the substituents on the ring with the peri hydrogens destabilize the corresponding aromatized isomers. This high-stability hypothesis also explains the fact that in the reactions of $EtOH/Et_3N$, NaOEt/EtOH, and $NaN_3$ with **80a**−**f**, only **80f** bearing an isopropyl group at C10 afforded mixtures of anthracene products and dearomatized compounds (Scheme 20; entry 6 in Table 11).

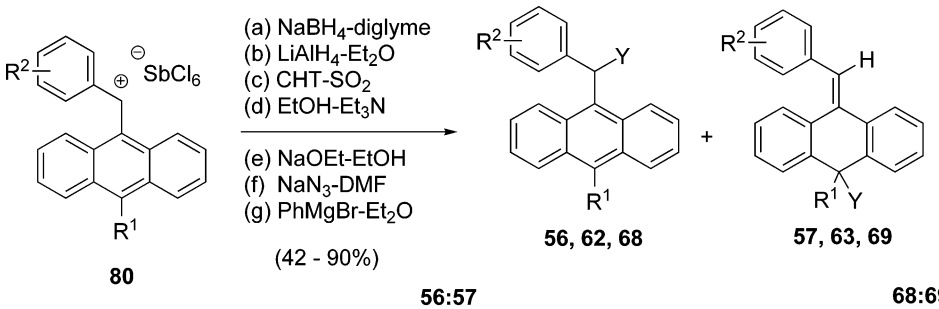
## 3.4. Chloromethylbenzenes and Chloromethylnaphthalenes

In sharp contrast to the limited scope of the alkylation processes previously mentioned, Yamamoto and co-workers devised a very efficient method for the allylative dearomatization of chloromethylbenzenes **87** and -naphthalenes **88** based on a different approach: transfer of the allyl group of allyltributylstannane in the presence of Pd(0) catalyst. The mild and neutral reaction conditions used allowed the isolation of the dearomatized products **89** and **90** without isomerization to the corresponding aromatized compounds (Scheme 23; Table 12).[89] For the ortho-, meta-, and para-methyl-substituted derivatives of **87** slightly longer reaction times were required in comparison with the unsubstituted system. As expected, allylation of the naphthalene ring of **88** occurred much more rapidly than for the phenyl system (Scheme 23). *p*-Bromobenzyl and *p*-methoxybenzyl chlorides afforded mixtures of doubly allylated products **89g** and **91a**, with the dearomatized compound being the major component of the mixture (Table 12, entries 7 and 8). Double and triple allylation of benzene derivatives containing two, **87i**, and three, **87j**, benzyl chloride groups, respectively, proceed smoothly as well (Scheme 23). In a similar way, allylic−benzylic coupling products were formed in these cases. In fact, **91b** was the major product of the reaction of **87i**, probably due to steric congestion. The mechanism proposed for the allylative dearomatization involves the oxidative coupling of the aryl chloride to the Pd(0) catalyst to give a Pd(II) complex, which is in equilibrium with the corresponding $\pi$-allyl derivative. The latter reacts with the allyltributylstannane, furnishing a bis-$\pi$-allylpalladium intermediate that upon reductive coupling yields the dearomatized product and Pd(0).

### *4. Aryl Ethers*

Not unexpectedly, nucleophilic addition to aryl ethers is practically unfeasible unless the ring charge density increase caused by the ether moiety is compensated by binding electron-withdrawing substituents to the aromatic system. Two representative examples of the activation of these aryl ethers toward nucleophilic attack are the complexation with electrophilic transition metal groups[13,90] and the incorporation of nitro groups into the ring (see section 14.1).[91] A particular dearomatization of an unactivated aryl ether was observed in the lithiation of **92** with *tert*-butyl-lithium (Scheme 24). The reaction afforded a mixture of the naphthyl derivatives **97** and **98** together with the ketone **99** resulting from the ring expansion of one of the fused phenyl rings of the naphthalene system (Scheme 24).[92] The formation of compounds **97**−**99** has been explained through the intermediate anion **93**, generated by lithium−bromine exchange. Protonation by the solvent produces debrominated ether **97**, an unwanted process probably favored by the relatively high temperature of the reaction. Transformation of anion **93** into **98** involves a proton exchange to the allyl-lithium species **94**, which then undergoes a [1,2]-Wittig rearrangement to the alkoxide **95** and subsequent hydrolysis. Alternatively, anion **94** may evolve via an α-elimination followed by carbene insertion into a carbon−carbon double bond of the naphthalene to give the dearomatized lithium enolate **96**. Ring expansion and double-bond migration, perhaps during hydrolysis, give rise to ketone **99**.

**Scheme 20**




| 80 | $R^2$ | $R^1$ |
|---|---|---|
| **a** | *p*-Me | H |
| **b** | H | H |
| **c** | *p*-Cl | H |
| **d** | *m*-Cl | H |
| **e** | H | Ph |
| **f** | H | *i*-Pr |

**56:57** 100:0 to 40:60

| 56/57 | $R^2$ | $R^1$ | Y |
|---|---|---|---|
| **b** | *p*-Me | H | H |
| **c** | H | H | H |
| **d** | *p*-Cl | H | H |
| **e** | *m*-Cl | H | H |
| **i** | H | Ph | H |
| **n** | H | *i*-Pr | H |

**62:63** 14:86

| 62/63 | $R^2$ | $R^1$ | Y |
|---|---|---|---|
| **o** | H | H | Ph |

**68:69** 100:0 to 27:73

| 68/69 | $R^2$ | $R^1$ | Y |
|---|---|---|---|
| **i** | H | Ph | OEt |
| **z** | H | *i*-Pr | OEt |
| **aa** | H | *i*-Pr | $N_3$ |

**Table 10. Distribution of Products in the Reaction of (9-Anthryl)benzylhexachloroantimonates 80b, 81, and 82 with Nucleophiles[a]**

| | | | SM **80b**[b] | | SM **81**[c] | | SM **82**[c] | |
|---|---|---|---|---|---|---|---|---|
| entry | nucleophile | solvent | yield (%) | ratio $S_N$:$S_N'$ | yield (%) | ratio **83**:**84** | yield (%) | ratio **85**:**86** |
| 1 | $LiAlH_4$ | $Et_2O$ | 62 | **56c**:**57c**, 60:40 | 77 | **a**, 67:33 | 90 | **a**, 100:0 |
| 2 | $NaBH_4$ | $Et_2O$ | 40 | **56c**:**57c**, 54:46 | 74[d] | **a**, 50:50 | 85 | **a**, 100:0 |
| 3 | CHT | $SO_2$ | 90 | **56c**:**57c**, 43:57 | 80 | **a**, 65:35 | | |
| 4 | $NaN_3$ | DMF | 60 | **68m**:**69m**, 100:0 | 70 | **b**, 88:12 | 70 | **b**, 100:0 |
| 5 | NaSCN | DMF | | | 80 | **c**, 88:12 | | |
| 6 | NaSPh | DMF | 37 | **68ab**:**69ab**, 100:0 | 70 | **d**, 30:70 | 70 | **c**, 100:0 |
| 7 | KOH | $H_2O$-dioxan | 80 | **68ac**:**69ac**, 100:0 | 92 | **e**, 0:100 | 80 | **d**, 100:0 |
| 8 | MeOH | MeOH | | | 70 | **f**, 0:100 | | |
| 9 | NaOMe | MeOH | 60 | **68w**:**69w**, 100:0 | 80 | **f**, 0:100 | | |
| 10 | EtOH | EtOH | 60 | **68i**:**69i**, 100:0 | 93 | **g**, 0:100 | | |
| 11 | NaOEt | EtOH | 96 | **68i**:**69i**, 100:0 | 80 | **g**, 0:100 | 95 | **e**, 0:100 |
| 12 | MeMgI | $Et_2O$ | | | 46 | **h**, 0:100 | | |
| 13 | PhMgBr | $Et_2O$ | 42 | **62o**:**63o**, 14:86 | 44 | **i**, 0:100 | | |

[a] Reactions performed at 20 °C for 5−120 min. [b] Data taken from ref 82. [c] Data taken from ref 88. [d] Reaction performed in tetrahydrofuran.

**Table 11. Distribution of Products in the Reaction of (9-Anthryl)arylmethyl Hexachloroantimonates 80 with Nucleophiles[a]**

| | | | | Nu = EtOH[b] | | Nu = NaOEt[c] | | Nu = $NaN_3$[d] | | $NaBH_4$/diglyme[e] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| entry | SM | Ar | $R^1$ | yield (%) | ratio **68**:**69** | yield (%) | ratio **68**:**69** | yield (%) | ratio **68**:**69** | yield (%) | ratio **56**:**57** |
| 1 | **80a** | 4-Me-$C_6H_4$ | H | 69 | **b**, 100:0 | 83 | 100:0 | 61 | **l**, 100:0 | 59 | **b**, 89:11 |
| 2 | **80b** | $C_6H_5$ | H | 60 | **c**, 100:0 | 95 | 100:0 | 60 | **m**, 100:0 | 73 | **c**, 80:20 |
| 3 | **80c** | 4-Cl-$C_6H_4$ | H | 76 | **d**, 100:0 | 85 | 100:0 | 65 | **n**, 100:0 | 80 | **d**, 65:35 |
| 4 | **80d** | 3-Cl-$C_6H_4$ | H | 69 | **e**, 100:0 | 69 | 100:0 | 59 | **o**, 100:0 | 82 | **e**, 73:27 |
| 5 | **80e** | $C_6H_5$ | $C_6H_5$ | 70 | **i**, 100:0 | 74 | 100:0[f] | 65 | **s**, 100:0 | 90 | **i**, 100:0 |
| 6 | **80f** | $C_6H_5$ | *i*-Pr | 70 | **z**, 31:69 | 73 | 27:73[f] | 86 | **aa**, 52:48 | 74 | **n**, 40:60 |

[a] Data taken from ref 80. [b] Reaction performed in the presence of 3 equiv of triethylamine at 20 °C for 5 min. [c] Three equivalents of sodium ethoxide in ethanol at 20 °C for 5 min. [d] Three equivalents of sodium azide in DMF at 20 °C for 5 min. [e] Reaction performed at 20 °C. [f] Almost the same ratio of methoxy derivatives was obtained in the reaction with 10 equiv of sodium methoxide in methanol at 20 °C.

It is interesting to note that compound **97** is an aryl allyl ether, a type of substrate that is known to react with Grignard reagents through addition of the nucleophile to the allylic carbon−carbon double bond and subsequent $\beta$-elimination leading to products derived from the cleavage of the ether linkage.[93]

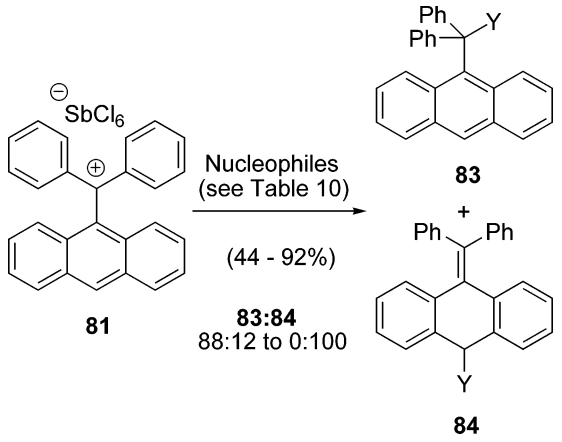
## 5. Aldehydes and Ketones

Two strategies have been used to simultaneously promote the attack of a nucleophile to the ring of aromatic aldehydes and ketones and prevent the competing [1,2] addition to the carbonyl linkage. The first strategy makes use of the increase of crowding around the CO group, whereas the second is based on the decrease of the aromatic stabilization through the use of larger conjugated $\pi$ systems.

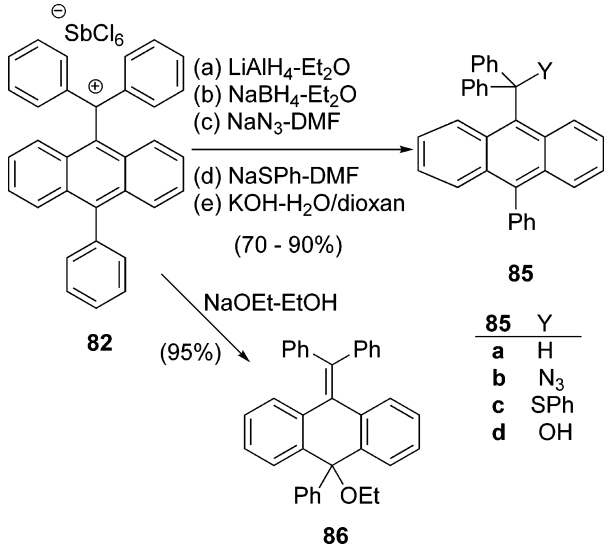
### 5.1. Hindered Carbonyl Functional Groups

Steric hindrance was soon recognized as a factor of prime importance to direct the attack of the incoming nucleophile to the aromatic nucleus. This idea has pervaded most of the subsequent nucleophilic dearomatization reactions described so far. Aromatic ketones afforded the earliest examples of dearomatizing reactions through nucleophilic addition.[25] As a note of historical interest, it is remarkable that the first conjugate addition of an organometallic to an aromatic nucleus was effected on a phenyl ring, normally the most

**Scheme 21**




**Scheme 22**




reluctant to participate in this type of reaction. Schmidlin and Wohl reported in 1910 the synthesis of what they thought to be pentaphenylethanol, through the addition of phenylmagnesium iodide to $\beta$-benzopinacolone **100** (Scheme 25).[94] However, the actual reaction product was dihydro ketone **101** arising from the [1,4] addition of the carbanion to the starting ketone, a discovery that passed unnoticed until Mosher and Huber reinvestigated the reaction 43 years later and gave convincing evidence of the structure assigned to **101** (among others, dehydrogenation of **101** with palladium on charcoal affords aromatized ketone **102**; Scheme 25).[95] A similar situation occurred in the series of condensed aromatic compounds. Thus, [1,2] addition of a phenyl Grignard reagent to 3-ethoxy-1-benzonaphthen-1-one described by Calderaro[96] in 1913 was corrected more than three decades later by Koelsch and Rosenwald.[97] They showed that the addition was of the [1,4] type, involving an aromatic ring. The true nature of the new conjugate reactions was first appreciated by Kohler and Nygaard in 1930, who demonstrated that, under forcing conditions, phenylmagnesium bromide undergoes addition in both [1,2] and [1,4] manner to tetraphenylpropenone **103**, yielding **104** (Scheme 25).[98] It is noticeable that again a phenyl ring has undergone dearomatization.

Fuson and co-workers were among the pioneers who contributed to generalize the strategy based on crowding around the carbonyl group of aromatic ketones as a method of promoting Michael addition reactions onto the aromatic ring. For instance, trityl-,[99] **105**, mesityl-,[100] **106**, and duryl-,[101] **107**, aryl ketones underwent conjugate addition to an aromatic nucleus upon treatment with Grignard reagents, giving rise to isolable dearomatized alkylated products **108**, **109**, and **110**, respectively (Scheme 26). Moreover, the treatment of phenyl duryl ketone **107** with benzyl- and *p*-chlorobenzylmagnesium chloride in diethyl ether at reflux afforded mixtures of di-**110** (diastereoselectivity and stereochemistry not given) and monobenzylated **111** compounds in low yields (Scheme 26). Careful exclusion of oxygen from the reaction was essential for preventing aromatization.[102] Another remarkable example is the formation of **113** by treating the *o*-alkoxy ketones **112** with benzylmagnesium chloride (Scheme 26). Benzylation occurred in a [1,6] manner, rather uncommon for Grignard reagents and was accompanied by the cleavage of the ether linkage. $S_NAr$ displacement of the alkoxy substituent to give **114** was observed to a very small extent (<7%).[103]

Fuson and co-workers also reported the first alkylation of aromatic ketones with *n*-BuLi (Scheme 26, bottom). [1,6] Adducts were obtained in the reaction with mesityl, phenyl, and naphthyl ketones.[104] A dihydro compound **117** was identified only for the naphthyl derivative **116**, albeit in very low yield (7%). The phenyl adducts underwent aromatization in the reaction medium. The [1,2] and [1,4] addition of aryllithiums to aryl ketones had been previously described; however, the attack of an alkyl-lithium in a [1,6] manner was unprecedented.[105] Grignard reagents that are hindered at the carbanionic center (*i*-PrMgBr, *t*-BuMgCl) also gave [1,6] aromatized addition products,[106] whereas *n*-BuMgBr failed to react.

The elaboration of the dearomatized compounds was limited to aromatization reactions, usually by heating in the presence of Pd/carbon (e.g., formation of **102**, **115**, and **118** in Schemes 25 and 26).

## 5.2. Bulky Lewis Acid Catalysts

Almost three decades later, Yamamoto and co-workers proposed a new strategy for promoting the regioselective conjugate addition of organolithiums to simple aromatic aldehydes and ketones **119**. The method is based on the use of a very bulky Lewis acid, aluminum tris(2,6-diphenylphenoxide) (ATPH), which, by coordinating to the carbonyl group, gives rise to a complex **120** that hinders the [1,2] nucleophilic attack and, at the same time, increases the electrophilicity of the aromatic ring.[107] The reaction of standard organolithiums RLi (R = *n*-Bu, *s*-Bu, *t*-Bu) with benzaldehyde **119a** and acetophenones **119b**,**c** gave dearomatized [1,6] addition products **121** and rearomatized derivatives **122**, together with small amounts of [1,2] adducts. Yields were very high (80−93%) except for the less hindered nucleophile, *n*-BuLi (~45%) (Scheme 27; Table 13).[108] These were the first reported examples of conjugate additions to an aromatic aldehyde. The ratio of dearomatized to rearomatized products **121**:**122** was found to be dependent on the solvent and quenching method used. The highest ratio was obtained when the complexation of the carbonyl compound with ATPH was carried out in toluene/THF (1:1 v/v) and the quench was done with concentrated HCl. In contrast, in $CH_2Cl_2$ as solvent, and using diluted HCl for quenching the reaction, compounds **122** are obtained almost exclusively (entries 4 and 13 in Table 13). The application of the same procedure to 1-acenaphthone **125a** produced high yields of dearomatized compounds **126** and/or **127**. However, the

**Scheme 23**

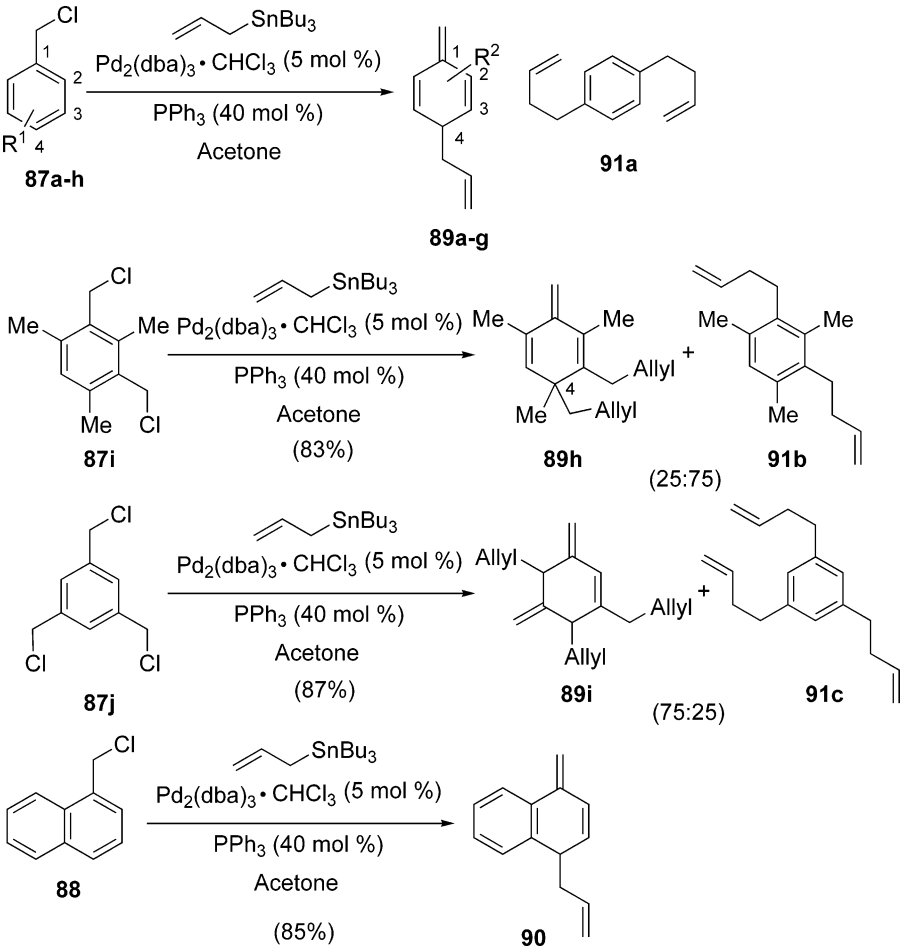



**Table 12. Products Obtained in the Dearomatization Reaction of Benzylic Chlorides 87 with Allyltributylstannane**[a]

| entry | 87 | $R^1$ | time (h) | products (ratio) | $R^2$ | yield (%) |
|---|---|---|---|---|---|---|
| 1 | **a** | H | 24 | **89a** | H | 80 |
| 2 | **b** | 2-Me | 32 | **89b** | 2-Me | 82 |
| 3 | **c** | 3-Me | 35 | **89c** | 3-Me | 80 |
| 4 | **d** | 4-Me | 37 | **89d** | 4-Me | 76 |
| 5 | **e** | 4-Ph | 60 | **89e** | 4-Ph | 71 |
| 6 | **f** | 4-*i*-Pr | 34 | **89f** | 4-*i*-Pr | 79 |
| 7 | **g** | 4-Br | 35 | **89g**:**91a** (83:17) | 4-Allyl | 82 |
| 8 | **h** | 4-MeO | 43 | **89g**:**91a** (89:11) | 4-Allyl | 85 |

[a] Data taken from ref 89.

regiochemistry varied as a function of the nucleophile used, from exclusive [1,6] addition for *t*-BuLi, **126** ($R^3$ = *t*-Bu), to exclusive [1,4] addition for MeLi, **127** ($R^3$ = Me). The intermediate enolates resulting from the conjugate addition step to **119b** and **125a** were also trapped with MeOTf, furnishing **124** and **128**, respectively.

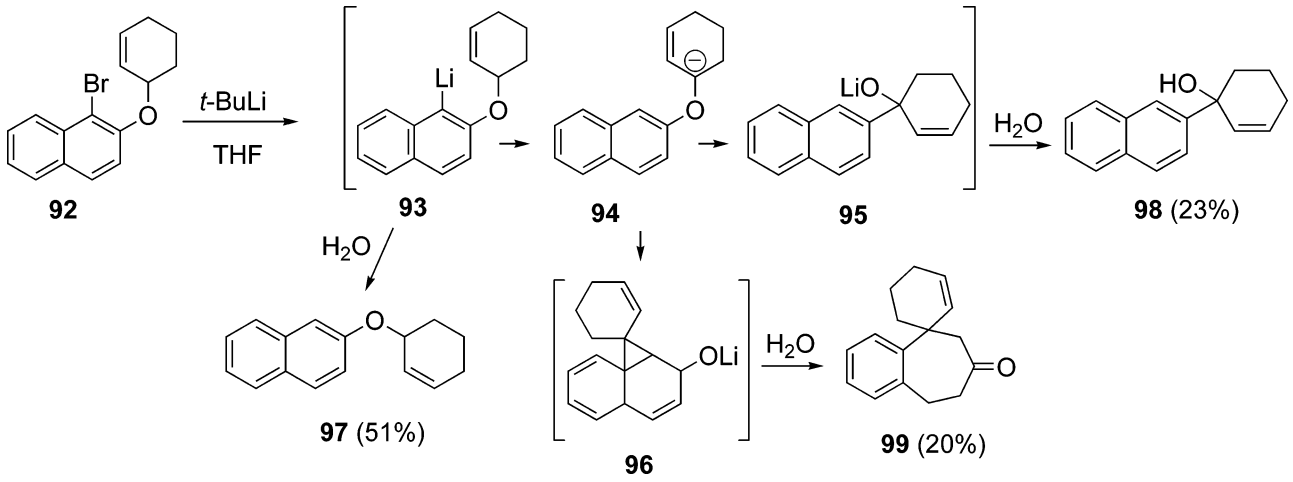
The method was successfully extended to nucleophiles such as lithium enolates[109] (Scheme 28) and silyl-lithium reagents (Scheme 29).[110] The results of the reactions of a series of ester enolates **129** with phenyl-, **119**, and naphthyl-, **125**, carbonyl compounds are collected in Table 14. The lithium enolate of isobutyrates **129a**,**b** showed total [1,6] selectivity with all aromatic aldehydes and ketones assayed. However, the reactions of benzaldehyde **119a** with propionate enolates **129c**−**h** gave mixtures of dearomatized products **130**, aromatized derivatives **131**, and [1,2] adducts **132**. The yield of byproducts **131**−**132** diminished with increasing bulkiness of the alkoxy moiety of the ester (entries 3−9, Table 14). Such steric effect was not operative in the reactions of acetate enolates **129i**,**j** with benzaldehyde **119a** and 1-naphthaldehyde **129b**, which afforded only products of [1,2] addition **132** and **134** (Table 14, entries 10 and 20). This limitation could be overcome by using the lithium enolate of α-trimethylsilylacetate **129m** as nucleophile. Treatment of the precomplexed salt of PhCHO and ATPH with lithium α-trimethylsilylacetate produced solely the [1,6] addition derivative in 54% yield (entry 14, Table 14). The silyl group was later removed with TBAF. Compounds **130** and **133** represent the first examples of the conjugate addition of lithium enolates to electron-deficient phenyl and naphthyl rings, respectively, due to the binding to a carbonyl functional group.

Phenyldimethylsilyl-lithium underwent selective [1,6] addition to benzaldehyde **119a** in the presence of ATPH to give **135** (Scheme 29).[110] However, the application of the same procedure to ketones **119b** ($R^1$ = Me), **119f** ($R^1$ = *i*-Pr), and **119g** ($R^1$ = *t*-Bu) resulted in the formation of mixtures of [1,6], **135**, [1,4] addition products **136**, and small amounts of silylated aromatized compounds **137**. Additionally, only products of [1,6] attack on **138** were observed in the reactions of lithiated silyl reagents with the precomplex of 1-acenaphthone **125a** and 1-naphthaldehyde **125b** with ATPH (Scheme 29).

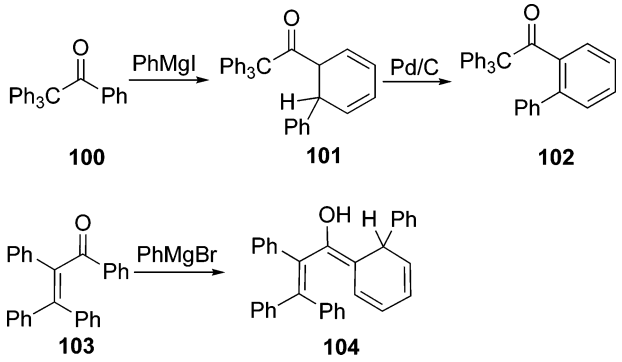
## 5.3. Polycyclic Compounds

Methods of nucleophilic conjugate addition to aromatic systems developed slowly throughout the first half of the past century, focusing mainly on polycyclic ketones. The

**Scheme 24**




**Scheme 25**




literature up to 1957 has been reviewed by Fuson.[25] Rio and Sillion provided some new examples of this chemistry. Treatment of 9-anthryl phenyl ketone **139** with benzylmagnesium chloride, either in the presence or in the absence of $PhCH_2Cl$, afforded a mixture of [1,6] adducts **140** and **141** resulting from the attack of the Grignard reagent to the anthracene and the phenyl ring, respectively (Scheme 30).[111] The preferred formation of **141** indicates that the electron deficiency is larger at the phenyl ring than at the anthracene system due to a greater conjugation with the CO linkage. Steric hindrance prevents the coplanarity of the carbonyl group with the anthracene ring, decreasing the efficiency of the delocalization. Introducing a cyano group at the C10 position of the anthracene ring of **139** produced a significant change in the reactivity toward $PhCH_2MgCl$. In the reaction of $PhCH_2MgCl$ with **142** in the absence of $PhCH_2Cl$ and subsequent hydrolysis, the starting substrate was recovered together with anthraquinone and small quantities of the 9,10-DHA derivative **144**. This product originated from the reduction of the anthracene ring of **142** via intermediate **143** and was also obtained when **142** was treated with *i*-PrMgBr and *t*-BuMgCl (Scheme 30). Consistent with the participation of **143** in the process, when the reaction is performed in the presence of benzyl chloride or quenched with 4-Cl-$C_6H_4$-$CH_2Cl$, dearomatized products **145a**,**b** are respectively isolated.

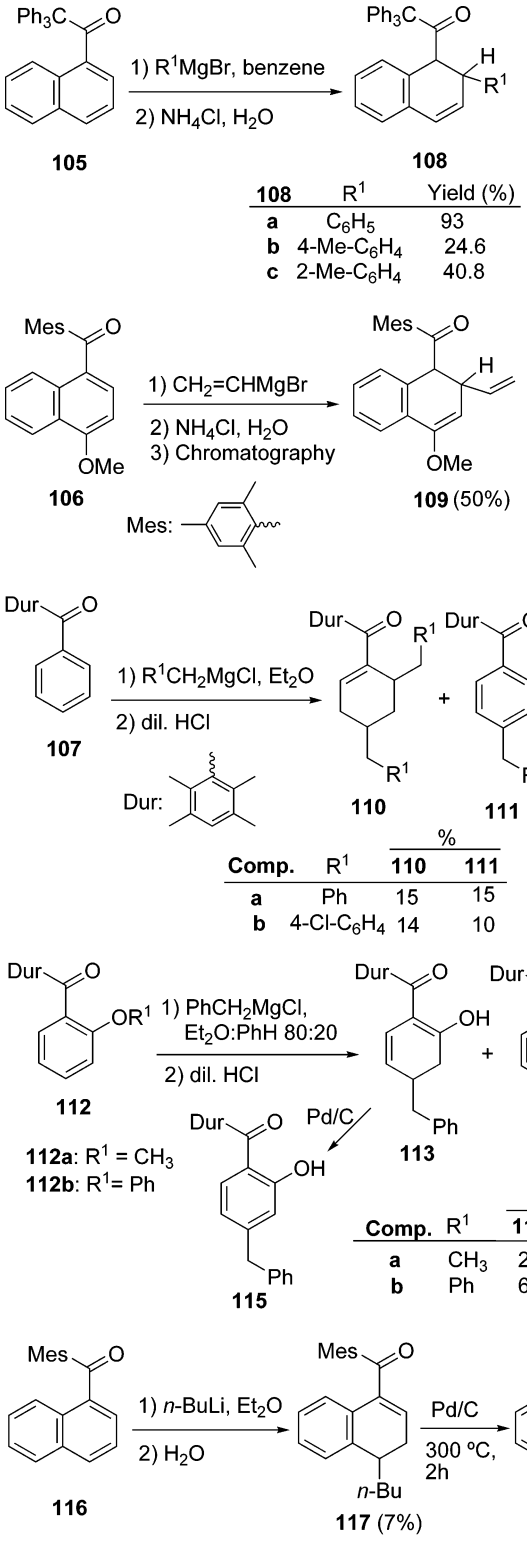
Cava and Lee investigated the reactivity of some 7,12-dihydropleidenes toward Grignard reagents. They observed the formation of products resulting from [1,4] conjugate addition to an aromatic ring, which underwent oxidation during workup and chromatographic purification to give aromatized derivatives. Only in the reaction of 1-methyl-7,12-dihydropleidene-7-one **146** with PhMgBr was a very small amount (2%) of a dearomatized compound **149** isolated, together with the products of [1,4], **147**, and [1,2] addition, **148** (Scheme 31).[112] Compound **149** was converted into 7,12-dihydropleidenone **147** by oxidation with chloranil.

## 6. Imines

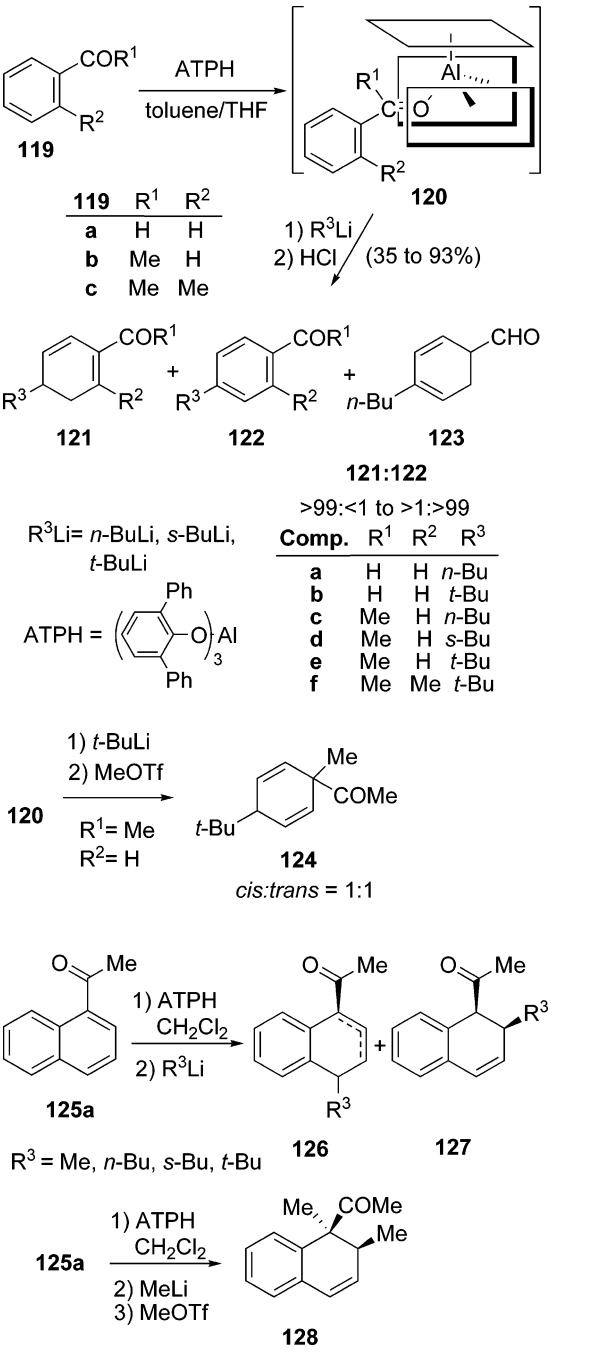
Arylimines were also among the first substrates for which conjugate addition to an aromatic ring was reported. Gilman et al. showed that the product of the reaction between phenylisocyanate **150** and an excess of phenylmagnesium bromide (6 equiv), under forcing conditions (refluxing toluene/diethyl ether), was *o*-phenylbenzohydrylaniline **154**. Its formation implied the participation of an intermediate species **153** derived from the [1,4] addition of the Grignard reagent to the phenyl group of the imine **152** (Scheme 32).[113] Although some qualitative proofs indicated that the dearomatized precursor **153** was stable in solution, the compound was not isolated. Gilman attributed to steric hindrance the reason for this new reaction mode, alternative to the expected [1,2] addition to the C═N linkage.

Since this pioneering work, more than half a century elapsed until arylimines received renewed interest as targets for nucleophilic conjugate addition. In the late 1980s, A. I. Meyers extended to naphthylimines his highly efficient oxazoline-substituted naphthalene methodology for preparing functionalized dihydronaphthalenes (vide infra). As a result, it was found that the addition of organolithiums RLi (R = *n*-Bu, *s*-Bu, *t*-Bu, *i*-Pr, $PhCH_2$, $CH_3C{=}CH_2$) to the imine of 1-naphthaldehyde and cyclohexylamine **155a** at −78 °C in THF proceeded in a [1,4] manner in high yields to give, after acid hydrolysis, cis-1,2-disubstituted dihydronaphthalenes **156** (Scheme 32). For methyl lithium, it was necessary to use HMPA as cosolvent and to increase the temperature of the reaction to −10 °C, to obtain an acceptable yield of the [1,4] adduct (Table 15); otherwise, only [1,2] addition was observed.[114] Aldehydes **156** were converted into alcohols **157** by reduction with $NaBH_4$. Trans derivatives **160** and **161** were obtained in a similar manner except that the quench of the intermediate lithium adduct was carried out with isopropanol. The lithium isopropoxide generated in the reaction medium is responsible for the epimerization of **158**. The asymmetric version of the process was attained by using chiral imine **155b** derived from 1-naphthaldehyde and (*S*)-*O*-*tert*-butyl valinol (Scheme 32). In this case, good yields and high enantiomeric excesses of dearomatized compounds

**Scheme 26**




**Scheme 27**




**160** were obtained only for *i*-PrLi, *n*-BuLi, and *t*-BuLi. Methyl-lithium, 2-propenyl-lithium, and benzyl-lithium gave exclusively addition to the C═N (Table 15).[115]

In later work it was shown that organomagnesium reagents ($R^4MgX$, where $R^4$ = Me, Et, *i*-Pr, vinyl, Ph) underwent reaction with 3-methoxynaphthalen-2-yl imines **162** also via [1,4] nucleophilic addition.[116] The intermediate aza-enolates were trapped with MeI and subsequently hydrolyzed to give aldehydes **163** (Scheme 33). Interestingly, no substitution of the methoxy group was observed. The tandem addition reactions proceeded in moderate yields (from 12 to 65%, Table 16) due to competing [1,2] addition of the Grignard to the imino group. Increasing the bulkiness of the 2-alkyl substituent of the 1,2-aminoalcohol present in imines **162a**−**g** produced lower yields of aldehydes **163**. [1,2] addition became the exclusive process observed in the case of the reaction of *tert*-leucinol imine **162e** ($R^2$ = *t*-Bu; $R^3$ = H, *n* = 1) with *i*-PrMgCl. The reaction of EtMgBr, *i*-PrMgCl, and PhMgBr with imine **162c** ($R^2$ = H; $R^3$ = Ph, *n* = 1) containing the chiral auxiliary (*R*)-phenylglycinol afforded aldehydes **163b,c,e** in 33−56% yield with enantiomeric excesses ranging from 82 to 95% (Table 16, entries 7−9). The hydroxy group of imines **162** may not be essential for the conjugate addition to occur but contributes to increase the rate of the addition. Treatment of imine **162h** ($R^1$ = $C_6H_{11}$) not bearing appended OH with 2 equiv of *i*-PrMgCl at 0 °C and subsequent addition of MeI gave aldehyde **163c**

**Table 13. Conjugate Alkylation of 119 with Organolithium Reagents**[a]

| entry | $R^1$ | $R^2$ | $R^3$ | solvent (time, h) | yield (%) | ratio **121**:**122** |
|---|---|---|---|---|---|---|
| 1 | H | H | *n*-Bu | toluene/THF (2) | 47 | 99:1[b,c] |
| 2 | H | H | *t*-Bu | toluene/THF (3) | 81 | 99:1[b] |
| 3 | H | H | *t*-Bu | toluene/THF (3.5) | 69 | 10:90[d] |
| 4 | H | H | *t*-Bu | $CH_2Cl_2$ (5) | 49 | 1:99[e] |
| 5 | Me | H | *n*-Bu | toluene/THF (7) | 45 | 99:1[b] |
| 6 | Me | H | *n*-Bu | toluene/THF (7.5) | 41 | 73:27[e] |
| 7 | Me | H | *s*-Bu | toluene/THF (1.5) | 80 | 99:1[b] |
| 8 | Me | H | *t*-Bu | toluene/THF (0.5) | 74 | 91:9[d] |
| 9 | Me | H | *t*-Bu | toluene/THF (3) | 93 | 99:1[b] |
| 10 | Me | H | *t*-Bu | toluene/THF (7.5) | 92 | 74:26[e] |
| 11 | Me | H | *t*-Bu | toluene/$Et_2O$ (3) | 74 | 88:12[b] |
| 12 | Me | H | *t*-Bu | toluene/$Me_2O$ (4) | 35 | 54:46[e] |
| 13 | Me | H | *t*-Bu | $CH_2Cl_2$ (2.5) | 43 | 1:99[e] |
| 14 | Me | H | *t*-Bu | $CH_2Cl_2$ (12) | 71 | 53:47[b] |
| 15 | Me | Me | *t*-Bu | toluene/THF (12) | 89 | 99:1[b] |

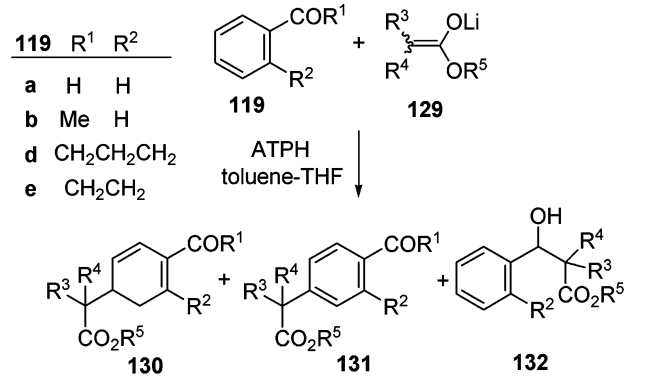
[a] Conditions: ATPH (1.5 equiv) and organolithium (2 equiv) at −78 °C. Data taken from ref 108. [b] Workup with concentrated HCl. [c] Compound **123** was also obtained in a yield of 13%. [d] Workup with AcOH. [e] Workup with 1 N HCl.

in 39% yield (Table 16, entry 12). The yield of **163c** increased to 65% when a 3-fold excess of Grignard was used and the temperature was raised to 25 °C. The aza-enolate resulting from the addition of *i*-PrMgCl to imine **162f** ($R^2$ = H; $R^3$ = H, $n$ = 2) was quenched also with methyl chloroformate. Acid hydrolysis of the adduct afforded aldehyde **164** subsequently deformylated with KCN in refluxing methanol yielding ester **165**. Dihydronaphthyl derivative **165** represents the formal chemoselective addition of *i*-PrMgCl or *i*-PrLi to the naphthalene nucleus of 3-methoxy-2-carbomethoxynaphthalene, a process normally not possible because of the preferred attack of the organometallic reagents on the ester moiety. Further elaboration of **165** allowed the synthesis of chiral 3,4-dialkyl-disubstituted 2-tetralones **166** (Scheme 33).

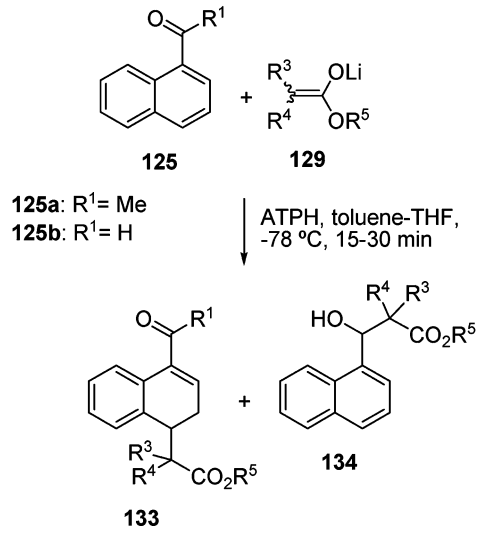
Tomioka et al. investigated the addition of a series of organolithium reagents (MeLi, *n*-BuLi, *t*-BuLi, PhLi) to naphthyl imines using $C_2$ symmetric chiral diether ligands as catalysts for asymmetric induction. They found that ligands **167** promoted the conjugate addition of RLi to *N*-cyclohexyl-[117,118] **155a** and *N*-(1-adamantyl)[119] imine **155c** of 1-naphthaldehyde and to control the stereochemical course of the reaction (Scheme 34; Table 17). Acid hydrolysis of the aza-enolate afforded dihydronaphthyl aldehydes **170**, subsequently reduced to alcohols **171** with $NaBH_4$ (Scheme 34). Yields and enantiomeric excesses varied in a wide range (Table 17, entries 1, 3, 5, and 7), with the best results obtained for the bulkiest 1,2-diethers (*R*,*R*)-**167d**,**e** (Table 17, entries 7−10). Other structurally related $C_2$ chiral ligands **168** and **169** proved to be much less efficient (Table 17, entries 11 and 12). The sense of the asymmetric induction implies that the organolithium attacks the top face of the imine. The preference for this attack was rationalized on the basis of a mixed aggregate formed by complexation of the organolithium with the imine and the chiral ligand.

The regioselectivity of the addition step was dependent on the nature of the imine. In sharp contrast to *N*-alkyl imines **155a**,**c**, the reaction of *N*-aryl imines of 1-naphthaldehyde with alkyl- and aryl-lithiums resulted in the nearly exclusive [1,2] addition to the C=N bond. The same trend was observed when the reaction was performed in THF in the absence of chiral auxiliaries.[120] Interestingly, in the case of alkyl and aryl imines of 1-fluoronaphthalene-2-carbaldehyde,

**Scheme 28**




| 129 | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|
| **a** | Me | Me | Me |
| **b** | Me | Me | (+)-menthyl |
| **c** | H | Me | Me |
| **d** | H | Me | Et |
| **e** | H | Me | *i*-Pr |
| **f** | H | Me | *i*-Pr |
| **g** | H | Me | Cy |
| **h** | H | Me | $CPh_3$ |
| **i** | H | H | Me |
| **j** | H | H | *t*-Bu |
| **k** | H | Et | Me |
| **l** | H | *t*-Bu | Me |
| **m** | H | $Me_3Si$ | OEt |




$S_NAr$ products derived from [1,4] addition were exclusively obtained.[121] MP3 and ab initio (HF/STO-3G, HF/3-21G) calculations showed a direct correlation between the relative magnitude of the LUMO coefficients and the N-substituent dependence of the observed regioselectivity. For *N*-alkyl imines, the coefficient is larger at the 4-position than at the 2-position, whereas for *N*-aryl derivatives both coefficients are either of similar size or the 2-position coefficient is larger than the 4-position one.[120,122] In this context, it is worth mentioning the reaction of some cyclic arylketimines **172** with *tert*-butyl-lithium, where a variety of alkylated and oxidized dearomatized byproducts **173**−**175** were isolated, and whose formation was consistent with the participation of SET processes (Scheme 35).[123]

**Scheme 29**

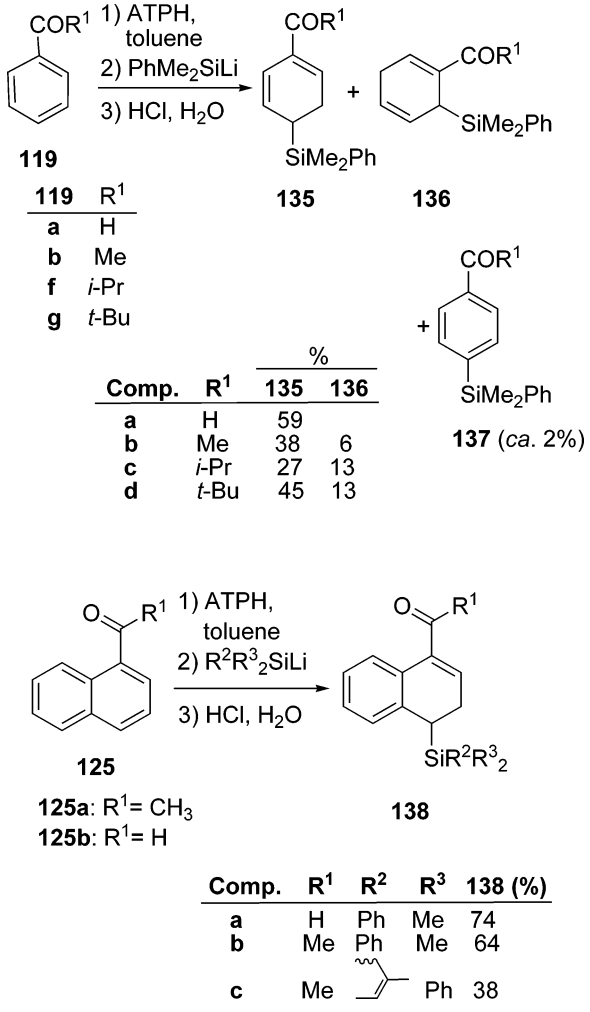



**Table 14. Product Composition (in Percent) in the Reactions of Lithium Ester Enolates 129 with Aromatic Carbonyl Compounds 119 and 125[a]**

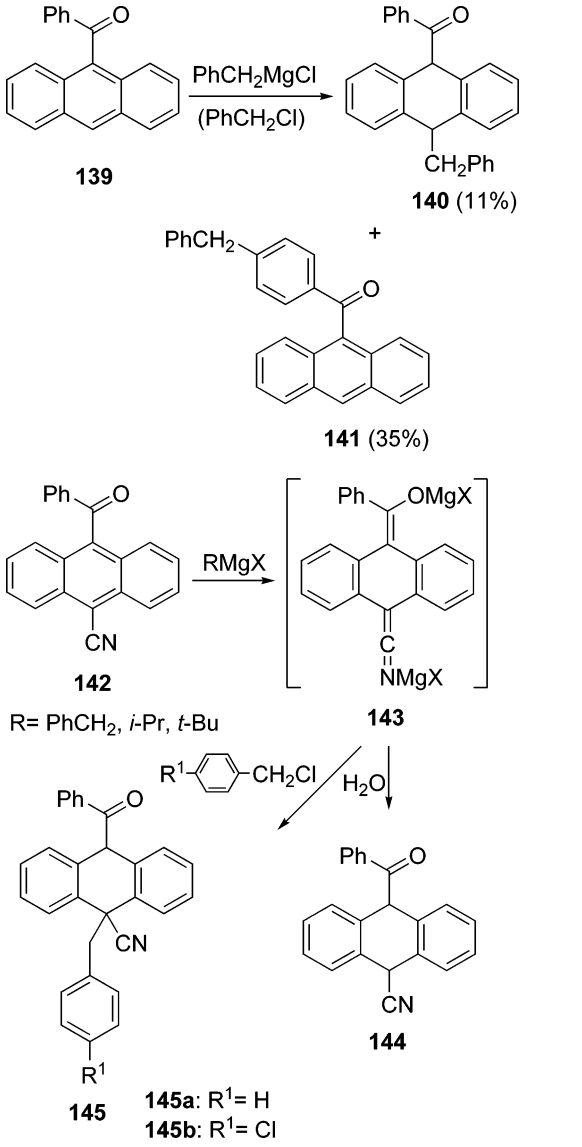
| entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | **130** | **131** | **132** | **133** | **134** |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | Me | Me | Me | 77 | | | | |
| 2 | H | H | Me | Me | (+)-menthyl | 77[b] | | | | |
| 3 | H | H | H | Me | Me | 23 | 19 | 57 | | |
| 4 | H | H | H | Me | Et | 20 | 20 | 40 | | |
| 5 | H | H | H | Me | *i*-Bu | 45 | 15 | 33 | | |
| 6 | H | H | H | Me | *i*-Pr | 61 | 7 | 27 | | |
| 7 | H | H | H | Me | Cy | 58 | 12 | 22 | | |
| 8 | H | H | H | Me | *t*-Bu | 83 | 3 | 13 | | |
| 9 | H | H | H | Me | $CPh_3$ | 81 | 3 | 9 | | |
| 10 | H | H | H | H | Me | | | 99 | | |
| 11 | H | H | H | H | *t*-Bu | | | 98 | | |
| 12 | H | H | H | Et | Me | 16 | 15 | 51 | | |
| 13 | H | H | H | *t*-Bu | Me | 30 | 8 | 3 | | |
| 14 | H | H | H | $Me_3Si$ | Et | 54 | | | | |
| 15 | Me | H | Me | Me | Me | 88 | | | | |
| 16 | $CH_2CH_2CH_2$ | | Me | Me | Me | 94 | | | | |
| 17 | $CH_2CH_2$ | | Me | Me | Me | 90 | | | | |
| 18 | H | | Me | Me | Me | | | | 78 | |
| 19 | H | | H | Me | Me | | | | 85[c] | |
| 20 | H | | H | H | Me | | | | | 90 |
| 21 | Me | | Me | Me | Me | | | | 82 | |

[a] Stoichiometry **119**/**125**:ATPH:**129** of 1:1.5:2. Data taken from ref 109. [b] de = 3%. [c] Diastereomeric ratio = 1:1.

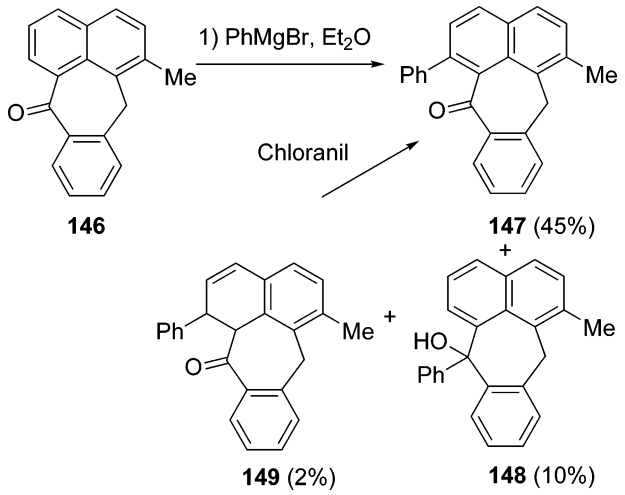
## 7. Carboxylic Acids

There are merely two studies showing the feasibility of conjugate addition to an aromatic nucleus activated by an unprotected carboxylic acid functional group. Alkylation of

**Scheme 30**




**Scheme 31**




1-naphthoic acid **176** with 2.2 equiv of *n*-BuLi or *s*-BuLi, followed by electrophilic quench (MeI, EtI, $Me_2S_2$), gave rise to dihydronaphthalene derivates **179** in good yields (Scheme 36; Table 18).[124] 2-Naphthoic acid **177** underwent reaction in a similar manner to give 1,2,2-trisubstituted 1,2-

**Scheme 32**

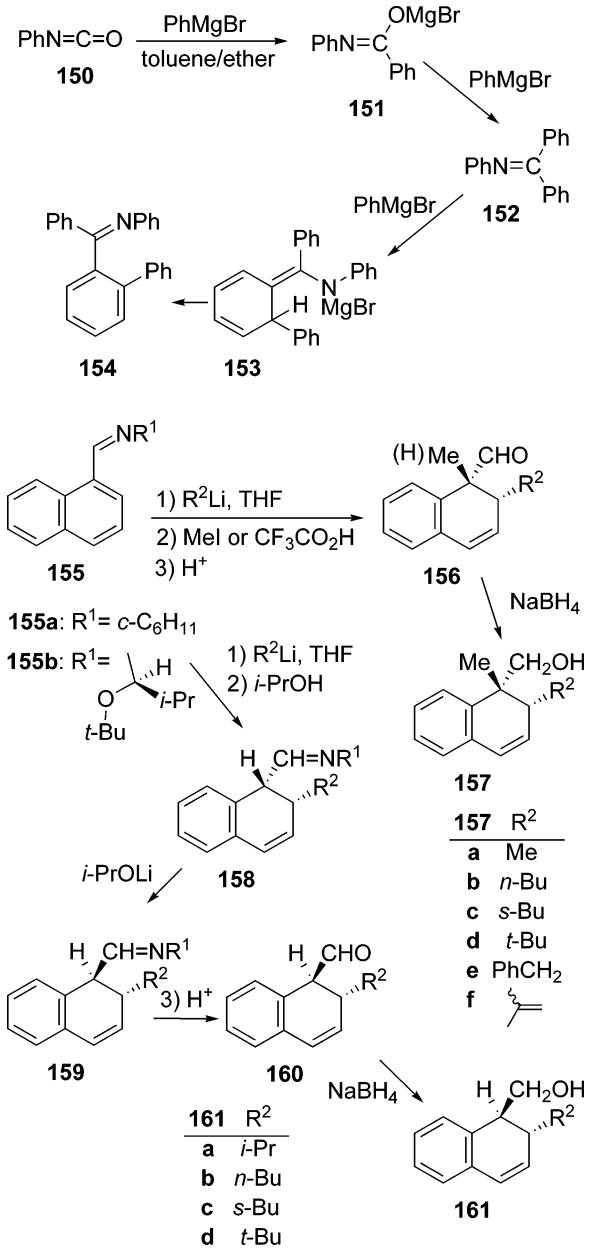



**Table 15. Addition of Organolithium to Naphthylimines 155[a]**

| | | | 157 | | 161 | |
|---|---|---|---|---|---|---|
| entry | SM | $R^2Li$ | $R^2$ | yield (%) [ee][e] | $R^2$ | yield (%) [ee][e] |
| 1 | **155a** | MeLi[b] | Me | 60 | | |
| 2 | **155a** | *i*-PrLi | | | *i*-Pr | 89 |
| 3 | **155a** | *n*-BuLi | *n*-Bu | 87 | *n*-Bu | 81 |
| 4 | **155a** | *s*-Bu | *s*-Bu | 86 | *s*-Bu | 78 |
| 5 | **155a** | *t*-BuLi | *t*-Bu[c] | 87 | *t*-Bu | 91 |
| 6 | **155a** | $PhCH_2Li$ | $PhCH_2$ | 55 | | |
| 7 | **155a** |  |  | 80 | | |
| 8 | **155b**[d] | *i*-PrLi | | | *i*-Pr | 78 [95] |
| 9 | **155b**[d] | *n*-BuLi | *n*-Bu | 85 [95] | *n*-Bu | 78 [95] |
| 10 | **155b**[d] | *t*-Bu | *t*-Bu | 75 [95] | *t*-Bu | 85 [95] |

[a] Data taken from ref 114. [b] Reaction performed in the presence of 2.5 equiv of HMPA. [c] Acid hydrolysis to give aldehyde **156** took 8−10 days at 25 °C. [d] Data taken from ref 115. [e] Determined using Mosher ester.

dihydronaphthalenes **181**. [1,2] addition was minimal at −78 °C (5−12%, entries 1−7). The yield of ketone byproduct **182** increased at higher temperatures (entry 8). In all

**Scheme 33**

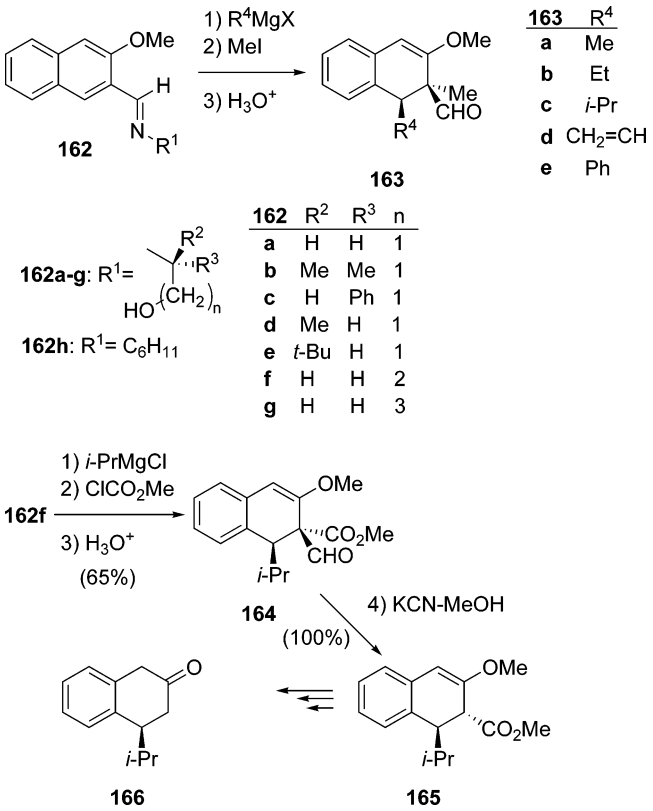



**Table 16. Addition of Organomagnesium to Naphthylimines 162[a]**

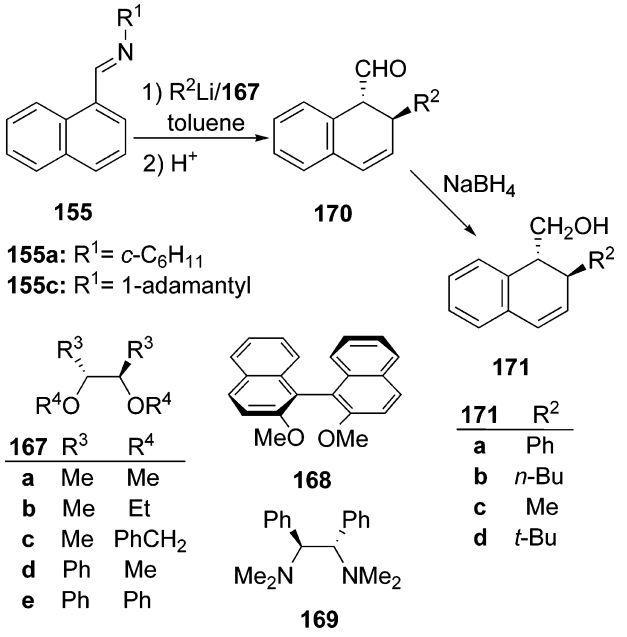
| entry | SM | product | $R^4$ | yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | **162a** | **163a** | Me | 20 | |
| 2 | **162a** | **163b** | Et | 52 | |
| 3 | **162a** | **163c** | *i*-Pr | 63 | |
| 4 | **162a** | **163d** | $CH_2$=CH | 65 | |
| 5 | **162a** | **163e** | Ph | 57 | |
| 6 | **162b** | **163c** | *i*-Pr | 12 | |
| 7 | **162c** | **163b** | Et | 56 | 82 |
| 8 | **162c** | **163c** | *i*-Pr | 33 | 95 |
| 9 | **162c** | **163e** | Ph | 40 | 92 |
| 10 | **162f** | **163c** | *i*-Pr | 27 | |
| 11 | **162g** | **163c** | *i*-Pr | 44 | |
| 12 | **162h** | **163c** | *i*-Pr | 39 | |

[a] Reactions performed at 0 °C. Data taken from ref 116.

cases, cis-1,2-disubstituted dihydronaphthalenes were obtained. However, for *s*-BuLi two diastereoisomers were formed, differing in the configuration of the stereogenic center of the branched alkyl chain. The temperature of the quenching step had a negligible effect on the diastereoselectivity, and the use of additives such as HMPA and TMEDA did not affect the efficiency of the reaction. Apparently, carboxylate is a much better ligand for the organolithiums than these coordinating agents. Methyl- and phenyl-lithium failed to undergo reaction with **176** and **177**, and the use of hexachloroethane as quenching agent afforded aromatized products **183** and **184**, respectively (Scheme 36).

The dearomatized lithium enolate arising from the addition of *s*-BuLi to the naphthoic acids **176** and **177** was trapped with trifluoroacetic acid, rendering lower regio- and/or stereoselectivity. The alkylation−protonation of **176** leads to a mixture of diastereoisomeric 1,2-disubstituted dihydronaphthalenes **185**−**186**, derived from pairs of cis and trans epimers at the stereogenic center of the *s*-butyl substitutent.

**Scheme 34**




| 167 | $R^3$ | $R^4$ |
|---|---|---|
| **a** | Me | Me |
| **b** | Me | Et |
| **c** | Me | $PhCH_2$ |
| **d** | Ph | Me |
| **e** | Ph | Ph |

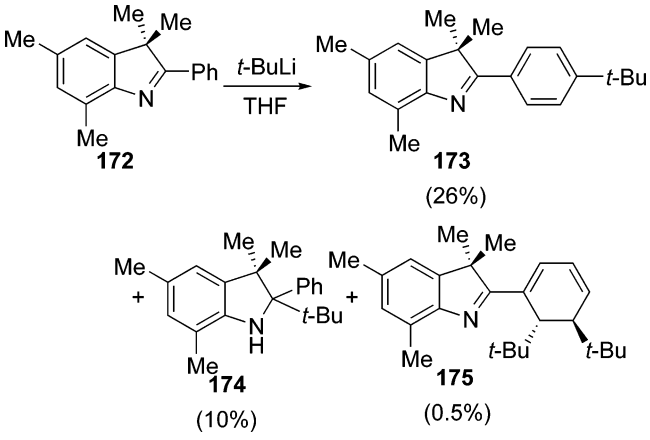
| 171 | $R^2$ |
|---|---|
| **a** | Ph |
| **b** | *n*-Bu |
| **c** | Me |
| **d** | *t*-Bu |

**Table 17. Addition of Organolithium to Naphthylimines 155a,c in the Presence of Chiral $C_2$ Symmetric Ligands**[a]

| entry | 155 | chiral ligand | temp (°C) | time (h) | $R^2$ | [1,4] adduct product | yield (%) | ee (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **a** | (*S*,*S*)-**167a** | −45 | 13 | Ph | (*1S*,*2R*)-**171a** | 68 | 90 |
| 2 | **a** | (*R*,*R*)-**167a** | −78 | 2 | *n*-Bu | (*1R*,*2S*)-**171b** | 92 | 53 |
| 3 | **a** | (*S*,*S*)-**167b** | −45 | 15 | Ph | (*1S*,*2R*)-**171a** | 64 | 33 |
| 4 | **a** | (*S*,*S*)-**167b** | −78 | 5 | *n*-Bu | (*1S*,*2R*)-**171b** | 83 | 28 |
| 5 | **a** | (*S*,*S*)-**167c** | −45 | 12 | Ph | (*1S*,*2R*)-**171a** | 26 | 20 |
| 6 | **a** | (*S*,*S*)-**167c** | −78 | 2 | *n*-Bu | (*1R*,*2S*)-**171b** | 89 | 15 |
| 7 | **a** | (*R*,*R*)-**167d** | −45 | 13 | Ph | (*1R*,*2S*)-**171a** | 82 | 94 |
| 8 | **a** | (*R*,*R*)-**167d** | −78 | 6 | *n*-Bu | (*1R*,*2S*)-**171b** | 80 | 91 |
| 9 | **a** | (*R*,*R*)-**167e** | −45 | 13 | Ph | (*1R*,*2S*)-**171a** | 82[b] | 94 |
| 10 | **a** | (*R*,*R*)-**167e** | −78 | 6 | *n*-Bu | (*1R*,*2S*)-**171b** | 80[b] | 91 |
| 11 | **a** | (*S*)-**168** | −78 | 7 | *n*-Bu | (*1R*,*2S*)-**171b** | 46 | 6 |
| 12 | **a** | (*S*,*S*)-**169**[c] | −78 | 4 | *n*-Bu | (*1S*,*2R*)-**171b** | 26 | 11 |
| 13 | **c** | (*S*,*S*)-**167a** | −45 | 16 | Ph | (*1S*,*2R*)-**171a** | 80 | 92 |
| 14 | **c** | (*R*,*R*)-**167d** | −45 | 22 | Ph | (*1R*,*2S*)-**171a** | 76 | 95 |
| 15 | **a** | (*R*,*R*)-**167d** | −23 | 20 | Me | (*1R*,*2R*)-**171c** | 19[d] | 64 |
| 16 | **a** | (*R*,*R*)-**167d** | −78 | 1 | *t*-Bu | (*1R*,*2S*)-**171d** | 79 | 59 |
| 17 | **a** | none | −78 | 3 | *n*-Bu | **171b** | 22 | |

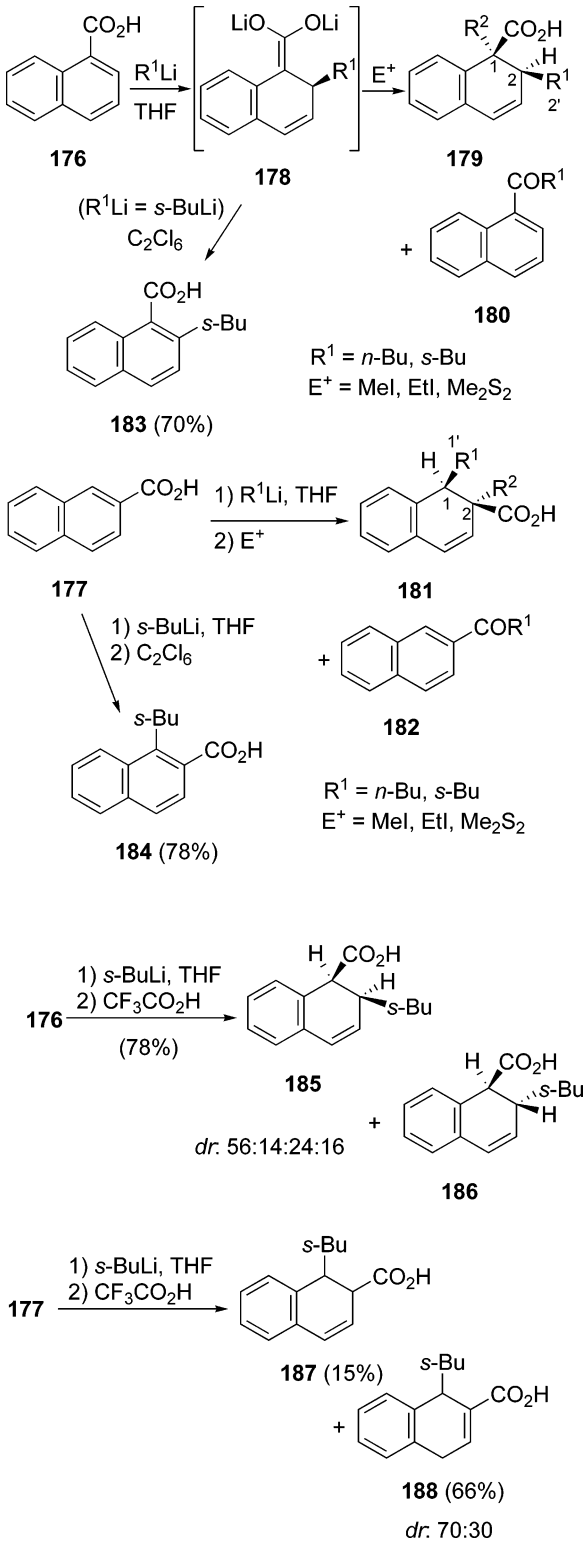
[a] Data taken from ref 119. [b] Data taken from ref 117. [c] In diethyl ether. [d] Forty-nine percent of the 1,2-adduct was also obtained.

**Scheme 35**




When 2-naphthalenecarboxylic acid **177** was used as starting material, products of α, **187**, and γ protonation, **188**, with respect to the $CO_2H$ group were obtained (Scheme 36).[125]

**Scheme 36**




## 8. Carboxylic Esters

### 8.1. Hindered Esters

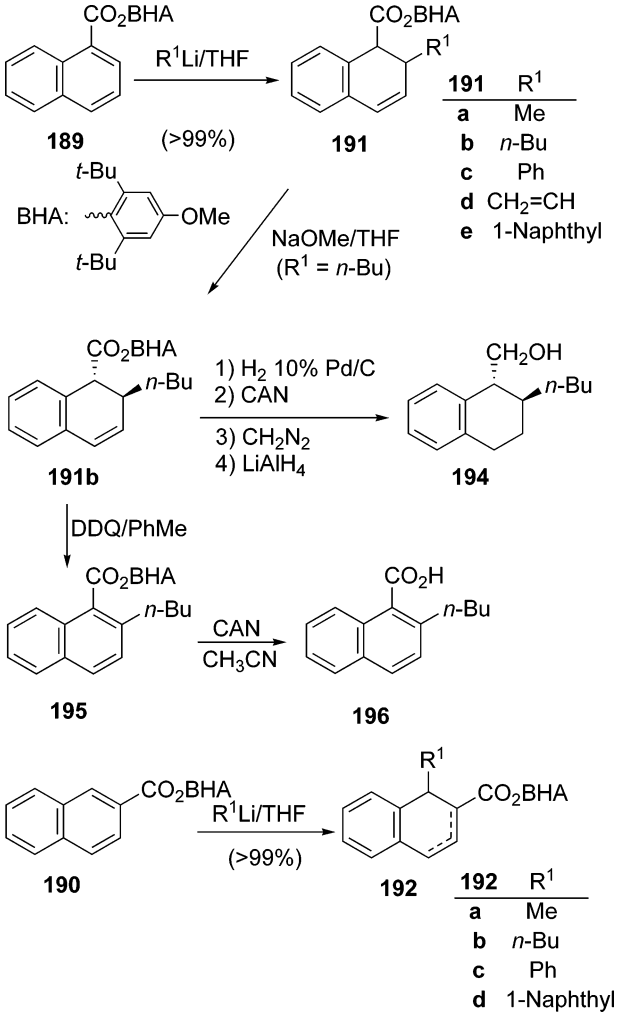
The general strategy for the regioselective addition of organometallics to aromatic carboxylic esters is equally based on the steric inhibition of the access to the carbonyl carbon. Following the work of Cook, who demonstrated the steric suppression of carbonyl reactivity in α,β-unsaturated esters of 2,6-di-*tert*-butyl-4-methoxyphenol (BHA),[126] Tomioka and co-workers described the first example of the Michael

**Table 18. Addition of Organolithium to Naphthoic Acids 176 and 177**[a]

| entry | SM | temp (°C) | $R^1$Li | $E^+$ | $R^1$ | $R^2$ | [1,4]-adduct product yield (%, dr ratio) | $R^1$ | [1,2]-adduct product yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **176** | −78 | *n*-BuLi | MeI | *n*-Bu | Me | **179a** (36) | *n*-Bu | **180a** (8) |
| 2 | **176** | −78 | *s*-BuLi | MeI | *s*-Bu | Me | **179b**,**b′** (80, 90:10)[b] | *s*-Bu | **180b** (8) |
| 3 | **176** | −78 | *s*-BuLi | EtI | *s*-Bu | Et | **179c**,**c′** (44, 75:25) | *s*-Bu | **180b** (12) |
| 4 | **176** | −78 | *s*-BuLi | $Me_2S_2$ | *s*-Bu | MeS | **179d**,**d′** (82, 65:35) | *s*-Bu | **180b** (10) |
| 5 | **177** | −78 | *n*-BuLi | MeI | *n*-Bu | Me | **181a** (38) | *n*-Bu | **182a** (5) |
| 6 | **177** | −90 | *s*-BuLi | MeI | *s*-Bu | Me | **181b**,**b′** (60, 75:25)[c] | *s*-Bu | **182b** (10) |
| 7 | **177** | −78 | *s*-BuLi | MeI | *s*-Bu | Me | **181b**,**b′** (90, 70:30) | *s*-Bu | **182b** (7) |
| 8 | **177** | −45 | *s*-BuLi | MeI | *s*-Bu | Me | **181b**,**b′** (50, 69:31) | *s*-Bu | **182b** (35) |

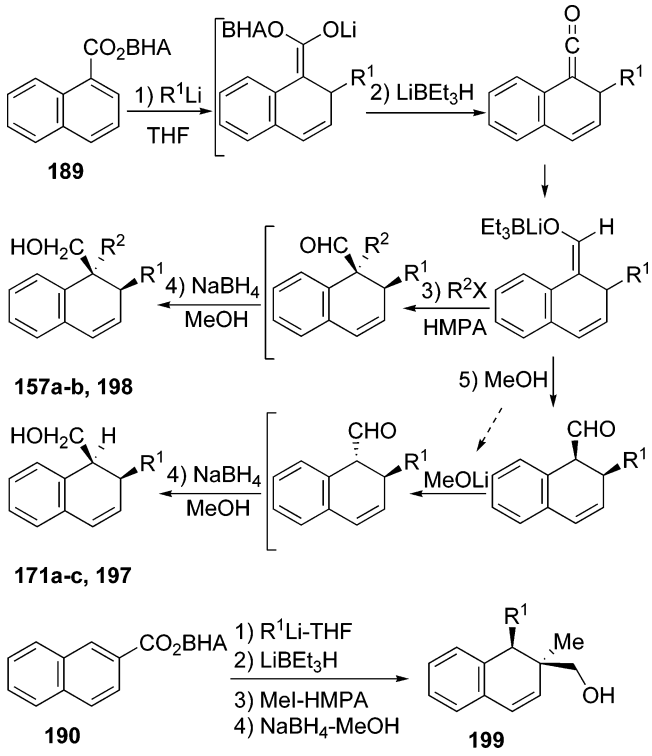
[a] Data taken from ref 124. [b] **179b**, (*1S**,*2S**,*2′S**); **179b′**, (*1S**,*2S**,*2′R**). [c] **181b**, (*1R**,*2R**,*1′S**); **181b′**, (*1R**,*2R**,*1′R**).

**Scheme 37**




addition of organolithiums to 2,6-di-*tert*-butyl-4-methoxyphenylnaphthalenecarboxylates **189** and **190** (Scheme 37).[127,128] Nearly quantitative yields of dihydro-1,2-disubstituted naphthalenes **191** and **192** were obtained in the reactions of **189** and **190**, respectively, with a series of RLi (R = Me, *n*-Bu, $CH_2$=CH, Ph, 1-naphthyl) reagents (Scheme 37). Nucleophiles such as *n*-butylmagnesium chloride and lithium ethyl acetate proved to be unreactive. It is noteworthy that the bulky *tert*-butyl ester of 1-naphthoic acid provided mainly the [1,2] adduct (73%). In sharp contrast with the results of Fuson and Berlin,[99] naphthyl trityl ketone also failed to act as Michael acceptor. Esters **191** consisted of mixtures of cis/trans stereoisomers (cis/trans ratio ranging from 1.8 to 3.6), except for **191e** ($R^1$ = 1-naphthyl), which was obtained exclusively as the cis isomer. The mixtures led entirely to trans derivatives by treatment with NaOMe in THF at room

**Scheme 38**




temperature. As previously noted in the dearomatization−protonation of 2-naphthalenecarboxylic acid, the analogous reaction of **190** provided also mixtures of [1,2]- and [1,4]-dihydro derivatives in a ratio ranging from 2 to 4.3. The dearomatized ester **191b** ($R^1$ = *n*-Bu) was further converted into alcohol **194** and carboxylic acid **196** (Scheme 37).

The scope of the reaction was improved by designing a one-pot process involving a sequence of five reactions going from **189** or **190** to trialkylated dihydronaphthalene compounds **157a,b**, **171a**−**c**, and **197**−**199** (Scheme 38).[129] The sequence consists of (1) Michael addition of an organolithium to the naphthalene nucleus, (2) ketene formation from the lithium enolate of the BHA ester, (3) in situ reduction of the ketene with $LiEt_3BH$ to lithium aldehyde enolate, (4) electrophilic quench with methanol or an alkyl halide in the presence of HMPA, and, finally, (5) reduction of the resulting aldehyde to the corresponding alcohol with $NaBH_4$ in methanol (Scheme 38; Table 19). In the protonation with methanol, the LiOMe generated promoted the epimerization of the *cis*-dihydronaphthyl aldehyde to the trans isomer. PM3 calculations of the LUMO coefficients of phenyl 1- and 2-naphthalenecarboxylates indicated that the magnitude of the coefficients does not fully account for the experimentally observed regioselectivity, suggesting that precomplexation

**Table 19. One-Flask Synthesis of 1,1,2- and 1,2,2-Trisubstituted Dihydronaphthalenes**[a]

| entry | SM | $R^1$ | electrophile | [1,4] adduct product | yield (%) |
|---|---|---|---|---|---|
| 1 | **189** | Ph | MeOH | **171a** | 85[b] |
| 2 | **189** | *n*-Bu | MeOH | **171b** | 81 |
| 3 | **189** | Me | MeOH | **171c** | 71 |
| 4 | **189** | $CH_2$═CH | MeOH | **197a** | 61 |
| 5 | **189** | 1-naphthyl | MeOH | **197b** | 82[c] |
| 6 | **189** | Me | MeI | **157a** | 55 |
| 7 | **189** | *n*-Bu | MeI | **157b** | 75 |
| 8 | **189** | *n*-Bu | BnBr | **198a** | 53 |
| 9 | **189** | $CH_2$═CH | MeI | **198b** | 42 |
| 10 | **189** | Ph | MeI | **198c** | 65 |
| 11 | **190** | Me | MeI | **199a** | 45 |
| 12 | **190** | *n*-Bu | MeI | **199b** | 93 |
| 13 | **190** | $CH_2$═CH | MeI | **199c** | 52 |
| 14 | **190** | Ph | MeI | **199d** | 66[d] |
| 15 | **190** | 1-naphthyl | MeI | **199e** | 51[e] |

[a] Data taken from ref 128. [b] In the presence of **167e**: yield of 80% and ee of 84%. [c] In the presence of **167e**: yield of 82% and ee of 91%. [d] In the presence of **167e**: yield of 54% and ee of 90%. [e] In the presence of **167e**: yield of 40% and ee of 95%.

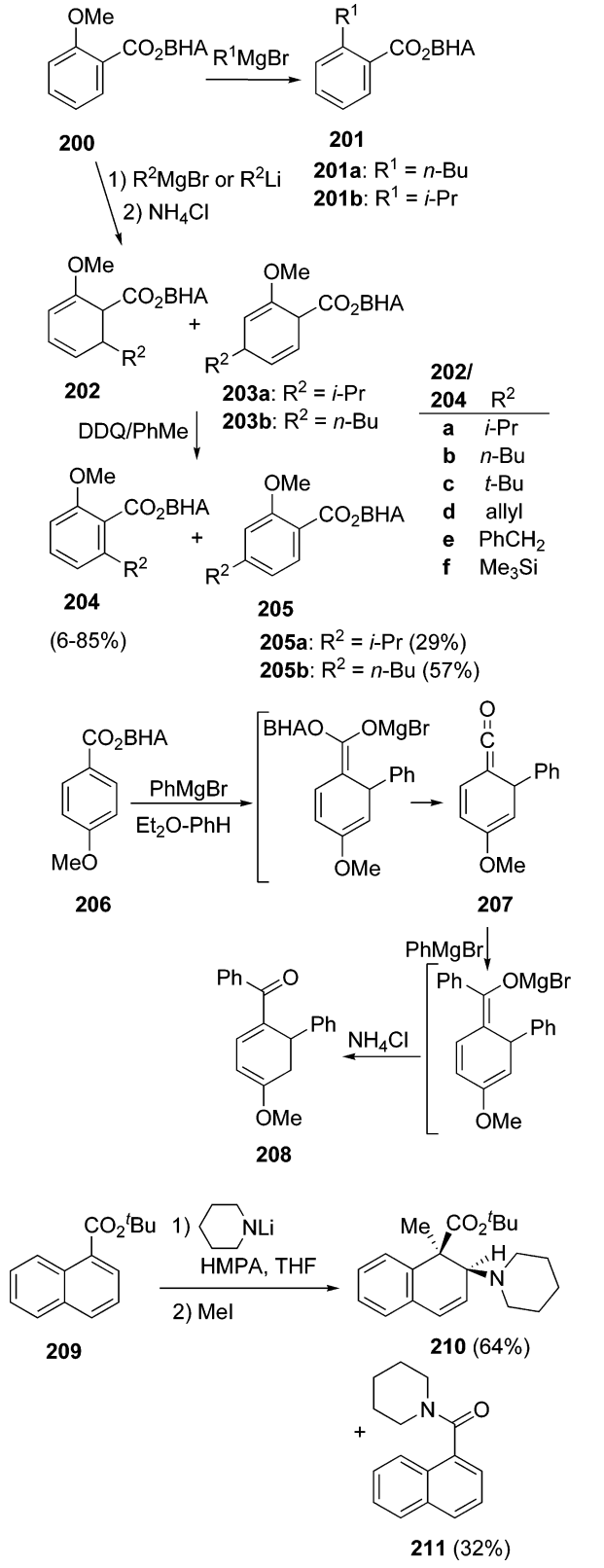
of the reagents plays a significant role in driving the reaction.[128]

The asymmetric induction methodology developed for naphthyl imines, that is, the use of $C_2$ symmetric chiral diether ligands, was also successfully applied to BHA esters **189** and **190**. Compounds **171a**, **197b**, and **199d**,**e** were obtained in good yields and with high enantioselectivities (ee from 84 to 95%) by carrying out the one-pot procedure in the presence of 1.1 equiv of the chiral ether **167e**.[130] The enantiomeric excesses decreased to 63−75% when 20 mol % of **167e** was used, whereas the reaction time increased almost 3-fold.

Miyano et al. showed that with the appropriate choice of organometallic reagent and/or reaction conditions, phenyl esters of the bulky phenol BHA also react as Michael acceptors. The reaction of 2-methoxybenzoate **200** with butyl- and *iso*-propylmagnesium bromide in diethyl ether−benzene at a given temperature led exclusively to methoxy substitution products **201**. In contrast, *t*-BuMgBr and $PhCH_2$-MgBr, under the same conditions, favored the formation of 1,4-cyclohexadienes **202** and **203** derived from [1,4] and [1,6] conjugate addition, respectively. Due to difficulties in the purification of **202**−**203**, they were rearomatized to **204**−**205** by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 39).[131,132] Addition of HMPA resulted in an increase in the yield of dearomatized compounds. It was concluded that the dearomatization proceeded via a mechanism SET.

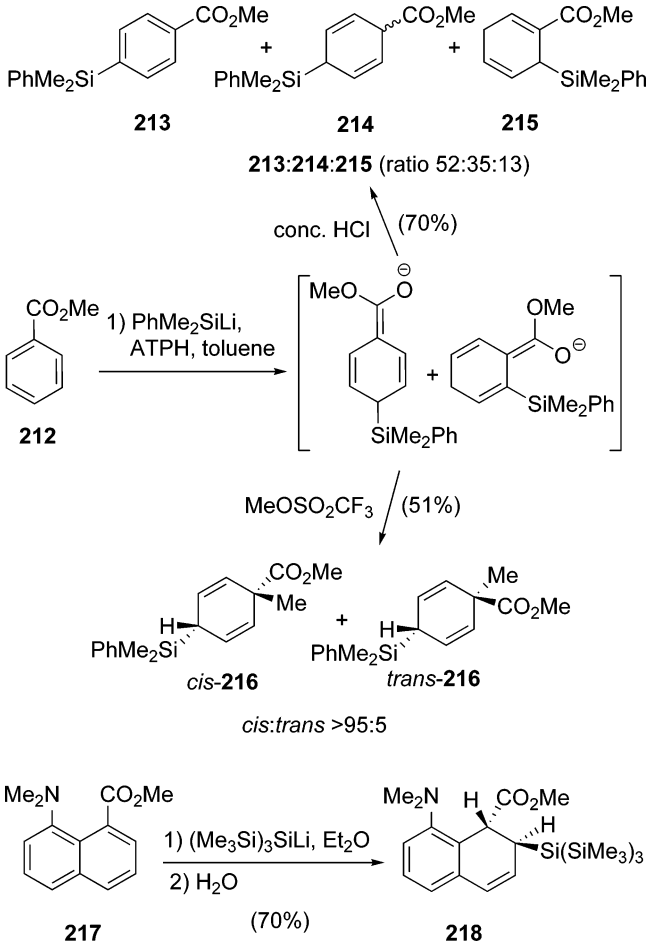
The introduction of a methoxy or halo substituent at the 3-position of the ring greatly accelerated the $S_NAr$ process rate. However, when the methoxy substituent is in the para position to the ester, no substitution products were observed. Refluxing **206** with benzylmagnesium bromide for 24 h led to 98% recovery of the starting material. In the analogous reaction with PhMgBr ketone **208** was isolated in 23% yield. The formation of **208** implies that 2 equiv of the Grignard reagent have been incorporated to **206**. [1,4] conjugate addition of 1 equiv produces dearomatized ketone **207**, which, after [1,2] addition of a second equivalent of organomagnesium and subsequent hydrolysis, would give the ketone **208**.[133]

**Scheme 39**




An additional example of the conjugate addition to bulky esters was provided by Meyers and Shimano (Scheme 39). While investigating the dearomatizing amination of naphthyloxazolines (see section 12.2), these authors observed that the sequential addition of lithium piperidide and methyl iodide to *tert*-butyl 1-naphthalenecarboxylate **209** in the presence of HMPA furnished the [1,4] adduct **210** in good yield, together with a large amount of the amide **211** (Scheme 39).[134]

**Scheme 40**




## 8.2. Bulky Lewis Acid Catalysts

Protection of the carbonyl group of the ester with the bulky ATPH Lewis acid developed by Yamamoto represents an alternative for directing the attack of a nucleophile to the ring of an aromatic ester. The reaction of phenyldimethylsylil-lithium with methyl benzoate **212** in the presence of ATPH followed by protonation with concentrated HCl afforded mixtures of [1,6], **213**−**214**, and [1,4] addition products, **215** (Scheme 40). The dihydrobenzene derivative **214** was obtained as a mixture of cis/trans isomers in a ratio 1:3.1.[110] Interestingly, quenching the intermediate dienolates with methyl triflate gave almost exclusively *cis*-**216**. Methylation occurs in the α-position with respect to the carbonyl, and with very high anti selectivity to the silyl substituent (cis/trans ratio > 95:5) (Scheme 40).

## 8.3. Bulky Nucleophiles

There is one particular example in which the size of the nucleophile may be considered responsible for the change in the reaction pattern with an aromatic ester from the normal [1,2] to the [1,4] addition. Tris(trimethylsilyl)silyl-lithium undergoes reaction with methyl 8-dimethylamino-1-naphthoate **217** in ether at −78 °C to give the dihydronaphthalene **218** in a yield of 70%. The formation of the expected acyl-*tris*(trimethylsilyl)silane derived from nucleophilic attack at the carbonyl group was completely inhibited in this case (Scheme 40).[135]

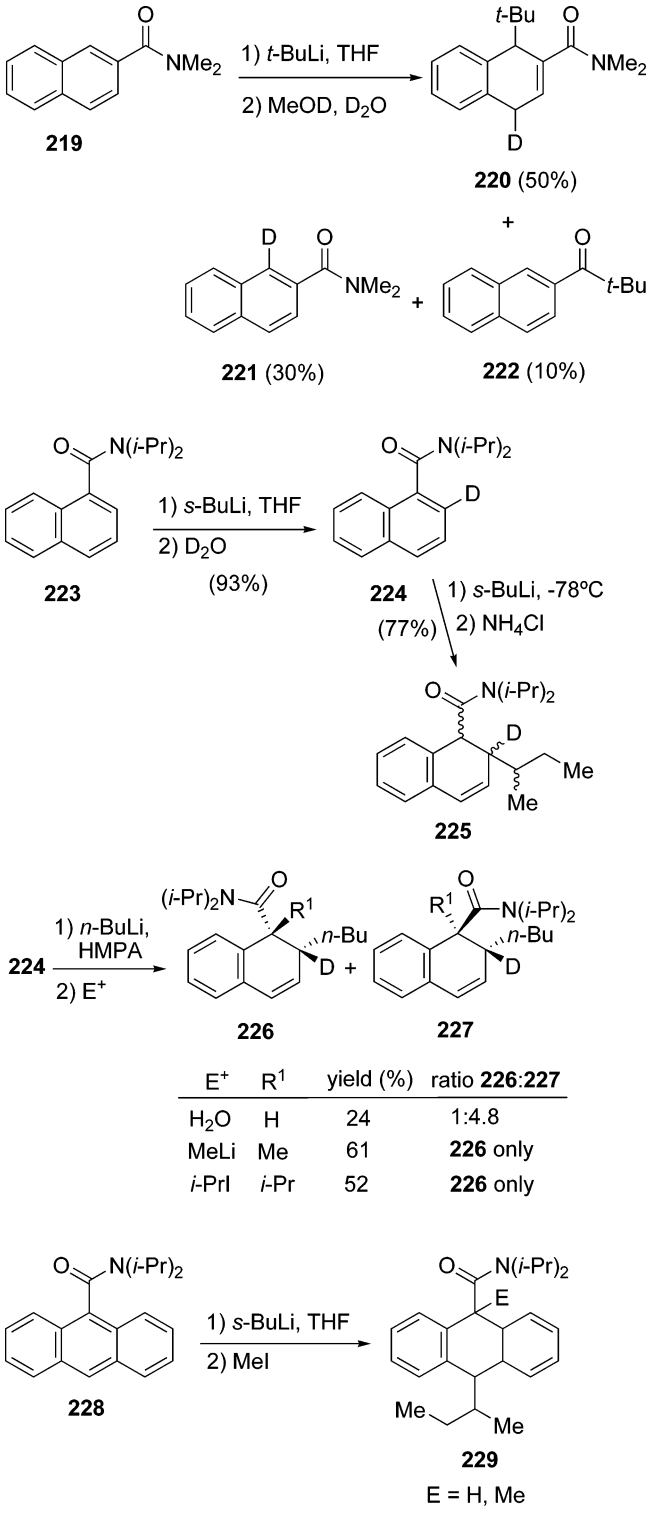
# *9. Amides*

## 9.1. Intermolecular Nucleophilic Dearomatizing Reactions

Tertiary amide substituents are acknowledged in the chemistry of aromatic compounds as one of the best directors of ortho-lithiation.[14−20,136−138] In sharp contrast, their use as activating groups for intermolecular nucleophilic addition to an aromatic ring has received much less attention. In pioneering work, Meyers and co-workers showed that *t*-BuLi undergoes addition to the aromatic nucleus of *N*,*N*-dimethyl-2-naphthamide **219** to give, after quenching with deuterated water, the [1,4] adduct **220** in 50% yield, together with the products derived from ortho-lithiation **221** and [1,2] addition **222** (Scheme 41).[139] Dihydronaphthalenes **220** aromatized spontaneously, and no further investigations were pursued. Ten years later, while searching for a possible method to achieve peri-lithiation of 1-naphthamides, Clayden et al. found a way of favoring conjugate addition over the generally preferred ortho-lithiation of the ring: the use of *ortho*-deuterium-labeled amides as a way of slowing the metalation reaction due to a kinetic isotopic effect.[140] Deuterated naphthalenecarboxamide **224** was prepared by lithiation of **223** with *s*-BuLi, followed by a quench with $D_2O$. Treatment of **224** with *s*-BuLi at −78 °C and subsequent protonation with $NH_4Cl$ led to the formation of all possible stereoisomeric dihydronaphthamides **225** in 77% yield (Scheme 41). On the basis of the deuterated starting material recovered, a primary kinetic isotope effect of $k_H/k_D > 80$ in the ortho-lithiation process was estimated.[141] The less nucleophilic *n*-BuLi also undergoes addition to the ring, albeit in the presence of HMPA and at a temperature of −50 °C. Again, protonation afforded mixtures of diastereoisomers **226** and **227**. However, the sequence butylation−alkylation with MeI or *n*-PrI resulted in the exclusive formation of **226**. In contrast, aromatic addition was found to be only marginal for MeLi and *t*-BuLi, and the use of HMPA or higher temperatures did not improve the results. Deuterium protection was not necessary when anthracenecarboxamide **228** was used as starting material. The sequence of *s*-BuLi addition−methylation with MeI provided a mixture of products tentatively assigned as diastereoisomers of **229** on the basis of mass spectrometry analysis (Scheme 41).

Intermolecular dearomatization of benzamides proved to be also feasible by making use of the strategy based on steric hindrance as a means of controlling nucleophilic attack to the ring system in preference to either addition to the carboxamide or ortho-lithiation.[142] A series of 2,2,6,6-tetramethylpiperidinyl (TMP) benzamides **231** were synthesized through standard methods using benzoyl chlorides **230** and allowed to react with simple alkyllithiums (MeLi, *n*-BuLi, and *s*-BuLi). The enolate formed in the alkyl-lithium addition stage was trapped with a small range of electrophiles. Amides **231a**−**c** gave products of [1,4] addition **232**. For benzamide **231d** with a methoxy group in the meta position, the conjugate addition of the organolithium takes place in the para position, leading to the [1,6] addition product **233** (Scheme 42; Table 20). Protonation afforded mixtures of regio- and stereoisomers (entry 8). Alkylation (MeI, BnBr, EtI, cyclobutanone) was, however, fully stereoselective for the *trans*-cyclohexadiene derivatives **232**. Moreover, in the reaction with *s*-BuLi only two of the four possible diastereoisomers were formed.[143] Amides of TMP are characterized by a low barrier to C−N rotation as a consequence of the bulkiness of the amine moiety. This

**Scheme 41**




feature renders relatively easy a conformation in which carbonyl conjugation with the aromatic ring facilitates the conjugate addition, whereas the carbonyl linkage remains effectively shielded by the methyl substituents of TMP. Deprotection of the carboxamide was finally effected by ring opening of TMP by treatment of the dearomatized product with iodotrimethylsilane in the dark.

## 9.2. Intramolecular Nucleophilic Dearomatizing Reactions

No doubt, the major contributions to the dearomatization of arylamides came from a new approach developed by

**Scheme 42**

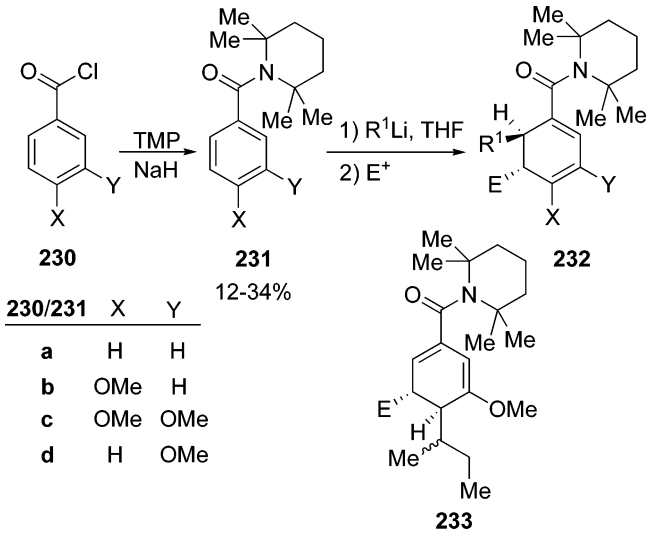



**Table 20. Addition of Organolithium−Electrophilic Quench of TMP Benzamides 231**[a]

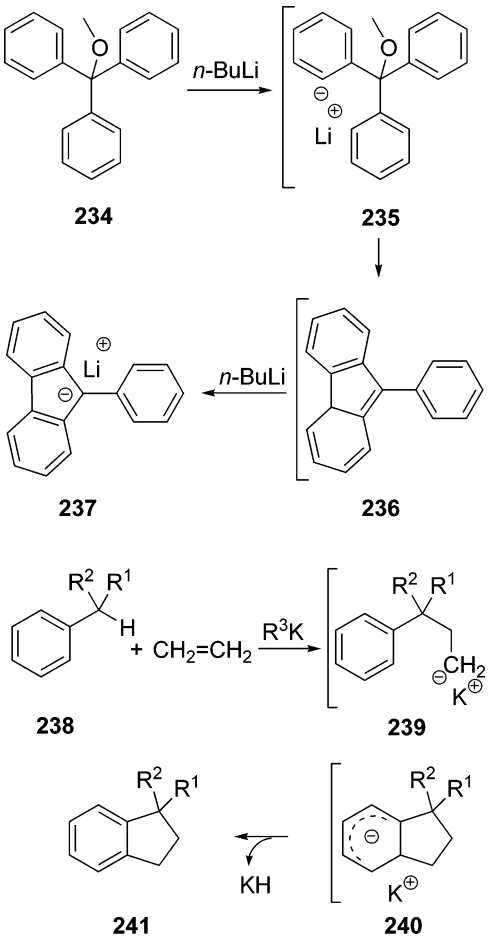
| entry | product | X | Y | $R^1$ | $E^+$ | yield (%) |
|---|---|---|---|---|---|---|
| 1 | **232a** | H | H | *s*-Bu | MeI | 55 |
| 2 | **232b** | OMe | H | Me | MeI | 22 |
| 3 | **232c** | OMe | H | *n*-Bu | MeI | 40 |
| 4 | **232d** | OMe | H | *s*-Bu | MeI | 71[b] |
| 5 | **232e** | OMe | H | *s*-Bu | EtI | 51[b] |
| 6 | **232f** | OMe | H | *s*-Bu | BnBr | 61[b] |
| 7 | **232g** | OMe | H | *s*-Bu | $Me_2CO$ | 32[b] |
| 8 | **232h** | OMe | H | *s*-Bu | $NH_4Cl$ | 76[b,c] |
| 9 | **232i** | OMe | OMe | *s*-Bu | MeI | 12 |
| 10 | **233a** | H | OMe | *s*-Bu | MeI | 23 |
| 11 | **233b** | H | OMe | *s*-Bu | $NH_4Cl$ | 15 |

[a] Data taken from ref 142. [b] A 3:1 mixture of diastereoisomers at CH(Me)Et. [c] Mixture of $\gamma$ and $\epsilon$ protonated regiosiomers.

Clayden's group: anionic cyclization. This approach consists of the metalation of an acyclic precursor, which then undergoes an intramolecular carbon−carbon bond-forming reaction through addition to a suitable functional group. Quenching the reaction with a variety of electrophiles allows the synthesis of substituted carbocyclic and heterocyclic systems, generally, with high regio- and stereocontrol.[34,35,144] Early examples of anionic cyclization onto an unactivated aromatic ring are shown in Scheme 43. Ortho-lithiation of trityl methyl ether **234** produced an aryl anion **235**, which undergoes intramolecular addition to an adjacent phenyl ring followed by elimination of LiOMe.[145] The resulting fluorenyl derivative **236** undergoes further lithiation to give the anion **237**, which afforded 9-phenylfluorene (20%) on hydrolysis. Pines and Schaap obtained alkylated indan derivatives **241** in the potassium-mediated reaction of simple olefins with arylalkanes **238**.[146] A reasonable mechanism involves the participation of alkyl anions **239** formed by addition of a benzylic anion to the olefin. Anionic cyclization of **239** gives the dearomatized anions **240**, which affords the carbocycles **241** by elimination of hydride.

In the previous examples, aromatized products are isolated as a result of the harsh reaction conditions used and/or the absence of electron-withdrawing substituents in the ring capable of stabilizing the dearomatized metalated species. Clayden and co-workers first applied this strategy to aromatic tertiary *N*-benzyl amides in the late 1990s. They demonstrated that amide-substituted naphthyl[147] **242** or phenyl[148]

**Scheme 43**




**243** rings are good acceptors for intramolecular nucleophilic conjugate addition. The amide group also stabilizes the intermediate dearomatized organolithium, making possible the isolation of dihydroaromatic derivatives **246**−**250** by trapping with a variety of electrophiles (Scheme 44; Table 21). The literature has been recently surveyed,[35,149] and the essentials of this methodology are shown in Schemes 44−46.

The reaction conditions first developed for the anionic cyclization of aromatic amides consisted in the metalation with *t*-BuLi in THF in the presence of HMPA or 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) at low temperature during 16 h.[147] Deuterium-labeling studies[150] indicate that the benzylic anion **245** required for the intramolecular conjugate addition is formed in two ways: through direct deprotonation in the benzylic position or via a tandem process starting with the ortho-lithiation of the aromatic ring directed by the carboxamide moiety to give **244** and subsequent proton exchange[151] to give **245** (Scheme 44). On the basis of trapping experiments with MeI, it was suggested that these anions are in equilibrium. The presence of HMPA or DMPU drives the equilibrium to the benzylic anion and accelerates the cyclization step, for which a disrotatory electrocyclic ring closure rather than an intramolecular conjugate addition was proposed.[152]

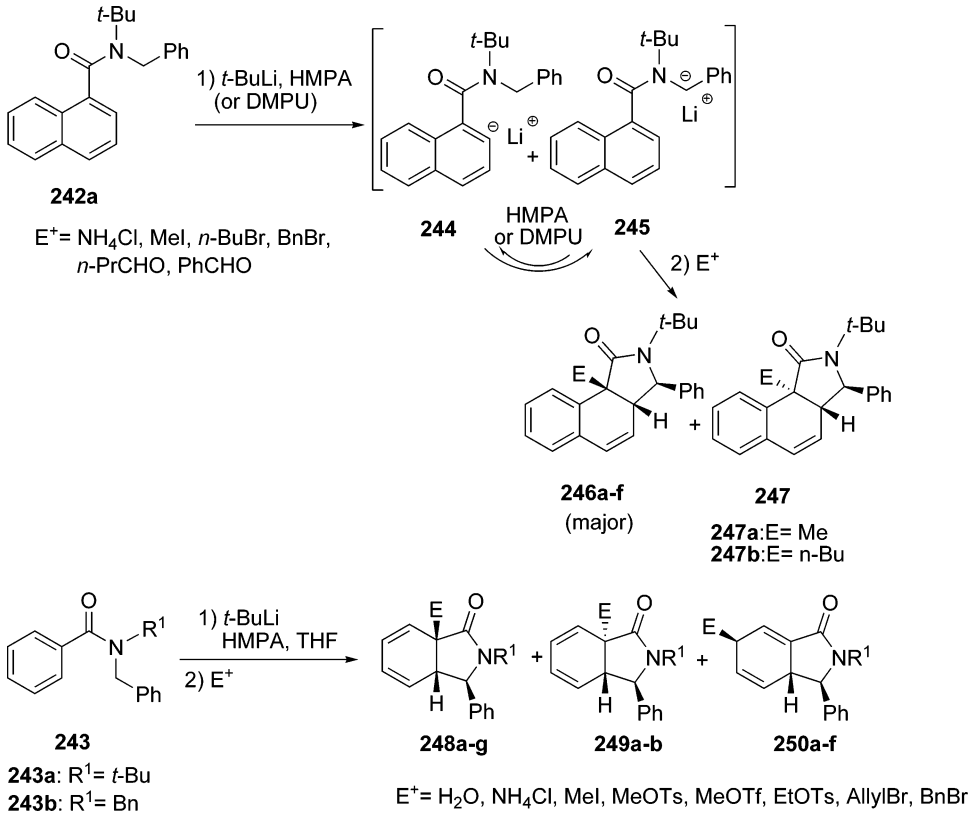
The use of tertiary *N*-benzyl benzamides **243c**−**q** substituted with either electron-withdrawing or electron-donating groups allowed the reaction to be carried out under much milder conditions: lithiation with LDA, absence of cosolvents, and temperatures ranging from 0 to 25 °C (Scheme 45).[153] The best diastereoselectivities were obtained when bulky nitrogen substituents (*tert*-butyl or cumyl) were used. The resulting dearomatized products **251a**,**b**/**d**,**e** containing a methyl vinyl ether moiety were further converted into heterocycles **252**−**255** upon dilute acid hydrolysis. The process leading to **252**−**255** can be performed in a one-pot manner. The cyano-substituted amide **243p** gave a 1:2 mixture of **251h** and the aromatized product **256** (Table 21, entry 30). Significantly, the presence of a methoxy group ortho/para with respect to the position of attack of the benzylic anion prevented the cyclization. This limitation was overcome by performing the metalation with *t*-BuLi in THF in the presence of HMPA at −40 °C.[154] In this way, **251e** and the corresponding product of hydrolysis **253** were obtained, indicating that only the regioisomers resulting from anionic cyclization through position 2 have been formed. Amide **243f** gave a mixture of two products, the α,*β*- and *β*,*γ*-enone derivatives **254** and **255** (Table 21, entry 20). Protonation of the dearomatized enolate resulting from the anionic cyclization of amide **243q** occurred at the α and *γ* positions with respect to the carbonyl group, providing compounds **251d** (63% yield) and **257** (13% yield), respectively. Hydrolysis of the mixture afforded cyclohexenone **252k** in 80% yield (Table 21, entry 31). The methodology was also successfully applied to unsubstituted 1-naphthamide **242b** and 2-naphthamide **259**, leading to **246g** (Table 21, entry 7) and **260**, respectively. The absence of a stabilizing effect from the substituents is compensated by the lower aromatic stabilization of the naphthalene ring with respect to the benzene derivatives. Anionic cyclization of **259** with LDA is particularly advantageous because the deprotonation with *t*-BuLi is accompanied by addition of the base to the 1-position. Additionally, the cumyl protecting group was easily removed by treatment with trifluoroacetic acid, as shown in Scheme 45 with the transformation of **246g** into the N-unsubstituted pyrrolidinone **258**.

Dearomatizing anionic cyclization also works well on amides alkyl branched at the *N*-α-benzylcarbon **261**. In this case, the deprotonation was again performed with *t*-BuLi. The tricyclic products **262** contain a quaternary carbon adjacent to the nitrogen. Remarkably, only one diastereoisomer is formed and in yields ranging from 53 to 73%.[155]

Besides *N*-benzylamides, aromatic amides derived from allylamines[156] and oxazolidines[152] were also efficiently dearomatized. In the case of *N*-allylnaphthamides **263**, the main product formed in the dearomatizing reaction results from the *γ*-attack of the allylic moiety. After electrophilic quench, tetrahydroazepinones **264** were obtained in yields ranging from 22 to 73% (Scheme 46). Compounds **264** constitute the first examples of an organolithium cyclization leading to seven-membered rings. Amides **263** having one phenyl at the allylic position do not undergo cyclization. The additional stabilization of the anion provided by the delocalization through the phenyl group prevents the intramolecular Michael-type addition.

Tertiary *N*-allylbenzamides failed to give dearomatized products under analogous reaction conditions.[149] In contrast, *N*-benzoyl oxazolidines **266** are smoothly transformed into dearomatized tricyclic products **267** or **268**, in moderate yields (Scheme 47; Table 22). By treating **267**/**268** with 2 M HCl in diethyl ether diastereoisomers **269**/**270** were quantitatively obtained, except for **267b**. In this case, dihydroisoindolone **271** was the major product isolated in the reaction. The epimerization at the carbon adjacent to the nitrogen promoted by the action of HCl indicates that cis-fused products are formed under kinetic control. On the basis of this isomerization, it was proposed that the anionic

**Scheme 44**




cyclization takes place through a pericyclic mechanism,[152] although no additional support for this hypothesis was provided.

Recently, amide activation of an aromatic nucleus toward conjugate addition and anionic cyclization were made possible as two separate events on the same substrate: the alkyl fragment amenable for the anionic intramolecular attack was linked to a naphthyl nucleus bearing a carboxamide group. This synthetic strategy allows for annelating the five-membered rings shown in Scheme 48.[157] Tin−lithium exchange in naphthamide **272** with MeLi in THF in the presence of TMEDA and subsequent protonation afforded the dearomatized heterocycle **273**, albeit in low yield. The method proved to be more efficient when the activation of the aromatic ring was performed with an oxazoline ring (see section 12).

## 9.3. Asymmetric Dearomatizing Anionic Cyclization

Asymmetric induction in dearomatizing anionic cyclizations has been attained in two ways: carrying out the reaction on chiral substrates or using chiral bases for performing the deprotonation of achiral amides. Both methods have been applied to the synthesis of products of the kainic acid family (see section 19).

### *9.3.1. Chiral Aromatic Carboxamides*

Anionic cyclization of amides (−)-**274** and *meso*-**274** afforded the respective dearomatized products, (+)-**275** and (±)-**275**, as single diastereoisomers (Scheme 49).[155] These results indicate that the reaction is stereospecific and proceeds with retention of the configuration at the lithiated benzylic site. The origin of the stereospecificity was assigned to the presence of a chiral naphthalene−CO axis.[151] Under the same conditions, enantiomerically pure amide **276** cyclized to give tricyclic derivative **277**. In this remarkable reaction the trisubstituted stereogenic center of the starting material becomes a quaternary carbon and two additional stereogenic carbons adjacent to the tetrasubstituted center are created in a stereospecific manner. Furthermore, the stereospecifity in the formation of (±)-**275** suggests that the chiral center at the N-substituent of (−)**274** and *meso*-**274**, not involved in the cyclization, has little effect on the reaction course.

The insignificant effect of chiral auxiliaries linked to the nitrogen on the asymmetric induction in the deprotonation of the *N*-benzylamides was evidenced by the low diastereomeric excesses observed in the cyclization of amides **278a**,**b**. In both cases, a mixture of two diasteroisomers **279a**,**b** and **280a**,**b** in a 60:40 ratio was obtained (Scheme 50).[158] However, the diastereoselectivity increased to >90:10 for amides (*R*)-**278c**,**d** containing the phenylglycinol moiety as chiral auxiliary and dropped again to 67:33 for the cyclization of amide (*S*)-**278e**, which incorporates a methoxy group in the para position of the benzyl-lithium species. The reasons for the differences noted in the stereocontrol of the anionic cyclization of amides **278** remain unclear. Further manipulations of the dearomatized products included the conversion of methyl vinyl ether derivatives to ketones such as **281** by mild acid hydrolysis and the removal of the chiral auxiliary to give tricyclic products **282**.

Asymmetric dearomatizing anionic cyclization was also successful for chiral benzamides **283a**−**i** (Scheme 51).[159] The products **284**−**288** obtained are collected in Table 23. The regioselectivities observed were similar to those found for achiral amides.[153] Quenching the dearomatized lithium intermediate with alkyl halides led to mixtures of products of attack α, **284f**−**h**, and γ, **288a**−**c** with respect to the carbonyl group (entries 8−10, Table 23). The use of

**Table 21. Dearomatizing Anionic Cyclization of Amides 242 and 243**

| | | starting material | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| entry | compd | $R^1$ | $R^{2a}$ | $R^{3a}$ | Ar | $E^+$ | E | yield (%) of products | | |
| 1 | **242a** | *t*-Bu[b] | H | H | Ph | $NH_4Cl$ | H | **246a** (82) | | |
| 2 | **242a** | *t*-Bu[b] | H | H | Ph | MeI | Me | **246b** (69) | **247a** (23) | |
| 3 | **242a** | *t*-Bu[b] | H | H | Ph | *n*-BuBr | *n*-Bu | **246c** (68) | **247b** (13) | |
| 4 | **242a** | *t*-Bu[b] | H | H | Ph | BnBr | Bn | **246d** (72) | | |
| 5 | **242a** | *t*-Bu[b] | H | H | Ph | *n*-PrCHO | *n*-PrCHOH | **246e** (84)[c] | | |
| 6 | **242a** | *t*-Bu[b] | H | H | Ph | PhCHO | PhCHOH | **246f** (81) | | |
| 7 | **242b** | cumyl[d,e] | H | H | Ph | $NH_4Cl$ | H | **246g** (88) | | |
| 8 | **243a** | *t*-Bu[f] | H | H | Ph | $NH_4Cl$ | H | **248a** (75) | **249a** (5) | |
| 9 | **243a** | *t*-Bu[f] | H | H | Ph | MeI | Me | **248b** (22) | **249a** (13) | **250b** (36) |
| 10 | **243a** | *t*-Bu[f] | H | H | Ph | MeOTs | Me | **248b** (43) | **249a** (5) | **250b** (8) |
| 11 | **243a** | *t*-Bu[f] | H | H | Ph | MeOTf | Me | **248b** (34) | **249a** (13) | |
| 12 | **243a** | *t*-Bu[f] | H | H | Ph | EtOTs | Et | **248c** (30) | | |
| 13 | **243a** | *t*-Bu[f] | H | H | Ph | allylBr | allyl | **248d** (46) | **250c** (27) | |
| 14 | **243a** | *t*-Bu[f] | H | H | Ph | BnBr | Bn | **248e** (61) | **250d** (4) | |
| 15 | **243b** | Bn[f] | H | H | Ph | $H_2O$ | H | **248f** (68) | **250e** (21) | |
| 16 | **243b** | Bn[f] | H | H | Ph | MeI | Me | **248g** (25) | **249b** (15) | **250f** (33) |
| 17 | **243c** | *t*-Bu[d] | 4-OMe | H | Ph | $NH_4Cl$ | H | **252a** (73) | | |
| 18 | **243d** | *t*-Bu[g] | 4-OMe | H | 4-$MeOC_6H_4$ | $NH_4Cl$ | H | **252b** (100) | | |
| 19 | **243e** | *t*-Bu[g] | 3-OMe | H | Ph | $NH_4Cl$ | H | **253** (70) | | |
| 20 | **243f** | *t*-Bu[g] | 2-OMe | H | Ph | $NH_4Cl$ | H | **254** (25) | **255** (32)[j] | |
| 21 | **243g** | cumyl[d] | 4-OMe | H | Ph | $NH_4Cl$ | H | **252c** (53) | | |
| 22 | **243h** | prenyl[d,h] | 4-OMe | H | Ph | $NH_4Cl$ | H | **252d** (53)[i] | | |
| 23 | **243i** | Bn[d] | 4-OMe | H | Ph | $NH_4Cl$ | H | **252e** (37)[j] | | |
| 24 | **243j** | *p*MB[d,k] | 4-OMe | H | Ph | $NH_4Cl$ | H | **252f** (37)[j] | | |
| 25 | **243k** | cumyl[d] | 4-Ph | H | Ph | $NH_4Cl$ | H | **252g** (88) | | |
| 26 | **243l** | cumyl[d] | 2-MeO | H | Ph | $NH_4Cl$ | H | **251c** (60) | | |
| 27 | **243m** | cumyl[d] | 4-MeO | 2-MeO | Ph | $NH_4Cl$ | H | **252h** (62) | | |
| 28 | **243n** | cumyl[d] | 4-Br | H | Ph | $NH_4Cl$ | H | **252i** (59) | | |
| 29 | **243o** | cumyl[d] | 3-Br | H | Ph | $NH_4Cl$ | H | **252j** (44) | | |
| 30 | **243p** | cumyl[d] | 4-CN | H | Ph | $NH_4Cl$ | H | **251h** (20) | **256** (40%) | |
| 31 | **243q** | *t*-Bu[g] | 4-OMe | 2-Me | Ph | $NH_4Cl$ | H | **252k** (80) | | |

[a] Position with respect to the carboxamide group. [b] Data taken from ref 147. [c] Mixture of diastereoisomers. [d] Data taken from ref 153. [e] Cumyl = 1,1-dimethylphenylmethyl. [f] Data taken from ref 148. [g] Data taken from ref 154. [h] Prenyl = 3-methylbut-2-enyl. [i] Thirteen percent of the trans-fused product was also obtained. [j] The trans-fused product was also obtained in 9% yield. [k] *p*MB = *p*-methoxybenzyl.

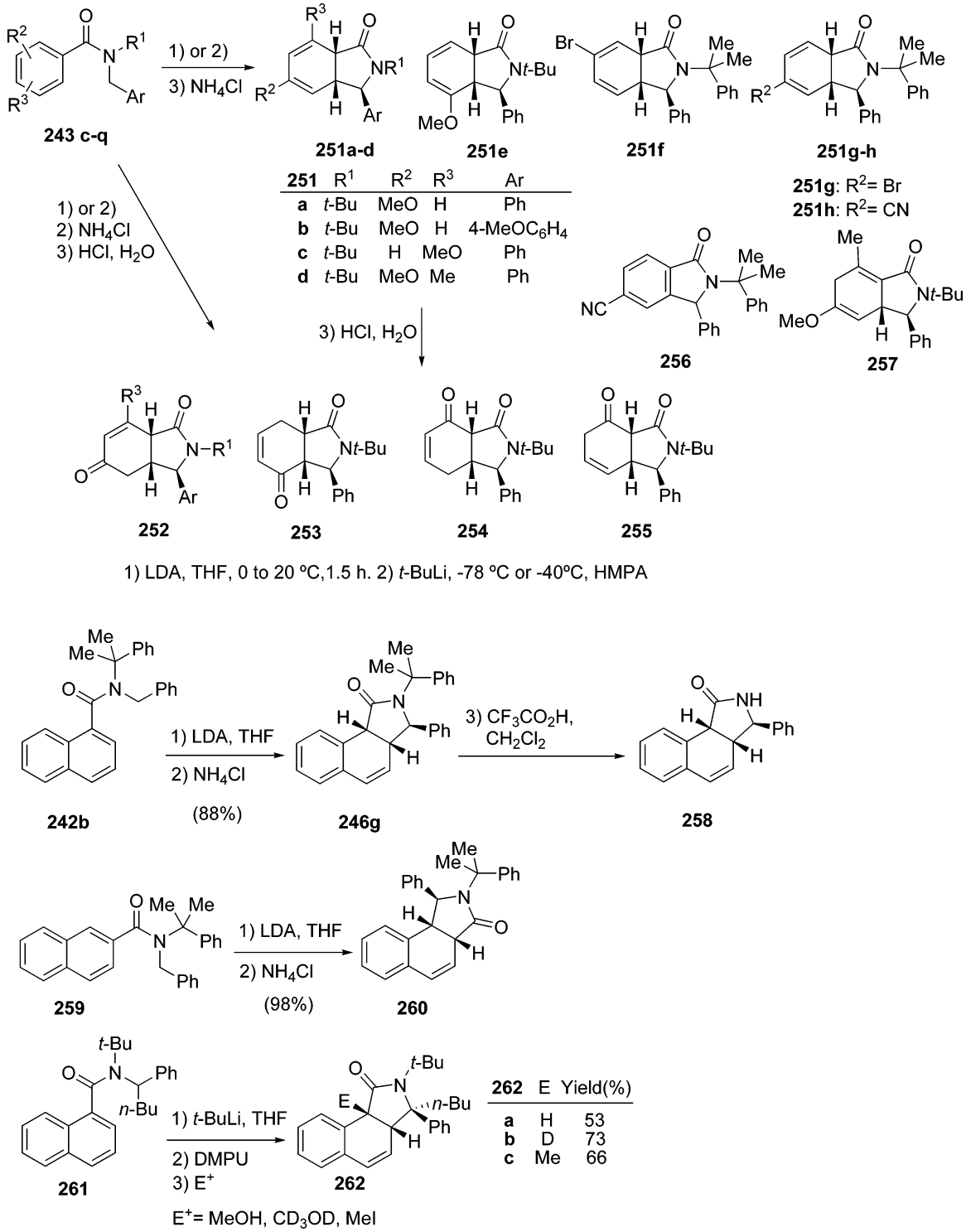
benzaldehyde as electrophile (entry 11, Table 23) produced **284i** ($R^1$ = 4-OMe; $R^2$ = H) as a single stereoisomer in very high yield. Compound **284i** contains four stereogenic centers, two of them tetrasubstituted, and it represents a nice example of the performance of the reaction. As in the related naphthamide series, the process involves the stereospecific formation and cyclization of a tertiary benzyl-lithium intermediate. This anion must be configurationally stable in the time scale of the anionic cyclization because the chiral center present in the starting amide is the source of such stereospecificity. Cyclizacion of (*R*,*R*)-**289a**,**b** and *meso*-**289a**,**b** afforded diastereomeric products **290**−**291** and **292**−**293**, respectively (Scheme 52).[160] The discrimination between two similar benzylic groups in the cyclization of amide (*R*,*S*)-**294** proved to be rather low, rendering compounds **295** and **296** in 74% yield and a ratio of 4:1 (Scheme 52).

The scope of the anionic dearomatization of amides has been further extended by replacing the electrophilic quench step by a photochemical reaction. The irradiation with a 500 W tungsten-filament halogen lamp ($h\nu$ >500 nm) of the enolates **297** obtained upon lithiation of amides **283a**−**h** and **289a** effects a rearrangement leading to the stereospecific formation of norcaradienes **298** (52−94% yield) or cycloheptatrienes **299** (20−94% yield) (Scheme 53; Table 24).[161] Bicycles **298** are the precursors of cycloheptatriene derivatives **299** via isomerization through a six-electron disrotatory ring-opening reaction. For amide **283e** containing an *o*-MeO substituent, the rearrangement followed a different pathway, affording ketone **300**. The conversion of amides **283a**−**h** and **289a** onto dearomatized compounds **298** and **299** represents the formal insertion of a chiral carbenoid into a benzene ring through a sequence of reactions involving deprotonation, cyclization, and rearrangement that preserves the chiral integrity in each step. The significant structural modification of the starting material has been accomplished by using two simple reagents: a base and a lamp. Anionic cyclization−photochemical rearrangement of achiral *N*-benzyl-*N*-*tert*-butylamides **243** proceeds in a similar manner. However, in this case two possible regioisomeric norcaradienes **301** and **303** were formed together with their corresponding rearranged cycloheptatrienes **302** and **304** (Scheme 53).

### 9.3.2. Enantioselective Deprotonation with Chiral Bases

Intermolecular transfer of asymmetry by sequential asymmetric deprotonation of a prochiral methylene group and electrophilic quench has become a valuable synthetic tool for obtaining chiral compounds in high enantiomeric excesses.[162] Enantioselective deprotonation is generally achieved through the use of the chiral base *s*-BuLi/(−)-sparteine in nonpolar solvents[163] or by the action of a suitable chiral lithium amide.[164,165] The metalation of benzamide **243c** with *s*-BuLi/(−)-sparteine in THF afforded the racemic dearomatized product **252a**. As mentioned previously, tertiary arylamides could be deprotonated at the benzylic position by treatment with LDA.[153] When the metalation of **243c**,**g**,**w**,**x** was performed with the chiral lithium amides **305**−**308** and the crude reaction mixture was hydrolyzed with dilute hydrochloric acid, bicyclic enones **252a**,**c**,**m**,**n** were obtained in good yield and with moderate ee (Scheme 54; Table 25).[166] In the absence of a methoxyvinyl ether moiety as in **243y**, the product isolated after protonation with aqueous ammonium chloride was **251i**. In general, lithium amides **306** and **307** proved to be

**Scheme 45**

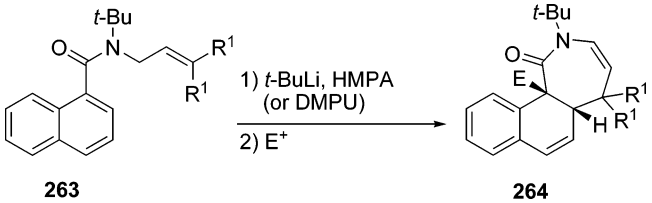



more efficient as chiral transfer reagents than the simplest phenethylamine derivative **305** or the doubly lithiated amide **308** (Table 25). However, the reaction proceeded with either low yields or low enantioselectivities with *N*-benzyl-*N*-*tert*-butyl-2-methoxybenzamide **243f** and *N*-benzyl-*N*-*tert*-butyl-1-naphthamide **242a**. These poor results have been attributed to the possibility that these amides may be chiral at low temperature due to atropisomerism.[151] As expected, when the enolate formed in the asymmetric deprotonation of **243c** with **306** was irradiated prior to the quenching with aqueous $NH_4Cl$, the rearranged product obtained, **301a** (69%), was enantiomerically enriched (ee 78%) (Scheme 53).[161]

Deuterium-labeling studies on **243c** indicated that chiral lithium amides deprotonated amides enantioselectively. The resulting benzylic anions were configurationally stable on the time scale of the cyclization, which proceeds stereospecifically.

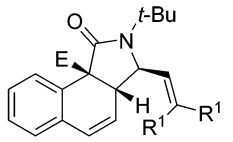
Enantioselective dearomatizing anionic cyclization of amides **243** through asymmetric deprotonation represents a significant improvement with respect to intramolecular transfer of chirality processes described above. The method allows the use of achiral starting amides. Asymmetric induction originates on a reagent that is readily available and may be quantitatively recovered from the acidic fraction of the

**Scheme 46**




$R^1$= H, Me
$E^+$= $NH_4Cl$, MeI, EtI, BnBr, PhCHO

| | | | 264 | 265 |
|---|---|---|---|---|
| Comp | $R^1$ | E | Yield (%) | Yield (%) |
| **a** | H | H | 73 | 17 |
| **b** | H | Me | 56 | 25 |
| **c** | H | Et | 66 | 27 |
| **d** | H | Bn | 68 | 23 |
| **e** | H | PhCHOH | 48 | 9 |
| **f** | Me | H | 22 | 18 |




**Scheme 47**

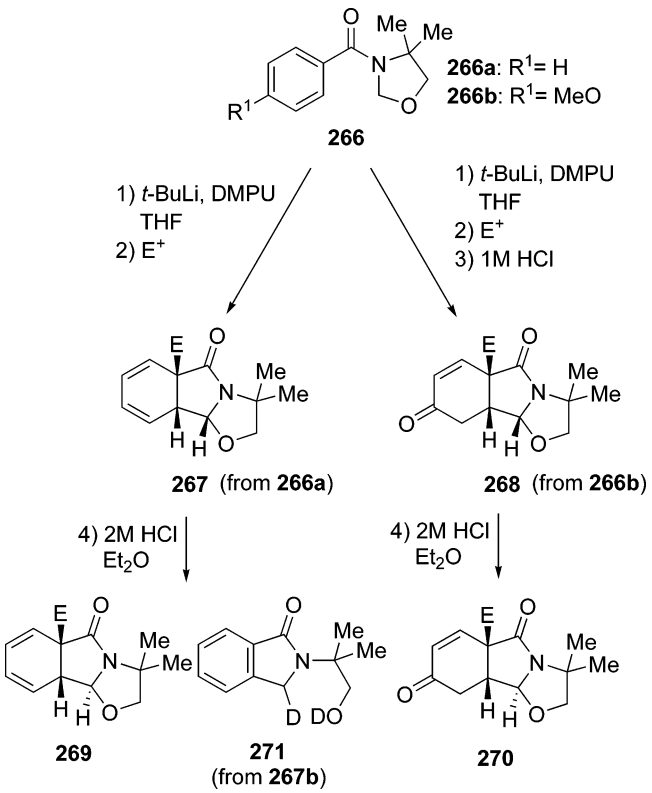


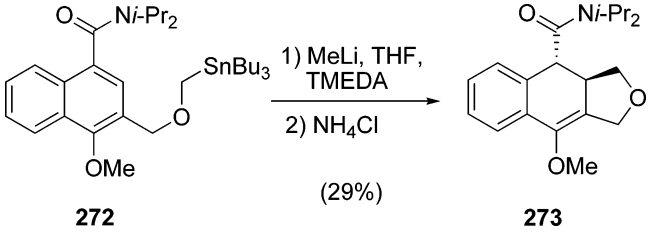

**Table 22. Dearomatizing Anionic Cyclization of Amides 266**[a]

| entry | SM | $E^+$ | E | yield (%) |
|---|---|---|---|---|
| 1 | **266a** | $NH_4Cl$ | H | **267a** (60) |
| 2 | **266a** | $CD_3OD$ | D | **267b** (60) |
| 3 | **266a** | MeI | Me | **267c** (53) |
| 4 | **266a** | BnBr | Bn | **267d** (45) |
| 5 | **266a** | 4-$BrC_6H_4CH_2Br$ | 4-$BrC_6H_4CH_2$ | **267e** (41) |
| 6 | **266b** | 1 M HCl | H | **268a** (55) |
| 7 | **266b** | MeI | Me | **268b** (48) |

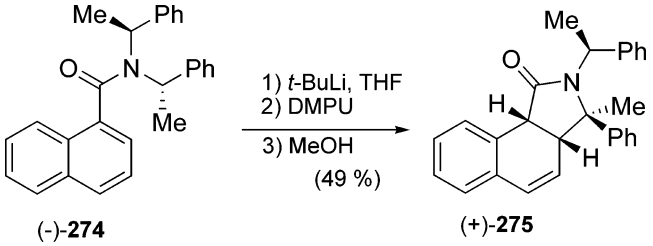
[a] Data taken from ref 152.

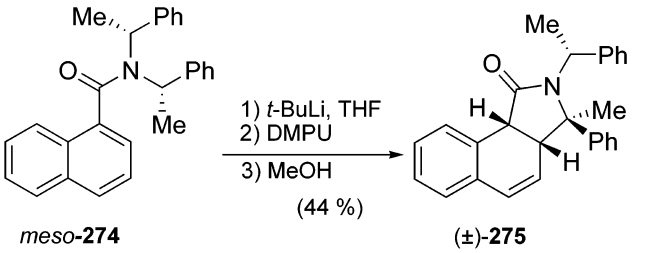
aqueous workup. Although the enantiomeric excesses attained are not very high, a single recrystallization leads to products with ee > 99%. The dearomatized compounds obtained contain a chiral trisubstituted N−$C_\alpha$ carbon. Therefore, this methodology complements the previous synthesis of chiral bicyclic enones (e.g., **284**−**286**) via anionic cyclization

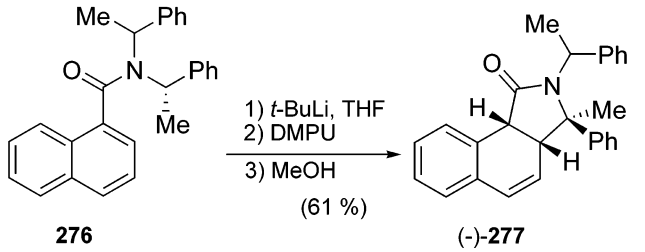
**Scheme 48**




**Scheme 49**



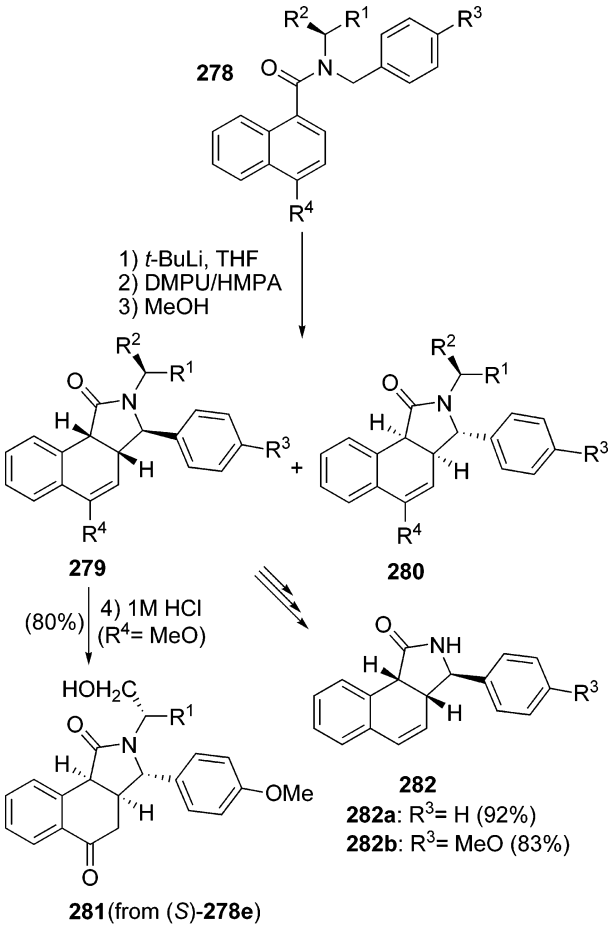




of chiral arylamides, which affords products with a quaternary chiral carbon adjacent to the nitrogen.

## *10. Acid Halides*

$D_NAr$ of aromatic acid halides has been achieved only via the methodology developed by Yamamoto et al.: complexation of benzoyl or 2-naphthoyl chloride with ATPH in toluene at −78 °C followed by addition of the nucleophile. Starting with PhCOCl **309**, treatment with $R^1M$ reagents and workup with concentrated HCl afforded mixtures of [1,6] and [1,4] cyclohexadienyl carboxylic acids **311** and **312**, respectively (Scheme 55).[167] Performing the hydrolysis with HCl/MeOH gave the corresponding esters **313** and **314**. The range of nucleophiles that undergo addition to the ring include simple alkyl-lithiums (MeLi, *t*-BuLi, PhLi, $CH_2$=CHLi, $CH_2$=$CHCH_2$Li), lithium enolates, and Grignard reagents (*i*-PrMgBr, *t*-BuMgCl). Compared with the analogous reaction of benzaldehyde, the ATPH·PhCOCl complex **310** shows enhanced selectivity (no [1,2] adducts were detected) and reactivity (*i*-PrMgBr and *t*-BuMgCl failed to add to the ATPH−PhCHO complex). These differences in chemical behavior correlated with the differences observed in the X-ray structures of both complexes. These results suggest an increased $\pi$-deficiency and a higher congestion of the carbonyl moiety of PhCOCl in **310** than that of PhCHO in **120** (see

**Scheme 50**



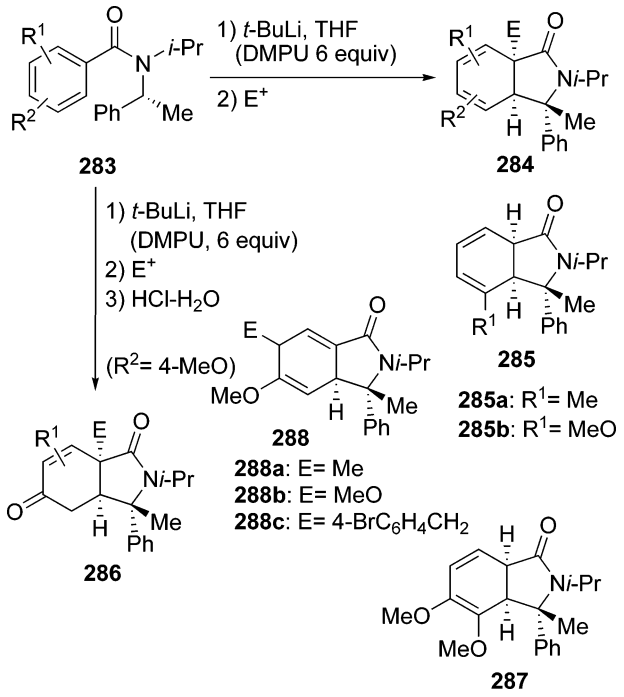

| SM/ Comp | $R^1$ | $R^2$ | $R^3$ | $R^4$ | 279 Yield(%) | 279:280 Ratio |
|---|---|---|---|---|---|---|
| **a** | Ph | Me | H | H | 52 | 60:40 |
| **b** | 1-Naph | Me | H | H | 52 | 60:40 |
| **c** | Ph | $CH_2OH$ | H | H | 66 | 91:9 |
| **d** | Ph | $CH_2OH$ | MeO | H | 52 | >90:10 |
| **e**[a] | Ph | $CH_2OH$ | MeO | MeO | 32 | 67:33 |

[a] (*S*)-**278e**

Scheme 27). Benzoyl chloride afforded predominantly or exclusively moderate to good yields of [1,6] regioisomers **311** or **313** (Table 26). The same regioselectivity was observed in the reaction of alkyl-substituted benzoyl chlorides **315a**,**b** with bulky nucleophiles such as *t*-BuLi (entries 16 and 18). However, MeLi attacked solely the ortho position of the carbonyl group, giving a mixture of cyclohexadiene isomers **316** and **317** derived from protonation at the $\beta$ or $\delta$ position with respect to the incoming nucleophile (entries 15 and 17). *tert*-Butylation of 4-chlorobenzoic acid chloride **319** with an excess of *t*-BuMgBr is a remarkable reaction that gives a mixture of di-*tert*-butylbenzoic acids **320** and **321**. Their formation was explained via a tandem process involving a [1,6] conjugate addition of *t*-BuMgBr to the aromatic nucleus, followed by aromatization and chloride elimination from the intermediate enolate formed and subsequent [1,4] addition of the Grignard reagent.

The complex of 2-naphthoic chloride **322** and ATPH also undergoes nucleophilic addition onto the ring. However, mixtures of [1,4] and unprecedented [1,8] conjugate addition products **324** and **323** were formed in this case. [1,8] Regioselectivity predominated with *t*-BuLi (entry 19, Table

**Scheme 51**




26). Curiously, the hydrolysis with concentrated HCl was assisted by HMPA. The analogous reaction with the lithium enolate of 2-methylpropionate, in the absence of HMPA during acid hydrolysis, afforded high yields of the [1,4] regioisomer **324b** (entry 20). In sharp contrast, 2-naphthaldehyde was unreactive under the same conditions.

## *11. Nitriles*

The cyano group is characterized by its strong electron-withdrawing nature, making arylnitriles prone to react with nucleophiles through [1,2] addition to the CN. Nevertheless, there are a number of examples for which the regioselectivity predominantly observed corresponds to attack on the aromatic ring.

### 11.1. Reactions with Hydride Transfer Agents

There is only one report on the conjugate addition of hydride to an aromatic nitrile. Stirring a DMF solution of 9-cyanoanthracene **325a** with sodium borohydride at room temperature for 2 h gave 9,10-dihydro-9-cyanoanthracene **326a** in 65% yield (Scheme 56).[168] However, the analogous reduction of 9,10-dicyanoanthracene produced exclusively the substitution of a cyanide group yielding **325a** (50%).

### 11.2. Reactions with Grignard Reagents

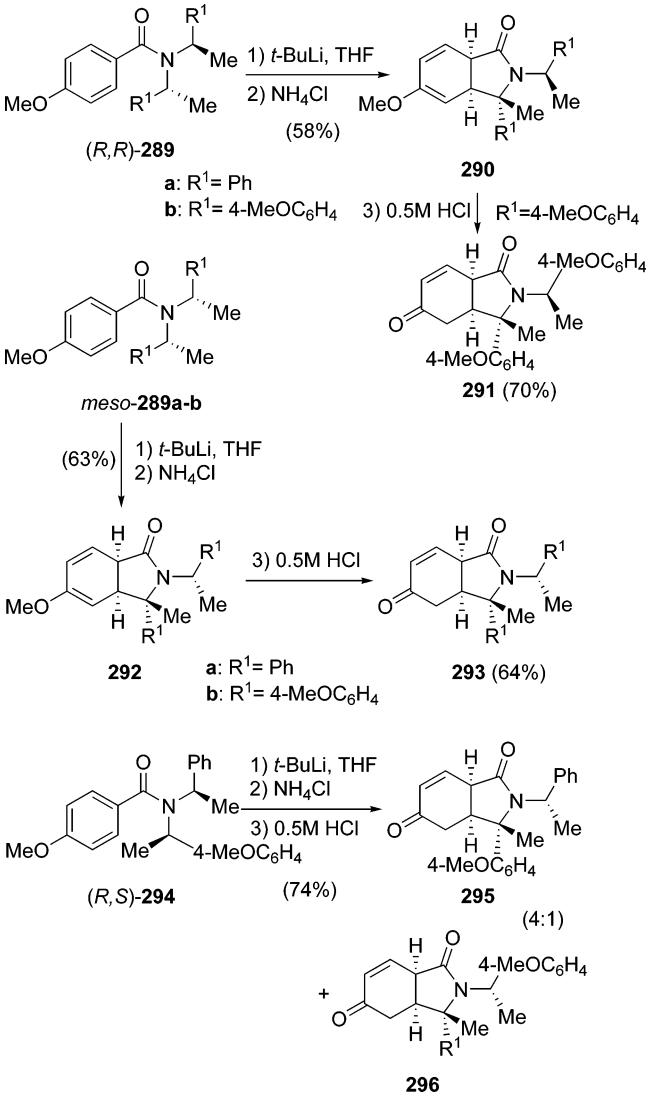
Generally, organomagnesiums undergo reaction with arylnitriles via [1,2] addition to give imines in good yields. However, the reduced stabilization energy of the central ring of 9-cyanoanthracene **325a** with respect to an isolated phenyl ring opens the way to alternative reactivity patterns with Grignard reagents. Organomagnesiums can be classified into four groups based on the products obtained in their reactions with **325**: (i) Grignard reagents that afford normal [1,2] adducts, as is the case for MeMgBr and PhMgBr;[169] (ii) linear

**Table 23. Dearomatizing Anionic Cyclization of Amides 283**[a]

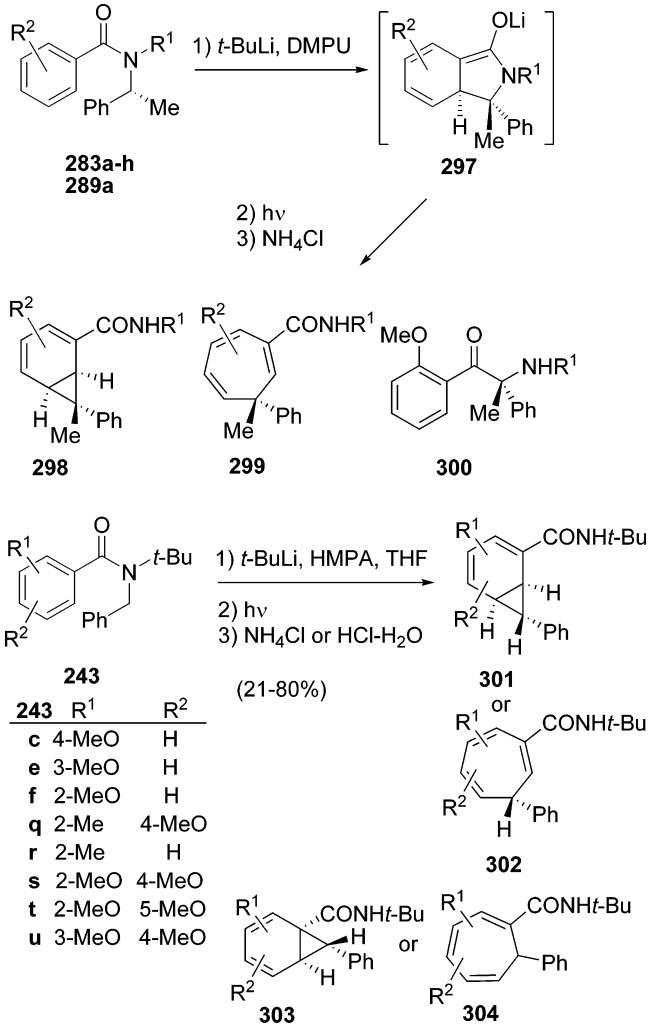
| | starting material | | | products | | | |
|---|---|---|---|---|---|---|---|
| entry | **283** | $R^1$ | $R^2$ | $E^+$ | E | yield (%) | ee (%) |
| 1 | **a** | H | H | $NH_4Cl$ | H | **284a** (70) | |
| 2 | **b** | 2-Me | H | $NH_4Cl$ | H | **284b** (60) | |
| 3 | **c** | 3-Me | H | $NH_4Cl$ | H | **284c** (23)[b] | |
| 4 | **d** | 4-Me | H | $NH_4Cl$ | H | **284d** (75) | |
| 5 | **e** | 2-MeO | H | $NH_4Cl$ | H | **284e** (74) | >99 |
| 6 | **f** | 3-MeO | H | $NH_4Cl$ | H | **285b** (66) | >99 |
| 7 | **g** | 4-MeO | H | HCl | H | **286a** (80) | >99 |
| 8 | **g** | 4-MeO | H | MeI | Me | **284f** (28)[c] | |
| 9 | **g** | 4-MeO | H | BnBr | Bn | **284g** (48)[d] | |
| 10 | **g** | 4-MeO | H | $4\text{-BrC}_6H_4CH_2Br$ | $4\text{-BrC}_6H_4CH_2$ | **284h** (61)[e] | |
| 11 | **g** | 4-MeO | H | PhCHO | (*S*)-PhCHOH | **284i** (96) | |
| 12 | **h** | 2-MeO | 4-MeO | $NH_4Cl$ | H | **286b** (52) | |
| 13 | **i** | 3-MeO | 4-MeO | $NH_4Cl$ | H | **284j** (41)[f] | 93 |

[a] Data taken from refs 159 and 160. [b] Compound **285a** was also formed in 23% yield. [c] Compound **288a** was also formed in 48% yield and separated before acid hydrolysis. [d] Compound **288b** was also formed in 29% yield and separated before acid hydrolysis. [e] Compound **288c** was also formed in 30% yield and separated before acid hydrolysis. [f] Compound **287** was also formed in 10% yield.

**Scheme 52**




**Scheme 53**




| 243 | $R^1$ | $R^2$ |
|---|---|---|
| **c** | 4-MeO | H |
| **e** | 3-MeO | H |
| **f** | 2-MeO | H |
| **q** | 2-Me | 4-MeO |
| **r** | 2-Me | H |
| **s** | 2-MeO | 4-MeO |
| **t** | 2-MeO | 5-MeO |
| **u** | 3-MeO | 4-MeO |

chain organomagnesiums (EtMgBr, *n*-PrMgBr, *n*-BuMgBr, $n\text{-}C_7H_{15}MgBr$, and $PhCH_2CH_2MgBr$) leading to the formation of dihydrodimer **329** via radical coupling reactions; (iii) branched organomagnesiums (*i*-PrMgBr, *s*-BuMgBr, CyMgBr) giving rise to mixtures of dihydrodimers and dearomatized conjugate addition compounds;[170,171] (iv) Grignards such as $PhCH_2MgCl$ and *t*-BuMgCl characterized by the exclusive formation of [1,6] addition products.

Thus, the reaction of **325a** with an excess of EtMgBr affords a mixture of the normal [1,2] addition product **327** (<10%), the 10-ethyl-substituted anthryl ethyl ketimine **328** (35%),[172] and the dihydrodimer **329** (50%, mixture of two stereoisomers)[173] (Scheme 56). Compound **328** results from the consecutive [1,2] and [1,6] addition of the organomagnesium to the [1,2]- and [1,6]-positions of the conjugated

**Table 24. Dearomatizing Anionic Cyclization−Photochemical Rearrangement of Benzamides 283a−h and 289a[a]**

| entry | SM | $R^1$ | $R^2$ | yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | **283a** | *i*-Pr | H | **299a** (80) | >99 |
| 2 | **283b** | *i*-Pr | 2-Me | **299b** (49) | 80 |
| 3 | **283c** | *i*-Pr | 3-Me | **299c** (40) | 92 |
| 4 | **283d** | *i*-Pr | 4-Me | **298a** (85) | 86 |
| 5 | **283e** | *i*-Pr | 2-MeO | **300** (55) | nd |
| 6 | **283f** | *i*-Pr | 3-MeO | **299d** (20) | 90 |
| 7 | **283g** | *i*-Pr | 4-MeO | **298b** (94) | >99 |
| 8 | **283g** | *i*-Pr | 4-MeO | **299e** (94) | nd |
| 9 | **283h** | *i*-Pr | 2,4-di-MeO | **298c** (53) | 92 |
| 10 | **289a** | (*S*)-CH(Me)Ph | 4-MeO | **298d** (52) | >98 (de) |

[a] Data taken from ref 161.

**Scheme 54**

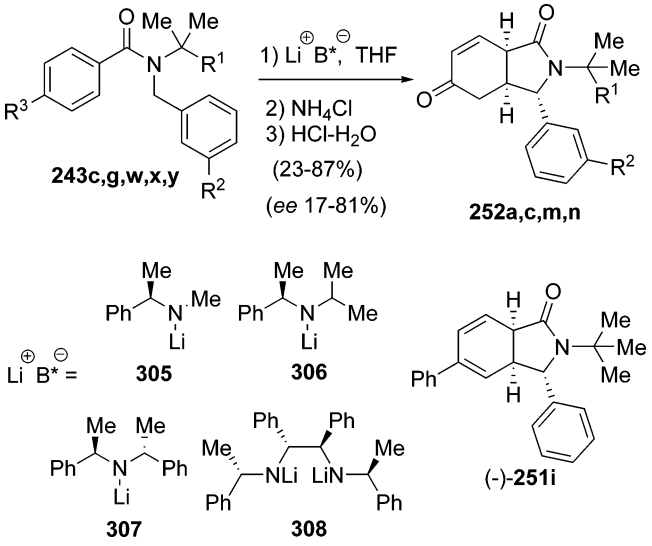



**Table 25. Asymmetric Deprotonation and Cyclization of Amides 243[a]**

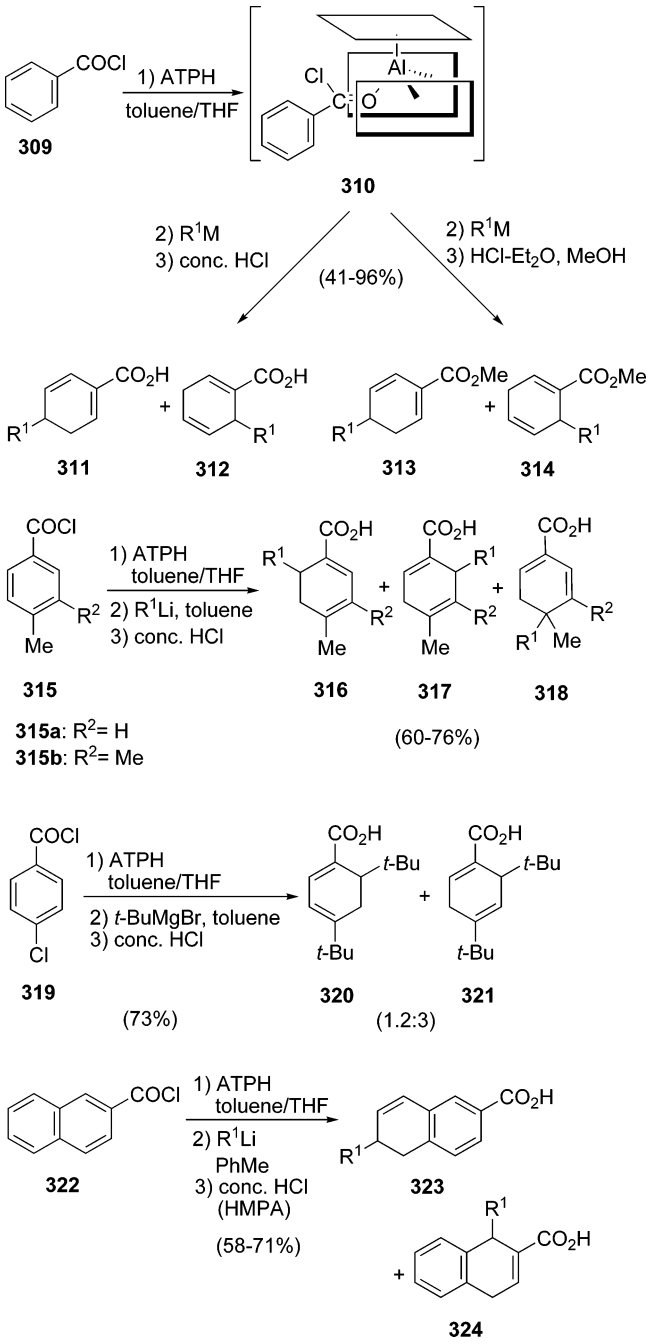
| entry | SM | $R^1$ | $R^2$ | $R^3$ | $Li^+B^*$ | yield (%) | ee (%) |
|---|---|---|---|---|---|---|---|
| 1 | **243c** | Me | H | MeO | **305** | (−)-**252a** (72) | 17 |
| 2 | **243c** | Me | H | MeO | **306** | (−)-**252a** (72) | 80 |
| 3 | **243c** | Me | H | MeO | **307** | (−)-**252a** (73) | 80 |
| 4 | **243c** | Me | H | MeO | **308** | (+)-**252a** (38) | 75 |
| 5 | **243g** | Ph | H | MeO | **307** | (−)-**252c** (59) | 73 |
| 6 | **243w** | Me | MeO | MeO | **306** | (−)-**252m** (72) | 81 |
| 7 | **243w** | Me | MeO | MeO | **307** | (−)-**252m** (64) | 75 |
| 8 | **243w** | Me | MeO | MeO | **308** | (+)-**252m**(23) | 30 |
| 9 | **243x** | Ph | MeO | MeO | **305** | (-)-**252n** (87) | 84 |
| 10 | **243y** | Me | H | Ph | **305** | (-)-**251i** (70) | 60 |

[a] Data taken from ref 166.

system defined by the central aromatic ring of the anthracene linked to the cyano group. On the other hand, it has been suggested that dearomatized dimer **329** is the result of a radical process initiated also by the [1,6] addition of EtMgBr to the starting nitrile.

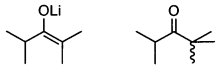
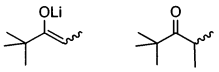
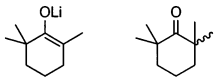
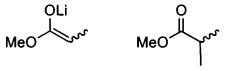
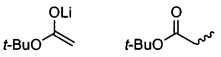
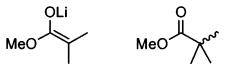
Martynoff described the first dearomatization of an arylnitrile, 9-cyanoanthracene **325a**, through the reaction of a Grignard reagent, *t*-BuMgCl. The product isolated, **326b**, was considered to result from a [1,2] addition of *t*-BuMgCl to the cyano group followed by migration of the *t*-Bu moiety to the carbon C10 of the anthracene system (Scheme 56).[174] However, Lalande and Calas[169] showed that **326b** was formed by the intermolecular conjugate [1,6] addition of the Grignard to the aromatic nitrile **325a**. Benzylmagnesium chloride reacted also with **325a**, leading to **326c** (67%),[169] identified in a later work as a mixture of two stereoisomers.[175]

**Scheme 55**



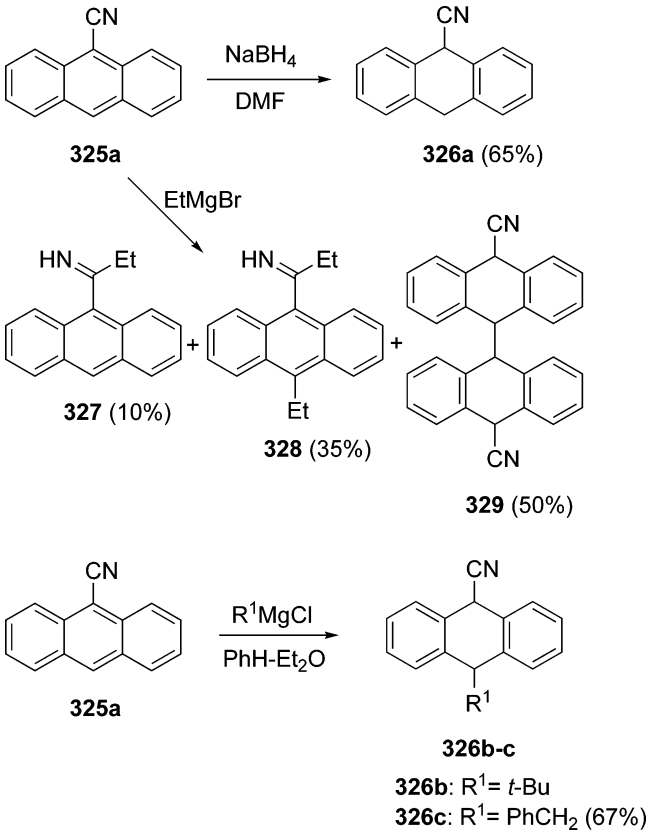

The presence of an alkyl substituent in the para position with respect to the cyano group as in 9-cyano-10-methylanthracene **325b** prevents the attack of the less reactive Grignard reagents on the ring. For instance, the reaction of EtMgBr with **325b** produced a mixture of imine **330** and a dimer assigned as **331** (Scheme 57).[176] However, $PhCH_2$-MgCl added smoothly to 9-cyano-10-ethylanthracene **325c**, 10-benzyl-9-cyanoanthracene **325d**, and 9-cyano-10-phenylanthracene **325e**, to give, after electrophilic trapping with alkyl halides, dearomatized products **326f−i** in yields ranging from 26 to 63%.[177,178] The same organomagnesium added in a [1,6] manner to 9,10-dicyanoanthracene **325f** and 9-cyano-10-methoxyanthracene **325g**. In both cases, a first equivalent of $PhCH_2MgCl$ displaced the cyano or methoxy substituent at the C10 position, and then [1,6] addition of a second equivalent of $PhCH_2MgCl$ to the in situ generated benzylated cyanoanthracene derivative **325d**, producing a

**Table 26. Conjugate Addition to Aromatic Acid Halides 309, 315, and 322**[a]

| Entry | SM | $R^1M$ | $R^1$ | $R^2$ | Yield (%) [ratio] |
|---|---|---|---|---|---|
| 1 | **309** | MeLi | Me | | **311a:312a** (99) [1.6:1] |
| 2 | **309** | *n*-BuLi | *n*-Bu | | **311b:312b** (ng)[b] [4.5:1] |
| 3 | **309** | *s*-BuLi | *s*-Bu | | **311c:312c** (ng)[b] [14:1] |
| 4 | **309** | *t*-BuLi | *t*-Bu | | **311d:312d** (ng)[b] [39:1] |
| 5 | **309** | PhLi | Ph | | **311e:312e** (96) [>99:1] |
| 6 | **309** |  | | | **311f:312f** (41) [>99:1] |
| 7 | **309** |  | | | **311g:312g** (72) [>99:1] |
| 8 | **309** |  | | | **311h:312h** (46) [>99:1] |
| 9 | **309** |  | | | **311i:312i** (75) [>99:1] |
| 10 | **309** | *i*-PrMgBr | *i*-Pr | | **311j:312j** (71) [13:1] |
| 11 | **309** | *t*-BuMgBr | *t*-Bu | | **311d:312d** (90) [15:1] |
| 12 | **309** | $CH_2$=CHLi | $CH_2$=CH | | **313a:314a** (53) [8.5:1] |
| 13 | **309** | $CH_2$=$CHCH_2$Li | $CH_2$=$CHCH_2$ | | **313b:314b** (68) [3.4:1] |
| 14 | **309** |  | | | **313c:314c** (78) [7.9:1] |
| 15 | **315a** | MeLi | Me | H | **316a:317a** (76) [1:1] |
| 16 | **315a** | *t*-BuLi | *t*-Bu | H | **317b:318a** (63) [1:8.1] |
| 17 | **315b** | MeLi | Me | Me | **316b:317c** (60) [1:1.7] |
| 18 | **315b** | *t*-BuLi | *t*-Bu | Me | **318b** (70) [100] |
| 19 | **322** | *t*-BuLi | *t*-Bu | | **323a:324a** (58) [2.9:1] |
| 20 | **322** |  | | | **323b:324b** (71) [1:13.3] |

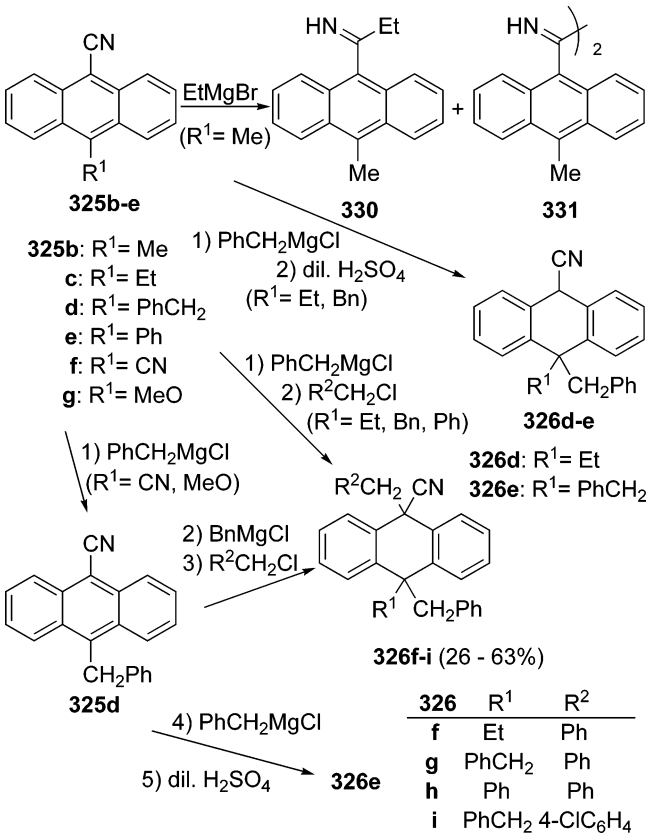
[a] Data taken from ref 167. [b] Yield not given.

**Scheme 56**




dearomatized anion. This intermediate anion can be protonated with dilute $H_2SO_4$ or alkylated with benzylic halides ($PhCH_2Cl$, 4-Cl-$C_6H_4CH_2Cl$), affording dihydroanthracenes **326e** and **326g**,**i**, respectively. The less reactive ethyl iodide

**Scheme 57**




| 326 | $R^1$ | $R^2$ |
|---|---|---|
| **f** | Et | Ph |
| **g** | $PhCH_2$ | Ph |
| **h** | Ph | Ph |
| **i** | $PhCH_2$ | 4-$ClC_6H_4$ |

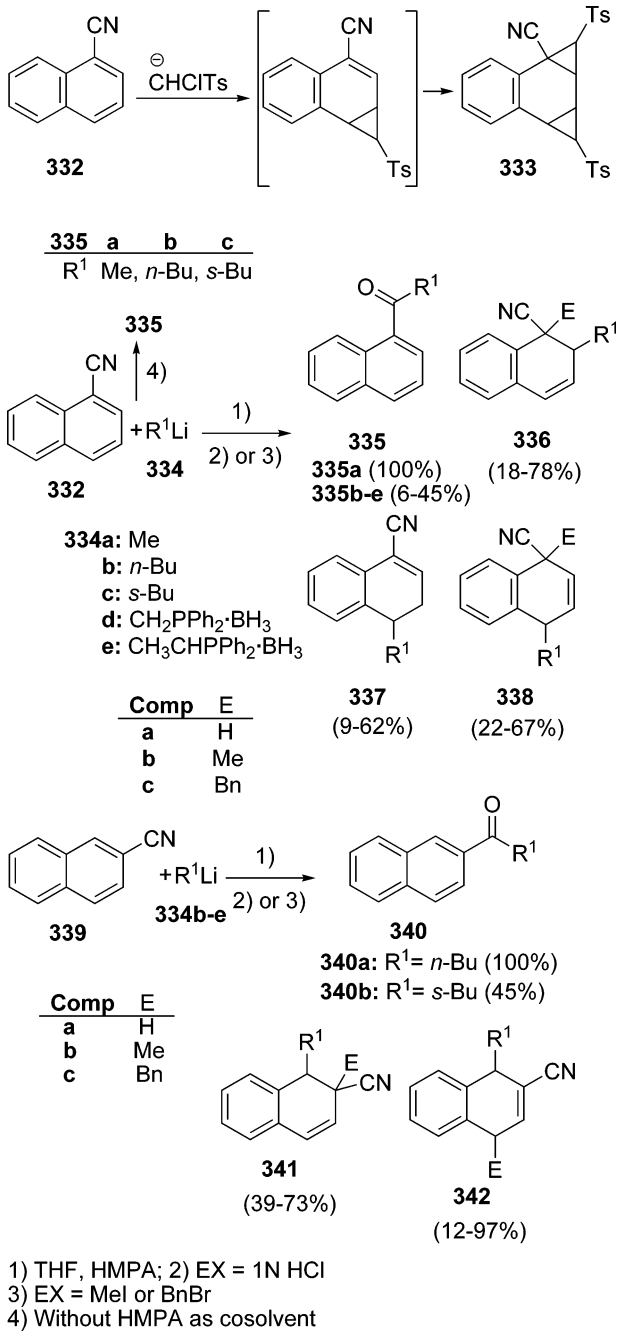
failed to add to the dearomatized organomagnesium intermediate. Alternatively, the treatment of **325f**,**g** with an excess of $PhCH_2MgCl$ in the presence of benzyl chloride affords directly **326g** in good yields. The method described here represents an interesting entry to 9,10-dihydroanthracenes tetrasubstituted at positions 9 and 10. It is worth recalling that introducing a carbonyl substituent in the C10 carbon of anthracene-9-carbonitrile as in compound **142** (section 5.3) induced a change of reactivity toward Grignard reagents, leading to 9,10-dihydroanthryl derivatives **144** and **145** resulting from the initial reduction of the central ring of **142**.[111]

## 11.3. Reactions with Organolithium Reagents

The cyano group is a known precursor of 1,3-oxazolines,[179] one of the activating groups most widely applied for the conjugate addition of organolithiums to naphthalenes (see section 12). However, the use of arylnitriles as Michael acceptors in dearomatizing reactions with RLi reagents has remained practically unexplored. As for Grignard reagents, the normal reaction of organolithiums with aromatic nitriles consists of a [1,2] addition to give imines,[180] ketones,[181] amines,[182,183] enamidines,[184] and triazines.[185] Until recently, the only report on the dearomatization of an aromatic ring bearing a cyanide substituent was the attempted vicarious nucleophilic substitution[31,33,186] between 1-cyanonaphthalene **332** and the carbanion of chloromethyl *p*-tolyl sulfone. Instead of the expected $S_NAr$ product, the bisannulated compound **333** was obtained. The formation of **333** was explained via two consecutive additions of the carbanion to naphthalene followed by intramolecular nucleophilic displacement of chloride (Scheme 58).[187]

Very recently, it has been shown that organolithium reagents undergo conjugate addition to both naphtho- and

**Scheme 58**




1) THF, HMPA; 2) EX = 1N HCl
3) EX = MeI or BnBr
4) Without HMPA as cosolvent

benzonitriles when the reaction is carried out in the presence of HMPA at low temperature. Simple alkyl-lithiums and lithium phosphine borane complexes **334** have proved to be suitable nucleophiles for the dearomatization of 1-cyanonaphthalene **332** and 2-cyanonaphthalene **339** (Scheme 58).[188] Protonation or alkylation of the anionic intermediates gave mixtures of ketones **335/340** and dihydronaphthalenes **336**−**338/341**−**342**. Increasing the nucleophilicity and bulkiness of the incoming anion favored the [1,6] addition to **332** over the competing [1,4] and [1,2] addition products. Thus, for E = H the ratio **337**:**336** increased in the series *n*-BuLi < *s*-BuLi < $LiCH_2PPh_2{\cdot}BH_3$ < $LiCH(CH_3)PPh_2{\cdot}BH_3$ from 1:5 to 3.4:1. The distribution of products obtained after electrophilic quench indicated that the lithium adducts to the cyano group are in equilibrium with those formed by attack at the naphthalene nucleus. The latter were alkylated more quickly, leading to mixtures of dihydronaphthalenes **336b**,**c** and **338b**,**c** in good yields. Nucleophiles **334d**,**e** added regiospecifically to the α position of the naphthalene ring of nitrile **339**. Protonation of the metalated dearomatized adducts occurred predominantly or exclusively at the γ position with respect to the cyano group, leading to dihydronaphthalene derivatives **342**. When MeI or BnBr is used as electrophile, the major products obtained, **341**, result from the reaction through the α position of the CN linkage.

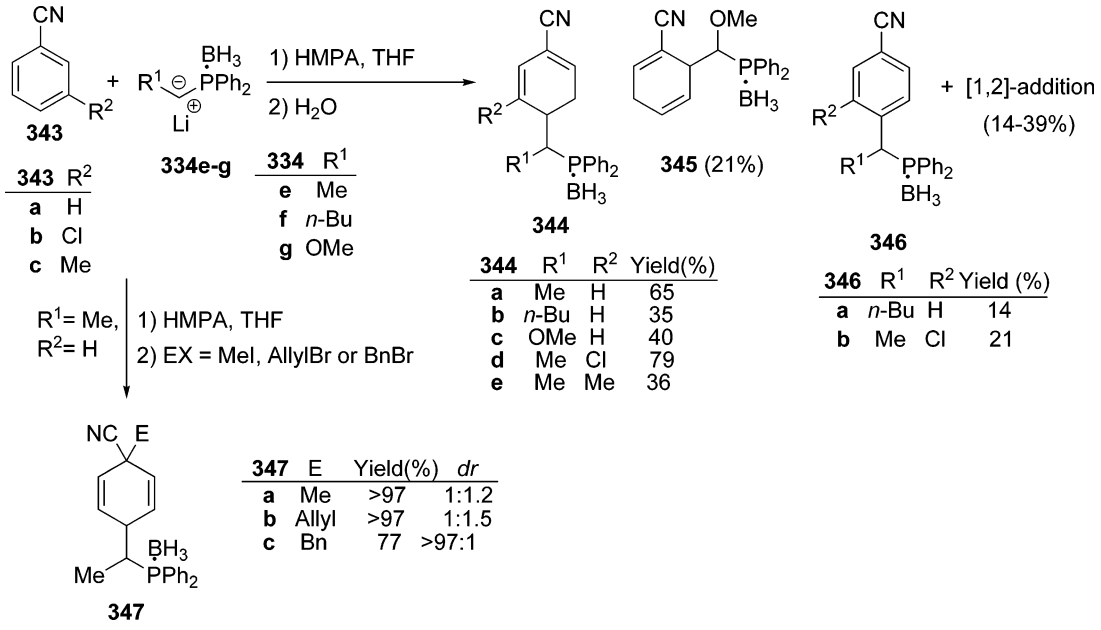
Additionally, nucleophilic conjugate addition to benzonitriles is feasible only with lithium phosphine borane complexes **334e**−**g** having a secondary carbanionic center. *n*-BuLi and *s*-BuLi add exclusively to the CN group of benzonitrile **343a**, affording the respective ketones quantitatively. The primary carbanion **339d** also failed to attack the aromatic ring of **343a**, probably due to insufficient nucleophilicity. [1,6] Addition of **334e**−**g** to **343** in THF at −90 °C in the presence of HMPA is preferred over the normal [1,2] attack at the CN (Scheme 59).[189] The dearomatized species were trapped with water and alkyl halides. Protonation afforded 2-cyano-1,3-cyclohexadienes **344** in moderate to good yields (35−79%, mixtures of two diastereoisomers). Only in the reaction of **334g** with **343a** was a significant amount of the product of [1,4] addition **345** (21%) observed. The lower regioselectivity shown by **334g** was ascribed to the higher nucleophilicity as compared with the other nucleophiles used. In addition, small amounts of rearomatized products **346** were observed in two cases (Scheme 59). Alkylation with MeI, AllylBr, BnBr, and the [1,6] adduct via reaction of **334e** with benzonitrile **343a** furnished 1,4-cyclohexadienes **347** in very high yield.

The processes described above represents not only the first examples of the conjugate addition of lithium reagents to arylnitriles but also the first examples of the participation of phosphorus-stabilized anions[190] **334d**−**g** in $D_NAr$ reactions. Further elaboration of the cyano and phosphine borane functional groups present in the dearomatized products may give access to interesting products. Functionalized cyclohexane derivatives are frequently found in numerous biologically active substances.[191]

## 12. Oxazolines

Nucleophilic conjugate additions to an aromatic ring based on the ring electrophilicity induced by oxazoline substituents represent the method of widest generality for the dearomatization of a naphthalene nucleus. The sequence of reactions, developed by Meyers and co-workers, involves [1,4] and [1,6] additions of organolithiums and organomagnesiums to oxazoline-substituted naphthalenes followed by trapping of the resulting azaenolate intermediate with an electrophile, which invariably enters trans to the organometallic reagent. As activating groups, oxazolines offer an immediate intrinsic advantage: the heterocycle is readily accessible in a chiral form and, therefore, it can impart asymmetry to the successive transformations affecting the naphthalene ring. Conversion of the oxazoline moiety of the dearomatized product to an aldehyde allows the recovery of the chiral auxiliary and affords a functionalized dihydronaphthalene containing two adjacent stereocenters, which can be further functionalized. Yields and stereoselectivities are generally very high. Furthermore, for electrophiles other than protons, one of the stereocenters formed is quaternary. The literature up to 1993 has been covered in detail.[14,16] Some additional contributions may be found in a recent review by Meyers.[29] In the following sections we will present the main achievements of the method classified according to the incoming nucleo-

**Scheme 59**




phile. Synthetic applications will be discussed in section 19.

## 12.1. Reactions with Carbon Nucleophiles

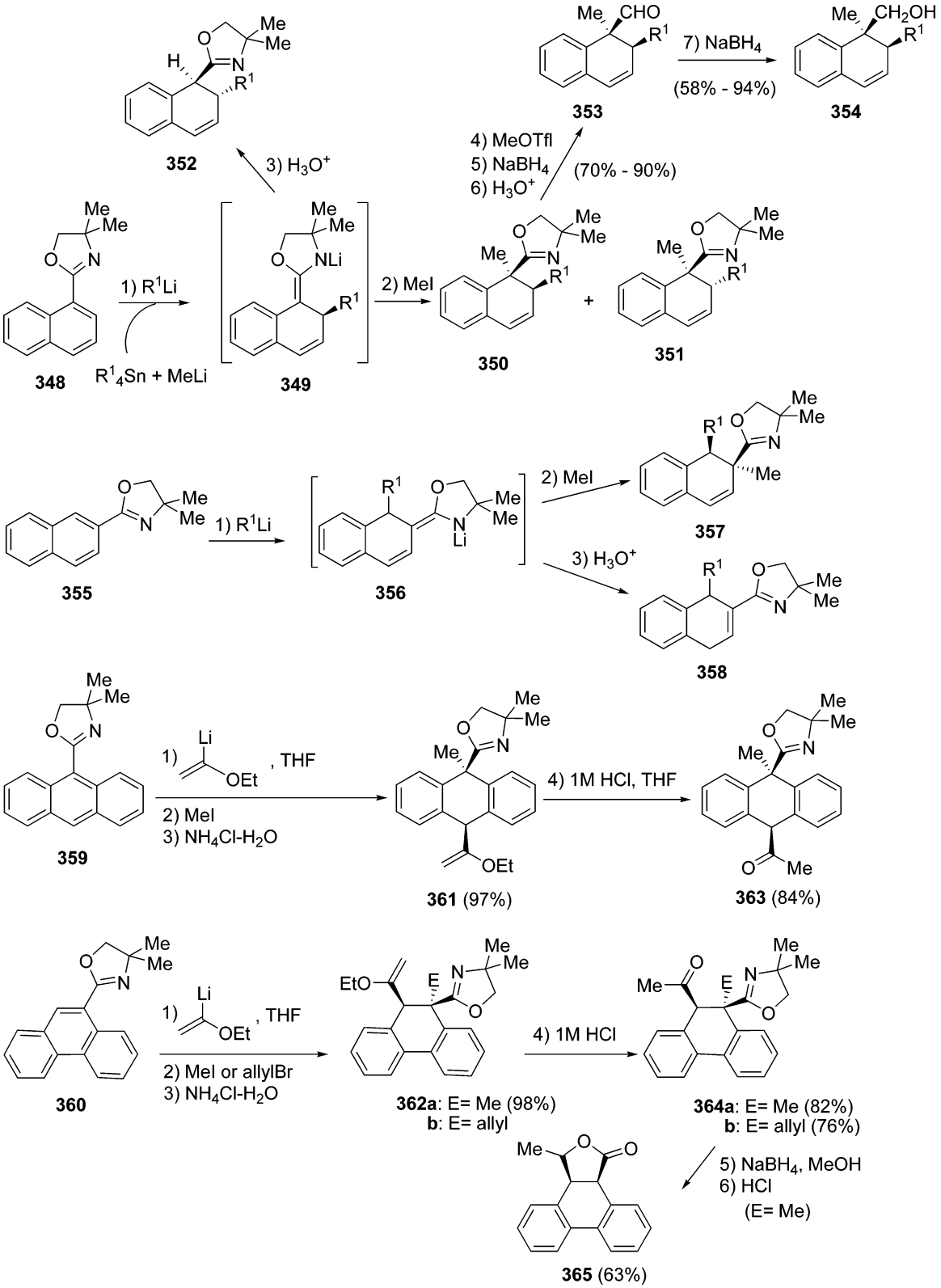
The tandem conjugate organolithium addition−electrophilic trapping of naphthyloxazolines is illustrated in Scheme 60 for the 1-isomer, **348**, and 2-isomer, **355**. Treatment of **348** and **355** with a series of $R^1$Li reagents in THF, followed by acidic quench or addition of methyl iodide, gave dihydronaphthyl derivatives **350**−**352**, **357**, and **358** via azaenolates **349** and **356**, respectively (Table 27).[139] Protonation with isopropanol produced large amounts of rearomatized or trans-epimerized products. Similar base-promoted isomerization has been observed in the analogous dearomatization reaction of naphthyl imines (Scheme 32). In a number of cases, the addition could be achieved only when organolithiums were prepared in situ through trans-metalation of tetrasubstituted stannanes with MeLi. The differences in the behavior of the organolithium reagents were explained in terms of possible changes in the aggregation state. In line with this argument, it was observed that the reaction rate increased when HMPA was added to the reaction mixture prior the addition of methyl-lithium. Further improvement resulted from the use of lithium 4,4′-di-*tert*-butylbiphenyl (LiDBB) for the generation of the requisite lithium reagents. In this way, comparable yields were obtained in significantly shorter reaction times.[192] The oxazoline ring of compounds **350** was converted into an aldehyde by sequential quaternization of the nitrogen with methyl trifluoromethanesulfonate, reduction with sodium borohydride, and acidic hydrolysis. Additional reduction of dihydronaphthalenes **353** to the carbinols **354** was performed to facilitate the separation of stereoisomers.

The remarkable conjugate addition of ethoxyvinyl-lithium to **348** and **355** (Table 27, entries 13 and 21) represents the first examples of addition of an acyl equivalent to an aromatic ring. The lithio intermediates thus generated were trapped with methyl iodide, furnishing **350j** and **357d**, respectively, which were transformed into the corresponding methyl ketones by mild acid hydrolysis.[193] This chemistry was extended to anthracene-oxazolines, **359**, and phenanthrene-oxazolines, **360**. High yields of dearomatized compounds **361** and **362**, respectively, were obtained. Treatment of these vinyl ether derivatives with 1 M HCl provided the ketones **363** and **364**. Reduction of the carbonyl group of **364a** (E = Me) with sodium borohydride and subsequent removal of the oxazoline with hydrochloric acid afforded the lactone **365**. Compounds **361** and **362** represent the only examples of dearomatized products of aryloxazolines in which the aromatic system is not a naphthalene ring.

When the nucleophilic and electrophilic centers are present in the same reagent as in haloalkyl lithium **366**, the tandem conjugate anionic dearomatization−electrophilic alkylation furnishes annelated dihydronaphthalene **368** (Scheme 61; Table 27, entry 17).[194] Addition to the naphthalene nucleus takes place at −78 °C, whereas cyclization occurs at temperatures above 0 °C. Protonation of the adduct **367** at −45 °C affords dihydronaphthyl derivative **369**. Further elaboration of **368**, as previously described for **350**, leads to aldehyde **370** and carbinol **371**. The annelation of a saturated five-membered carbocycle and heterocycle (pyrrolidine and furan) to the aromatic system of suitably substituted naphthyloxazolines has also been accomplished very efficiently through anionic cyclization.[149] Lithiation of **372** via iodine−lithium (for **372a**) or tin−lithium exchange (for **372b**,**c**, in the presence of TMEDA) and subsequent treatment of the intermediate azaenolates **373** with ammonium chloride, alkyl halides (MeI, allylBr, BnBr), or benzaldehyde gives dihydronaphthalene derivatives **374** and **375** in good yields and, in general, with excellent stereocontrol (Scheme 61; Table 28).[157]

For naphthyloxazolines bearing a methoxy substituent, the reaction with nucleophiles follows two different pathways depending on the position of the methoxy group. Dearomatization dominates when both substituents are separated,[195] whereas essentially $S_NAr$ products are obtained if both substituents occupy adjacent 1,2-positions in the naphthalene nucleus.[196] The exception to this rule are the [1,6] adducts **378**, **379**, and **381** formed in the reaction of **376** and **377** with allyl-lithium reagents (Scheme 62).[197,198] The scope of the process was extended by trapping the dearomatized azadienolate with a variety of carbon electrophiles. In this case, excellent yields of diastereomerically pure 1,4-dihy-

**Scheme 60**



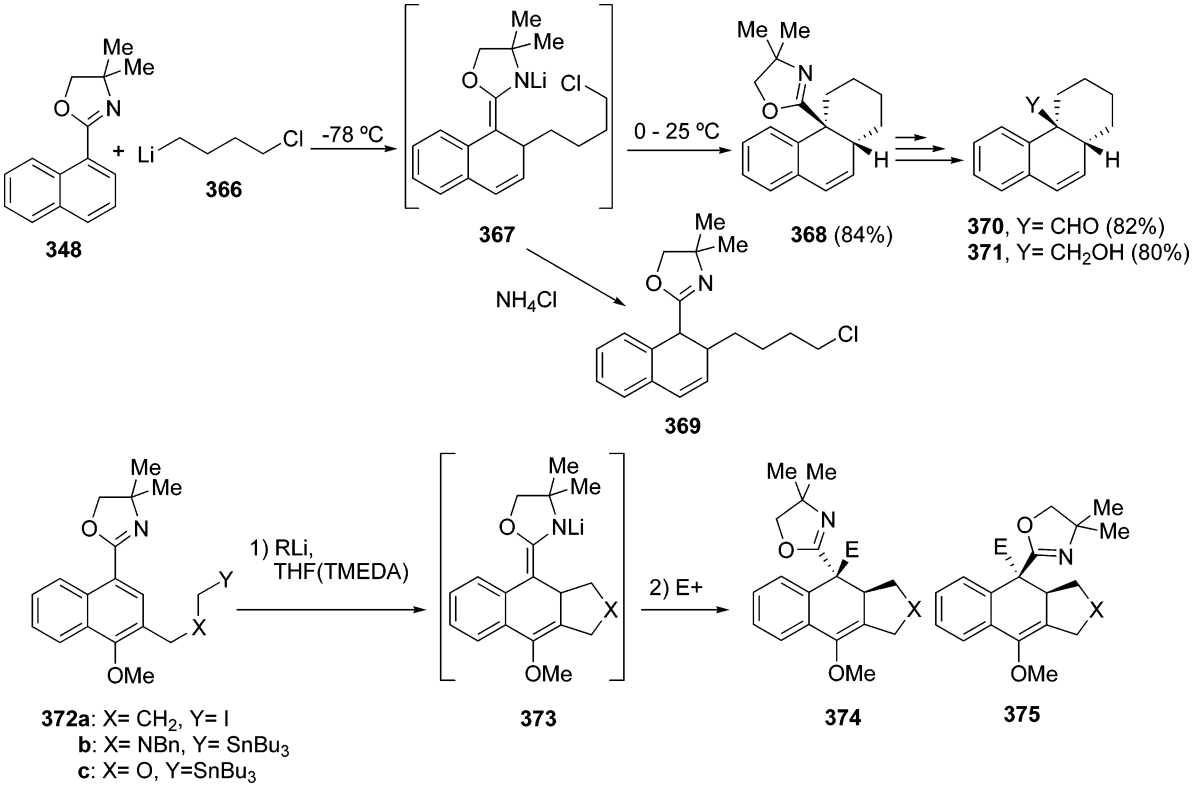

dronaphthalenes **379a**−**f** were obtained (Scheme 62; Table 27, entries 24−29).[199] The remarkable stereocontrol exerted by the remote allylic system was assigned to the existence of a major azadienolate conformer having the alkyl substituent in a pseudoaxial orientation that minimizes steric interactions with the peri hydrogen. The presence of the axial group appears to prevent the attack of the incoming electrophile from the same face, thus explaining the trans relationship between the two alkyl substituents in 1,4-positions of the products. Furthermore, the exclusive addition of the electrophile to the carbon adjacent to the oxazoline ring of the lithio intermediate was assumed to be the result of a complex-induced proximity effect (CIPE)[200] due to chelation of the lithium cation to the oxazoline nitrogen and the methoxy substituent. Coordination of the electrophile to the lithium ion of this chelate places the electrophilic center close to carbon C1 of the naphthalene. Upon standing in air, dihydronaphthalenes **379** undergo oxidation to give naph-

**Table 27. Conjugate Addition of Carbon Nucleophiles to Achiral Naphthyloxazolines**

| entry | SM | $R^1Li$ | addition temp (°C) | $R^1$ | $E^+/H^+$ | yield (%) [ratio] |
|---|---|---|---|---|---|---|
| 1 | **348**[a] | $CH_2$=CHLi | −80 | $CH_2$=CH | $CF_3CO_2H$ | **352a** (95) |
| 2 | **348**[a] | $CH_2$=$CHCH_2Li$ | −80 | $CH_2$=$CHCH_2$ | $H_2O$:*i*-PrOH 1:1 | **352b** (90) |
| 3 | **348**[a] | $CH_2$=C(Li)$CH_3$ | −80 | $CH_2$=$CCH_3$ | HCl | **352c** (90) |
| 4 | **348**[a] | MeLi | −20 | Me | MeI | **350a** (65) |
| 5 | **348**[b] | *i*-PrLi[c] | −78 | *i*-Pr | MeI | **350b** (81) |
| 6 | **348**[b] | *c*-$C_3H_5Li$[c] | −78 to −30 | *c*-$C_3H_5$ | MeI | **350c** (78) |
| 7 | **348**[a] | *n*-BuLi | −45 | *n*-Bu | MeI | **350d** (90) |
| 8 | **348**[a] | *s*-BuLi | −45 | *s*-Bu | MeI | **350e** (94) |
| 9 | **348**[a] | *t*-BuLi | −45 | *t*-Bu | MeI | **350f** (99) |
| 10 | **348**[a] | $CH_2$=$CHCH_2Li$ | −80 | $CH_2$=$CHCH_2$ | MeI | **350g**:**351a** (85) [62:38] |
| 11 | **348**[a] | $CH_2$=C(Li)$CH_3$ | −80 | $CH_2$=$CCH_3$ | MeI | **350h** (95) |
| 12 | **348**[b] | $CH_3CH_2$=CHLi[c] | −30 | $CH_3CH_2$=CH | MeI | **350i** (70) |
| 13 | **348**[d] | $CH_2$=C(Li)OEt | −10 | $CH_2$=COEt | MeI | **350j** (50) |
| 14 | **348**[a] | $PhCH_2Li$ | −80 | $PhCH_2$ | MeI | **350k** (91) |
| 15 | **348**[a] | PhCαC$CH_2Li$[e] | −40 | PhC≡$CCH_2$ | MeI | **350l**:**351b** (90) [70:30] |
| 16 | **348**[a] | $THPOCH_2CH$=CHLi[e] | −40 | $THPOCH_2CH$=CH | MeI | **350m**:**351c** (74) [84:16] |
| 17 | **348**[f] | $LiCH_2CH_2CH_2CH_2Cl$ | −78 | $CH_2CH_2CH_2CH_2$ | | **368** (84) |
| 18 | **355**[a] | *n*-BuLi | −45 | *n*-Bu | MeI | **357a** (90) |
| 19 | **355**[a] | *s*-BuLi | −45 | *s*-Bu | MeI | **357b** (91) |
| 20 | **355**[a] | *t*-BuLi | −45 | *t*-Bu | MeI | **357c** (90) |
| 21 | **355**[d] | $CH_2$=C(Li)OEt | −10 | $CH_2$=COEt | MeI | **357d** (98) |
| 22 | **376**[g] | $CH_2$=$CHCH_2Li$ | −40 | $CH_2$=$CHCH_2$ | $NH_4Cl$ | **378a** (88) |
| 23 | **376**[g] | $Me_3SiCH$=$CHCH_2Li$ | −40 | $Me_3SiCH$=$CHCH_2$ | $NH_4Cl$ | **378b** (90) |
| 24 | **376**[h] | $CH_2$=$CHCH_2Li$ | −78 | $CH_2$=$CHCH_2$ | MeI | **379a** (97) |
| 25 | **376**[h] | $Me_3SiCH$=$CHCH_2Li$ | −78 | $Me_3SiCH$=$CHCH_2$ | MeI | **379b** (95) |
| 26 | **376**[h] | $Me_3SiCH$=$CHCH_2Li$ | −78 | $Me_3SiCH$=$CHCH_2$ | $I(CH_2)_4Cl$ | **379c** (96) |
| 27 | **376**[h] | $Me_3SiCH$=$CHCH_2Li$ | −78 | $Me_3SiCH$=$CHCH_2$ | $Me_2C$=$CH(CH_2)_2Br$ | **379d** (92) |
| 28 | **376**[h] | $Me_3SiCH$=$CHCH_2Li$ | −78 | $Me_3SiCH$=$CHCH_2$ | $I(CH_2)_3CO_2Et$ | **379e** (89)[i] |
| 29 | **376**[h] | $Ph_3SiCH$=$CHCH_2Li$ | −78 | $Ph_3SiCH$=$CHCH_2$ | MeI | **379f** (97) |
| 30 | **377**[j] | $Me_3SiCH$=$CHCH_2Li$ | −78 | $Me_3SiCH$=$CHCH_2$ | MeI | **381** (98) |

[a] Data taken from ref 139. [b] Data taken from ref 192. [c] Generated by reaction of the corresponding bromide with LiDBB. [d] Data taken from ref 193. [e] Reaction performed in the presence of 2 equiv of HMPA. [f] Data taken from ref 194. [g] Data taken from ref 197. [h] Data taken from ref 199. [i] Yield decreased to 52% when $Br(CH_2)_3CO_2Et$ was used as electrophile. [j] Data taken from ref 198.

**Scheme 61**




thalenones **380** in high yield. The transformation can be accelerated by performing the oxidation with singlet oxygen.

An alternative to prevent the nucleophilic displacement of a methoxy group contiguous to an oxazoline moiety is to place both substituents in 2,3-positions of the naphthalene

**Table 28. Dearomatizing Anionic Cyclization of Naphthyloxazolines 372**[a]

| entry | SM | X | $E^+$ | $R^1$ | yield (%) [ratio] |
|---|---|---|---|---|---|
| 1 | **372a** | $CH_2$ | $NH_4Cl$ | H | **374a**:**375a** (85) [>96:4] |
| 2 | **372a** | $CH_2$ | MeI | Me | **374b**:**375b** (71) [<4:96] |
| 3 | **372a** | $CH_2$ | $CH_2$=$CHCH_2Br$ | $CH_2$=$CHCH_2$ | **374c**:**375c** (67) [50:50] |
| 4 | **372a** | $CH_2$ | $PhCH_2Br$ | $PhCH_2$ | **374d**:**375d** (65) [<4:96] |
| 5 | **372a** | $CH_2$ | PhCHO | $PhCH_2OH$ | **374e**:**375e** (60)[b] [<4:96] |
| 6 | **372b** | NBn | $NH_4Cl$ | H | **374f**:**375f** (73) [>96:4] |
| 7 | **372b** | NBn | MeI | Me | **374g**:**375g** (71) [>96:4] |
| 8 | **372b** | NBn | $CH_2$=$CHCH_2Br$ | $CH_2$=$CHCH_2$ | **374h**:**375h** (67) [>96:4] |
| 9 | **372b** | NBn | $PhCH_2Br$ | $PhCH_2$ | **374i**:**375i** (65) [>96:4] |
| 10 | **372b** | NBn | PhCHO | $PhCH_2OH$ | **374j**:**375j** (60)[c] [>96:4] |
| 11 | **372c** | O | $NH_4Cl$ | H | **374k**:**375k** (74) [>96:4] |
| 12 | **372c** | O | MeI | Me | **374l**:**375l** (79) [>96:4] |
| 13 | **372c** | O | $PhCH_2Br$ | $PhCH_2$ | **374m**:**375m** (75) [75:25] |
| 14 | **372c** | O | PhCHO | $PhCH_2OH$ | **374n**:**375n** (68)[c] [>96:4] |

[a] Data taken from ref 157. [b] Mixture of epimers in the CHOH in a ratio of 3:1. [c] Mixture of epimers in the CHOH in a ratio of 3:2.

ring. In this substitution pattern, the formation of the lithium $\sigma$-complex precursor of the $S_NAr$ product would perturb the whole aromatic system, whereas the intermediate participating in the [1,4] addition would retain a benzene ring unaffected. As a result, the dearomatization reaction would be kinetically favored. This hypothesis was experimentally confirmed by treating naphthyloxazolines **382** with a series of alkyl-lithiums in THF and subsequent trapping of the dearomatized adducts with methyl iodide. The process furnished mixtures of [1,2] and [1,4] addition products **384** and **383**, respectively (Scheme 62).[116] Attack on the aromatic ring predominated for *n*-BuLi, *s*-BuLi, and PhLi with yields ranging from 75 to 95%. For MeLi the major product obtained was the ethyl ketone **385a** (65%), the formation of which may be understood through deprotonation with MeLi followed by methylation of an intermediate imine resulting from ring−chain tautomerism of **384a**. The bulky *t*-BuLi led to the exclusive addition to the carbon−nitrogen double bond of the oxazoline. When *n*-BuLi was used as nucleophile, a small amount of the 1-methylnaphthyloxazoline derivative **386** (5%) arising from the ortho-lithiation of **382** was also obtained. Significantly, no displacement of the methoxy group of the starting substrate was observed.

The sequence of reactions of nucleophilic addition−electrophilic trapping of naphthaleneoxazolines can be readily performed in an asymmetric manner by using chiral oxazolines as auxiliaries.[14,16,201] The application of this synthetic strategy to the transformations described in section 12.1 allows the synthesis of 1,1,2- and 1,2,2-trisubstituted enantiomerically pure dihydronaphthalenes having two chiral centers, with generally high diastereoselectivity and predictable absolute configuration. The methodology is illustrated in Scheme 63 for naphthalene oxazolines **387**−**388**, and the results obtained are summarized in Tables 29 and 30.[202,203] The oxazoline moiety of the dearomatized products **391** and **395** can be transformed into a carbaldehyde group producing the corresponding derivatives **393** and **396** via a very efficient three-step procedure involving quaternization of the nitrogen followed by reduction and subsequent acid hydrolysis as already mentioned in the dearomatization of achiral oxazolines. Further reduction of the carbonyl group with $LiAlH_4$ or $NaBH_4$ gives the corresponding carbinols **394**.

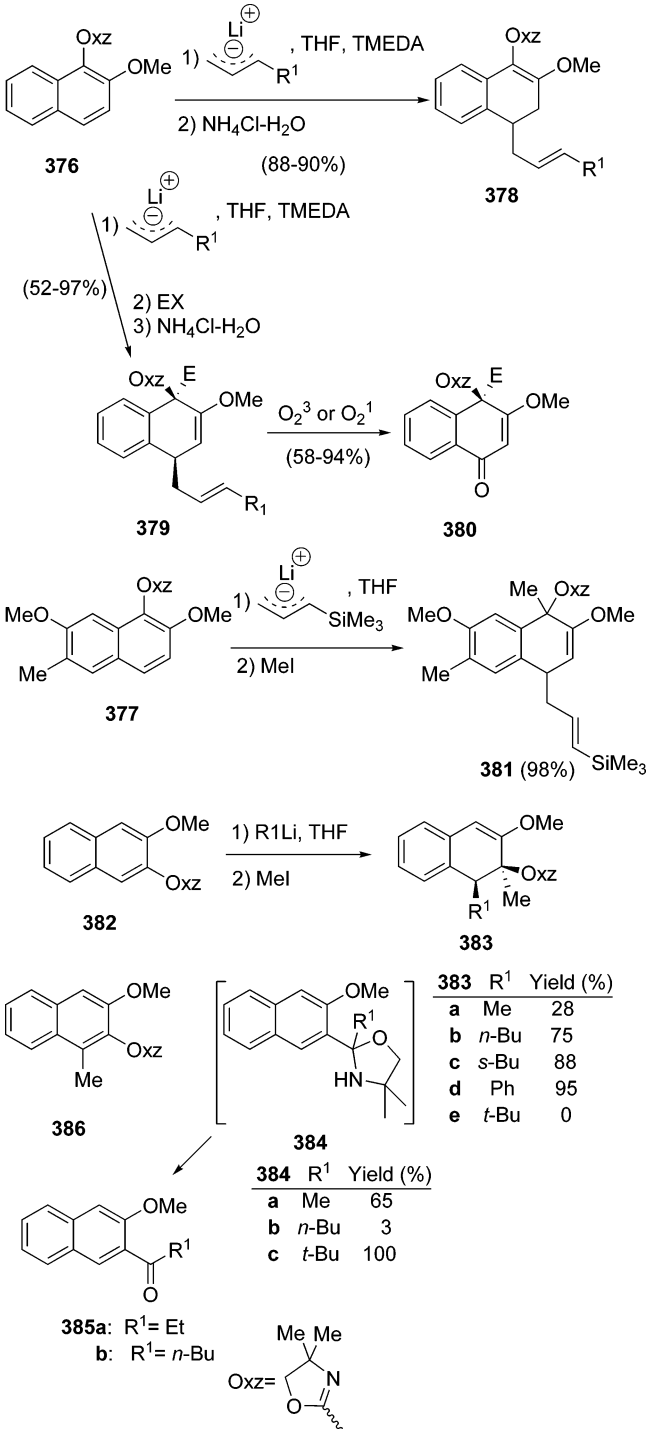
Annulation of **387a** by reaction with 4-chloro-1-butyllithium proceeded stereospecifically to give tricyclic system **399** in good yield (75%) (Scheme 64; Table 29, entry 15).[194] Acidic removal of the oxazoline auxiliary and subsequent treatment with lithium aluminum hydride afforded alcohol **400**. Additional intramolecular processes involved the formation of **403** and **404** through cyclization with the lithium derivatives of the diethylacetals of 3-chloropropanal- and 4-chlorobutanal formed by treatment with LiDBB. In this case, the annulation was performed by the addition of $BF_3$.

In all cases, the two diastereomers obtained result from the attack of the electrophile on the intermediate dearomatized azaenolate from the side opposite the organolithium reagent. The quench of these intermediates with protonating agents followed the same stereochemical course. However, as in the achiral series, epimerization occurred during workup and/or postprocessing steps. Protonation was best achieved with trifluoroacetic acid. In the case of **387a**,**c**, the workup procedure caused ring opening of the oxazoline auxiliary leading to the amino ester salts **397**. Lithium aluminum hydride reduction of the latter gave enantiomerically pure carbinols **398** in good yields (Scheme 63).[195,204]

The facial selectivity observed for the incoming nucleophile is determined by the stereocenter at C4 in the oxazoline auxiliary. Interestingly, the presence of a phenyl substituent at position C5 in oxazolines **I** (Scheme 63) produced a reversal of the configuration of the stereocenters created in the naphthalene nucleus with respect to the oxazolines **II**−**IV**. A model explaining the stereochemical course of the sequential nucleophilic addition−alkylation process for the threonine-derived oxazolines **I**−**IV** is shown in Scheme 63. A complex is formed between the chiral auxiliary and the organolithium in which the lithium cation is coordinated to the nitrogen of the heterocycle and the oxygen of the sidearm at C4. Assuming a tetracoordination for the lithium, the carbanionic ligand $R^4$ may undergo exchange between two positions, one almost parallel to the naphthalene ring and a second one giving complex **389** with the requisite alignment to undergo a suprafacial 1,5-sigmatropic rearrangement, which would lead to azaenolate **390**. Electrophilic attack on the latter would occur preferentially through the less hindered $\alpha$-face affording **391**.

Chelation is not the only pathway for the stereocontrolled addition of the nucleophile to naphthyloxazolines. Bulky alkyl substituents at C4 of the auxiliary, as in oxazolines **V** and **VI**, block nucleophilic attack to the $\alpha$-face, thus favoring complexation of the organolithium through the $\beta$-face. Addition of methyl iodide to the resulting azaenolates led to dihydronaphthalenes **391** with the same stereochemistry obtained with chiral oxazolines having a chelating sidearm and with similar or even superior stereoselectivities (Scheme 63).[205] The reaction shows interesting temperature effects;

**Scheme 62**




| 383 | $R^1$ | Yield (%) |
|---|---|---|
| a | Me | 28 |
| b | *n*-Bu | 75 |
| c | *s*-Bu | 88 |
| d | Ph | 95 |
| e | *t*-Bu | 0 |

| 384 | $R^1$ | Yield (%) |
|---|---|---|
| a | Me | 65 |
| b | *n*-Bu | 3 |
| c | *t*-Bu | 100 |

for example, vinyl-lithium smoothly undergoes addition to **387h** (Oxz = **VI**) at 0 °C, whereas the process was completely inhibited at −40 °C. Similarly, increasing the temperature of the addition of *n*-butyllithium from −78 °C to room temperature allowed a significant shortening of the reaction time without affecting the enantioselectivity of the products (Table 29, entries 37 and 38). Short reaction times were also observed when organolithium reagents generated in situ from LiDBB were used (Table 29, entry 34).[192] Chiral oxazoline **VI** proved to be also very efficient in the asymmetric tandem nucleophilic addition−methylation of the methoxy-substituted 2-naphthyloxazoline **412**. The dihydronaphthalene derivatives **413** ($R^4$ = *n*-Bu, Ph) were obtained as single stereoisomers (Scheme 64; Table 30, entries 11−12).[116]

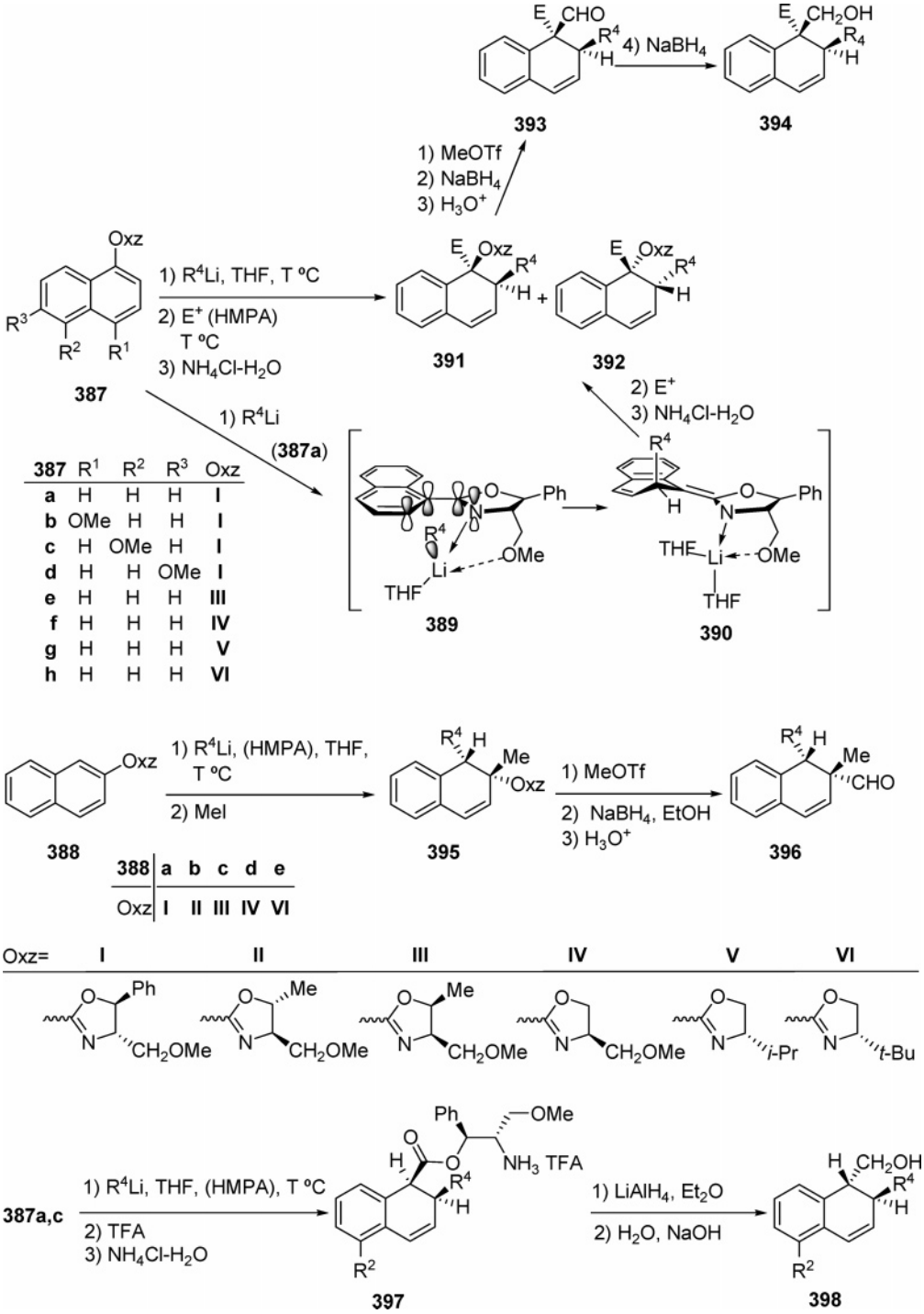
The chiral oxazolines **I**−**VI** (Scheme 63) provided high stereocontrol through either chelating or steric effects. However, these chiral auxiliaries were derived from amino acids and therefore gave access to only one enantiomer. This limitation was surmounted by designing a multigram synthesis of both enantiomers of methoxyaminoalcohol **411** starting from L-serine **405** (Scheme 64). The performance of the new auxiliaries in dearomatization−alkylation reactions proved to be comparable to those previously described (Table 29, entries 17−23).[206] Poor diastereoselectivities were observed only for *s*-BuLi and *t*-BuLi. Chromatographic separation of the mixture allowed the isolation of the major stereoisomer in high purity.

## 12.2. Reactions with Nitrogen Nucleophiles

Meyers and Shimano achieved the first direct amination of a naphthalene nucleus by treating naphthyloxazolines **387h** and **388e**,**f** with lithium amides in THF in the presence of 1 equiv of HMPA (Scheme 65). The intermediate dearomatized anions formed, **414** and **416**, were trapped with alkyl halides, affording exclusively the respective [1,4] adducts **415** and **417** (Table 31).[134,207] In the absence of additive, the reaction yields were very low. An optimization study showed that the yields increased with increasing polarity of the solvent (DME > THF > $Et_2O$). Chelating amines such as TMEDA and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) produced a small decrease in yield with respect to pure THF, whereas DMPU was slightly less efficient than HMPA in promoting the conjugate addition.[134]

Interestingly, the amide addition step proved to be reversible. The reaction of **387h** with lithium piperidide and subsequent addition of methyl iodide led to **415d** as a single product. However, the use of diethyl carbonate as quenching electrophile resulted in the complete recovery of the starting material. Furthermore, addition of *n*-BuLi to the adduct of naphthyloxazoline **387h** and lithium piperidide followed by methylation with MeI produced the butyl derivative **391ca** exclusively. The reversibility of the reaction was attributed to steric effects in the dearomatized azaenolate intermediate, which would favor the rearomatization. Steric hindrance was considered also to be responsible for the absence of reaction between **387h** and lithium diethylamide, lithium diallylamide, lithium diisopropylamide, and lithium 2,2-dimethylaziridide. Lithium allylamide failed to give dearomatized products. In this case, the lack of reactivity correlates with the inability of lithium salts of primary amines to undergo conjugate additions to α,β-unsaturated carbonyl compounds. Azaenolate **414** may be the favored intermediate generated in the process. As in previous examples of nucleophilic addition to chiral naphthyloxazolines, the incoming nucleophile approches the β-face due to the blocked access of the α-face by the bulky *t*-Bu group. The nitrogen atoms of the adduct are proposed to chelate to the lithium cation, which would complete its tetracoordination through binding to a solvent molecule and to the bulky cosolvent HMPA. The latter would coordinate preferably through the β-face to avoid steric interactions with the *t*-Bu group. In this model, minor steric interactions are expected for the cyclic lithium piperidide and the lithium methylalkylamides. However, in the adducts of the lithium salts of diethylamine, diallylamine, and diisopropylamine, the alkyl groups of the amine moiety can freely rotate, causing unfavorable interactions with HMPA, *t*-Bu, and the solvated cation. Nevertheless, it cannot be discarded that the apparently unreactive lithium amides mentioned do

**Scheme 63**




indeed undergo addition to the naphthalene nucleus, but its bulkiness prevents the approach of the electrophile. Under such conditions, the lithiated azaenolate **414** and **416** may revert to the starting naphthyloxazolines simply on warming.

Aminated dihydronaphthalenes **415** and **417** were converted into $\beta$-amino acids **420**, **422**, **424**, and **425** as shown in Scheme 66. The piperidone acetal derivatives served as precursors of primary amino acids. 2-Amino-dihydronaphthalene **419** was further transformed into the $\beta$-lactam **421**. Surprisingly, in the case of **417d** hydrolysis of the chiral oxazoline and cleavage of the piperidone ring to give a $NH_2$ group took place in a single step under basic conditions and without the requisite activation of the heterocycle via alkylation as mentioned previously. Conversion of **415b**,**d**,**e** into the corresponding *N*,*N*-dialkyl $\beta$-amino acids **422** was achieved in the two-step procedure indicated in Scheme 66.

Interestingly, secondary lithium amides (diallyl, dibenzyl, etc.) that failed to react with the *tert*-leucine-derived naphthyloxazolines **387h** and **388e**,**f** smoothly added to achiral oxazoline **348** in the presence of 1 equiv of HMPA, to give [1,6] adducts when the amount of HMPA was increased to 8−10 equiv (Scheme 67; Table 31).[208,209] The reversibility of the addition of lithium amides to naphthaleneoxazolines, together with difficulties for the [1,4] attack arising from steric effects of the bulky nucleophiles $LiNR_2$, is a feature

**Table 29. Conjugate Addition of Carbon Nucleophiles to Chiral 1-Naphthyloxazolines 387**

| entry | SM | $R^4Li$ | addition temp (°C) | $E^+/H^+$ | yield (%) [ratio 389:387] | $R^1$ | $R^2$ | $R^3$ | Oxz | $R^4$ | E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **387a**[a] | MeLi | −45 | $(PhS)_2$ | **391a** (56) [86:14] | H | H | H | **I** | Me | PhS |
| 2 | **387a**[b] | EtLi | −45 | MeI | **391b** (92) [94:6] | H | H | H | **I** | Et | Me |
| 3 | **387a**[b] | *n*-BuLi | −45 | MeI | **391c** (97) [94:6] | H | H | H | **I** | *n*-Bu | Me |
| 4 | **387a**[a] | *n*-BuLi | −45 | $MeO_2CCl$ | **391d** (99) [94:6] | H | H | H | **I** | *n*-Bu | $CO_2Me$ |
| 5 | **387a**[b] | *n*-BuLi | −45 | $(PhS)_2$ | **391e** (91) [94:6] | H | H | H | **I** | *n*-Bu | PhS |
| 6 | **387a**[c] | $Me_2C(Li)CH_2CH_3$ | −85 | MeI | **391f** (75) [96:4] | H | H | H | **I** | $Me_2C(Li)CH_2CH_3$ | Me |
| 7 | **387a**[b] | $CH_2$═CHLi | −80 | MeI | **391g** (79) [90:10] | H | H | H | **I** | $CH_2$═CH | Me |
| 8 | **387a**[b] | $CH_2$═C(Li)$CH_3$ | −80 | MeI | **391h** (75) [88:12] | H | H | H | **I** | $CH_2$═$CCH_3$ | Me |
| 9 | **387a**[b] | $C_5H_7Li$ | −80 | MeI | **391i** (73) [89:11] | H | H | H | **I** | 1-cyclopentenyl | Me |
| 10 | **387a**[a] | PhLi | −45 | MeI | **391j** (99) [83:17] | H | H | H | **I** | Ph | Me |
| 11 | **387a**[d] | MeLi[e] | −45 | $CF_3CO_2H$ | **397a** (42) [84:16][f] | H | H | H | **I** | Me | H |
| 12 | **387a**[d] | *i*-PrLi | −78 | $CF_3CO_2H$ | **397b** (73) [96:4][f] | H | H | H | **I** | *i*-Pr | H |
| 13 | **387a**[d] | *n*-BuLi | −78 | $CF_3CO_2H$ | **397c** (73) [94:6][f] | H | H | H | **I** | *n*-Bu | H |
| 14 | **387a**[d] | PhLi | −45 | $CF_3CO_2H$ | **397d** (62) [85:15][f] | H | H | H | **I** | Ph | H |
| 15 | **387a**[g] | $Cl(CH_2)_4Li$ | −78 | $Cl(CH_2)_4Li$ | **399** (75) [>99:1] | H | H | H | **I** | $CH_2CH_2CH_2CH_2$ | |
| 16 | **387e**[b] | PhLi | −45 | MeI | **391k** (94) [30:70] | H | H | H | **III** | Ph | Me |
| 17 | **387f**[h] | EtLi | −78 | MeI | **391l** (66) [4:96] | H | H | H | **IV** | Et | Me |
| 18 | **387f**[h] | *n*-BuLi | −78 | MeI | **391m** (94) [5:95] | H | H | H | **IV** | *n*-Bu | Me |
| 19 | **387f**[b] | *n*-BuLi | −78 | MeI | **391m** (93) [8:92] | H | H | H | **IV** | *n*-Bu | Me |
| 20 | **387f**[h] | *s*-BuLi | −78 | MeI | **391n** (72) [23:77] | H | H | H | **IV** | *s*-Bu | Me |
| 21 | **387f**[h] | *t*-BuLi | −78 | MeI | **391o** (79) [36:64] | H | H | H | **IV** | *t*-Bu | Me |
| 22 | **387f**[h] | $CH_2$═CHLi | −40 | MeI | **391p** (73) [3:97] | H | H | H | **IV** | $CH_2$═CH | Me |
| 23 | **387f**[h] | PhLi | −78 | MeI | **391q** (78) [9:91] | H | H | H | **IV** | Ph | Me |
| 24 | **387b**[b] | *n*-BuLi | −80 | MeI | **391r** (95) [97:3] | MeO | H | H | **I** | *n*-Bu | Me |
| 25 | **387b**[b] | *t*-BuLi | −80 | MeI | **391s** (95) [65:35] | MeO | H | H | **I** | *t*-Bu | Me |
| 26 | **387b**[b] | $CH_2$═$CH(CH_2)_3Li$ | −80 | MeI | **391t** (90) [97:3] | MeO | H | H | **I** | $CH_2$═$CH(CH_2)_3$ | Me |
| 27 | **387b**[b] | $Me_2C$═$CH(CH_2)_2Li$ | −80 | MeI | **391u** (90) [97:3] | MeO | H | H | **I** | $Me_2C$═$CH(CH_2)_2$ | Me |
| 28 | **387c**[b] | *n*-BuLi | −78 | MeI | **391v** (95) [97:3] | H | MeO | H | **I** | *n*-Bu | Me |
| 30 | **387c**[b] | $CH_2$═CHLi | 0 | MeI | **391w** (80) [80:20] | H | MeO | H | **I** | $CH_2$═CH | Me |
| 31 | **387c**[b] | $CH_2$═$CH(CH_2)_3Li$ | −78 | MeI | **391x** (80) [95:5] | H | MeO | H | **I** | $CH_2$═$CH(CH_2)_3$ | Me |
| 32 | **387c**[d] | EtLi | −78 | $CF_3CO_2H$ | **397e** (85) [97:3][f] | H | MeO | H | **I** | Et | H |
| 33 | **387d**[b] | $C_5H_7Li$ | −80 | MeI | **391y** (50) [85:15] | H | H | MeO | **I** | 1-cyclopentenyl | Me |
| 34 | **387g**[i] | *n*-BuLi | −78[j,k] | MeI | **391z** (97) [97:3] | H | H | H | **V** | *n*-Bu | Me |
| 35 | **387g**[i] | $CH_2$═CHLi | −10 | MeI | **391aa** (89) [94:6] | H | H | H | **V** | $CH_2$═CH | Me |
| 36 | **387g**[i] | PhLi | −40 | MeI | **391ba** (87) [87:13] | H | H | H | **V** | Ph | Me |
| 37 | **387h**[i] | *n*-BuLi | −78[j] | MeI | **391ca** (99) [>99:1] | H | H | H | **VI** | *n*-Bu | Me |
| 38 | **387h**[i] | *n*-BuLi | 25[l] | MeI | **391ca** (99) [>99:1] | H | H | H | **VI** | *n*-Bu | Me |
| 39 | **387h**[i] | $CH_2$═CHLi | 0 | MeI | **391da** (94) [>99:1] | H | H | H | **VI** | $CH_2$═CH | Me |
| 40 | **387h**[i] | PhLi | −40 | MeI | **391ea** (81) [95:5] | H | H | H | **VI** | Ph | Me |

[a] Data taken from ref 202. [b] Data taken from ref 195. [c] Data taken from ref 192. [d] Data taken from ref 204. [e] Three equivalents of HMPA added. [f] Carbinol formed upon addition of $LiAlH_4$ to the product of protonation **395**. [g] Data taken from ref 194. [h] Data taken from ref 206. [i] Data taken from ref 205. [j] Reaction time = 2 h. [k] Reaction time < 1 min, temperature = 0 °C for *n*-BuLi generated via LiDBB.[192] [l] Reaction time = 0.25 h.

**Table 30. Conjugate Addition of Carbon Nucleophiles to Chiral 2-Naphthyloxazolines 388 and 412**

| entry | SM | $R^4Li$ | addition temp (°C) | yield (%) [ratio] | Oxz | $R^4$ |
|---|---|---|---|---|---|---|
| 1 | **388a**[a] | MeLi | −30 | **395a** (67) [91:9] | **I** | Me |
| 2 | **388a**[a] | *n*-BuLi | −78 | **395b** (85)[b] [98:2] | **I** | *n*-Bu |
| 3 | **388b**[a] | *n*-BuLi | −78 | **395b** (87) [6:94] | **II** | *n*-Bu |
| 4 | **388d**[a] | *n*-BuLi | −78 | **395b** (96) [7:93] | **IV** | *n*-Bu |
| 5 | **388a**[a] | *t*-BuLi | −100 | **395c** (74) [73:27] | **I** | *t*-Bu |
| 6 | **388a**[a] | PhLi | −30 | **395d** (89) [90:10] | **I** | Ph |
| 7 | **388b**[a] | PhLi | −78 | **395d** (90) [9:91] | **II** | Ph |
| 8 | **388c**[a] | PhLi | −78 | **395d** (93) [25:75] | **III** | Ph |
| 9 | **388d**[a] | PhLi | −78 | **395d** (90) [9:91] | **IV** | Ph |
| 10 | **388e**[c] | *n*-BuLi | −78 | **395b** (94) [99:1] | **VI** | *n*-Bu |
| 11 | **412**[d] | *n*-BuLi | −78 | **413b** (56) [>99:1] | **VI** | *n*-Bu |
| 12 | **412**[d] | PhLi | −78 | **413d** (56) [>99:1] | **VI** | Ph |

[a] Data taken from ref 195. [b] Increased to 92% in the presence of HMPA (1 equiv). [c] Data taken from ref 205. [d] Data taken from ref 116.

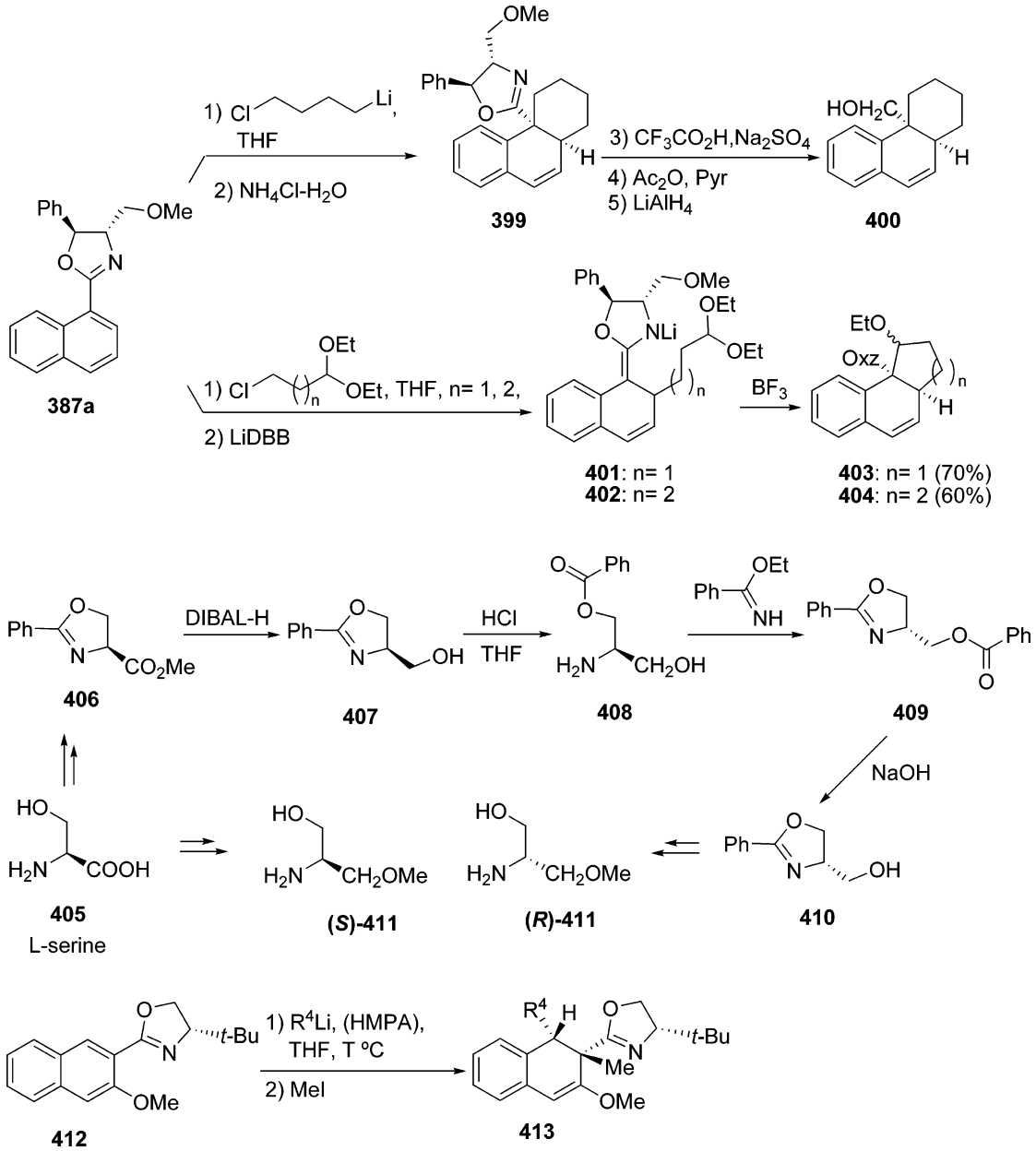
that favors the alternative [1,6] addition pathway. Nevertheless, the reaction of **348** with lithium monoalkylamides and pyrrolidides still occurred in a [1,4] manner when an excess of additive was used. Quenching the reaction with a series of alkylating agents afforded mixtures of dearomatized products alkylated at the α position to the oxazolines **426** and **427**, in preference to the $\gamma$ position, **428**, with moderate to good stereoselectivities. The utility of the major products **426** as precursors of $\delta$-amino esters was demonstrated by the efficient transformation of **426g**,**h** into **430a**,**b** in a three-step process indicated in Scheme 67. A mechanistic study of the reaction revealed that [1,4] and [1,6] adducts existed in equilibrium through the parent compound. The [1,4] derivatives were identified as the products of kinetic control, whereas formation of the [1,6] amino adducts was observed under thermodynamic control.[209] Acidity and bulkiness of the secondary amine, together with the use of a large excess of HMPA, were found to be the major factors responsible for the observed regioselectivity. Other bulky lithium amides such as lithium bis(trimethylsilyl)amide, lithium benzyltrimethylsilylamide, and lithium benzophenone imine did no undergo reaction with naphthaleneoxazoline **348**.

$\beta$-Amino acids **420** and **424** and $\gamma$-amino acids **430** obtained are conformationally restricted due to the dihydronaphthalene system. These types of amino acids have attracted great interest. Peptide analogues constructed from $\beta$- and $\gamma$-amino acids are currently intensively investigated. They give rise to well-defined secondary structures, some of them not commonly found in nature, with short chain lengths. Besides structural stability, they show stability toward enzymatic degradation. These features render $\beta$- and $\gamma$-peptides attractive targets for drug design.[210−214]

## 12.3. Reactions with Silicon Nucleophiles

The sequential addition of trimethylsilyllithium and methyl iodide to **387a** proceeded in good yield (70%), giving mixtures of **431a** and **432a** in a ratio of 1.5:1 (Scheme 68; Table 32).[195,202] The poor selectivity observed was attributed to the coordinating effect of the HMPA, an additive required for the generation of the lithiosilane from hexamethylsilane. To avoid the use of HMPA, the silylation was performed with

**Scheme 64**



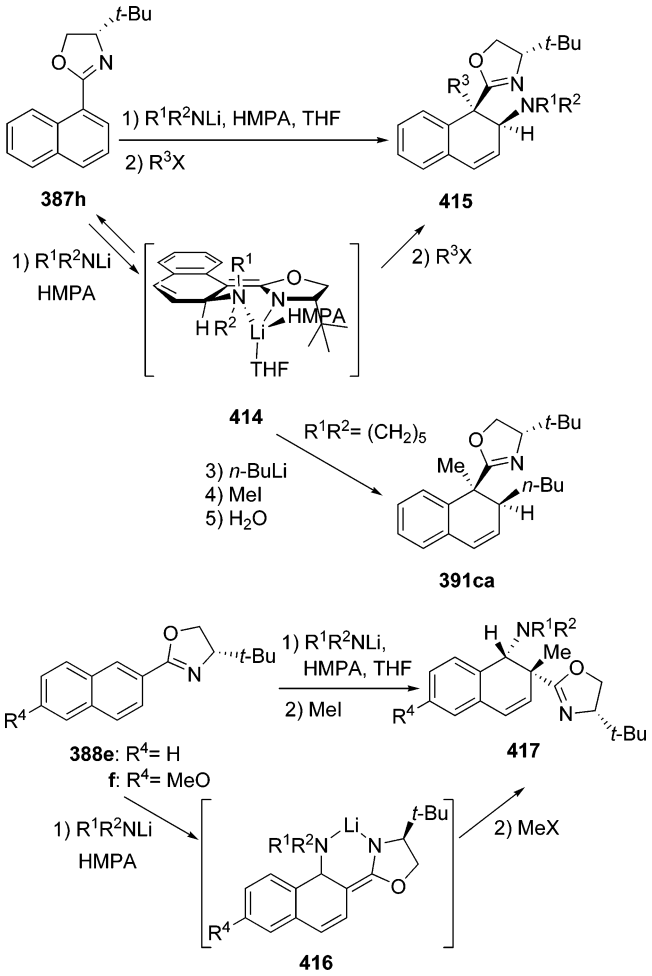

lithiodimethylphenylsilane generated by the reaction of PhMe$_2$SiCl with lithium wire. However, when the naphthaleneoxazolines **387g**−**i** were treated with this reagent in THF at low temperature and the azaenolate formed was captured with MeI, a mixture of diastereomers **431** and **432** was obtained in high yield, but again with low diastereoselectivities (Table 32, entries 2−4). Apparently, as in the case of HMPA, the solvent still competes strongly with the chiral oxazoline moiety for complexing the lithium reagent. This aspect was confirmed by reducing the coordinating ability and polarity of the solvent. The reaction of **387g** with lithiodimethylphenylsilane at −78 °C in diethyl ether/THF (3:1) and subsequent quench of the intermediate dearomatized anion with a series of alkyl halides leads to the dihydronaphthyloxazolines **431** with high diastereoselectivity (entries 5−7).[215] The silyl group could be efficiently replaced by a proton upon treatment with tetrabutylammonium fluoride to afford **433** together with small amounts of the $\Delta^3$-isomer **434** (7−9%). The mixture was converted quantitatively into **434** by treatment with Wilkinson's catalyst in toluene at 110 °C. Additional transformations of **433** involved hydrogenation of the isolated double bond and/or removal of the chiral oxazoline moiety to give quaternary substituted aldehydes **435** and **436**.

Silylation of methoxynaphthyloxazoline **386** with phenyldimethylsilyl-lithium followed by addition of methyl iodide gave ketone **385c** as the major product, which derives from [1,2] addition. The dearomatized oxazoline **437** was obtained in only 30% yield (Scheme 68).[116]

## 13. Oxazolidines

Parallel to Meyers' studies on the reactivity of nucleophiles toward naphthyloxazolines, Pridgen and co-workers found that the saturated oxazolidine ring was also capable of promoting nucleophilic conjugate addition to a naphthalene ring. The reaction of Grignard reagents with the naphthyloxazolidine **438** provided exclusively [1,4] addition products. Lithium, cerium, and copper organometallic reagents under

**Scheme 65**




went exclusively [1,2] addition.[216] Although considered by the authors as the first report of organomagnesium reagents adding to a naphthalene ring, such dearomatizing reactions are among the first examples described in the literature (see section 5.1). Trapping the dearomatized intermediate species **440** with a series of electrophiles proceeded in the same manner as that reported by Meyers, leading to dihydronaphthalenylcarbaldehydes **441**−**442** in high yields and, generally, with excellent enantioselectivities (Scheme 69; Table 33).[217] First, 1 equiv of Grignard reagent effects metalation of the oxazoline ring of **438**, which then undergoes a $\beta$-elimination to give the imine **439** with an alkoxy sidearm. This intermediate acts as the effective directing group of the nucleophilic attack of a second equivalent of organomagnesium to the aromatic ring. Conjugate addition of the nucleophile takes place through the less hindered face, that opposite the phenyl group of the chiral auxiliary. Interestingly, although the configuration of the chiral auxiliary of **438** is the opposite of that of Meyers's naphthyloxazolines **387g**,**h** (Scheme 63), the products **441**−**442** obtained show the same sense of chiral induction as the dihydronaphthyloxazolines **391** resulting from the [1,4] addition of *n*-BuLi, $CH_2$═CHLi, and PhLi to **387g**,**h** (Table 29).

In principle, the use of this methodology for the enantioselective synthesis of di- and trisubstituted dihydronaphthalenes **441**−**442** presents several advantages over the addition of organolithium reagents. On the one hand, the process is simpler because no stannylated precursors of the nucleophile are necessary to achieve the addition step efficiently. On the other, the transformation of the oxazolidine ring into the corresponding aldehyde can be readily performed in a one-pot manner by mild acid hydrolysis of the reaction mixture resulting from the nucleophilic dearomatization−electrophilic trapping process. Nevertheless, this methodology has been applied in only one additional case for the enantioselective synthesis of benzomorphans (see section 19).

**Table 31. Conjugate Addition of Nitrogen Nucleophiles to Naphthyloxazolines 348, 387h, and 388e,f**

| Entry | SM | $R^1R^2NLi$ | $R^3X$ | Yield (%) [ratio] |
|---|---|---|---|---|
| 1 | **387h**[a] | $Me_2NLi$ | MeI | **415a** (94) [98.5:1.5][b] |
| 2 | **387h**[a] | *n*-BuN(Li)Me | MeI | **415b** (93)[b] [>99:1] |
| 3 | **387h**[a] | *n*-$C_5H_{11}$N(Li)Me | MeI | **415c** (93) [>99:1] |
| 4 | **387h**[a] |  | MeI | **415d** (95) [>99:1] |
| 5 | **387h**[a] |  | AllylBr | **415e** (92) [>99:1] |
| 6 | **387h**[a] |  | BnBr | **415f** (67) [>99:1] |
| 7 | **387h**[a] |  | MeI | **415g** (96) [>99:1] |
| 8 | **388e**[a] | $Me_2NLi$ | MeI | **417a** (91) [97.5:2.5] |
| 9 | **388e**[a] |  | MeI | **417b** (94) [>99:1] |
| 10 | **388e**[a] |  | MeI | **417c** (94) [>99:1] |
| 11 | **388e**[a] |  | MeI | **417d** (94) [>99:1] |
| 12 | **388f**[a] | *n*-$C_5H_{11}$N(Li)Me | MeI | **417e** (90) [>99:1] |
| 13 | **348**[c] | $Bn_2NLi$ | MeI | **426a** (69) [78:15:7][d] |
| 14 | **348**[e] | $Bn_2NLi$ | AllylBr | **426b** (84) [91:<1:9][d] |
| 15 | **348**[c] | $Bn_2NLi$ | BnBr | **426c** (93) [>98:1:1][d] |
| 16 | **348**[c] | BnN(Li)Me | AllylBr | **426d** (86) [89:<2:9][d] |
| 17 | **348**[e] | BnN(Li)Me | BnBr | **426e** (94) [>98:1:1][d] |
| 18 | **348**[e] | $Ph(CH_2)_2N(Li)Me$ | AllylBr | **426f** (44) [>99:1:1][d] |
| 19 | **348**[c] | $(Allyl)_2NLi$ | MeI | **426g**(66) [75:15:10][d] |
| 20 | **348**[c] | $(Allyl)_2NLi$ | MeOTf | **426g** (76) [83:17:<1][d] |
| 21 | **348**[e] | $(Allyl)_2NLi$ | MeOTs | **426g** (50) [83:17:<1][d] |
| 22 | **348**[e] | $(Allyl)_2NLi$ | MeOBs | **426g** (46) [83:17:<1][d] |
| 23 | **348**[c] | $(Allyl)_2NLi$ | AllylBr | **426h** (85) [91:<1:9][d] |
| 24 | **348**[e] | $(Allyl)_2NLi$ |  | **426i** (20) [43:<1:49][d] |
| 25 | **348**[c] | $(Allyl)_2NLi$ | BnBr | **426j** (92) [>98:1:1][d] |
| 26 | **348**[e] | $(n\text{-}Pr)_2N(Li)$ | MeI | **426k** (53) [74:22:4][d] |

[a] Data taken from ref 134. [b] The minor isomer was identified as the [1,6] amino adduct. [c] Data taken from ref 208. [d] Product ratio **426**:**427**:**428**. [e] Data taken from ref 209.

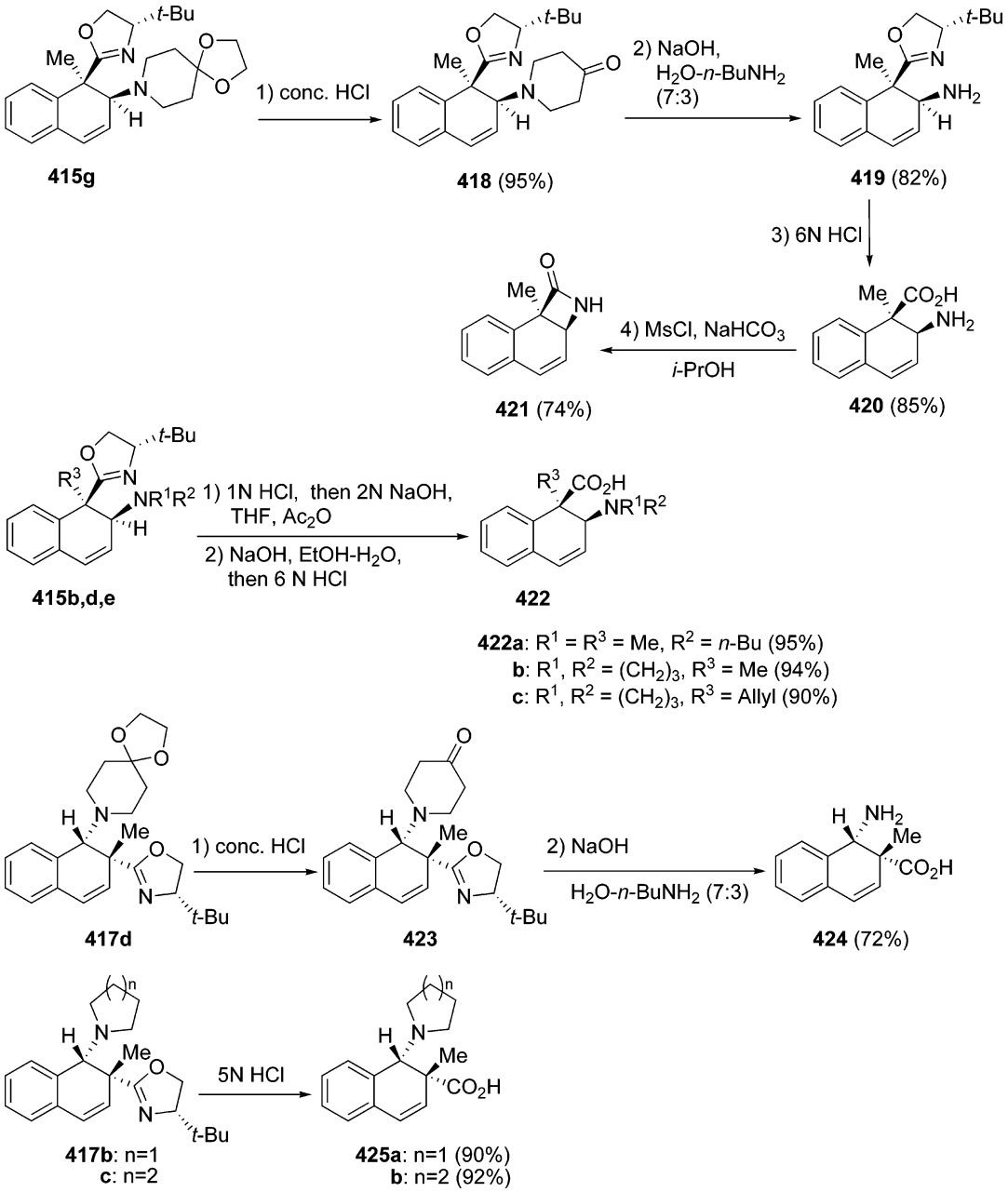
## *14. Aromatic Rings Linked to a Nitrogen Atom*

No doubt, the nitro group is the best substituent for making an aromatic ring electron-deficient, and a large body of knowledge has grown from the study of nucleophilic additions to nitroarenes. Besides this pivotal electron-withdrawing group, other nitrogenated functions such as diazo and triazine proved to be suitable for activating an aromatic nucleus toward nucleophilic attack.

### 14.1. Nitro Compounds

The addition of nucleophiles to aromatic nitro compounds to form $\sigma$-complexes (Meisenheimer[218] or Jackson−Meisenheimer[219] complexes for oxygen and nitrogen nucleophiles, Janovsky[220,221] complexes for carbon nucleophiles) has been known for more than a century. The topic has been covered in a number of reviews[31−33,222−226] and continues to attract great interest.[227,228] A wide variety of nucleophiles enter into this reaction, including hydride, carbanions, and reagents with nucleophilic heteroatoms such as nitrogen, oxygen, phos-

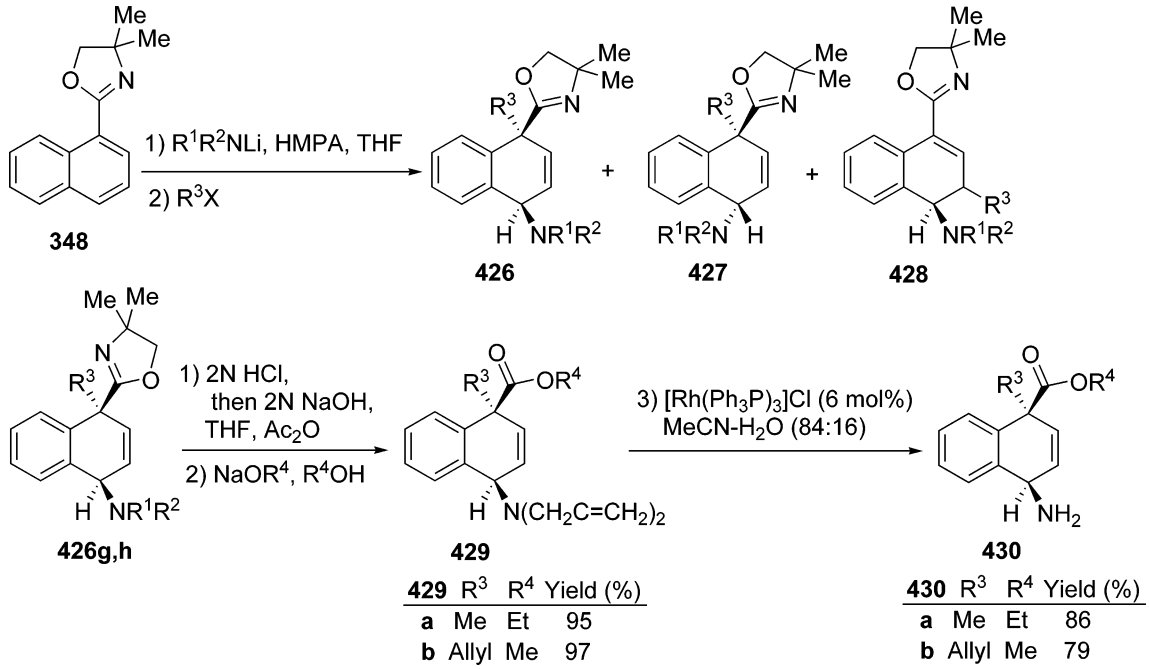
**Scheme 66**




phorus, and sulfur.[229−232] In general, stable σ-adducts result from the addition to aromatic rings of reduced aromaticity and/or when the nucleofuge is a poor leaving group. When a nucleophile attacks a nitroarene at a position bearing a good leaving group, rapid elimination of that group takes place, giving products of nucleophilic aromatic substitution.[233] However, when the nitronate formed proceeds from addition of the nucleophile to an unsubstituted carbon, then the rearomatization requires the departure of a hydride anion, *which is not a favored process*. These dearomatized anions can dissociate to starting reagents or can be converted to stable compounds by a variety of methods. Generally, rearomatization prevails, and the process represents a valuable route to the preparation of substituted nitroaromatic compounds.[30−33,234] Trapping reactions of Janovsky−Meisenheimer complexes with electrophiles may follow three directions: oxidation to the starting nitro compound, substitution of a nitro group, and formation of stable dearomatized compounds. The nature of the reacting agent and the substitution pattern in the complex define the preferred pathway.

Bartoli et al. studied extensively the scope of the conjugate addition of alkyl-Grignard reagents to mononitro aromatic compounds containing benzene, naphthalene, anthracene, and various heteroaromatic ring systems. Protonation or halogenation of the σ-complexes furnished cyclohexadiene compounds. The literature to 1982 has been reviewed.[26] From these studies some general patterns of alkylation have been found, which depend on the number of condensed aromatic cycles and the presence of substituents in reactive positions. Unsubstituted or alkyl-substituted nitrobenzenes and 1-nitronaphthalenes undergo alkylation to a similar extent in the ortho and para positions. Alkylation of 2-nitronaphthalene and 9-nitroanthracene occurs only at the α- and 10-positions, respectively. In systems having heterosubstituents in the ortho or para position, attack on the unsubstituted position is observed almost exclusively.[26] Addition to the position occupied by the heterosubstituent (ipso attack) takes place when it is the only reactive position. These features are illustrated in Scheme 70 by the reactions of benzylmagne-

**Scheme 67**




| 429 | $R^3$ | $R^4$ | Yield (%) |
|---|---|---|---|
| **a** | Me | Et | 95 |
| **b** | Allyl | Me | 97 |

| 430 | $R^3$ | $R^4$ | Yield (%) |
|---|---|---|---|
| **a** | Me | Et | 86 |
| **b** | Allyl | Me | 79 |

sium bromide with 4-methoxy-1-nitronaphthalene[235] **443** and 2-methoxy-2-nitronaphthalene[236] **444**. In both cases, acidic quench of the reaction mixture was used.

### *14.1.1. Reactions with Hydride Transfer Agents*

Aromatic nitro compounds may be converted into a variety of products by the action of sodium borohydride, the structures of which depend on the substrate and reaction conditions. The possible transformations include (a) reduction of the nitro group to an amine, azo, or azoxy moiety, (b) displacement of a nitro, halogen, or hydroxy group by hydrogen, or (c) selective reduction of the aromatic ring. In polynitro derivatives and in mononitro polycyclic systems, the conjugate addition of hydride ion to the aromatic ring gives Meisenheimer complexes. Electrophilic trapping of these adducts through protonation, halogenation, and alkylation furnishes dearomatized products showing a great structural diversity.

**14.1.1.a. Quenching with Protonating and Halogenating Reagents.** The substituted cyclohexenes **450** were obtained by reducing 1,3-dinitrobenzenes **447** with an excess of $NaBH_4$ and subsequent protonation with tartaric acid (Scheme 71, top).[237,238] The reduced tetrahydrobenzene derivatives **449** are formed via two succesive addition steps of hydride to the six-membered ring. The first addition produces the sodium salt of the *aci*-nitrocyclohexadiene **448**, which is transformed into the disodium di-*aci*-nitro-1-cyclohexene intermediate **449** upon attack of a second hydride to position 3. Meisenheimer complexes similar to **449** have been structurally characterized.[239,240] Similar to **447e** ($R^1 = CO_2H$), dinitrobenzoic acid **452** undergoes double reduction by $NaBH_4$ under basic conditions. In this case, the protonation of the intermediate dianionic species **453** with acetic acid and concentrated HCl results in the formation of the nitronic acid derivative **454**. Protonation of the hydride diadduct of 1,3-dinitrobenzene proved to be problematic. However, quenching the reaction with bromine allows the introduction of a bromide into the ring to give cyclohexene **451a** or **451b**.[237]

1,8-Dinitronaphthalene **455** undergoes reduction by a 6-fold excess of sodium borohydride in a mixture of THF−MeOH−$H_2O$ to give, after protonation with acetic acid, the [1,6] monoadduct **456**.[237] The latter can be converted into the tetrahydrodibrominated derivative **457** by treatment with a solution of bromine in methylene dichloride.[241] Introducing a phenol into the naphthalene nucleus as in compound **458** opens the possibility of new reaction pathways depending on the conditions used.[241] The reaction with $NaBH_4$ in the usual manner gives 3,4-dihydro derivative **459** stabilized as the keto-*aci*-nitro tautomer. However, when the reduction is performed with $LiBH_4$ as the source of hydride, the product isolated, **460**, corresponds to the formal substitution of the hydroxy group by a hydride ion (Scheme 71). The same compound was obtained in 21% yield when the dihydronaphthalene **459** was allowed to react with $LiBH_4$ in diglyme for 1 h at 15−20 °C. Similar to dinitronaphthalenes, 9-nitroanthracene **461** forms a Meisenheimer monoadduct **462** with $NaBH_4$ in DMF. The final products obtained depend again on the quenching conditions. Upon the action of hydrochloric acid, **462** afforded the anthraquinone **463** in 45% yield.[241] However, the use of an excess of acidic ion exchanger for protonating **462** allowed the isolation of 9,10-dihydroanthracene **464** in good yield (60%).[237]

Increasing the electrophilicity of the ring as in *sym*-trinitrobenzene (TNB) **465** promotes the complete reduction of the aromatic system by the action of sodium borohydride, affording 1,3,5-trinitrocyclohexanes **467** and **468** as mixture of stereoisomers. The reaction proceeds via successive addition of hydride to the ring of the nitro compound and quenching of the trisodium salt **466** with tartaric acid[237] and bromine,[242] respectively (Scheme 72). First reported by Severin and Schmitz, the synthetic applications of the process were further developed mostly by Atroshchenko et al.[243] Curiously, the analogous reduction of symmetrical trinitrobenzenes **469** containing one or two additional electron-withdrawing substituents furnished 1,3,5-trinitrocyclohexane **467** as the only isolable product (Scheme 72).[244] In contrast, trichloro derivative **473** underwent reaction with $NaBH_4$ to give the product of nitro displacement **474**. Apparently, $S_NAr$ processes are favored when the resonance interaction of the nitro groups and the benzene ring is minimal or nonexistent due to steric interactions, which seems to be the

**Scheme 68**

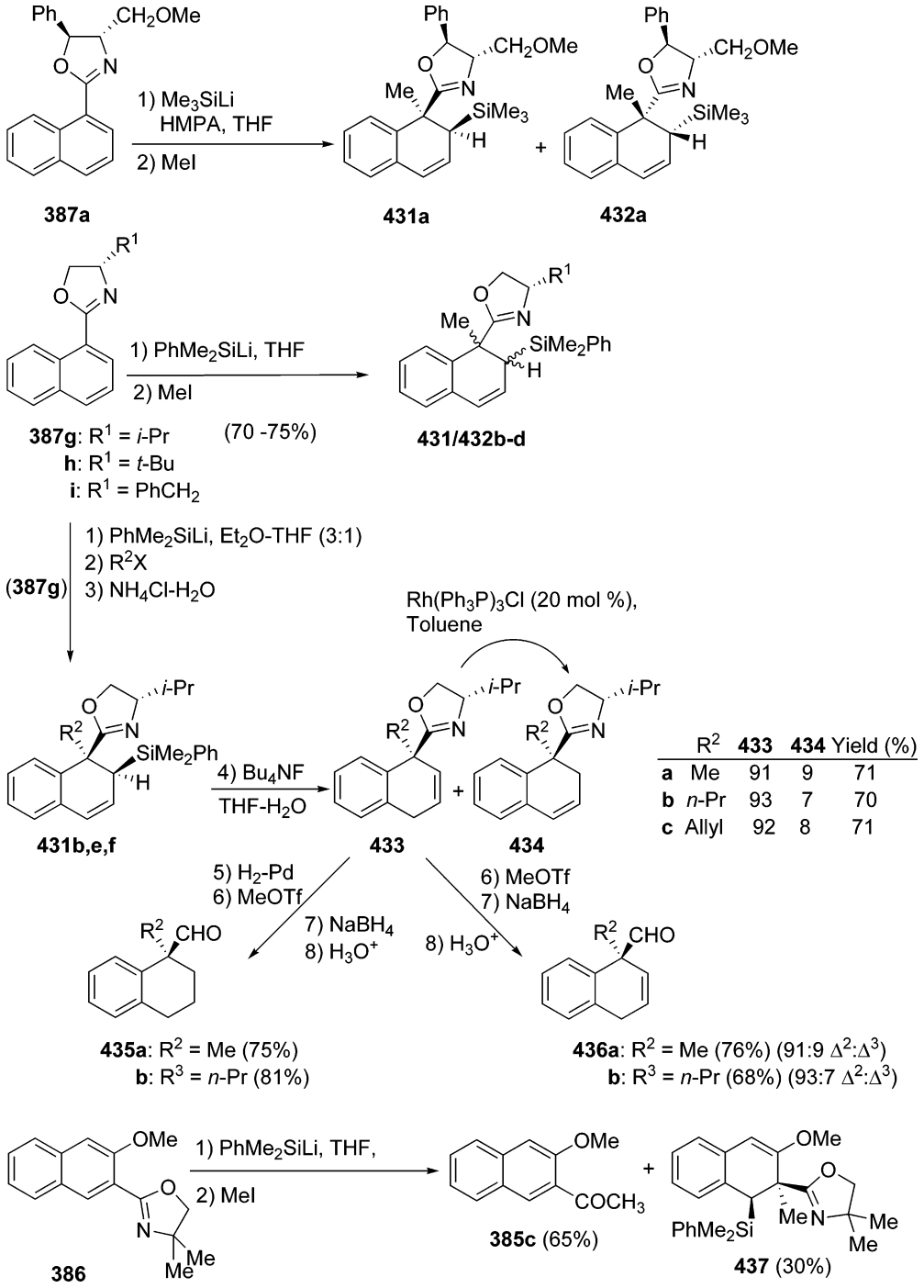



**Table 32. Conjugate Addition of Silicon Nucleophiles to Naphthyloxazolines 386−387**

| entry | SM | $R^1Me_2SiLi$ | $R^2X$ | yield (%) [ratio] |
|---|---|---|---|---|
| 1 | **387a**[a] | $Me_3SiLi$ | MeI | **431a**:**432a** (70) [60:40] |
| 2 | **387g**[b] | $PhMe_2SiLi$ | MeI | **431b**:**432b** (75) [25:75] |
| 3 | **387h**[b] | $PhMe_2SiLi$ | MeI | **431c**:**432c** (70) [40:60] |
| 4 | **387i**[b] | $PhMe_2SiLi$ | MeI | **431d**:**432d** (70) [40:60] |
| 5 | **387g**[b] | $PhMe_2SiLi$ | MeI | **431b**:**432b** (76) [95:5] |
| 6 | **387g**[b] | $PhMe_2SiLi$ | *n*-PrBr | **431e**:**432e** (66) [97:3] |
| 7 | **387g**[b] | $PhMe_2SiLi$ | allylBr | **431f**:**432f** (77) [95:5] |
| 8 | **386**[c] | $PhMe_2SiLi$ | MeI | **437** (30) |

[a] Data taken from ref 195. [b] Data taken from ref 215. [c] Data taken from ref 116. See text for explanations.

case in **473**. The crystal structure shows that the O−N−O planes of the nitro groups are rotated 76° out of the plane of the ring. When at least one of the $NO_2$ substituent can contribute to charge delocalization, succesive cycles of hydride ion addition−rearomatization reactions transform the nitro compounds **469** into TNB. The latter enters into a reduction sequence of reactions to give *sym*-trinitrocyclohexane **467**. The reaction course is shown in Scheme 72 for **469b** ($R^1 = R^2 = Cl$) and involves the participation of intermediates **470**−**472**. The transformation of alkyl-,[245] **469e**,**f**, or formyl-substituted,[246] **469g**, *sym*-trinitrobenzenes into the respective cyclohexanes **475** (quench with acetic acid) and **476** (quench with bromine) provides additional examples of this chemistry. As expected, under the reaction conditions the formyl group is also reduced to the corresponding alcohol.

Severin and Schmitz reported that the reduction−protonation of trinitroarenes containing a hydroxy substitutent in

**Scheme 69**

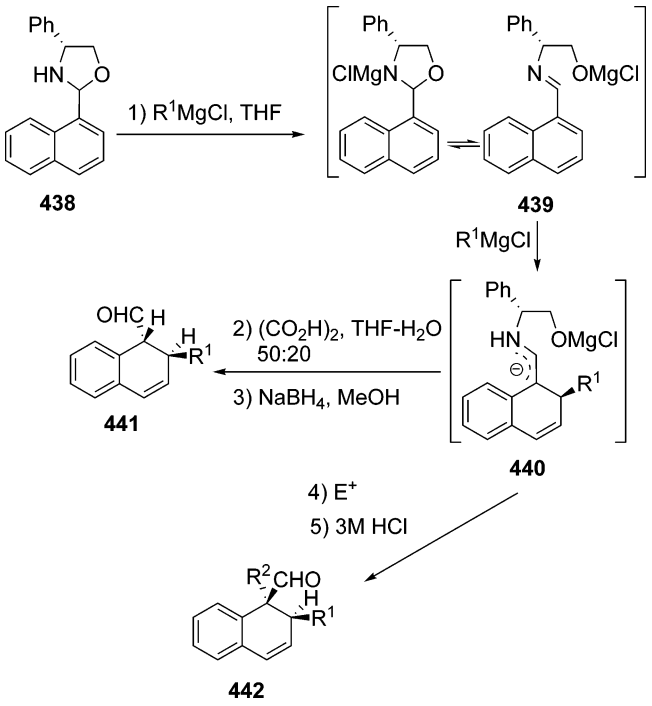
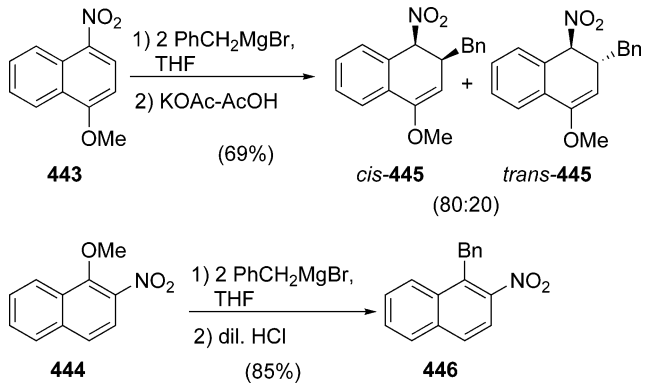



**Table 33. Conjugate Addition of Grignard Reagents to Naphthyloxazolidine 438**[a]

| entry | $R^1MgCl$ | $E^+$ | $R^2$ | yield (%) [ee] |
|---|---|---|---|---|
| 1 | Et | $(CO_2H)_2$ | H | **441a** (65) [96] |
| 2 | *n*-Bu | $(CO_2H)_2$ | H | **441b** (83) [93] |
| 3 | Ph | $(CO_2H)_2$ | H | **441c** (50) [93] |
| 4 | Me | MeI | Me | **442a** (31) [98] |
| 5 | Et | MeI | Me | **442b** (86) [97] |
| 6 | Et | allylBr | allyl | **442c** (82) [98] |
| 7 | Et | $ClCO_2Et$ | $CO_2Et$ | **442d** (89) [98] |
| 8 | *n*-Bu | MeI | Me | **442e** (87) [98] |
| 9 | vinyl | MeI | Me | **442f** (70) [74] |
| 10 | Ph | MeI | Me | **442g** (84) [99] |

[a] Data taken from refs 216 and 217.

**Scheme 70**




the ring followed a different pathway. The compound obtained by treatment of picric acid **469h** ($R^1$ = OH; $R^2$ = H) with $NaBH_4$ under basic conditions and subsequent quench with acetic acid was assigned as 1,3,5-trinitropentane **477** (Scheme 72).[237] Boldyrev and co-workers reinvestigated this reaction and found that the product formed was actually 1,3,5-trinitrocyclohexane **467** (yield of 33.5%),[247] in agreement with Kaplan's work.

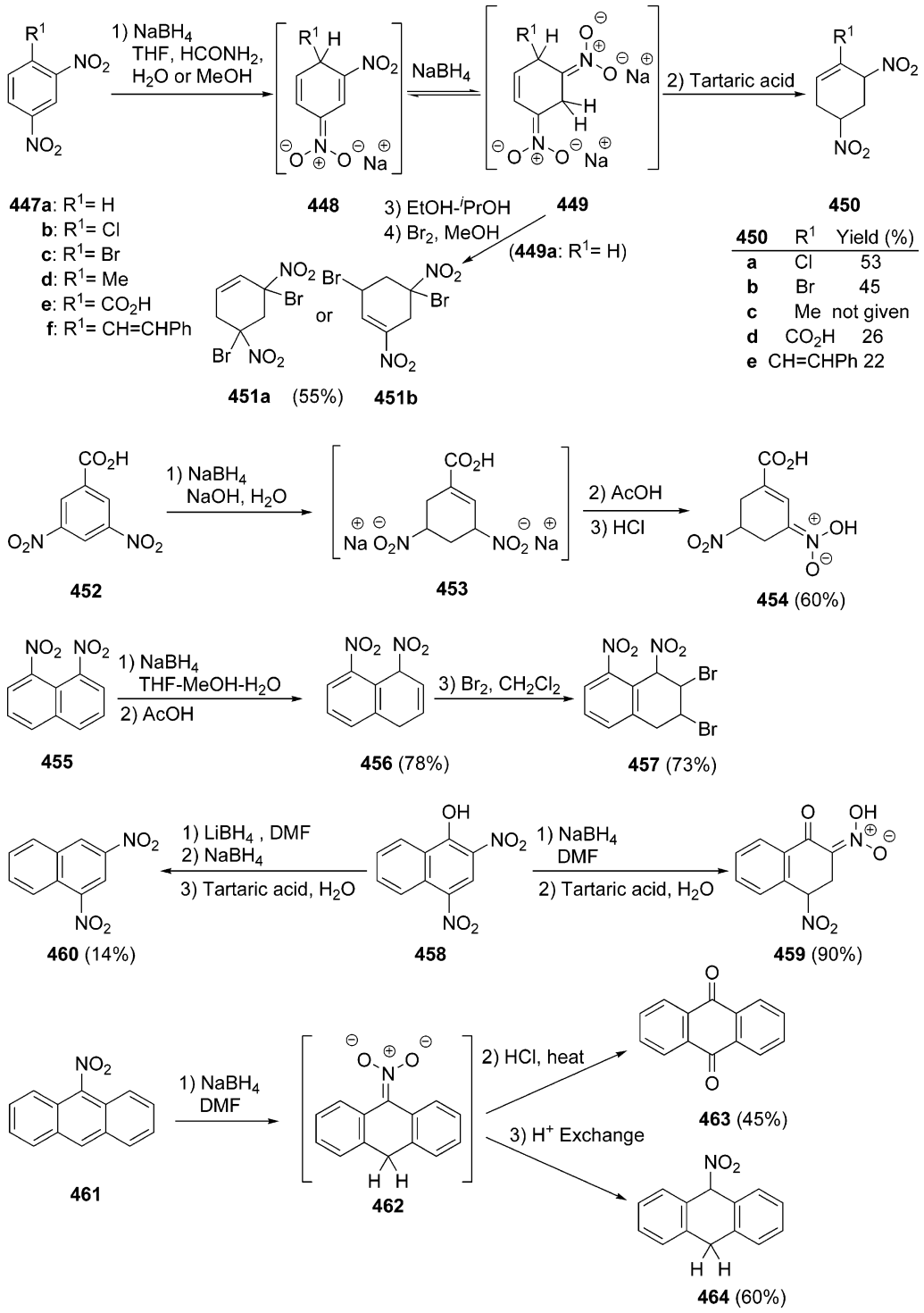
Meisenheimer monoadducts of 1,3,5-trinitrobenzenes may be obtained when an equimolar amount of nitro compound and reducing agent are allowed to react. Such monocomplexes have been prepared using different borohydrides as the source of hydride.[248−250] TNB **465** gave stable complex **478** when treated with tetramethylammonium tetrahydroborate. The protonation product of **478** with diluted sulfuric acid was stable in solution for a few hours at room temperature and was spectroscopically characterized as the nitronic acid **479**, although it was not isolated (Scheme 72).[251]

**14.1.1.b. Quenching with Aminoalkylating Reagents.** *σ*-Dianions proceeding from hydride attack to dinitro aromatic compounds may be alkylated via Mannich reactions. Thus, treating the hydride diadducts of dinitrobenzenes **447** with formaldehyde and piperidine and immediately afterward with acetic acid affords mono-, **480**, or diaminoalkylated compounds, **481**, depending on the substitution pattern of the aromatic ring, in moderate to good yield (Scheme 73).[252] In the particular case of *m*-dinitrobenzene, the resulting product was stabilized as the 3-*aci*-nitro-5-nitro tautomer **482**. Compounds **480b** ($R^1$ = Me) and **482** were rearomatized by reaction with tin dichloride under acidic conditions to give 2-methyl-5-piperidinomethylaniline **483** and 3-piperidinomethylaniline **484**, respectively.

Most importantly, using a primary amine in the Mannich condensation allowed trapping of the dianions in the form of 3-azabicyclo[3.3.1]nonanes (3-ABN) **485** (Scheme 73).[252] 3-ABNs are intermediate reagents in organic synthesis, and many derivatives of 3-ABN are biologically active substances.[253] The azabicyclic system also occurs in the skeleton of several diterpene alkaloids.[254] Following the discovery of the synthesis of 3-ABNs using dinitrobenzenes as starting materials, Wall[255] and, particulary, Atroshchenko and co-workers[256−261] demonstrated the wide scope of this reaction by preparing a large series of derivatives through variations in the substituents of the aromatic ring and the use of ammonia and functionalized aliphatic primary amines including haloamines, hydroxyamines, and amino acids. The results are collected in Table 34. Severin and co-workers found that 2,4-dinitrophenol **447g** ($R^1$ = OH; $R^2$ = H) adds only one hydride to give the ketone derivative **487** after aminoalkylation, whereas 2,4-dinitroanisole **447h** ($R^1$ = OMe; $R^2$ = H) affords, under the same conditions, a mixture of two regioisomers, **485** (27%) and **486** (8%), proceeding from the double reduction of the aromatic ring (entries 5 and 6, Table 34).[240] In contrast, Wall described the formation of small amounts of the bispidine **488** as a single product identified in the reduction and Mannich condensation of **447g** under the conditions used to prepare **485a** ($R^1$ = H; $R^2$ = H; $R^3$ = Me). The analogous reaction of 2,4-dinitronaphthol **458** furnished the expected 3-ABN derivative **490**. In this case, the aromatic ring of **490** presumably prevents the breakdown of the ABN system. Upon acid hydrolysis of the vinyl ether, products **485g−j** were transformed into keto compounds **489**.[240,255] In contrast to the *σ*-complexes **449b−f** (Scheme 71), protonation with acids of the hydride adducts of dinitrobenzenes having a hydroxy, **447g**, or methoxy, **447h**,**j**, substituent did not lead to isolable products.

Additionally, by using primary diamines in the process, bis-3-ABNs **491** were obtained linked through a hydrocarbon bridge of 2,[256,261] 4,[257,261] or 6[256] atoms (Scheme 73; Table 34, entries 63−67). In general, yields of mono- and bis-3-ABNs were low. A positive aspect of the synthesis is the simplicity of the process, as readily available starting materials take part in a one-pot reaction. 2,4-Dinitronaphthol **458** proceeds similarly, providing tricyclic compound **490**.

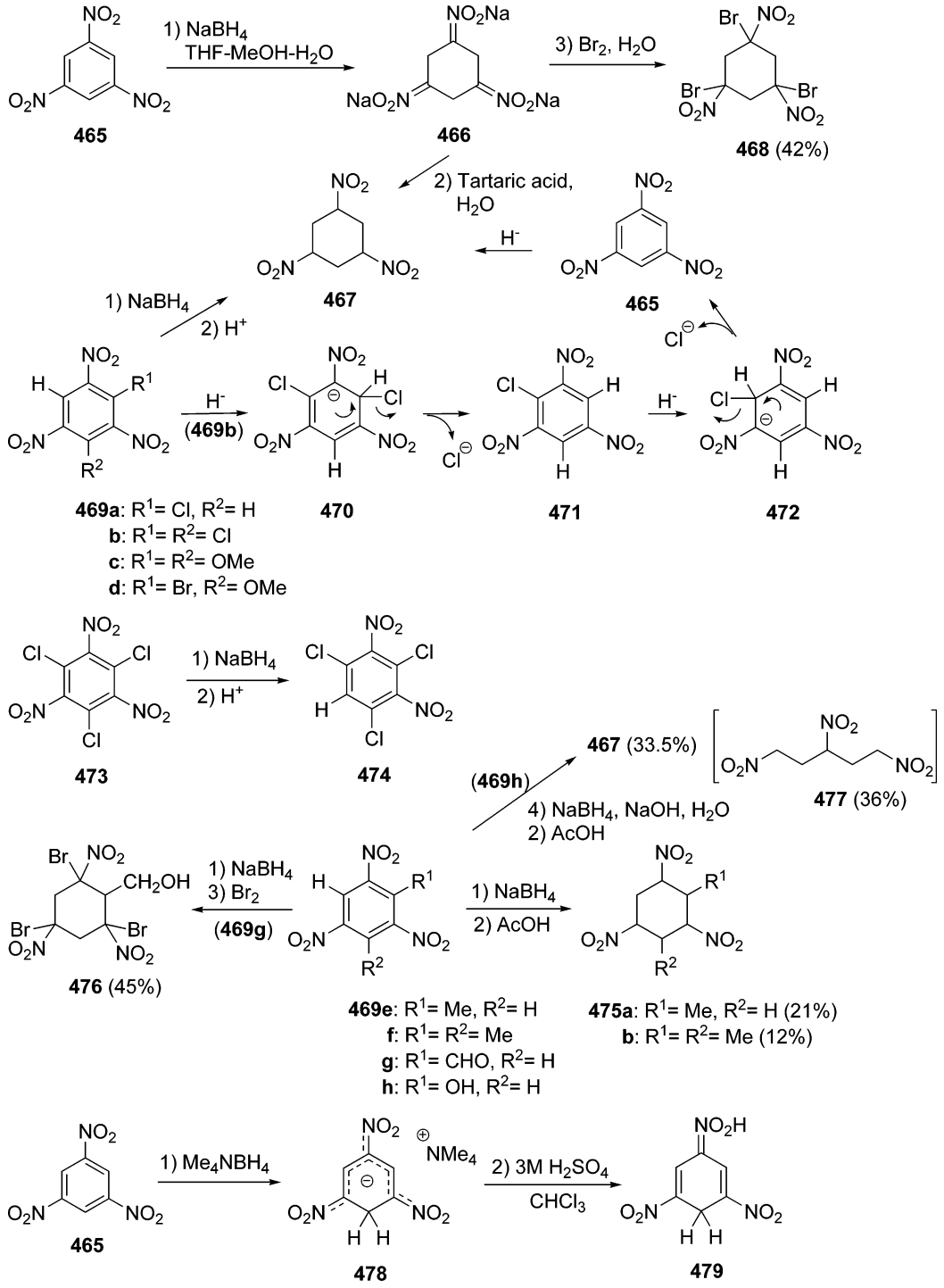
**Scheme 71**




However, the analogous reaction of 2,4-dinitrophenol gives a complex mixture of products.[255]

The $\sigma$-triadduct formed upon borohydride reduction of TNB **465** undergoes a triple Mannich aminoalkylation when treated with a mixture of formalin and ammonium nitrate. Under these conditions, 3,5,7-trinitro-1-azaadamantane **492a** was obtained in 15% yield (Scheme 74).[262] The synthesis of **492** can be accomplished stepwise starting with picric acid **469h**. First, the intermediate trianion of conjugate hydride addition was trapped by treatment with an excess of formaldehyde in the presence of concentrated phosphoric acid. Afterward, the resulting mixture of *cis*- and *trans*-tris-(hydroxymethyl)cyclohexanes **493** undergoes cycloconden-sation with aqueous ammonia to give **492a**, albeit in very low yield (8%).[263] Substitution of OH by hydrogen in picric acid had been described previously by Boldyrev and co-workers.[247] The same authors reported that the reduction−hydroxymethylation of picric acid proceeds efficiently to give *cis*-/*trans*-**493** in 76% yield. TNB **465** can also be converted into cyclohexanes **493**. Treating the borohydride complex formed in the reduction of TNB with formalin, followed by rapid addition of dilute orthophosphoric acid, provides *cis*-/*trans*-**493** in a yield of 58%.[264] The mixture of isomers were separated by precipitation from acetone. The isolated compounds isomerize into each other in the presence of catalytic amounts of a base to give mixtures of composition dependent

**Scheme 72**



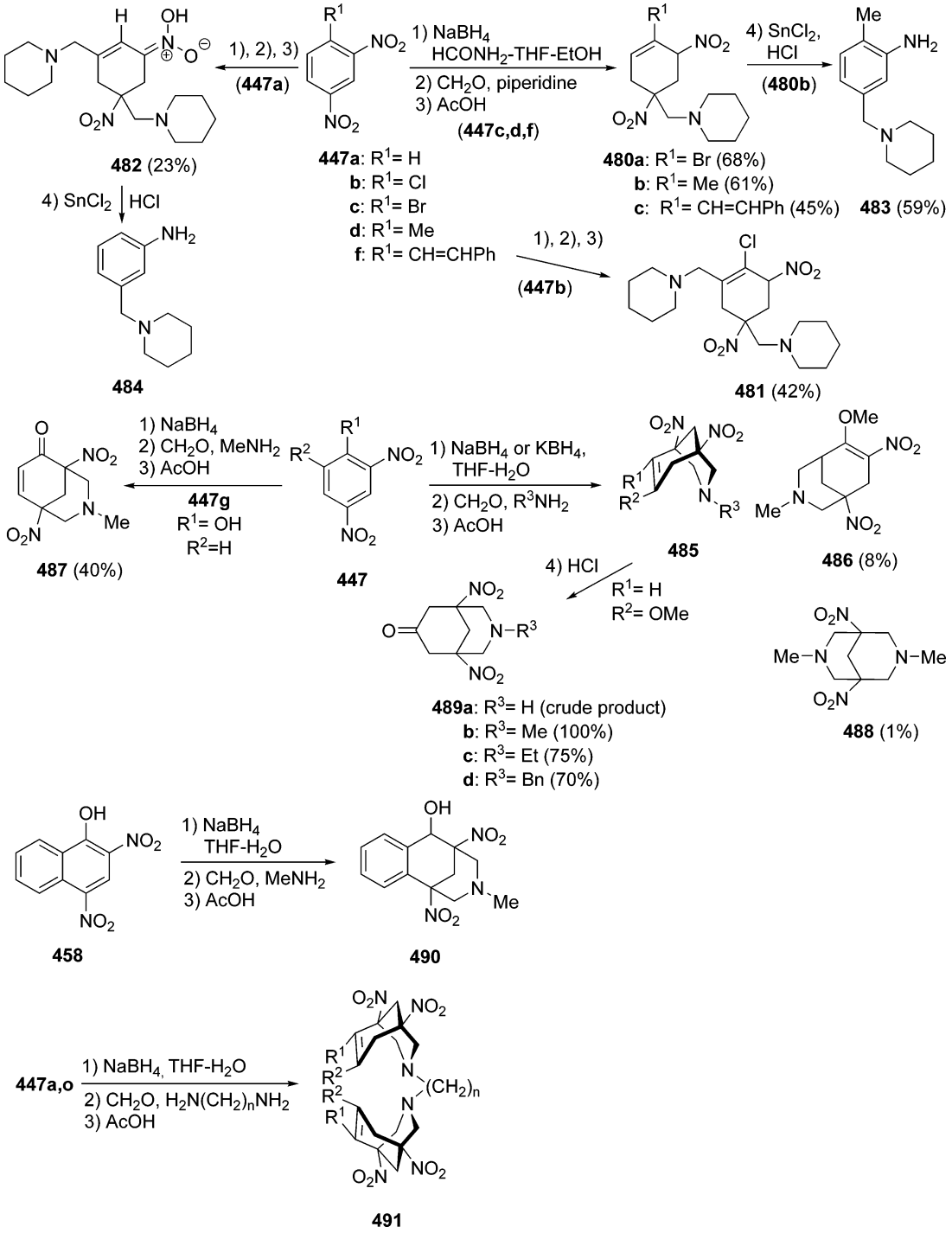

**465** **466** **468** (42%) **467** **465** **469a**: $R^1$= Cl, $R^2$= H; **b**: $R^1$= $R^2$= Cl; **c**: $R^1$= $R^2$= OMe; **d**: $R^1$= Br, $R^2$= OMe **470** **471** **472** **473** **474** **476** (45%) **469e**: $R^1$= Me, $R^2$= H; **f**: $R^1$= $R^2$= Me; **g**: $R^1$= CHO, $R^2$= H; **h**: $R^1$= OH, $R^2$= H **475a**: $R^1$= Me, $R^2$= H (21%); **b**: $R^1$= $R^2$= Me (12%) **465** **478** **479**

on the solvent and reaction conditions used.[265] Both isomers afforded trinitro-1-azaadamantane **492a** by the action of an excess of an aqueous solution of ammonia (yield of 50%). Cyclohexanes **475**, obtained in the hydride reduction−protonation of the aromatic precursors **469e**,**f** (Scheme 72), were also converted into adamantane derivatives **492b**,**c** by treatment with formaldehyde and ammonia under basic conditions (Scheme 74).[245] As already mentioned, the borohydride reduction of picryl aldehyde **469g** proceeds in the expected manner. Quenching the dearomatized hydride $\sigma$-triadduct with formaldehyde in the presence of ammonia gave 4-hydroxymethyl-3,5,7-trinitro-1-azaadamantane **492d** in a reasonable yield of 38%.[246]

### *14.1.2. Reactions with Nonstabilized Carbanions*

As mentioned above, electrophilic trapping of the nitronate adducts originating by the addition of Grignard reagents to mononitro compounds represents an interesting route for synthesizing alkylated cyclohexadienyl systems. The scope of this dearomatizing−alkylation process was extended by performing the decomposition of the $\sigma$-complexes with the reducing agent tris(dimethylamino)phosphine. Thus, treatment of 4-methoxy-1-nitronaphthalene **443** with a series of alkylorganomagnesiums in THF at 0 °C during 5 min, followed by the addition of $P(NMe_2)_3$ and stirring during 48 h, afforded, after quenching with aqueous ammonium chloride, the dihydronaphthalene oximes **495** in reasonable

**Scheme 73**




yields (Scheme 75; Table 35, entries 1−5).[266] Alternatively, quenching with HCl−MeOH produced the hydrolysis of the methoxyvinyl ether moiety, giving dihydronaphthoquinone oximes **496** (entries 6−10). In this case, minor amounts of 2-alkyl-1,4-naphthoquinones (4−10%) were also formed as byproducts. Phosphorus trichloride also effected the reduction of nitronates **494**. Quenching the reactions with HCl led to naphthylamines **497**. The exception was the reaction with *t*-BuMgCl, which gave oxime **496c**. The different chemical behavior of **494c** ($R^1 = t$-Bu) was attributed to the bulkiness of the substituent in position 2, which prevented the full reduction of the nitronic function.

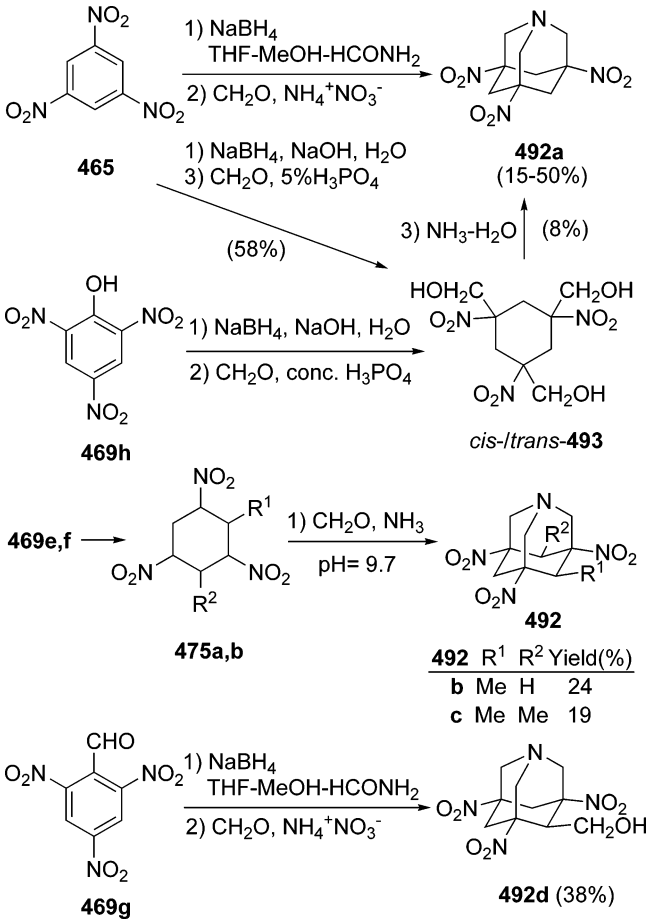
Addition of alkylorganomagnesiums to 9-nitroanthracene **461** in THF at room temperature results in the formation of only [1,6] adducts. Protonation of the nitronate intermediate **498** with dilute acetic acid (5%) occurs exclusively at the carbon bonded to the nitrogen to give *cis*-9-alkyl-10-nitro-9,10-dihydroanthracenes **499** (Scheme 75; Table 35, entries 11 and 12).[267] Curiously, although the resonance energy necessary for overcoming the aromaticity of the central anthracene ring is lower than that of a benzene or naphthalene nucleus, the conjugate addition to **461** requires larger excesses of the Grignard reagent and longer reaction times than that with nitrobenzenes and nitronaphthalenes. 9-Alkyl-9,10-DHAs exist in a boat conformation in which the alkyl substituent occupies a pseudoaxial position in order to minimize steric interactions with the peri hydrogens (see section 2.1.1). Such a conformation of **498** may cause

**Table 34. Conjugate Hydride Ion Addition−Mannich Condensation of Nitroaromatic Compounds 447**

| entry | SM | $R^1$ | $R^2$ | $R^3$ | yield (%) |
|---|---|---|---|---|---|
| 1 | **447a**[a] | H | H | Me | **485a** (79) |
| 2 | **447b**[a] | Cl | H | Me | **485b** (44) |
| 3 | **447d**[a] | Me | H | Me | **485c** (58) |
| 4 | **447f**[a] | CH=CHPh | H | Me | **485d** (52) |
| 5 | **447g**[b] | OH | H | Me | **487** (40) |
| 6 | **447h**[b] | OMe | H | Me | **485e** (27)[c] |
| 7 | **447i**[d] | H | Me | Me | **485f** (47) |
| 8 | **447j**[d] | H | OMe | H | **485g** (7) |
| 9 | **447j**[d] | H | OMe | Me | **485h** (66) |
| 10 | **447j**[d] | H | OMe | Et | **485i** (10) |
| 11 | **447j**[d] | H | OMe | Bn | **485j** (24) |
| 12 | **447k**[d] | H | $CO_2Me$ | H | **485k** (77) |
| 13 | **447l**[d] | H | $CO_2Et$ | Me | **485l** (98) |
| 14 | **447m**[d] | H | $CONH_2$ | H | **485m** (29) |
| 15 | **447m**[d] | H | $CONH_2$ | Me | **485n** (67) |
| 16 | **447a**[e] | H | H | Et | **485o** (51) |
| 17 | **447a**[e] | H | H | Bn | **485p** (50) |
| 18 | **447a**[e] | H | H | $(CH_2)_2Br$ | **485q** (25) |
| 19 | **447a**[e] | H | H | $CH(Et)CH_2OH$ | **485r** (59) |
| 20 | **447a**[e] | H | H | $CH_2CO_2H$ | **485s** (44) |
| 21 | **447a**[e] | H | H | $(CH_2)_2OH$ | **485t** (52) |
| 22 | **447b**[f] | Cl | H | $(CH_2)_2OH$ | **485u** (19) |
| 23 | **447c**[f] | Br | H | $(CH_2)_2OH$ | **485v** (21) |
| 24 | **447d**[f] | Me | H | $(CH_2)_2OH$ | **485w** (16) |
| 25 | **447h**[f] | OMe | H | $(CH_2)_2OH$ | **485x** (9) |
| 26 | **447n**[f] | $Cl(CH_2)_2O$ | H | $(CH_2)_2OH$ | **485y** (13) |
| 27 | **447e**[f] | $CO_2H$ | H | $(CH_2)_2OH$ | **485z** (12) |
| 28 | **447j**[f] | H | OMe | $(CH_2)_2OH$ | **485aa** (10) |
| 29 | **447o**[f] | H | $CO_2H$ | $(CH_2)_2OH$ | **485ab** (32) |
| 30 | **447m**[f] | H | $CONH_2$ | $(CH_2)_2OH$ | **485ac** (31) |
| 31 | **447p**[f] | H | CN | $(CH_2)_2OH$ | **485ad** (30) |
| 32 | **447k**[f] | H | $CO_2Me$ | $(CH_2)_2OH$ | **485ae** (24) |
| 33 | **447q**[g] | H | $CF_3CH_2O$ | Me | **485af** (55) |
| 34 | **447q**[g] | H | $CF_3CH_2O$ | Et | **485ag** (48) |
| 35 | **447q**[g] | H | $CF_3CH_2O$ | Bn | **485ah** (37) |
| 36 | **447q**[g] | H | $CF_3CH_2O$ | $(CH_2)_2Br$ | **485ai** (27) |
| 37 | **447q**[g] | H | $CF_3CH_2O$ | $(CH_2)_2OH$ | **485aj** (23) |
| 38 | **447q**[g] | H | $CF_3CH_2O$ | $CH_2CO_2H$ | **485ak** (25) |
| 39 | **447q**[g] | H | $CF_3CH_2O$ | $(CH_2)_2CO_2H$ | **485al** (26) |
| 40 | **447r**[g] | H | $CHF_2CF_2CH_2O$ | Me | **485am** (59) |
| 41 | **447r**[g] | H | $CHF_2CF_2CH_2O$ | Bn | **485an** (30) |
| 42 | **447s**[g] | H | $CHF_2(CF_2)_3CH_2O$ | Me | **485ao** (52) |
| 43 | **447b**[h] | Cl | H | $CH_2CO_2H$ | **485ap** (23) |
| 44 | **447c**[h] | Br | H | $CH_2CO_2H$ | **485aq** (36) |
| 45 | **447d**[h] | Me | H | $CH_2CO_2H$ | **485ar** (38) |
| 46 | **447h**[h] | OMe | H | $CH_2CO_2H$ | **485as** (33) |
| 47 | **447j**[h] | H | OMe | $CH_2CO_2H$ | **485at** (26) |
| 48 | **447k**[h] | H | $CO_2Me$ | $CH_2CO_2H$ | **485au** (42) |
| 49 | **447o**[h] | H | $CO_2H$ | $CH_2CO_2H$ | **485av** (40) |
| 50 | **447m**[h] | H | $CONH_2$ | $CH_2CO_2H$ | **485aw** (30) |
| 51 | **447t**[h] | H | $CONEt_2$ | $CH_2CO_2H$ | **485ax** (36) |
| 52 | **447u**[h] | H |  | $CH_2CO_2H$ | **485ay** (38) |
| 53 | **447v**[h] | H |  | $CH_2CO_2H$ | **485az** (48) |
| 54 | **447a**[h] | H | H | $(CH_2)_2CO_2H$ | **485ba** (53) |
| 55 | **447a**[h] | H | H | $CH(CO_2H)CH_2CO_2H$ | **485bb** (28) |
| 56 | **447a**[h] | H | H | $CH(CO_2H)CH_2CONH_2$ | **485bc** (19) |
| 57 | **447a**[h] | H | H | $CH(CO_2H)(CH_2)_2CO_2H$ | **485bd** (32) |
| 58 | **447o**[i] | H | $CO_2H$ | Me | **485be** (35) |
| 59 | **447o**[i] | H | $CO_2H$ | Et | **485bf** (45) |
| 60 | **447o**[i] | H | $CO_2H$ | *n*-Bu | **485bg** (19) |
| 61 | **447o**[i] | H | $CO_2H$ | $(CH_2)_2Br$ | **485bh** (52) |
| 62 | **447o**[i] | H | $CO_2H$ | $(CH_2)_2CO_2H$ | **485bi** (38) |
| 63 | **447a**[e] | H | H | $n = 2$ | **491a** (14) |
| 64 | **447a**[f] | H | H | $n = 4$ | **491b** (25) |
| 65 | **447a**[e] | H | H | $n = 6$ | **491c** (28) |
| 66 | **447o**[i] | H | $CO_2H$ | $n = 2$ | **491d** (43) |
| 67 | **447o**[i] | H | $CO_2H$ | $n = 4$ | **491e** (37) |

[a] Data taken from ref 252. [b] Data taken from ref 240. [c] Compound **486** was also obtained in 8% yield. [d] Data taken from ref 255. [e] Data taken from ref 256. [f] Data taken from ref 257. [g] Data taken from ref 258. [h] Data taken from ref 259. [i] Data taken from ref 261.

**Scheme 74**




protonation of the nitronic moiety from the less hindered opposite face. An alternative explanation of the total stereoselectivity of the protonation assumes the participation of product-like transition states. Attack trans to the alkyl group would be of lower energy. In this arrangement, the smallest group occupies the incipient pseudoequatorial position, thus minimizing the steric interactions with the peri hydrogens.

Increasing the electron deficiency of the aromatic system by introducing a second nitro group allows the double alkylation of the nitroarene. The reaction of 1,4-dinitrobenzene **500** with 2 equiv of alkylmagnesium or methyl-lithium in THF at −70 °C for 10 min, followed by oxidation with DDQ or sodium hypochlorite, gave *trans*-dialkylcyclohexa-1,3-dienes **504** in yields ranging from 17 to 56% (Scheme 76; Table 35, entries 13−19).[268] ESR monitoring of the reaction demonstrated the presence of the 1,4-dinitrobenzene radical anion **501**. Additionally, the formation of 2-methyl-1,4-dinitrobenzene (4−12%) when stoichiometric amounts of MeMgX (X = Cl, Br) or MeLi were used indicates that dialkylation occurs stepwise. In the first step, the addition of 1 equiv of nucleophile to **500** results in the formation of the radical anion **501** and the monoalkylated nitronate **502**. Subsequently, a second equivalent of $R^1MgX$ or MeLi undergoes addition to the ene-nitro moiety of **502**, leading to diadducts **503**. The oxidative quench of the reaction mixture transforms the reduced species **501** into the starting material, without affecting the cyclohexadiene derivatives. This mechanism also explains the exclusive formation of products with a trans configuration. The nucleophile approaches the ene-nitro function of **502** from the less hindered site, opposite the alkyl group. The fact that the yield of dialkylated products increases by using low-polar and highly viscous solvents (entries 13 and 16, Table 35) suggests that the reaction mechanism could be better interpreted as a continuous spectrum from pure polar to pure SET mechanisms. Mechanistic studies on the reaction of mononitrobenzenes with alkyl Grignard reagents also showed evidence of the participation of one-electron-transfer processes.[269]

Similar to the borohydride reduction of nitroarenes, the dialkylated σ-diadducts were also trapped through Mannich reactions. Thus, addition of formalin and methylamine to the Meisenheimer complexes obtained in the reaction of **447a**,**b** with an excess of Grignard reagents followed by treatment with acetic acid produced the 3-azabicyclo[3.3.1]-non-6-enes **505** in yields from 12 to 35% (Scheme 76).[270] For 5-methoxy-1,3-dinitrobenzene **447j** the expected bicyclic compound **506** was obtained in 37% yield. However, the reaction mixture had to be refluxed for 5 h; otherwise, unreacted **447j** was recovered.

Triple Grignard addition occurs in TNB **465**. Protonation with acetic acid and bromination of the intermediate trinitronate **507** affords trialkylated cyclohexanes[271,272] **508** (Table 35, entries 20−24) and **509**, respectively, as a mixture of stereoisomers. Moreover, Mannich condensation of **507** with a mixture of formaldehyde and ammonium nitrate furnishes trialkyltrinitroazaadamantanes **510** in yields of about 15% (Scheme 76).[262] The brominated derivatives **509** were isolated and dehydrobrominated by treatment with sodium iodide in refluxing acetone to afford cyclohexenes **511**.

An additional example of the addition of a non-delocalized carbon nucleophile to a polynitroaromatic compound was reported by Wennerström, who studied the reaction of 2,6-dimethoxyphenylsilver **512** with TNB **465**. This uncommon nucleophile was prepared by treating 2,6-dimethoxyphenyl-lithium with silver bromide. The organosilver compound **512** underwent reaction with TNB in pyridine to give, after addition of cold dilute HCl, the red Meisenheimer complex **513**. By $CHCl_3$ extraction of a suspension of **513** in dilute $H_2SO_4$, a neutral yellow product resulted, identified as the nitronic acid **514** on the basis of its spectroscopic data (Scheme 76).[273]

### *14.1.3. Reactions with Stabilized Carbanions*

This section covers the $D_NAr$ reactions in which the negative charge of the nucleophile is conjugated with some adjacent double bond. The anions involved can be grouped into three categories: aromatic hydrocarbons, aryloxides, and carbanions containing heteroatoms in the conjugated system (enolates and related systems, α-metalated nitriles, diazo compounds).

Wennerström and Moberg reported the only two known examples of adducts between carbanions derived from aromatic hydrocarbons and polynitroaromatic compounds that lead to isolable dearomatized products. The addition of indene **517** and cyclopentadiene **520** to a solution of TNB **465** and silver oxide in pyridine **515** in the dark at room temperature provides σ-complexes **518** and **521**, respectively (Scheme 77).[274] The reaction was followed by visible spectroscopy. A mixture of TNB and pyridine in the presence of silver oxide produced the same complex **516** observed in the initial stage of the reaction with indene, thus indicating that **516** can be thought of as an intermediate in the formation of **518**. This is not necessarily the case for cyclopentadiene. Under the same conditions, **520** underwent reaction 16 times more rapidly than indene, the addition of cyclopentadiene being also faster than the addition of pyridine. Complexes **518** and **521** were transformed into the corresponding nitronic

**Scheme 75**

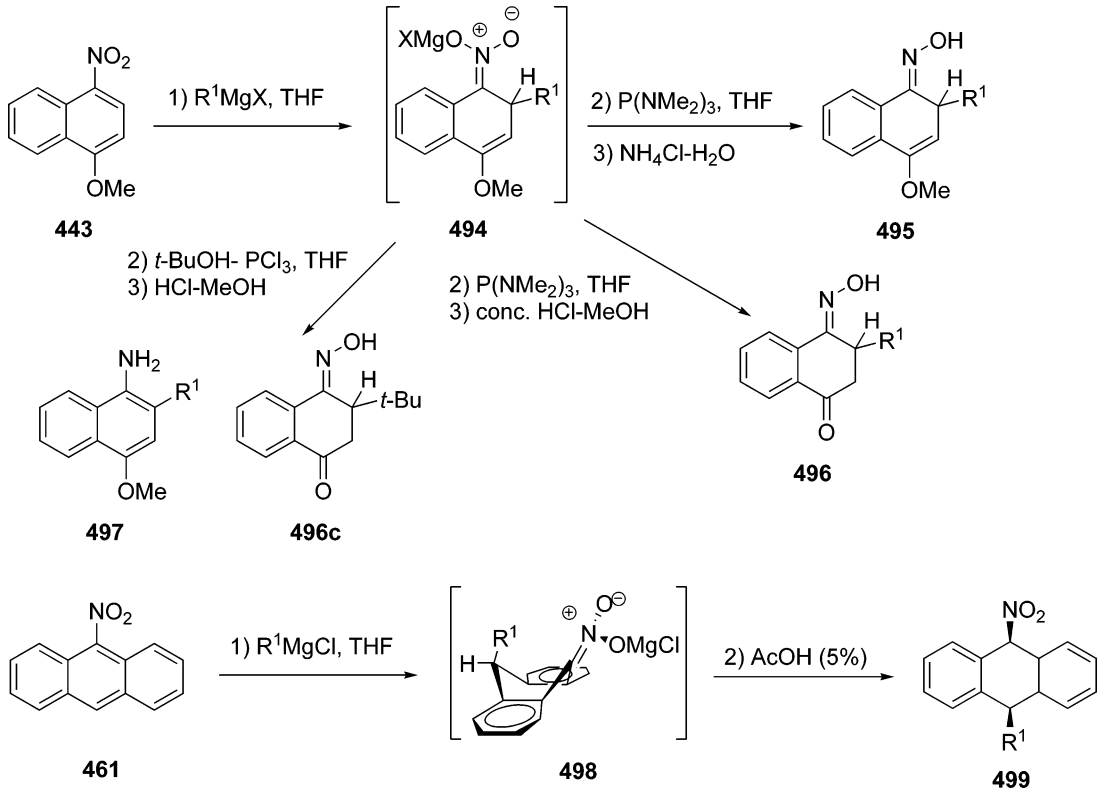



**Table 35. Conjugate Addition of Grignard Reagents and MeLi to Nitroarenes 443, 461, 500, and 465 and Acidic Quench**

| entry | SM | $R^1MgX$ | $H^+$ | yield (%) |
|---|---|---|---|---|
| 1 | **443**[a] | Me | $NH_4Cl$ | **495a** (46) |
| 2 | **443**[a] | *i*-Pr | $NH_4Cl$ | **495b** (45) |
| 3 | **443**[a] | *t*-Bu | $NH_4Cl$ | **495c** (48) |
| 4 | **443**[a] | *c*-$C_6H_{11}$ | $NH_4Cl$ | **495d** (51) |
| 5 | **443**[a] | $PhCH_2CH_2$ | $NH_4Cl$ | **495e** (42) |
| 6 | **443**[a] | Me | HCl | **496a** (44) |
| 7 | **443**[a] | *i*-Pr | HCl | **496b** (60) |
| 8 | **443**[a] | *t*-Bu | HCl | **496c** (57) |
| 9 | **443**[a] | *c*-$C_6H_{11}$ | HCl | **496d** (56) |
| 10 | **443**[a] | $PhCH_2CH_2$ | HCl | **496e** (40) |
| 11 | **461**[b] | Me | AcOH | **499a** (72) |
| 12 | **461**[b] | $PhCH_2$ | AcOH | **499b** (78) |
| 13 | **500**[c] | Me | $NH_4Cl$[d] | **504a** (56)[e] |
| 14 | **500**[c] | Me[f] | $NH_4Cl$[d] | **504a** (50) |
| 15 | **500**[c] | Et | $NH_4Cl$[d] | **504b** (30) |
| 16 | **500**[c] | $Me_3SiCH_2$ | $NH_4Cl$[d] | **504c** (17)[g] |
| 17 | **500**[c] | $CH_2{=}CH(CH_2)_2$ | $NH_4Cl$[d] | **504d** (36) |
| 18 | **500**[c] | $PhCH_2$ | $NH_4Cl$[d] | **504e** (20) |
| 19 | **500**[c] | $PhCH_2CH_2$ | $NH_4Cl$[d] | **504f** (34) |
| 20 | **465**[h] | Me | AcOH | **508a** (16) |
| 21 | **465**[h] | Et | AcOH | **508b** (22) |
| 22 | **465**[h] | *n*-Pr | AcOH | **508c** (20) |
| 23 | **465**[h] | *n*-Bu | AcOH | **508d** (24) |
| 24 | **465**[h] | *i*-Bu | AcOH | **508e** (19)[i] |

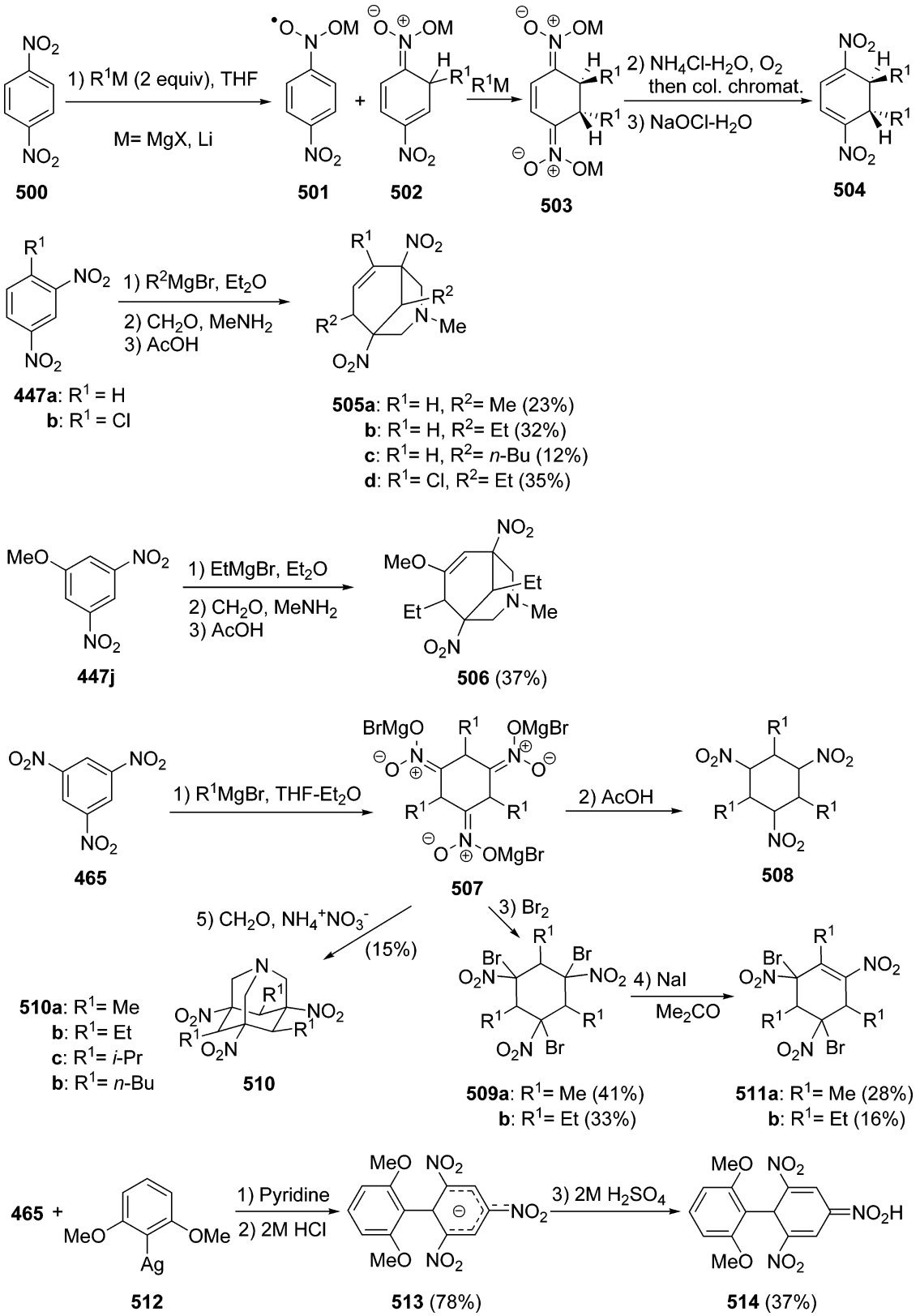
[a] Data taken from ref 266. [b] Data taken from ref 267. [c] Data taken from ref 268. [d] Then addition of NaOCl. [e] Yield increased to 65% when the reaction was performed in *t*-BuPh−PhH as solvent at −30 °C. [f] The nucleophile used was MeLi. [g] Yield increased to 24% when the reaction was performed in *t*-BuPh−PhH as solvent at −30 °C. [h] Data taken from ref 271. [i] Five percent of a second isomer was also isolated.

acids **519** and **522** by treatment with sulfuric acid. Compound **522** was characterized in the reaction mixture by analyzing its visible and $^1H$ NMR spectra, whereas the indenyl derivative **519** was isolated in 74% yield.

The reactions of nitroaromatic compounds with carbanions stabilized by charge delocalization through an adjacent carbonyl group (Janovsky complexes) have been extensively studied.[234] Phenolates can be considered as particular members of this family of nucleophiles. In a number of cases, electrophilic trapping provided dearomatized products. Severin was one of the pioneers in these investigations. In a series of three reports, he showed that *sym*-trihydroxybenzenes (phloroglucinol **523** and nitrophloroglucinol **524**) undergo reaction with TNB[275,276] **465** and *m*-dinitrobenzene[277] **447a** under basic conditions to give, after acidic quench, dearomatized polycyclic compounds **529**, **535**, and **536**, molecules formally constructed by connecting the starting reagents through their meta positions (Scheme 78). Interestingly, phloroglucinol **523** also undergoes addition to TNB in the presence of triethylamine with the formation of the 1:2:1 adduct of **523**, amine, and TNB, **533**. Treating this adduct with HCl in methanol afforded an acidic product for which structure could not be unequivocally assigned.[278]

Focusing on TNB **465** and phloroglucinol **523**, a reasonable mechanism for this remarkable transformation could begin with a carbon−carbon bond-forming reaction through attack of the aromatic enolate resulting from the deprotonation of phloroglucinol to position 2 of **465**. The intermediate **525** (Scheme 78) thus obtained undergoes an intramolecular C addition of a second enolate anion to a neighbor nitrovinyl moiety furnishing tricyclic salt **526**. Conjugate addition of a hydroxy anion to the remaining nitrovinyl functional group present in **526** [path (a)] generates the tetraanionic species **527**, which proceeds to give **528** by forming a hemiacetal bridge through intramolecular binding of the OH substituent to the nonconjugated carbonyl group. Alternatively, the formation of **528** may be explained by addition of $OH^-$ to the ketone group of **526** [Scheme 78, path (b)], followed by intramolecular attack at the nitrovinyl group. Protonation with aqueous sulfuric acid yields **529**. Some derivatives of **529** have been prepared by methylation with diazomethane, **530**, bromination, **531**, and reduction with tin dichloride in concentrated hydrochloric acid, **532**. The analogous reaction with *m*-dinitrobenzene **447a** gives

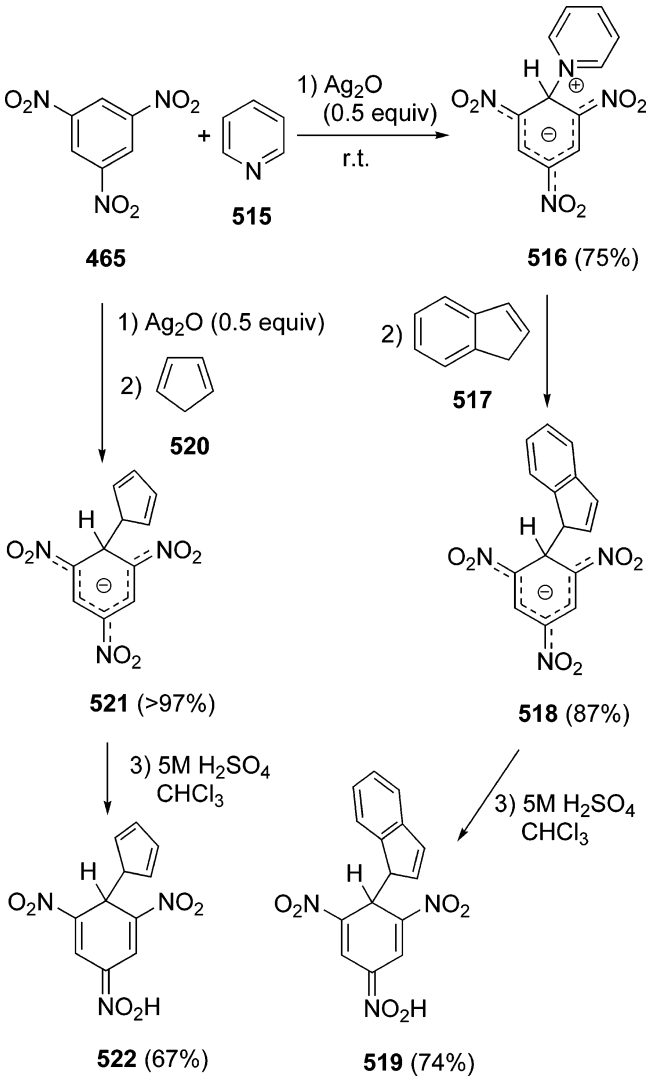
**Scheme 76**




trisodium salt **534**.[277] Hydrochloric acid addition to this salt results in reversion to the starting materials. However, protonation with HCl−MeOH caused the reduction of a nitro group to an oximino moiety and the replacement of a hydrogen by a chloro substituent, yielding **535** (Scheme 78). Introducing a nitro group into the enol-type reagent favors additional tandem reactions. TNB **465** and nitrophloroglucinol **524** undergo reaction in a similar manner in an alcoholic solution of KOH, leading to the adamantane-like potassium salt **536**, after treatment with acetic acid. Further elaboration of **536** included the reduction of the nitro substituents to amino groups, **537**, monodiazotation, and subsequent coupling with the sodium salt of **523** leading to the diazo dye **538**.

Mixing picric acid **469h** and phloroglucinol **523** in a solution of NaOH in MeOH−$H_2O$ also led to the 1:1 adduct

**Scheme 77**




**539**. However, acidification of the tricyclic salt resulted in the reversion to the initial reagents.[276]

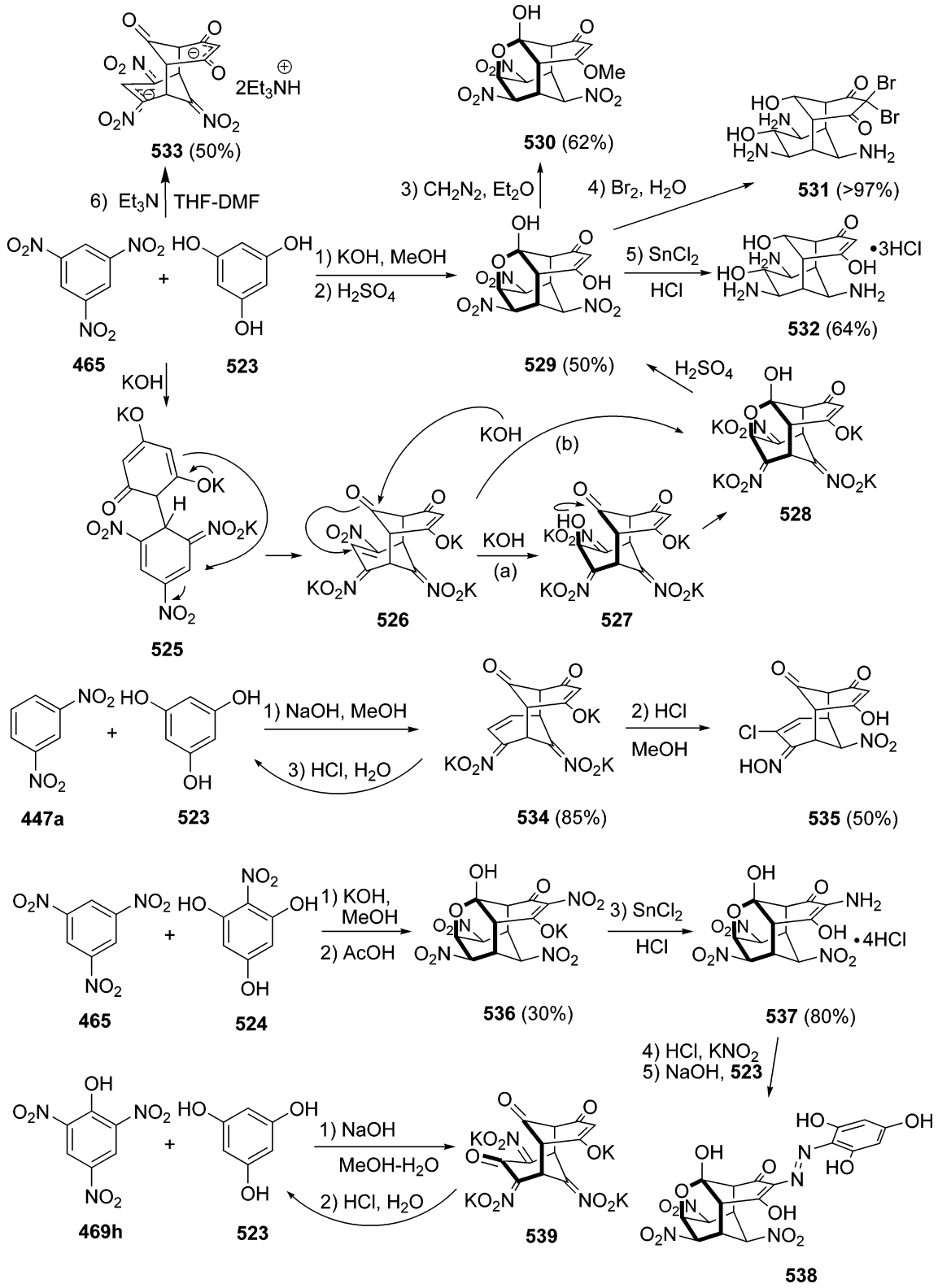
Phenolates are ambident nucleophiles. The simplest derivative, the phenoxide ion, acts as an oxygen nucleophile toward halo-nitroaromatic compounds, leading to the formation of diaryl ethers through displacement of the halide ion. However, the reaction of potassium phenoxide **540a** ($R^1$ = H) with TNB **465** affords $\sigma$-complex[279] **541**, where the phenoxide ion undergoes addition to the nitro-activated compound through the carbon at the para position (Scheme 79). Acidification of solutions of **541** in methanol, ethanol, or chloroform with dilute HCl or $H_2SO_4$ furnished a protonated derivative identified in situ as the nitronic acid **542** via IR, UV, and $^1$H NMR spectroscopic analysis of the reaction mixture.[280]

The reaction of phenoxide ion and alkyl-substituted phenolates with 1-X-2,4,6-trinitrobenzene derivatives can result in the formation of two isomeric $\sigma$-complexes by attack at the C3 and C1 carbons. The reactivity and regioselectivity observed depend on the substituents present in the reagents and the reaction conditions.[281,282] Typically, attack at C1 is kinetically preferred, whereas adducts at the C3 position are thermodynamically favored. NMR monitoring of the reaction of potassium phenoxide **540a** ($R^1$ = H) and potassium 2,6-di-*tert*-butylphenoxide **540b** ($R^1$ = *t*-Bu) with *N*,*N*-dimethylpicramide **543** showed the formation of $\sigma$-complexes **544**. Addition of trifluoroacetic acid to the reaction mixture rendered dearomatized compounds **545** (Scheme 79).[283] Derivative **545b** was prepared in almost quantitative yield by allowing **540b** to react with **543** for 30 min and subsequent protonation with HCl. The chemo- and regioselectivity observed could be anticipated on the basis of steric interactions. However, the protonation at C2 to give nitro compound **545** instead of the azinitro isomer was unexpected. The different behaviors in the protonation of **541** and **544** were ascribed to the inefficient charge delocalization in **544**. Steric hindrance between the C6 $NO_2$ group and the $NMe_2$ moiety prevents the coplanarity of the conjugated system.

Acid treatment of the $\sigma$-complexes of acetonates and nitroaromatic compounds generally leads to the breakdown of the complex into the starting components.[284] Curiously, treating the disodium salt **546** resulting from the reaction of picric acid **469h** and acetone under the Janovsky conditions[220,221] with acetic acid produced the monoanionic compound **547** (Scheme 79).[285] It was suggested that the formation of the product of protonation at C2, **547**, involves an intermediate species having the structure of a nitronic acid. We are aware of only one paper describing the isolation of a stable dearomatized product upon protonation of a Janovsky complex derived from a polynitroaromatic compound. Strauss and co-workers showed that cyclic ketones **548** undergo reaction with TNB in the presence of diethylamine to give monoanionic adducts **549**. Careful acidification of a methanolic solution of **549a** with HCl afforded the nitronic acid **550** in 40% yield (Scheme 79).[278] The same authors found that oxidizing the analogous complexes[286] **551** with 2 equiv of NBS results in the formation of the tricyclic isoxazoline *N*-oxides **552**, probably through bromination at the carbon adjacent to the carbonyl linkage and subsequent displacement of bromide ion by intramolecular attack of the oxygen of the nitronate moiety close to the electrophilic center.[287] Efforts made by Severin and co-workers to trap Janovsky complexes of TNB **465** and the sodium or potassium enolates of acetone, acetophenone, cyclopentanone, and cyclohexanone by successive treatment with sodium borohydride and bromine yielded 4,6-dinitro-2,3-dihydrobenzofurans **554** (Scheme 79).[242,288]

Dearomatized neutral products could be successfully isolated by alkylating the $\sigma$-complexes of 4-hydroxy-1,3-dinitrobenzene **447g** and the sodium ketonates of acetone **553a** ($R^1$ = Me, $R^2$ = H) and cyclohexanone **553b** [$R^1$−$R^2$ = $(CH_2)_4$] via Mannich condensation with formaldehyde and methylamine, in the same manner described in the quenching of hydride $\sigma$-adducts. In this way, new derivatives of 3-ABNs **555a**,**i** were obtained (Table 36[80], entries 1 and 10).[289] Additional examples of this chemistry were provided by Atroshchenko's group by using different ketones as precursors of the nucleophile as well as a variety of amines for the Mannich reaction (Scheme 80; Table 36).[290,291] The use of 1,4-butanediamine as the amine component in the aminoalkylation of Janovsky complex **554a** ($R^1$ = Me, $R^2$ = H) led to the formation of the bis-3-ABN **556**, albeit in very low yield (8%).[290] Introduction of a reduction step with sodium borohydride on the disodium salt **554a** prior to the Mannich condensation afforded tricyclic compound **557**.[289] This structure indicates that the carbonyl group of the side chain of complex **554a** was selectively reduced and the resulting hydroxy group underwent a [1,4] intramolecular addition to the vinyl ketone moiety. Subsequent Mannich reaction with formaldehyde and methylamine provides **557** in a yield of 65%. The labile bond of the α-nitroketone fragment of **557** was cleaved by treatment with NaOEt and

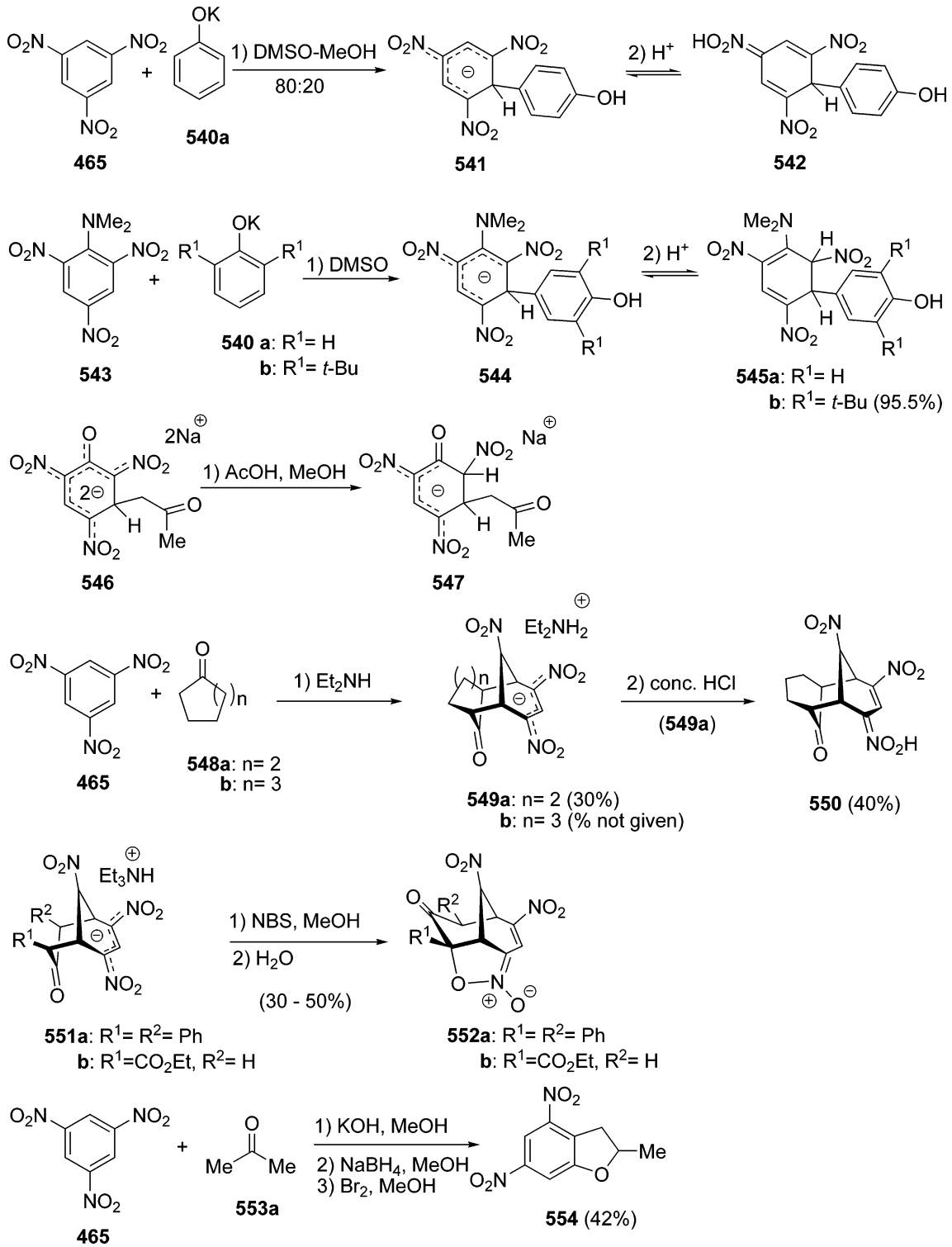
**Scheme 78**




$NaBH_4$ to give the nitrocarboxylic acid **558** and the nitroalcohol **559**, respectively. Mechanistic studies by NMR, UV, and quantum-chemical methods on the regioselectivity of the acetonate ion addition to 1,3-dinitro-5-$R^1$- and 1,3-di($R^1$)-5-nitro-benzenes ($R^1$ = H, CN, $CO_2Me$, $CONH_2CO_2^-$, $NO_2$) indicated that kinetic factors control the attack of the nucleophile to the C2 position, whereas addition to the C4 atom led to thermodynamically stable complexes.[292]

2,4-Dinitronaphthol **458** also undergoes this chemistry, generating 3-ABN derivatives **561** (Scheme 80). The synthesis was carried out in two steps. First, disodium salt **560** arising from the reaction of **458** with sodium ethoxide and acetone was immediately aminomethylated by treatment with formaldehyde and a primary amine. Second, an acidic quench was performed with orthophosphoric acid to furnish heterocyclic compounds **561** in moderate yields (Table 36). Similar

**Scheme 79**

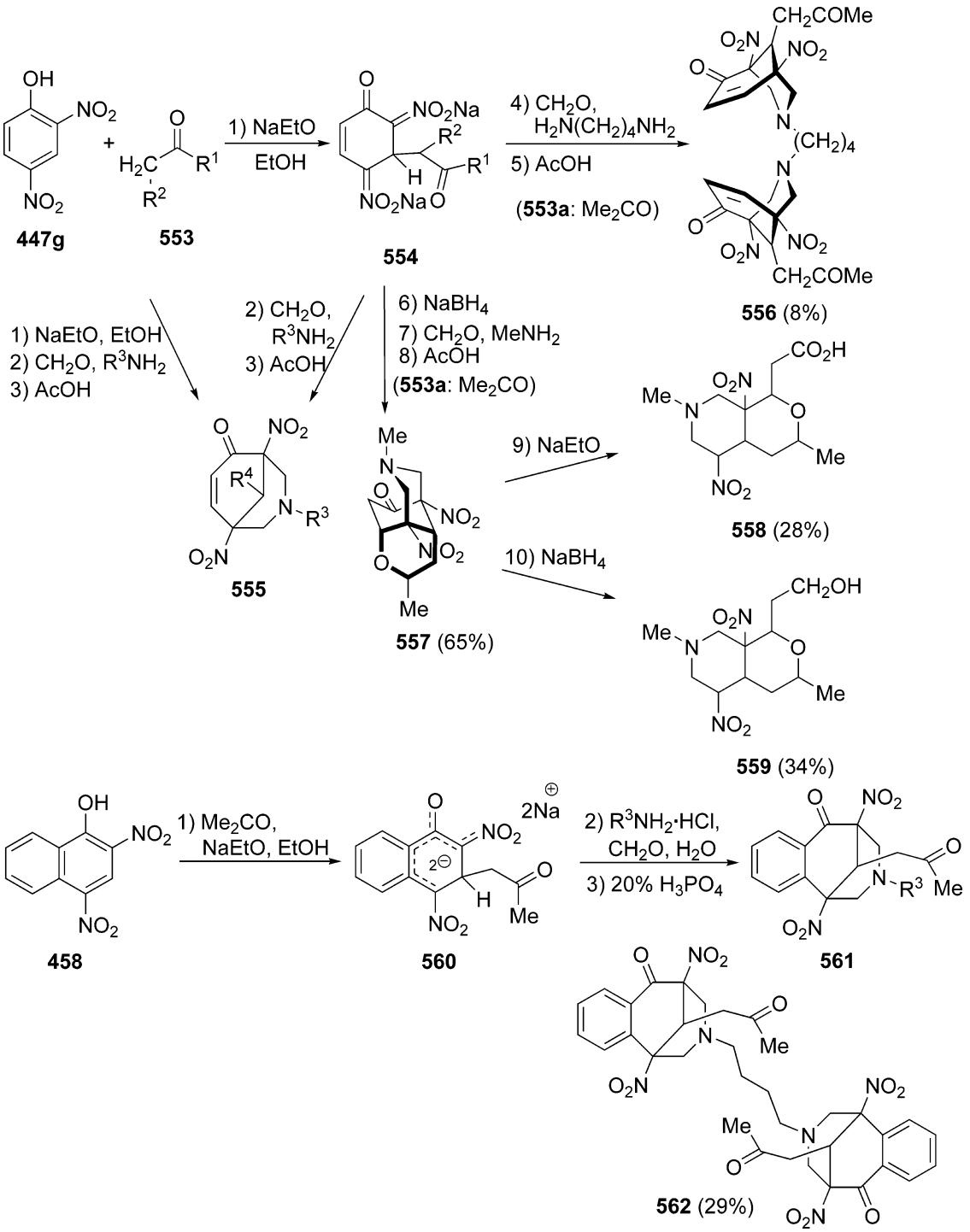



to the phenolate series, bis-ABN **562** was formed when 1,4-butanediamine was used in the Mannich condensation. On the basis of NMR studies and semiempirical calculations, it was concluded that the piperidine ring of **561a** ($R^3$ = Me) adopts predominantly a chair conformation with the *N*-methyl and oxopropyl groups occupying equatorial positions.[293]

Metalated ketones were also shown to form $\sigma$-complexes **563** with 9-nitroanthracene **461**.[294] Oxidation of the adducts proceeding from acetone, acetophenone, butanone, and methyl 1-naphthyl ketone with hydrogen peroxide gave 9-nitroanthracenes alkylated in position 10, **564a**−**c**,**h**. Surprisingly, in the analogous reaction with the anions of 2-hexanone and 3-methyl-2-butanone, the DHAs **499c** [$R^1$ = CH(*n*-Pr)$COCH_3$] and **499d** [$R^1$ = $C(CH_3)_2COCH_3$] were obtained, respectively (Scheme 81; Table 37 entries 1 and 2).[295] Apparently, in these two cases, the weak acid $H_2O_2$ effects protonation of the carbon atom linked to the *aci*-nitro group of the corresponding complexes. However, the reason for this different behavior as compared to the other ketones is not clear.

Anions stabilized by a nitro group, as well as doubly stabilized secondary and tertiary carbanions derived from diethyl malonate, diethyl methylmalonate, and malonodini-

**Scheme 80**




trile, also undergo addition to 9-nitroanthracene **461** in warm DMSO. Treatment of the resulting $\sigma$-adducts **563i**−**l** with HCl furnished *cis*-10-alkyl-9-nitro-9,10-DHAs **499e**−**h** (Scheme 81; Table 37, entries 3−6).[296] The dearomatized compounds **499f**,**g** were converted into 9-alkylanthracenes **565j**,**k** upon acid hydrolysis with boiling aqueous ethanolic HCl. $\sigma$-Complex formation seems to be disfavored in conventional protic solvents such as ethanol, and no reaction was observed when only a catalytic amount of base was used. Interestingly, dissolving **499h** [$R^1$ = $CH(CN)_2$] in pyridine caused the regeneration of the starting nitroanthracene. Alkylnitronates also undergo reaction with 1-nitronaphthalene **568** to give [1,4] adducts exclusively. Acidification of the nitromethyl $\sigma$-complex **569** formed by reaction of the anion of nitromethane with 1-nitronaphthalene **568** in DMSO afforded the dihydronaphthalene derivative **570** as a mixture of two diastereoisomers (Scheme 81).[297] Both isomers were transformed into 2-nitromethyl-1-nitronaphthalene **571** via a bromination−dehydrobromination procedure. Nitrobenzenes failed to react with the anion of nitromethane.

Alkylation of $\sigma$-adducts **563i**−**k** with benzyl halides[296] and **563a**−**g** with methyl iodide[298] followed by aqueous workup provided DHA oximes **567** in good yields (Scheme 81; Table 37, entries 7−16). In contrast to the oxidation with $H_2O_2$, the methylation of complexes **563a**−**c** proceeding from the addition of the anions of acetone, acetophenone, and butanone to nitroanthracene **461** produced also the corresponding dearomatized anthracene oximes **567a**−**c**. Treatment of

**Table 36. Conjugate Addition−Mannich Condensation of 447g and 458**

| entry | **553** | $R^1$ | $R^2$ | $R^3$ | $R^4$ | yield (%) |
|---|---|---|---|---|---|---|
| 1 | **a**[a] | Me | H | Me | $CH_2COCH_3$ | **555a** (62) |
| 2 | **a**[b] | Me | H | Et | $CH_2COCH_3$ | **555b** (30) |
| 3 | **a**[b] | Me | H | *n*-Bu | $CH_2COCH_3$ | **555c** (39) |
| 4 | **a**[b] | Me | H | Bn | $CH_2COCH_3$ | **555d** (28) |
| 5 | **a**[b] | Me | H | $(CH_2)_2Br$ | $CH_2COCH_3$ | **555e** (26) |
| 6 | **a**[b] | Me | H | $(CH_2)_2OH$ | $CH_2COCH_3$ | **555f** (32) |
| 7 | **a**[b] | Me | H | $CH_2CO_2H$ | $CH_2COCH_3$ | **555g** (38) |
| 8 | **a**[b] | Me | H | $(CH_2)_2CO_2H$ | $CH_2COCH_3$ | **555h** (37) |
| 9 | **a**[b] | Me | H | $(CH_2)_4NH_2$ | $CH_2COCH_3$ | **556** (8) |
| 10 | **b**[a] | $(CH_2)_4$ | | Me | 2-oxocyclohexyl | **555i** (48) |
| | **c**[c] | Ph | H | Me | $CH_2COPh$ | **555j** (48) |
| 11 | **c**[c] | Ph | H | Et | $CH_2COPh$ | **555k** (37) |
| 12 | **c**[c] | Ph | H | *n*-Bu | $CH_2COPh$ | **555l** (34) |
| 13 | **c**[c] | Ph | H | Bn | $CH_2COPh$ | **555m** (20) |
| | **c**[c] | Ph | H | $(CH_2)_2Br$ | $CH_2COPh$ | **555n** (26) |
| 14 | **c**[c] | Ph | H | $(CH_2)_2OH$ | $CH_2COPh$ | **555o** (23) |
| 15 | **c**[c] | Ph | H | $CH_2CO_2H$ | $CH_2COPh$ | **555n** (37) |
| 16 | **c**[c] | Ph | H | $(CH_2)_2CO_2H$ | $CH_2COPh$ | **555o** (20) |
| 17 | **458**[d] | | | Me | | **561a** (46) |
| 18 | **458**[d] | | | Et | | **561b** (57) |
| 19 | **458**[d] | | | *n*-Bu | | **561c** (53) |
| 20 | **458**[d] | | | Bn | | **561d** (54) |
| 21 | **458**[d] | | | $(CH_2)_2Br$ | | **561e** (63) |
| 22 | **458**[d] | | | $(CH_2)_2OH$ | | **561f** (50) |
| 23 | **458**[d] | | | $CH_2CO_2H$ | | **561h** (44) |
| 24 | **458**[d] | | | $(CH_2)_2CO_2H$ | | **561i** (30) |

[a] Data taken from ref 289. [b] Data taken from ref 290. [c] Data taken from ref 291. [d] Data taken from ref 293.

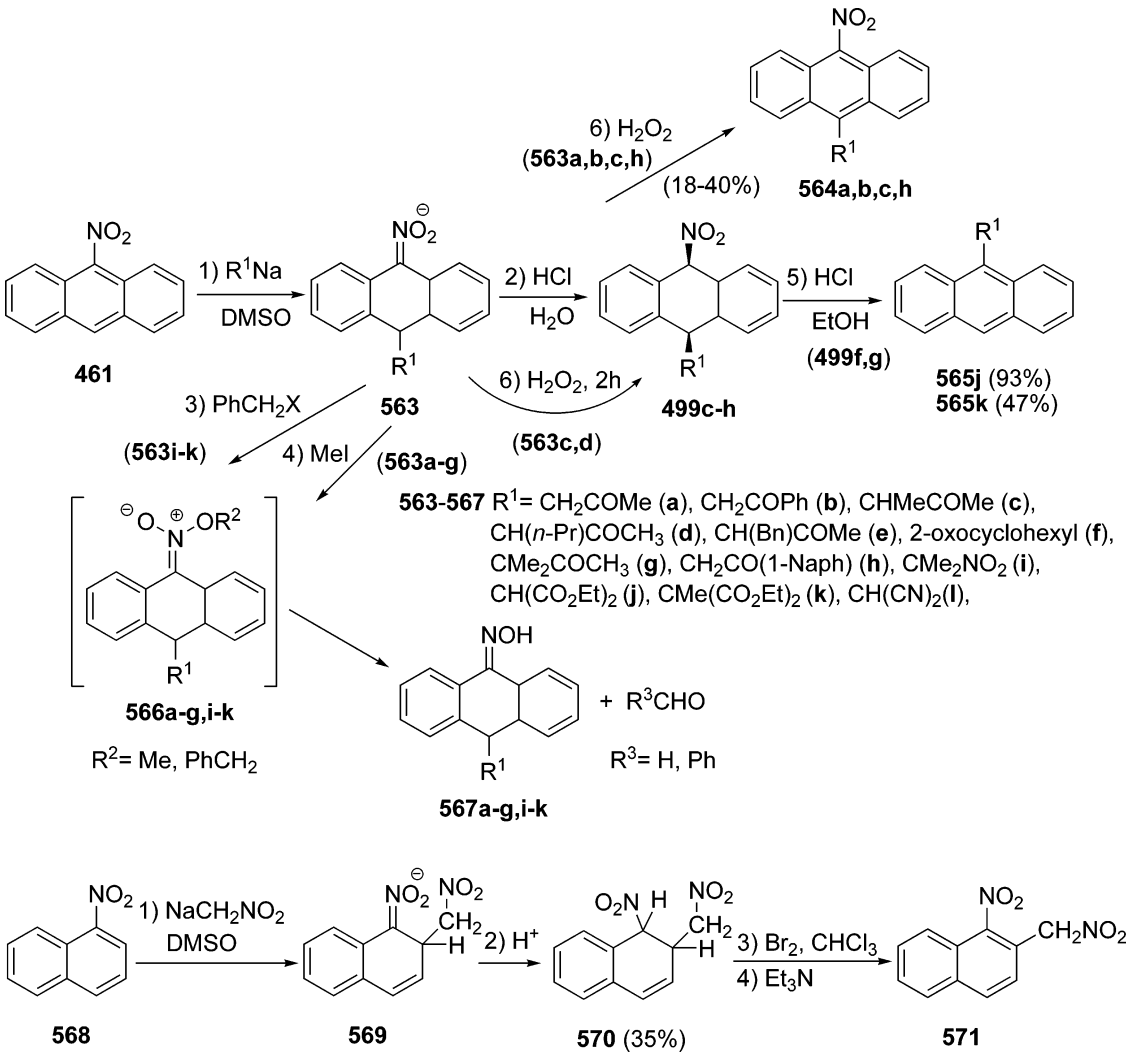
**Table 37. Conjugate Addition of Stabilized Cabanions to 9-Nitroanthracene 461**

| entry | $R^1$ | $E^+$ | yield (%) |
|---|---|---|---|
| 1 | CH(*n*-Pr)$COCH_3$ | HCl | **499c** (37)[a] |
| 2 | $CMe_2COCH_3$ | HCl | **499d** (43)[a] |
| 3 | $CMe_2NO_2$ | HCl | **499e** (76)[b] |
| 4 | $CH(CO_2Et)_2$ | HCl | **499f** (68)[b] |
| 5 | $CMe(CO_2Et)_2$ | HCl | **499g** (75)[b] |
| 6 | $CH(CN)_2$ | HCl | **499h** (70)[b] |
| 7 | $CH_2COCH_3$ | MeI | **567a** (40)[c] |
| 8 | $CH_2COPh$ | MeI | **567b** (18)[c] |
| 9 | $CHMeCOCH_3$ | MeI | **567c** (18)[c] |
| 10 | CH(*n*-Pr)$COCH_3$ | MeI | **567d** (3)[c] |
| 11 | CH(Bn)$COCH_3$ | MeI | **567e** (8)[c] |
| 12 | 2-oxocyclohexyl | MeI | **567f** (42)[c] |
| 13 | $CMe_2COCH_3$ | MeI | **567g** (6)[c] |
| 14 | $CMe_2NO_2$ | $PhCH_2Cl$ | **567i** (59)[b] |
| 15 | $CH(CO_2Et)_2$ | $PhCH_2Cl$ | **567j** (63)[b] |
| 16 | $CMe(CO_2Et)_2$ | $PhCH_2Br$ | **567k** (69)[b] |

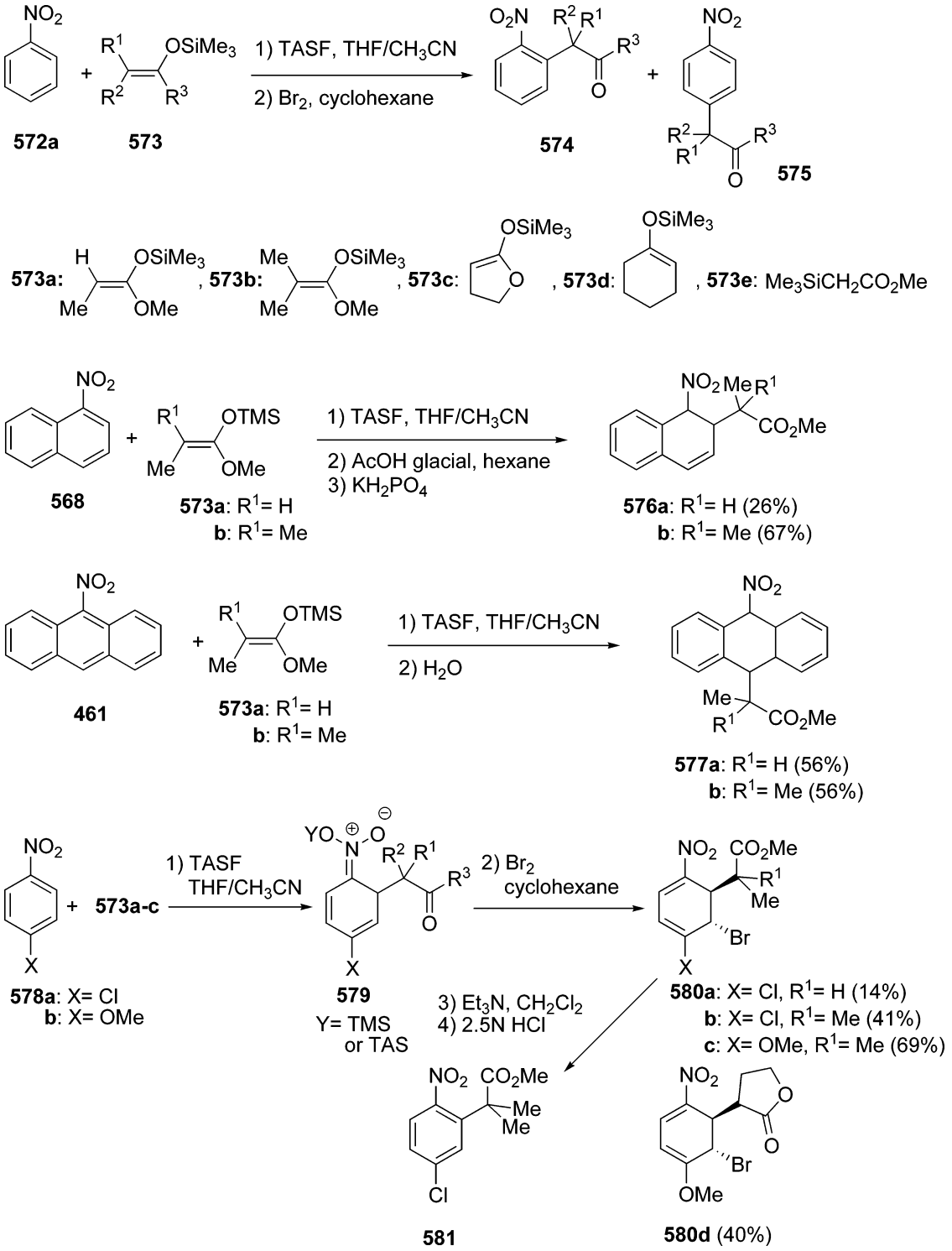
[a] Data taken from ref 295. [b] Data taken from ref 296. [c] Data taken from ref 298.

**563l** with benzyl chloride resulted in the complete reversion of the complex to the starting reagents. Some reversal was observed in the benzylation of **563k**, because 26% of nitroanthracene was recovered after recrystallization of the crude reaction mixture. The formation of oximes **567** is consistent with a mechanism involving O-alkylation of nitronates **563** to give the corresponding esters of nitronic

**Scheme 81**



**Scheme 82**




acids **566**, which decompose in a base-catalyzed process with loss of PhCHO or $CH_2O$.[299,300]

A significant contribution to the methodology aimed to introducing functionalized alkyl side chains into aromatic nitro compounds via nucleophilic conjugate addition reactions was the discovery by RajanBabu et al. of fluoride-assisted addition of silyl enol ethers and silyl ketene acetals to nitroarenes. The method consists of the reaction of silyl reagent **573** with the nitroarene in THF/$CH_3CN$ in the presence of 1 equiv of tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TASF) and subsequent oxidation with 1 equiv of bromine or DDQ (Scheme 82).[301,302] In this way, α-(nitroaryl)carbonyl compounds can be prepared in good yields. Products of attack ortho to the nitro group **574** predominate with sterically undemanding silyl reagents, whereas bulky reagents lead to the exclusive formation of para-substituted nitroarenes **575**. Yields decreased when tetrabutylammonium fluoride (TBAF) was used as fluoride source. The reacting nucleophiles are formed under neutral conditions, thus avoiding side reactions with substituents sensitive to nucleophiles prepared under basic conditions.

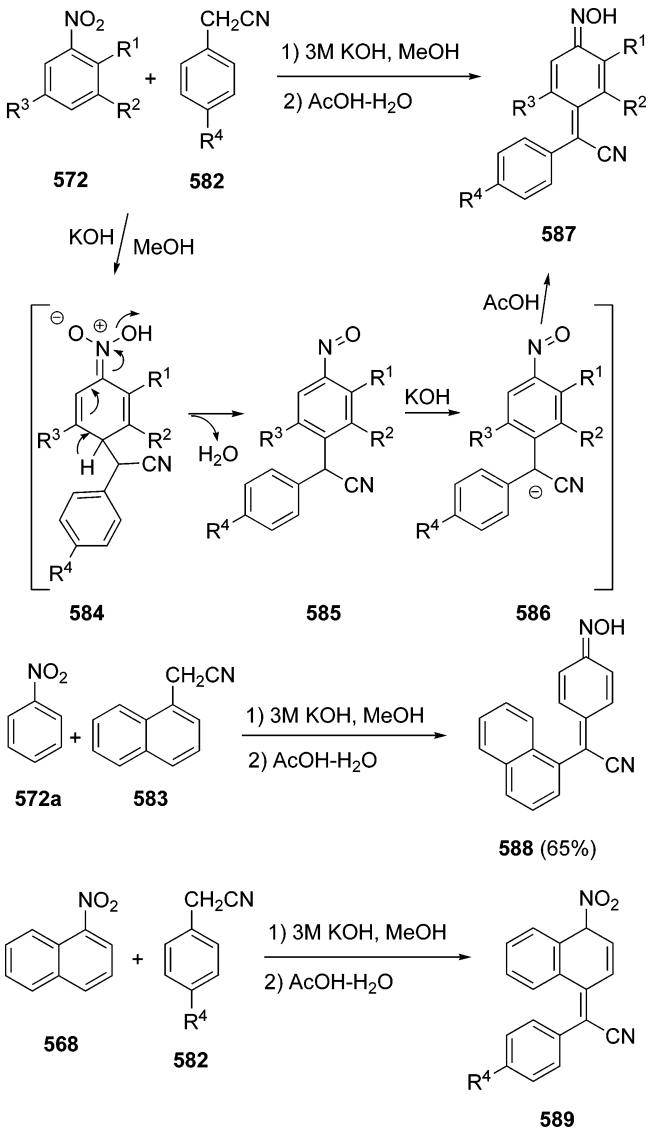
In systems of relatively low aromatic stabilization such as 1-nitronaphthalene **568** and 9-nitroanthracene **461** (as well as heteroaromatic compounds 5-nitroisoquinoline and 2-ni-

trothiophene) it was possible to isolate dihydroaromatic derivatives **576** and **577**, respectively, by quenching the nitronate adducts with a proton source. In the first case, the protonation was performed with glacial acetic acid, whereas water was used for quenching the $\sigma$-adducts leading to **577**. Nitronates **579** derived from nitrobenzenes could also be trapped when the extended conjugated system of the product was additionally stabilized by suitable substituents. Thus, 4-chloro-, **578a**, and 4-methoxynitrobenzenes, **578b**, underwent reaction with **573a**−**c** in the presence of TASF to give the functionalized 1,3-cyclohexadienes **580** upon quenching with bromine. Dehydrobromination to the aromatic alkylated compounds **581** was readily accomplished by treatment with triethylamine. Attempts to trap the dearomatized nitrobenzene $\sigma$-complexes with electrophiles such as aldehydes, alkylating agents, sulfur electrophiles, or *m*CPBA were unsuccessful. NMR monitoring of the reactions of nitrobenzene with **573b** and *p*-chloronitrobenzene with **573a** allowed the characterization of the corresponding $\sigma$-adducts. On the basis of these NMR studies and the absence of side products arising from the presence of radical ion intermediates in halo- and cyclopropyl-substituted nitrobenzenes, it was concluded that the reaction proceeds through a polar mechanism. Other electron-withdrawing groups ($CO_2Me$, CN, and $SO_2Ar$) failed to give this nucleophilic fluoride-assisted conjugate addition.

Anions stabilized by a cyano group are among the first charge delocalized nucleophiles used in dearomatizing reactions through nucleophilic conjugate addition to nitroarenes. Davis and co-workers demonstrated that aromatic mononitrobenzenes **572** unsubstituted in the para position to the nitro group and 1-nitronaphthalene **568** undergo condensation with phenylacetonitriles **582** and 1-naphthylacetonitrile **583** in methanolic potassium hydroxide solution to give dearomatized products having *p*-quinone-like **587**−**588** and naphthoquinone-like **589** structures (Scheme 83).[303,304] The mechanism proposed for this process involves the initial attack of the α-metalated nitrile to the para position of the nitroarene. The resulting $\sigma$-adduct is protonated at an oxygen atom of the *aci*-nitro group, affording the nitronic acid derivarive **584**, which undergoes water elimination with formation of the aromatized nitroso compound **585**. This intermediate has more acidic hydrogens than the starting nitrile and is deprotonated to give the highly delocalized anion **586**. Upon acidification with AcOH, **586** is protonated at the oxygen atom, yielding quinone oximes **587**−**588**. The excess of potassium hydroxide used may be necessary to ensure the precipitation of the potassium salt of the quinone-like products, thus preventing subsequent side reactions. The wide scope of the reaction was evidenced by preparing a large number of dearomatized derivatives containing either electron-donating or electron-withdrawing substituents (Table 38). The only limitation observed is the need for an unsubstituted nitroarene in the para position to the nitro group. When this position is occupied by a susbstituent, as in *p*-chloronitrobenzene and *p*-bromonitrobenzene, the metalated nitrile attacks the ortho position. However, the products obtained are 3-aryl-5-haloanthranils.[305,306]

Diazomethane is another carbon nucleophile capable of adding to polynitroaromatic compounds. The ability of diazomethane to react with trinitrobenzene derivatives having at least one hydrogen atom on the benzene ring (e.g., *sym*-trinitrobenzene, picryl chloride, pycril acetate, trinitrotoluene, trinitroxylene) was described as early as 1898.[307] By performing the reaction with a large excess of diazomethane,

**Scheme 83**




from 3 to 4 mol of the reagent was consumed depending on the substitution pattern on the aromatic ring. However, the structures of the products formed remained unclear. De Boer et al. addressed this issue about 70 years later and showed that treatment of TNB **465** with diazomethane **590** affords two products, **597** and **598**, via a tandem process in which the nitroarene undergoes reaction with three and four molecules of the diazoalkane, respectively (Scheme 84).[308−311] Thus, the molar ratio of the reactants was identified as an important factor in determining the final product. When the reaction was performed at −80 °C, a new product, **599**, was formed, also incorporating three methylene groups from diazomethane.[312,313] The mechanism proposed for rationalizing the formation of compounds **597**−**599** involves the sequential cyclopropanation of three carbon−carbon double bonds through the participation of diazonium betaines **591**, **594**, and **596**. Loss of nitrogen from these betaines furnishes the corresponding cyclopropanated compounds. The intermediate norcarane derivative **592** undergoes rearrangement to the seven-membered ring derivative **593**, which continues the chain of cyclopropanation reactions. Extensive charge delocalization in betaines **591**, **594**, and **596** seems to favor cyclopropanation over nitrogen retention with the formation of pyrazolines. In agreement with this reasoning, the reaction

**Table 38. Conjugate Addition of Potassium Arylacetonitriles to Nitroarenes 572 and 568[a,b]**

| entry | SM | $R^1$ | $R^2$ | $R^3$ | $R^4$ | yield (%) |
|---|---|---|---|---|---|---|
| 1 | **572a**[c] | H | H | H | H | **587a** (77) |
| 2 | **572a**[c] | H | H | H | Cl | **587b** (77) |
| 3 | **572a**[c] | H | H | H | MeO | **587c** (77) |
| 4 | **572b** | Cl | H | H | H | **587d** (92) |
| 5 | **572c** | Cl | H | H | Cl | **587e** (100) |
| 6 | **572d** | H | H | Cl | H | **587f** (53) |
| 7 | **572e** | H | H | Cl | Cl | **587g** (100) |
| 8 | **572f** | Me | H | H | H | **587h** (72) |
| 9 | **572g**[b] | Me | H | H | Cl | **587i** (60) |
| 10 | **572h** | H | H | Me | H | **587j** (76) |
| 11 | **572i** | H | H | Me | Cl | **587k** (33) |
| 12 | **572j** | MeO | H | H | H | **587l** (87) |
| 13 | **572k** | MeO | H | H | Cl | **587m** (80) |
| 14 | **572l**[d] | H | H | MeO | H | **587ln** (25) |
| 15 | **572**m | H | H | MeO | Cl | **587o** (89) |
| 16 | **572n** | Me | Cl | H | H | **587p** (82) |
| 17 | **572o** | Me | Cl | H | Cl | **587q** (80) |
| 18 | **572p** | Me | Cl | H | MeO | **587r** (80) |
| 19 | **572q** | Cl | Cl | H | H | **587s** (53) |
| 20 | **572r** | Cl | Cl | H | Cl | **587t** (92) |
| 21 | **572s** | Cl | Cl | H | MeO | **587u** (65) |
| 22 | **572t** | Cl | H | Cl | H | **587v** (93) |
| 23 | **572u** | Cl | H | Cl | Cl | **587w** (94) |
| 24 | **572v** | Cl | H | Cl | MeO | **587x** (91) |
| 25 | **572w** | MeO | H | MeO | H | **587y** (88) |
| 26 | **572x** | MeO | H | MeO | Cl | **587z** (80) |
| 27 | **572y** | MeO | H | MeO | MeO | **587aa** (65) |
| 28 | **572z** | Me | H | Me | H | **587ab**(53) |
| 29 | **572aa** | Me | H | Me | Cl | **587ac** (43) |
| 30 | **572ab** | Me | H | Me | MeO | **587ad** (69) |
| 31 | **572ac** | MeO | H | Cl | H | **587ae** (82) |
| 32 | **572ad** | MeO | H | Cl | Cl | **587af** (81) |
| 33 | **572ae** | MeO | H | Cl | MeO | **587ag** (84) |
| 34 | **572af** | Me | H | Cl | H | **587ah** (92) |
| 35 | **572ag** | Me | H | Cl | Cl | **587ai** (69) |
| 36 | **572ah** | Me | H | Cl | MeO | **587aj** (88) |
| 37 | **572ai**[d] | Cl | H | Me | H | **587ak** (77) |
| 38 | **572aj**[d] | Cl | H | Me | Cl | **587al** (77) |
| 39 | **572ak**[d] | Cl | H | Me | MeO | **587am** (80) |
| 40 | **568**[e] | | | | H | **589a** (33) |
| 41 | **568** | | | | Cl | **589b** (88) |
| 42 | **568**[e] | | | | MeO | **589a** (36) |

[a] Data taken from ref 303. [b] The configuration of the tetrasubstituted exocyclic carbon−carbon double bond has not been determined. [c] Data taken from ref 304. [d] Reaction performed at room temperature. [e] KOH (4.5 M) in methanol was used.

of diazomethane with compound **597** leads to the product of 1,3-dipolar addition **598**. The alternative betaine intermediate would have a limited charge delocalization. At low temperature, the loss of nitrogen from betaine **594** is effected by attack of the adjacent nitronate anion to give **599**.

Weak acids promote the isomerization of **598** to the tautomer **600**, which loses nitrous acid upon treatment with strong mineral acids. The resulting pyrazole derivative **601** is further oxidized to ketone **602**, which can be methylated by reaction with diazomethane to give *N*-methyl ketone **603**.[308]

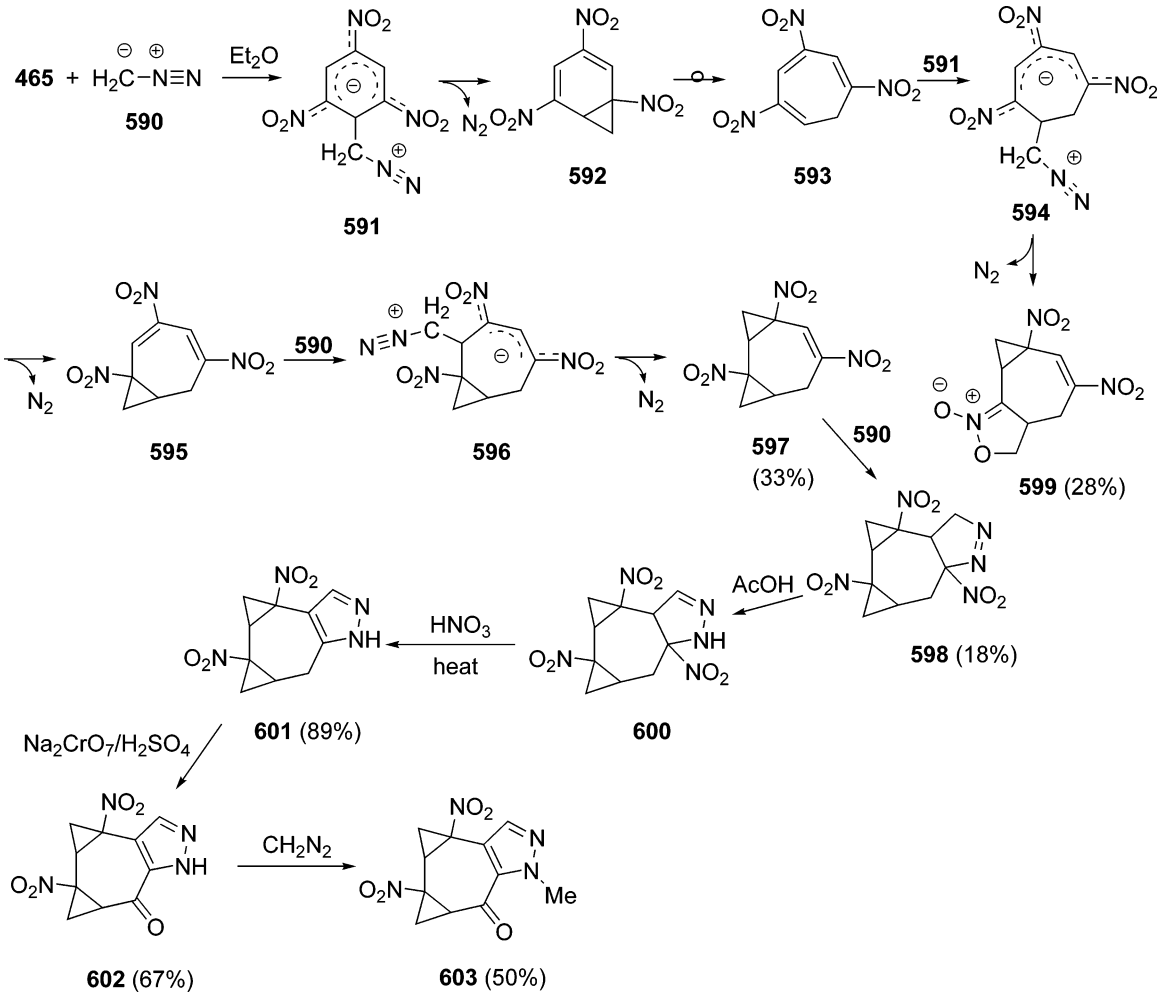
### *14.1.4. Reactions with Oxygen Nucleophiles*

Besides the carbon−carbon bond-forming reactions discussed in sections 14.1.1−14.1.3, $D_NAr$ reactions to nitroarenes may be used for the direct introduction of heteroatoms into the aromatic system. Around 1900, Jackson[219] and Meisenheimer[218] provided, independently, the correct structure of the red adducts obtained in the reaction of alkoxides with nitroaromatic compounds. As mentioned above, these type of covalent adducts became known as Meisenheimer and Jackson−Meisenheimer complexes, or simply $\sigma$-complexes. Since their discovery, $\sigma$-complexes have attracted an enormous activity.[222−226,229,231] In his classic study, Meisenheimer showed that the anionic adducts could be trapped by protonation and bromination to give dearomatized products **605**, **606a**, **608**, and **609** (Scheme 85). Interestingly, bromination of the ring prevailed over the formation of products of oxidation. The work also reformulated as dearomatized nitronic acids the structures proposed by other authors for the products resulting from the reaction of alkoxides and cyanide ion with some trinitrobenzene derivatives, for instance, compounds **610** and **611**. Although these early results demonstrated the feasibility of electrophilic trapping of $\sigma$-complexes, most investigations on the addition of nucleophiles to nitroaromatic compounds focused on features concerning the $\sigma$-complexes as pivotal intermediates in $S_N$Ar processes. Actually, the decomposition of Meisenheimer complexes by the action of an electrophile results generally in the formation of $S_NAr$ products.[314−317] Findings related to the preparation of dearomatized products are more of serendipitous nature than the result of a synthetic strategy designed for developing a new methodology or obtaining a preselected target compound.

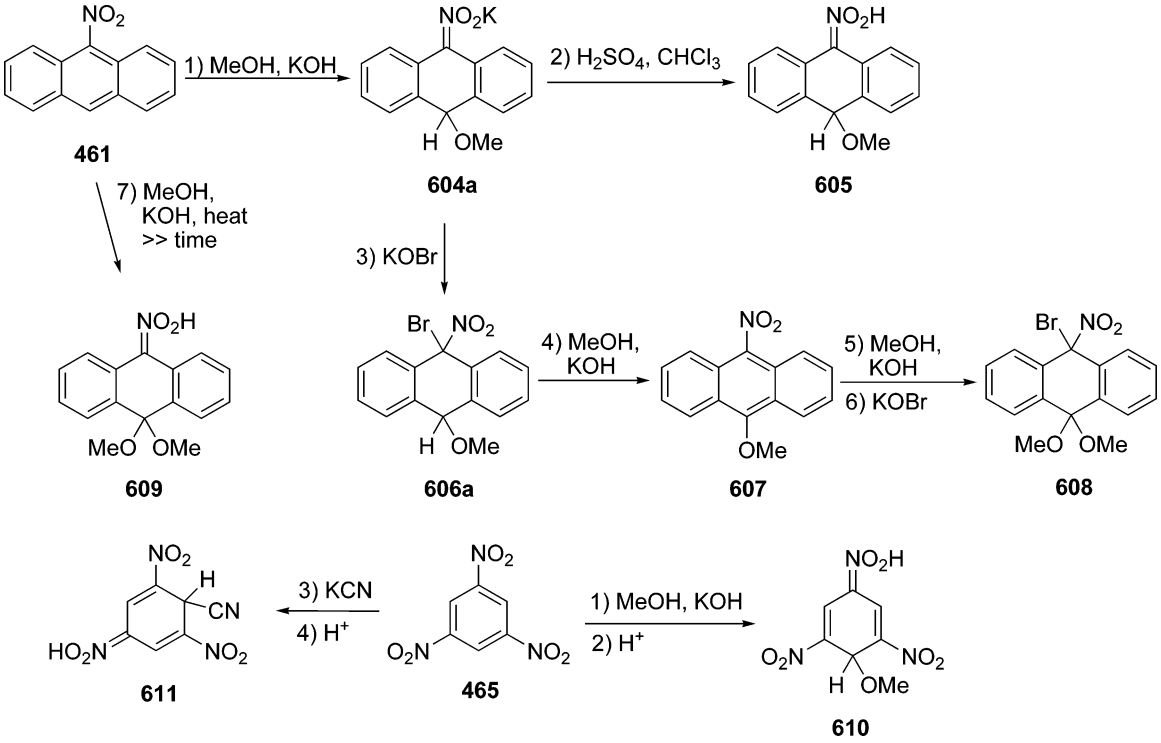
Nucleophilic addition to nitroanthracene became the origin of a long-lived and extremely fruitful subject, which continues to attract many investigations. Nearly a century later, renewed interest in this chemistry provided new examples of DHAs **606** (Scheme 86; Table 39, entries 1−5), using the same substrate as starting material and sodium hypochlorite or hypobromite as quenching reagent.[318] 9-Alkoxyanthracenes **612** also participate in the same way, leading to DHAs **613** with tetrasubstituted $sp^3$ carbons at positions 9 and 10 (Table 39, entries 6−11). The bromo derivative of the $\sigma$-complex of 9-nitroanthracene with the propoxide ion proved to be too unstable to be isolated and was characterized by $^1$H NMR spectroscopy. Compounds **606** were obtained as a single stereoisomer. It was assumed that the central ring adopts a boat conformation with the alkoxy and nitro substituents lying in pseudoaxial positions. However, no conclusions were drawn about the stereochemistry of the tetrasubstituted derivatives **613**.

Meisenheimer complexes **604** (**a**, $R^1$ = Me; **b**, $R^1$ = Et) may be methylated upon addition of methyl iodide, yielding 9,10-dihydro-10-alkoxy-9-anthroximes **614** (Scheme 86).[298,319] Similar to the analogous reactions with carbon nucleophiles, oxime formation occurs through O-methylation followed by loss of formaldehyde (see Scheme 81). Electrophilic attack at the carbon atom of the *aci*-nitro group of **604** was observed in the reaction of these $\sigma$-adducts with aromatic diazonium salts **615**, leading to the formation of 10-arylazo-9,10-DHAs **616** (Scheme 86; Table 39), which were further transformed into anthraquinone arylhydrazones **617** upon treatment with a base.[320,321] The formation of **616** is a remarkable process mainly for two reasons. On the one hand, the related reactions of $\sigma$-complexes of polynitroaromatic compounds afford rearomatized products through two competing pathways: oxidation to the polynitroarene and substitution of a nitro group by the aryldiazonium ion.[250,322−325] On the other hand, the conversion of **461** into **616** represents a procedure for introducing a phenylazo moiety into an electron-deficient aromatic system, which is not feasible through conventional diazo coupling reactions. The distinct behavior of $\sigma$-complexes **604** toward aromatic diazoniun salts as compared with

**Scheme 84**




**Scheme 85**




those derived from polynitrobenzenes and polynitronaphthalenes was attributed to the stability gained by the existence of **616** in a boat conformation, which minimizes the steric interactions between the substituents and the peri hydrogens.

**Scheme 86**

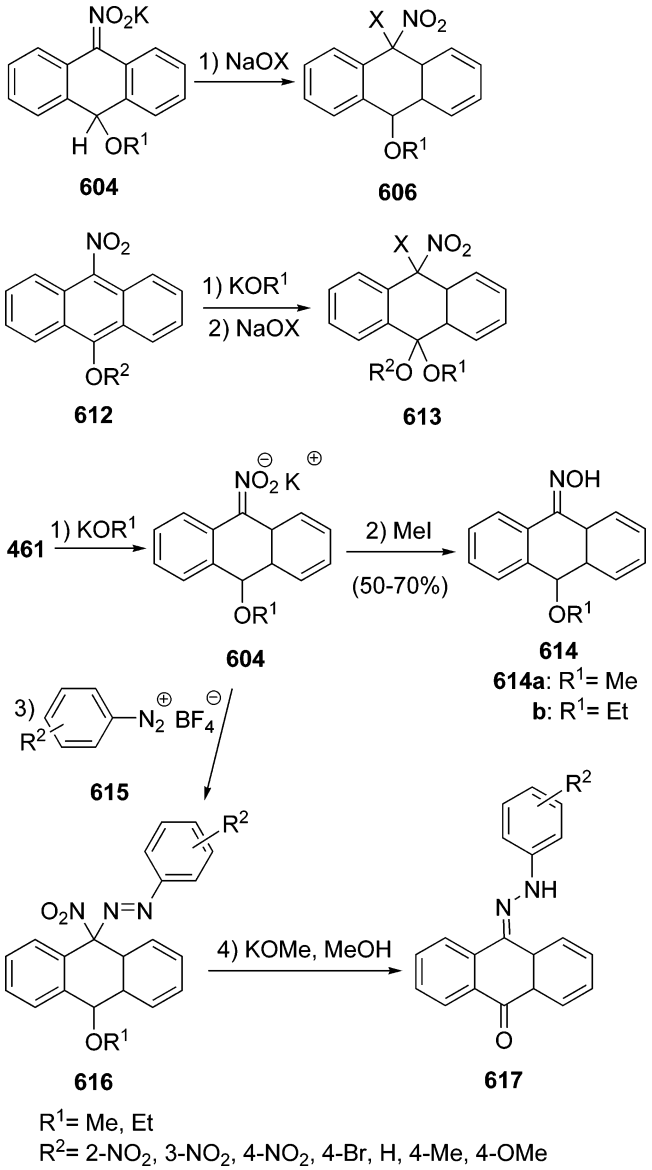



**Table 39. Conjugate Addition of Potassium Alcoholates to Nitroarenes 461 and 612**

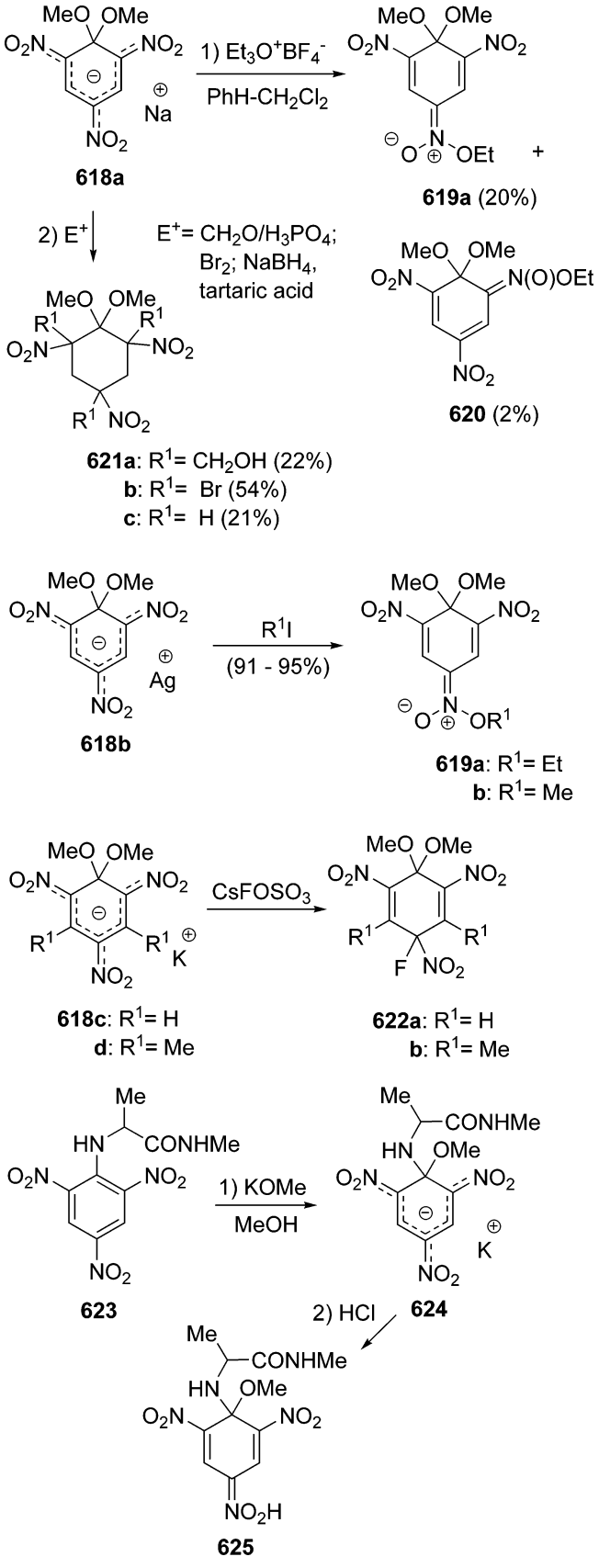
| entry | SM | $R^1$ | $R^2$ | X | yield (%) |
|---|---|---|---|---|---|
| 1 | **461**[a] | Me | | Br | **606a** (63) |
| 2 | **461**[a] | Me | | Cl | **606b** (66) |
| 3 | **461**[a] | Et | | Br | **606c** (72) |
| 4 | **461**[a] | Et | | Cl | **606d** (64) |
| 5 | **461**[a] | *n*-Pr | | Br | **606e**[b] |
| 6 | **612**[a] | Me | Me | Br | **613a** (56) |
| 7 | **612**[a] | Me | Me | Cl | **613b** (53) |
| 8 | **612**[a] | Me | Et | Br | **613c** (60) |
| 9 | **612**[a] | Me | Et | Cl | **613d** (52) |
| 10 | **612**[a] | Et | Et | Br | **613e**[b] |
| 11 | **612**[a] | Et | Et | Cl | **613f**[b] |
| 12 | **461**[c] | Me | 2-$NO_2$ | | **616a** (73) |
| 13 | **461**[c] | Me | 3-$NO_2$ | | **616b** (74) |
| 14 | **461**[c] | Me | 4-$NO_2$ | | **616c** (74) |
| 15 | **461**[c] | Me | 4-Br | | **616d** (32) |
| 16 | **461**[c] | Me | H | | **616e** (25) |
| 17 | **461**[c] | Me | 4-Me | | **616f** (21) |
| 18 | **461**[c] | Me | 4-MeO | | **616g** (14) |
| 19 | **461**[c] | Et | 2-$NO_2$ | | **616h** (65) |
| 20 | **461**[c] | Et | 3-$NO_2$ | | **616i** (68) |
| 21 | **461**[c] | Et | 4-$NO_2$ | | **616j** (70) |
| 22 | **461**[c] | Et | 4-Br | | **616k** (30) |
| 23 | **461**[c] | Et | H | | **616l** (24) |
| 24 | **461**[c] | Et | 4-Me | | **616m** (18) |
| 25 | **461**[c] | Et | 4-MeO | | **616n** (12) |

[a] Data taken from ref 318. [b] Yield not given. [c] Data taken from ref 321.

$\sigma$-Complexes formed by the addition of alkaline alkoxides to methyl picrate do not undergo reaction with conventional alkylating agents. However, alkylation becomes feasible when strong alkylating reagents are used or the alkali salts are previously converted into the corresponding silver derivatives. The reaction of the sodium salt **618a** with triethyloxonium fluoroborate furnished methyl picrate as the major product (73%), together with a mixture of nitronic esters **619a** ($R^1$ = Et) and **620** resulting from the O-alkylation of the nitro groups in the para and ortho positions (Scheme 87).[326] Interestingly, $\sigma$-complex **618a** underwent trialkylation by reaction with formalin at 25−40 °C to give trinitrocyclohexane **621a** in 22% yield after protonation with diluted phosphoric acid.[327] Monohydroxymethylation was also feasible by keeping the reaction temperature at 0 °C. Trapping **618a** with bromine, plus reduction with $NaBH_4$ followed by the addition of tartaric acid, afforded the respective cyclohexane derivatives **621b**,**c** in acceptable yields. In all cases, mixtures of the four geometrical isomers were obtained. The silver salt **618b** resulting from sodium−silver exchange of **618a** smoothly undergoes reaction with methyl iodide and ethyl iodide to give products of exclusive alkylation at the para position to the methoxy groups **619a**,**b** in excellent yields. Another example of electrophilic capture of Meisenheimer complexes of type **618** is provided by the reaction of potassium salts **618c**,**d** with cesium fluoroxysulfate. Fluorination occurred at the carbon atom in the para position to the methoxy groups to give **622** (Scheme 87).[328] The amino-substituted trinitrobenzene **623** also gave a 1-$\sigma$-complex **624** when treated with potassium methoxide in methanol. The salt **624** represents the first example of a Meisenheimer adduct formed by nucleophilic addition to a picramide. The same adduct, with an ammonium cation as counterion, was obtained by adding amines such as piperidine, morpholine, di-*n*-propylamine, and triethylamine to a methanolic solution of **623**. After reaction with 1 equiv of HCl, nitronic acid **625** was obtained.[329,330] In dimethyl sulfoxide solution, the neutral adduct rapidly reverted to the starting picryl derivative and methanol (Scheme 87).

Meisenheimer complexes with a spiro structure **628** arising from the intramolecular ipso attack of a nucleophilic center located in the side arm of a nitroaromatic compound **626** are considerably more stable than the corresponding open-chain salts. The spiro complex is in equilibrium with the ring-opened form **627** (Scheme 88). Negative charge delocalization in classical Meisenheimer complexes through the polynitro system reduces their reactivity with electrophilic agents. In the case of spiro $\sigma$-complexes **628**, electrophiles may attack either picrate **627** or the dearomatized salt **628**. The use of very strong alkylating reagents, such as methyl fluorosulfonate and triethyloxonium tetrafluoroborate, provided mixtures of nitronic esters **630a**,**b**/**636** and picryl ethers **631**/**637** derived from the O-alkylation of both anionic species (Scheme 88).[331] Small amounts of products derived from the attack at the oxygen atom of a nitro group in the ortho position, **632**, were also obtained. The formation of these byproducts could be avoided by performing the reaction in the presence of triethylamine. Interestingly, the substitution of the potassium cation by sodium favored the predominant or exclusive formation of picryl derivatives **631**. Introducing

**Scheme 87**




silver as counterion of the spiro dearomatized anion by treating the potassium salt **629a** with silver oxide or silver nitrate made it possible to effect the alkylation of the silver salts **629c** with conventional alkyl halides, due to halide ion displacement assisted by the metal ion (Scheme 88).[326,332]

No trace of the corresponding picryl derivatives **631** was observed. However, the increased reactivity produced a decrease in the regioselectivity of the electrophilic attack. As a result, mixtures of regioisomers **630** and **632** were formed (Table 40). The highest ratio of **630**:**632** was obtained when acetonitrile was used as solvent. The analogous reaction of $\sigma$-complexes of 9-nitroanthracene **461** with alkyl halides affords dihydroanthracene oximes **567** through decomposition of the nitronic ester intermediates initially formed (see Scheme 81).[296] Actually, nitronic esters **630** decompose upon heating to give the corresponding oxime **633**. Moreover, acid hydrolysis of **630** leads to the formation of the picryl ether **634**.

Heating a solution of nitronic ester **630f** in dibutyl ether promotes the elimination of benzaldehyde to give oxime **633**. The potassium salt formed upon metalation with potassium *tert*-butoxide **638** represents the first example of this type of spirocyclic complex having a nitroso group in the para position of the cyclohexadiene system. Alkylation of **638** with methyl fluorosulfonate and triethyloxonium tetrafluoroborate furnished mixtures of *O*-ethers of oximes **639** and nitrone **640**, whereas acylation with acetyl chloride occurred exclusively on the oxygen atom of the oxime moiety, yielding **641** (Scheme 89).[333]

Spiro Meisenheimer complexes containing only two nitro groups also undergo alkylation with methyl fluorosulfonate. In the 2,4-dinitrobenzene derivative **642** (Scheme 89), methylation occurs exclusively at the terminal oxygen atom of the ring-opened form of the 1,3-dioxolane ring, giving **643** in 77% yield.[334] However, the analogous reaction of potassium salt **644** gives a mixture of picryl ether **645** and O-methylated nitronic esters as a mixture of *Z* and *E* stereoisomers **646** and **647**, respectively. When the 2,4-dinitro substitution pattern was part of a spiro naphthalene complex **648**, methylation was effected exclusively on an oxygen atom of the nitro group at the ortho position to the dioxolane ring, leading to a pair of isomers, **650** and **651**, in moderate yield. A small amount of product **649** (23%) resulting from the loss of formaldehyde is also formed (Scheme 89).

### *14.1.5. Reactions with Nitrogen Nucleophiles*

Picryl ethers **652** (Scheme 90) lead to the formation of neutral Meisenheimer adducts **654** when they are allowed to react with equimolar amounts of *tert*-butylamine **653a** and 2-amino-2-methyl-1-propanol **653b** at low temperature in THF. Compounds **654** were characterized through their NMR spectra in solution. However, they could not be isolated. Warming the solution to room temperature leads to the decomposition of the adducts. It is interesting to note that although steric compression might be expected to occur between large groups on C1 and the nitro groups at C2 and C6, the ambident nucleophile **653b** attacks the ring through the nitrogen, the most hindered nucleophilic center (Scheme 90).[335] When the reaction was performed with 2 equiv of amine, rearomatized products **655** were obtained due to the elimination of alcohol.

Nucleophilic addition of 4-aryl-substituted 2-aminothiazoles[336] **656** and 3-amino-1,2,4-triazoles[337] **657** to picryl chloride **469a** has been reported to give also neutral Meisenheimer type adducts (Scheme 90). The dearomatized products were isolated and their structures determined. In both cases the reaction proceeds through ipso attack by the nucleophile to the carbon bearing the chlorine substituent. Thiazoles **656** reacted exclusively through the ring nitrogen

**Scheme 88**

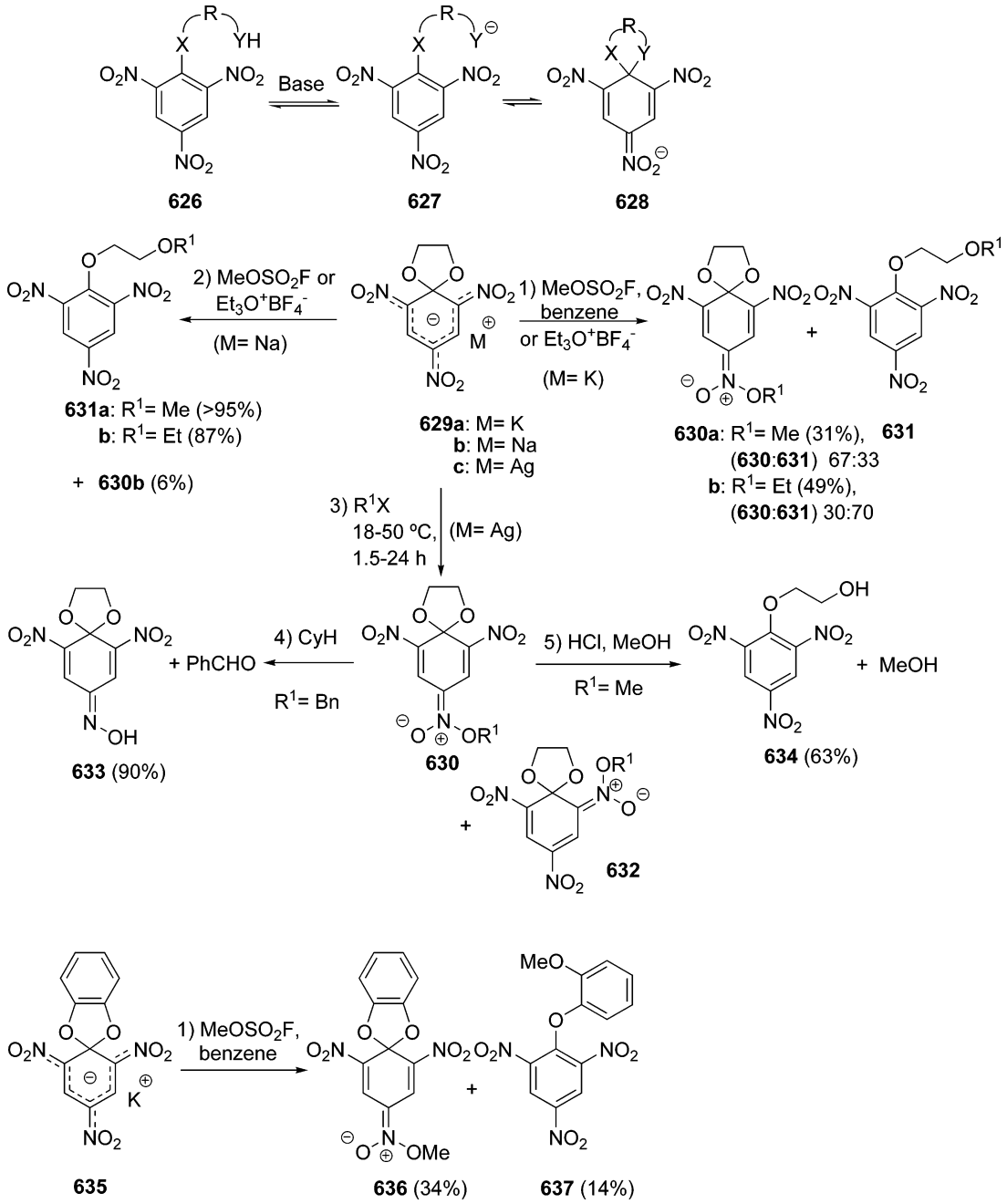



**Table 40. Alkylation of Silver Complexes 629c at 50 °C[a]**

| entry | compd | solvent | $R^1$ | X | yield (%) | ratio **630**:**632** |
|---|---|---|---|---|---|---|
| 1 | **a** | $C_6H_6$ | Me | I | 58[b] | 67:33 |
| 2 | **b** | $C_6H_6$ | Et | I | 60[b] | 80:20 |
| 3 | **b** | MeCN | Et | I | 56[c] | 89:11 |
| 4 | **b** | THF | Et | I | 45[c] | 91:9 |
| 5 | **b** | DMF | Et | I | 39[c] | 100:0 |
| 6 | **c** | $Me_2CO$ | *n*-Pr | I | 12[d] | 100:0 |
| 7 | **d** | MeCN | *i*-Pr | I | 49[c] | 75:25 |
| 8 | **e** | MeCN | allyl | I | 44[e] | 87:13 |
| 9 | **f** | MeCN | Bn | Br | 50[c] | 88:12 |

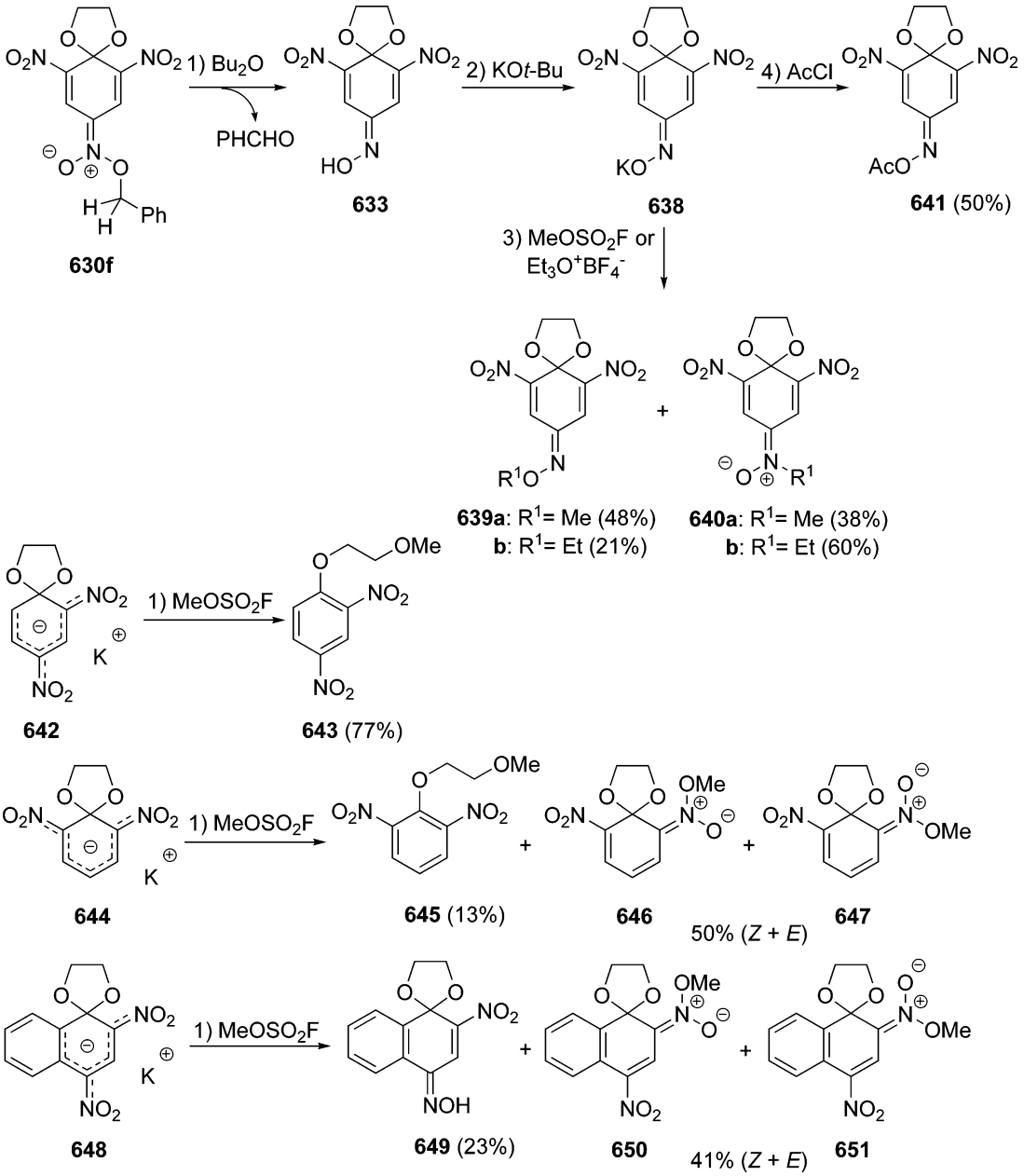
[a] Data taken from ref 326. [b] Reaction time of 2 h. [c] Reaction time of 1.5 h. [d] Reaction time of 10 h. [e] Reaction time = 24 h; temperature of the reaction = 18 °C.

to give **658**, whereas triazole derivative **657** afforded mixtures of products **659** and **660**.

### *14.1.6. Reactions with Phosphorus Nucleophiles*

Dialkyl and trialkyl phosphites are another class of heteroatom-centered nucleophiles that have been used for the generation of stable anionic $\sigma$-complexes with polynitroarenes.[338−341] However, there are very few examples of electrophilic trapping of the dearomatized adducts. TNB **465** and picryl derivatives **469e** ($R^1$ = Me) and **652a** ($R^1$ = OMe) led to the formation of monoadduct **661** and diadduct **662** with dialkyl phosphites in the presence of triethylamine, with the phosphite group entering meta to the substituent $R^1$ (Scheme 91).[342,343] The ability of alkyl phosphites to deoxygenate nitro compounds prompted additional transformations of the adducts. Thus, the reaction of an excess of dimethyl phosphite with nitronaphthalenes **568** ($R^1$ = H), **663** ($R^1$ = Me), and **664** ($R^1$ = Cl) in the presence of sodium methoxide provided heterocyclic compounds **670**. The Meisenheimer complexes **665** initially formed are deoxygenated by the

**Scheme 89**

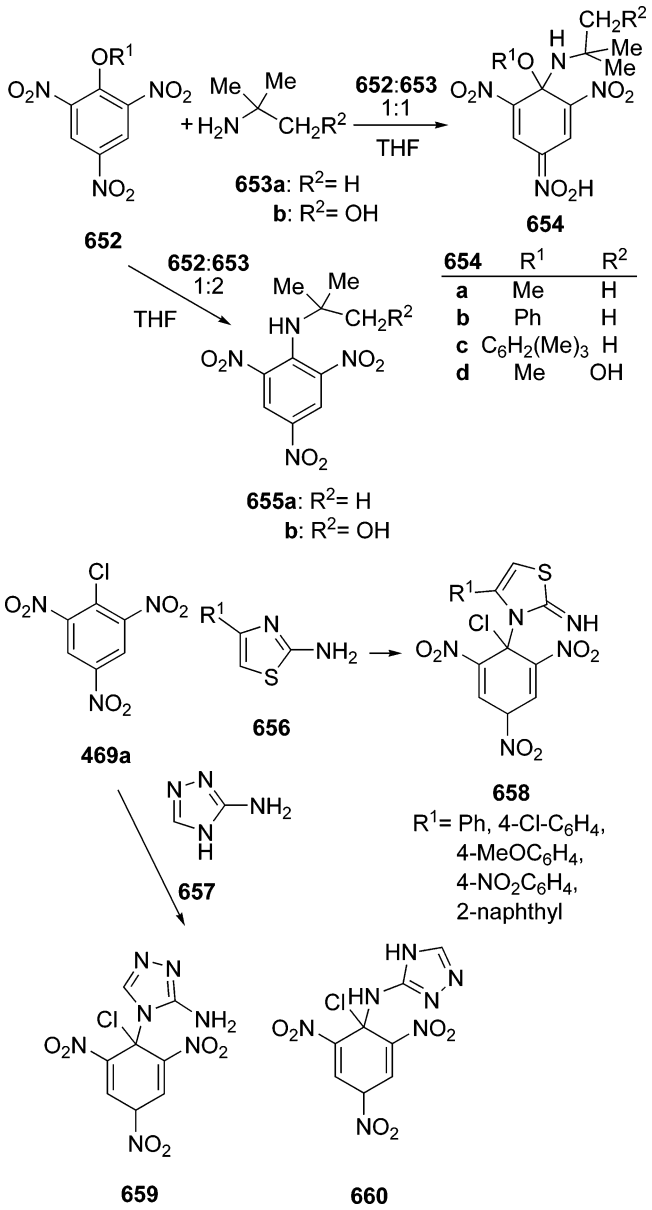



phosphite present in the reaction mixture to give nitrenes **666**. Reduction of this key intermediate or reaction with $HP(O)(OEt)_2$ furnishes the naphthalene derivatives **668** and **669**, respectively. Additionally, insertion into the phosphorus-substituted carbon−carbon double bond affords azirines **667**. Ring opening of **667** by nucleophilic attack of methoxide ion gives rise to benzazepine derivatives **670** (Table 41).[344] When the substituent $R^1$ is a methoxy group, the reaction follows a different course, leading to the formation of the dihydronaphthalene derivative **671**. It has been suggested that the electron-donating nature of the methoxy substituent determines a charge distribution of the nitrene intermediate **666**, which favors the addition of a second phosphite anion over other alternative reaction pathways.[345] The azirine intermediate could be intercepted by other nucleophiles. Performing the reaction in the presence of primary and secondary aliphatic amines affords amino-substituted benzazepines as mixtures of isomers **672** and **673** (Scheme 91; Table 41).[346] The analogous reaction with 2-nitronaphthalene **674** produces dimethyl 1*H*-2-benzazepine-1-ylphosphonates **675** in good yields.

## 14.2. Diazo Compounds

It has been shown in section 14.1.4. that diazonium salts may act as nitrogen electrophiles in trapping reactions of anionic $\sigma$-complexes. In addition to this reactivity, the $N_2^+$ function is one of the strongest activating groups for nucleophilic attack to an aromatic ring, and diazoarenes are known to participate in $S_NAr$ reactions.[347,348] Only in a few cases could dearomatized adducts be isolated, with most examples of reactions proceeding from 9-anthracenediazonium salts **679**. Diazotation of 9-aminoanthracene **676a** and 10-substituted derivatives **676b**−**d** is achieved by bubbling nitrogen oxide[349,350] or dinitrogen tetroxide[351] through a solution of the corresponding amine in diethyl ether or benzene (Scheme 92). Synthesis of derivative **678e** ($R^1 = NO_2$) needs the dioxime of anthraquinone **677** as starting material. Conventional diazotizing methods failed to give

**Scheme 90**




the expected diazonium salts. The counterion of the diazo compounds **678** thus obtained is the nitrate anion, which could be readily exchanged by anions such as $Cl^-$, $BF_4^-$, and $SO_4^{2-}$ by treating the nitrates with the respective acids, the tetrafluorborates **679** being the most stable salts.

Diazonium salts **679a** ($R^1$ = H) and **679c** ($R^1$ = OMe) proved to be too reactive. Once formed, they immediately undergo reaction with the amine present in the reaction crude, leading to products of coupling. Amine **676a** undergoes addition to diazonium salt **679a** through the para carbon, yielding the imine−diazonium salt **680**.[352] In **676c** this position is blocked by the methoxy substituent. Therefore, the coupling occurs by attack of the amine nitrogen at the 10-position of diazonium salt **679c**.[353] The derivative **681** thus formed spontaneously loses methanol to give diazoanthrimine **682**. Furthermore, when **676a** is allowed to react with NO for 5 h, the product isolated is the imine−oxime **683** proceeding from the action of nitrogen oxide on **679a**. The same product is obtained when diazoimine **680** is allowed to react with NO (Scheme 92).

Compounds **679b**,**d**,**e** undergo reaction in a similar manner with oxygen and nitrogen nucleophiles. However, the dearomatized adducts initially formed evolved through different pathways depending on the nature of the diazonium salt (Scheme 93; Table 42). The behavior of **679e** ($R^1$ = $NO_2$) is determined by the presence of a nucleofuge at position 10. The reaction of **679e** with water, methanol, or ethanol affords diazoanthrone **685** (entry 16, Table 42) via elimination of nitrous acid and the respective methyl and ethyl esters from adducts **684a**−**c**.[354] Analogously, treatment of an ethereal solution of **679e** with ammonia or aniline results in the formation of diazoanthrimine tetrafluorborates **686a**,**b** (entries 17 and 18, Table 42).

When 10-phenylanthracenediazonium tetrafluorborate **679b** ($R^1$ = Ph) was dissolved in water, methanol, or ethanol, azine **687a** was obtained (entry 4), together with byproducts such as azo compounds **688**, anthrones **689**, and anthracenes **690**.[355] The formation of azines **687** is catalyzed by acids as demonstrated by the isolation of adducts **684a**,**b** (entries 1 and 2, Table 42) when the reaction is performed in the presence of a base (NaOH or $Na_2CO_3$). These diazo derivatives **684** remain unchanged in a solution of methanol during 24 h. However, they are transformed very rapidly into the corresponding azines **687** by the addition of the salt **679b** to the methanolic solution.[356] Dimethylamine undergoes reaction with tetrafluorborate **679b** in a similar way. NMR and UV spectroscopic monitoring of the reaction evidenced the presence of mixtures of adduct **684c** and triazene **691a**. As the reaction progresses, compound **684c** disappears in favor of the aromatized product **691a** (entry 7, Table 42).

The diazonium salt **679d** ($R^1$ = $CO_2Me$) exhibited increased stability, facilitating its isolation and also affecting the reactivity. In contrast to **679b**, water solutions of **679d** afforded the hydroxydiazo compound **684d**, which showed a low tendency for the formation of azine **687d** (Scheme 93; cf. Table 42, entries 8 and 10).[357] Reaction of **679d** with dimethylamine and *p*-methoxyaniline also gave dearomatized products **684f** and **684g**, respectively (Table 42, entries 12 and 13). Isomerization of **684f** to triazene **691b** required the use of weak acids such as acetic acid or silica gel. On the other hand, **679d** underwent reaction with methanol in much the same manner as **679b**. In the presence of sodium carbonate, the diazoether **684e** was obtained (entry 9), whereas dissolving the diazonium salt in neutral methanol furnished the azine **687e** (entry 11). Successive saponification and acidic treatment of the triazene **691b** gave acces to a new diazonium salt **679f** ($R^1$ = $CO_2H$) bearing a $CO_2H$ substituent. Similar to the precursor **679d**, the treatment of **679f** with methanol in the presence of $Na_2CO_3$ produced the 9,10-dihydroanthracene derivative **684h** (Table 42, entry 15).

As far as we are aware, Panetta and co-workers reported the only example of a dearomatized spiro system formed by nucleophilic addition to a arenediazonium salt. While attempting to prepare nitrile **693** through a Sandmeyer-type reaction via diazotization of the amino terephthalate **692** and subsequent treatment with nickel cyanide, they obtained spiro compound **694** instead of the expected **693** (Scheme 94).[358] Apparently, the basic medium provided by the nickel cyanide [generated by reaction of nickel(II) nitrate hexahydrate with KCN in the presence of NaOH] promotes the intramolecular nucleophilic ipso attack of the oxygen atom in the hydroxyethoxy sidearm.

## 14.3. Triazo Compounds

Triazenes are another class of aromatic nitrogen compounds that have been recently used in carbon−carbon bond-

**Scheme 91**

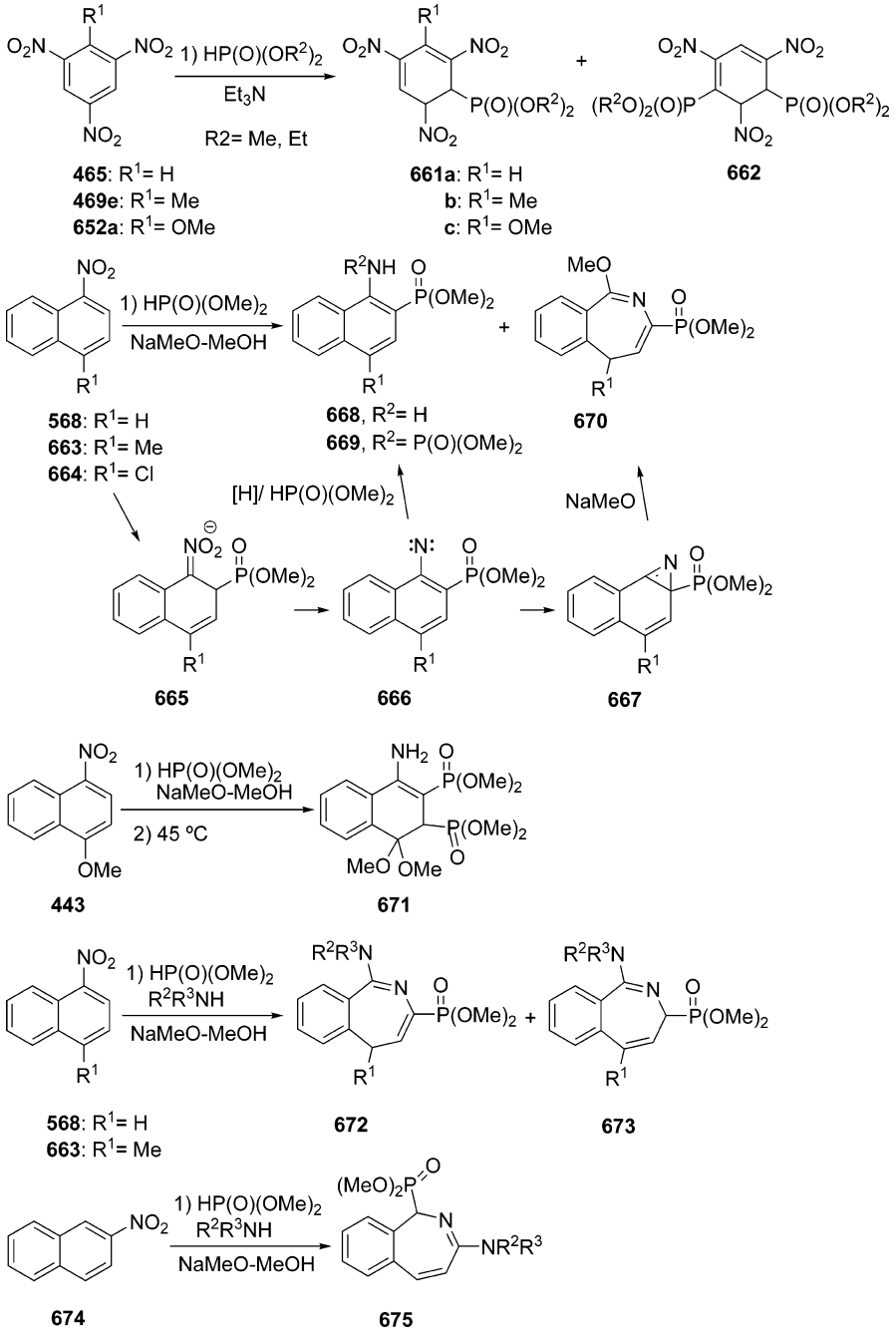



**Table 41. Conjugate Addition of Dialkyl Phosphite Anions to Nitroarenes**

| entry | SM | $R^1$ | $R^2$ | $R^3$ | | yield (%) | |
|---|---|---|---|---|---|---|---|
| 1 | **568**[a] | H | | | **668a** (24) | **669a** (18) | **670a** (30) |
| 2 | **663**[a] | Me | | | **668b** (12) | **669b** (51) | **670b** (2) |
| 3 | **664**[a] | Cl | | | **668c** (18) | **669c** (32) | **670c** (2) |
| 4 | **568**[b] | H | H | Et | **672a** (66) | **673a** (22) | |
| 5 | **663**[b] | Me | H | Et | **672b** (16) | **673b** (72) | |
| 6 | **568**[b] | H | Me | Me | **672c** (89) | | |
| 7 | **663**[b] | Me | Me | Me | **672d** (14) | **673c** (34) | |
| 8 | **568**[b] | H | $-(CH_2)_4-$ | | **672e** (69) | **673d** (7) | |
| 9 | **674**[b] | H | H | *n*-Bu | **675a** (81) | | |
| 10 | **674**[b] | H | Me | Me | **675b** (82) | | |

[a] Data taken from ref 344. [b] Data taken from ref 346.

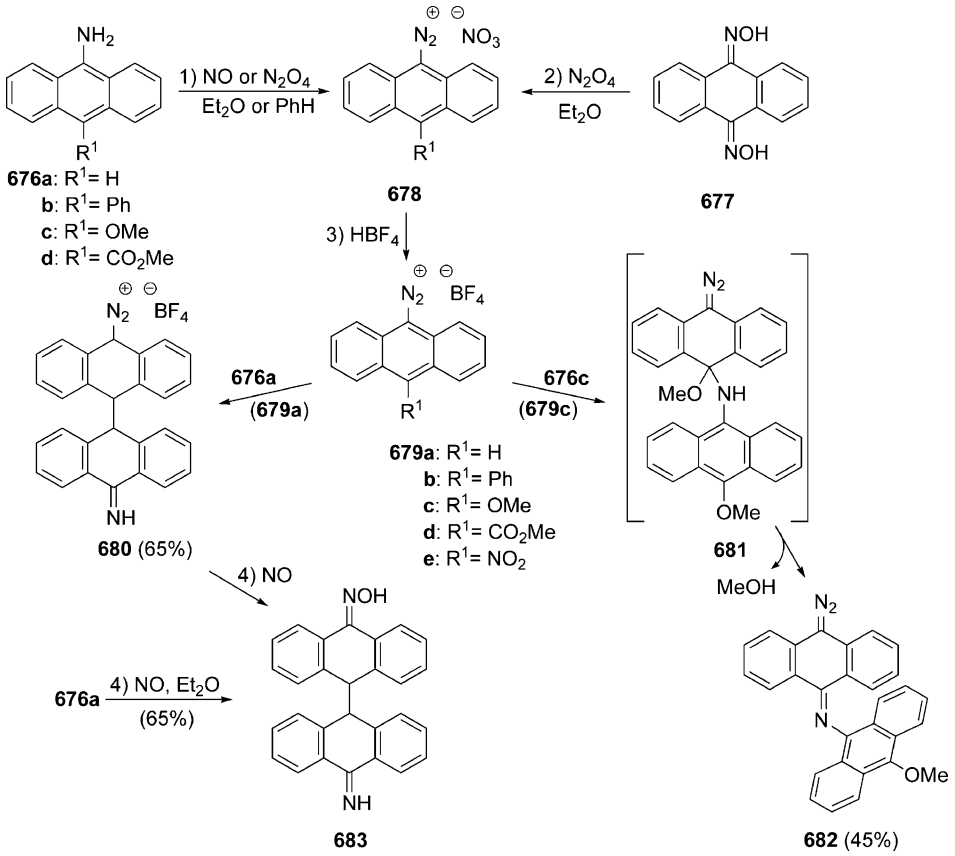
forming reactions involving dearomatization. The process is closely related to the Sommelet−Hauser rearrangement of benzylic ammonium salts caused by the action of base.[36,37]

In this case, the regioselective metalation of triazenes **695** in the α position with respect to the nitrogen, using *n*-BuLi, followed by the addition of $Boc_2O$, led to the formation of tetrahydrobenzotriazines **697** (Scheme 95; Table 43). The reaction pathway implies that, subsequent to the deprotonation, the anion attacks intramolecularly at the ortho position of the phenyl ring. The resulting dearomatized species **696** are then trapped by the reaction with $Boc_2O$. As expected, for triazenes unsubstituted at the ortho positions, the anionic cyclization was followed by rearomatization, and the products isolated are benzylamines **698**.[359]

## *15. Aromatic Rings Linked to a Phosphorus Atom*

Despite the rich chemistry of organophosphorus compounds, until recently, phosphorus-containing functionalities have been very rarely used as activating groups in nucleo-

**Scheme 92**




philic dearomatizing reactions.[360] Early examples are the result of a priori unexpected chemical behavior, therefore lacking generality. There are only two reports on intermolecular $D_NAr$ processes. They involve phosphonium salt and phosphine oxide functional groups and will be covered first. Dearomatizing reactions through anionic cyclization include ring activation by phosphorus ylide, phosphonamide, and phosphinamide moieties.

## 15.1. Phosphonium Salts

While investigating the reactivity of *N*,*N*-dibenzyltriphenylphosphonium bromide **699** with strong bases such as *t*-BuLi, Cristau and co-workers found that the organolithium underwent addition to one of the *P*-phenyl rings (Scheme 96).[361] Protonation of the adduct afforded an inseparable mixture of the cyclohexadiene derivative **700** and rearomatized product **701**. Using *p*-tolylaldehyde as trapping reagent caused the formation of small amounts of Wittig olefination products **703** and **704**, together with phosphonium salt **702** resulting from the alkylation−aromatization of a *P*-phenyl ring.

## 15.2. Phosphine Oxides

The attempted directed ortho lithiation of diphenyl(2-naphthyl)phosphine oxide **705** with *t*-BuLi led exclusively to the product of addition of the base to the α position of the naphthalene ring **706** (Scheme 96).[362] This reactivity was not further explored.

## 15.3. Dearomatizing Anionic Cyclization

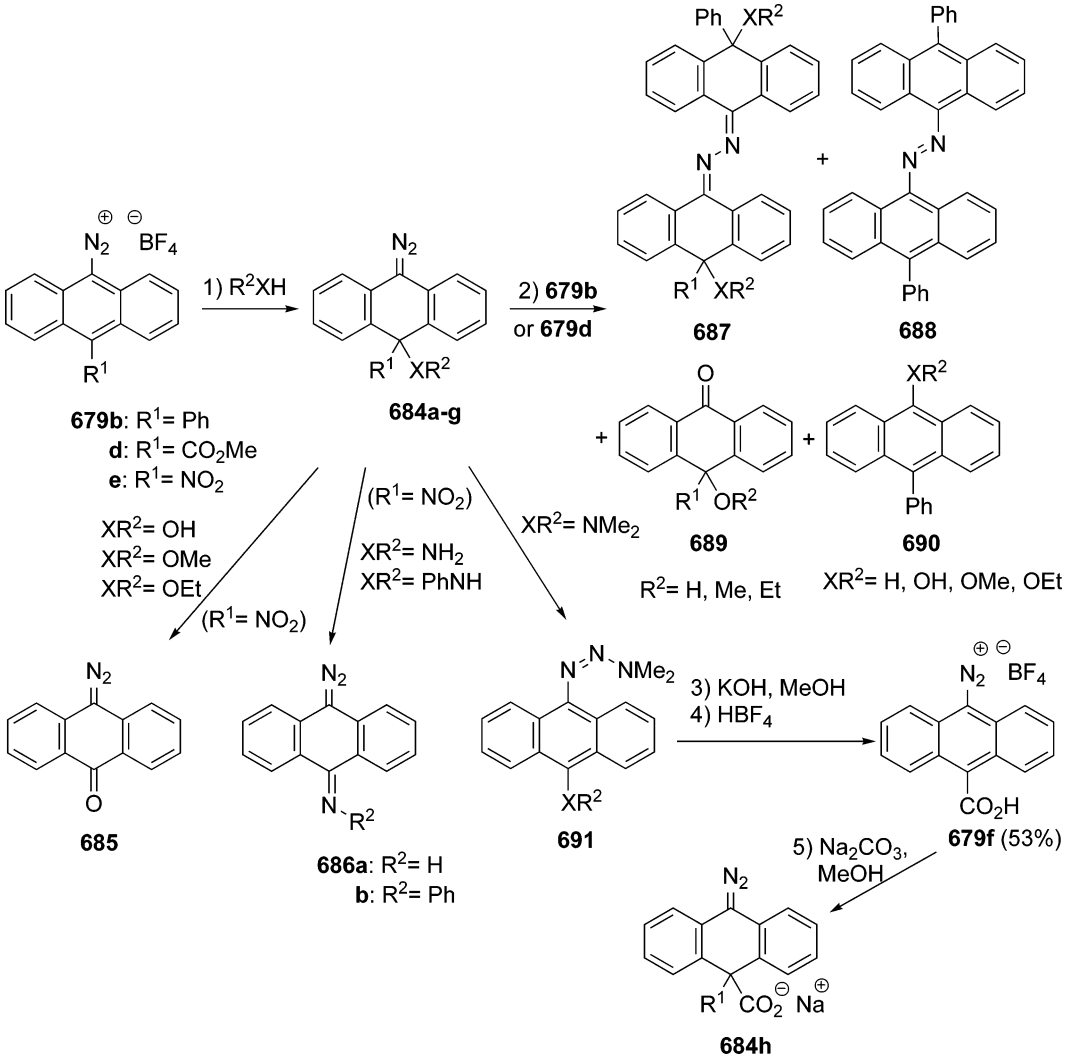
### *15.3.1. Phosphorus Ylides*

The first direct observation of an anionic dearomatization of a *P*-phenyl ring was provided by the lithiation of triphenylmethylenephosphorane **707** (Scheme 97). Within the framework of the debate between Corey[363,364] and Schlosser[365] on the structure of the species formed in the reaction of the simplest Wittig reagent **707** with *t*-BuLi, Schlosser and Schaub characterized by NMR spectroscopy the dearomatized species **709** formed by intramolecular attack of an ortho-lithiated phenyl ring to the ortho position of an adjacent *P*-phenyl substituent (Scheme 97).[366] Degradation of **709** by loss of benzene led to dibenzophosphole **710**. Recently, Sundermeyer and Korth suggested that the formation of **710** is also compatible with a mechanism involving the insertion of a nucleophilic carbene into the C−H bond of a phenyl ring.[367]

### *15.3.2. Phosphonamides*

Phosphinamide, phosphonamide, and phosphoramide functionalities are good groups for directing lithiations either at ortho[15] or benzylic positions.[368−373] Interestingly, in the reaction of *N*-benzyl-*N*-methyldiphenylthiophosphinamide with *s*-BuLi in THF/TMEDA, where both types of protons are available for metalation, only products of ortho lithiation are obtained.[374] In a trapping experiment of the ortho-lithiated phosphonamide **712** with benzonitrile, the dearomatized bicycle **716** incorporating 2 equiv of the electrophile was isolated in 83% yield (Scheme 97).[375] The mechanism proposed to explain the formation of **716** involves the reaction of the initial anion **712** with two molecules of the nitrile to give the 1:2 adduct **713**. Afterward, intramolecular Michael addition of the imine anion to the substituted ortho position of the *P*-phenyl ring affords dearomatized anion **714**, which undergoes rearrangement to the cyclopropane derivative **715**. Electrocyclic ring opening of the cyclohexadiene moiety of **715** and subsequent protonation rationalizes the formation of the isolated heterocycle **716**. This reaction

**Scheme 93**




represents the first example of an anionic cyclization of an organophosphorus compound leading to isolable dearomatized products.

### *15.3.3. Phosphinamides*

López-Ortiz and co-workers have initiated a systematic investigation of intramolecular $D_NAr$ reactions of *N*-alkyl-*N*-benzyldiphenylphosphinamides **717** as a key step for the synthesis of new $\gamma$-aminophosphinic acids (see section 19). Treatment of phosphinamides **717** with an excess of *s*-BuLi in THF at −90 °C in the presence of a strongly coordinating cosolvent, such as HMPA or DMPU, followed by electrophilic trapping, afforded tetrahydrobenzo[*c*]-1-aza-2$\lambda^5$-phospholes, for example, **718** and **722** (major products, Scheme 98).[376] These heterocycles may be converted into $\gamma$-aminophosphinic acids (see section 19.1, Scheme 115) through acid hydrolysis of the phosphinamide moiety present in the five-membered ring. The intermediate dearomatized species formed in the anionic cyclization were trapped with protonating and alkylating agents. Electrophilic attack at the cyclohexadienyl anion may occur at the $\alpha$, $\gamma$, and $\epsilon$ positions with respect to the phosphorus atom. The optimization of the reaction conditions allowed the azaphospholes to be obtained with high regio- and stereocontrol.

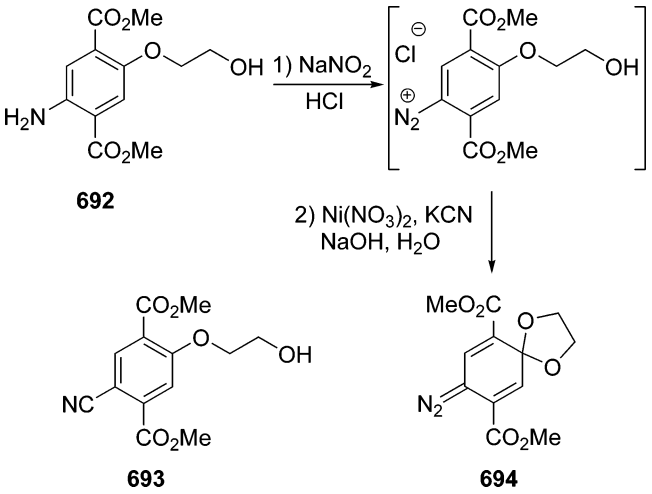
The protonation was performed at −90 °C during 30 min. The acids used include $D_2O$, methanol, isopropanol, *tert*-

**Table 42. Conjugate Addition of Oxygen and Nitrogen Nucleophiles to Diazoarenes**

| entry | SM | $R^1$ | $XR^2$ | yield (%) |
|---|---|---|---|---|
| 1 | **679b**[a] | Ph | OH | **684a**[b] |
| 2 | **679b**[a] | Ph | OMe | **684b**[b] |
| 3 | **679b**[a] | Ph | $NMe_2$ | **684c**[c] |
| 4 | **679b**[d] | Ph | OH | **687a** (48) |
| 5 | **679b**[d] | Ph | OMe | **687b** (37) |
| 6 | **679b**[d] | Ph | OEt | **687c** (58) |
| 7 | **679b**[a] | Ph | $NMe_2$ | **691a**[b] |
| 8 | **679d**[e] | $CO_2Me$ | OH | **684d** (68)[f] |
| 9 | **679d**[e] | $CO_2Me$ | OMe | **684e** (59)[f] |
| 10 | **679d**[e] | $CO_2Me$ | OH | **687d** (16)[g,h] |
| 11 | **679d**[e] | $CO_2Me$ | OMe | **687e** (98)[g,i] |
| 12 | **679d**[e] | $CO_2Me$ | $NMe_2$ | **684f** (71) |
| 13 | **679d**[e] | $CO_2Me$ | 4-$MeOC_6H_4NH$ | **684g** (66) |
| 14 | **679d**[e] | $CO_2Me$ | $NMe_2$ | **691b** (61)[j] |
| 15 | **691b**[e] | $CO_2^-$ | OMe | **684h** (77) |
| 16 | **679e**[k] | $NO_2$ | OH | **685** (94)[l] |
| 17 | **679e**[k] | $NO_2$ | $NH_2$ | **686a** (92) |
| 18 | **679e**[k] | $NO_2$ | PhNH | **686b** (54) |

[a] Data taken from ref 356. [b] Yield not given. [c] Observed through UV and NMR spectroscopy. [d] Data taken from ref 355. [e] Data taken from ref 357. [f] Reaction performed in the presence of $Na_2CO_3$. [g] Reaction performed under neutral conditions. [h] Mixture of stereoisomers in a ratio of 80:20. [i] Mixture of stereoisomers in a ratio of 56:44. [j] Catalyzed by $SiO_2$. [k] Data taken from ref 354. [l] Yield of 72% when the reaction is performed with methanol.

**Scheme 94**




**Scheme 95**

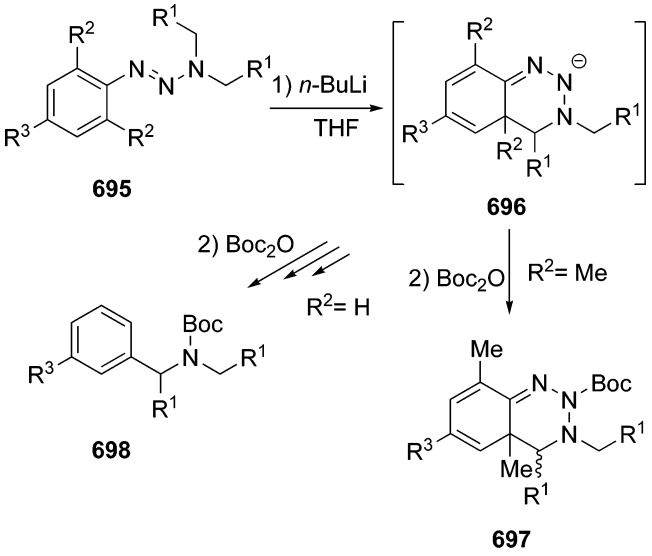


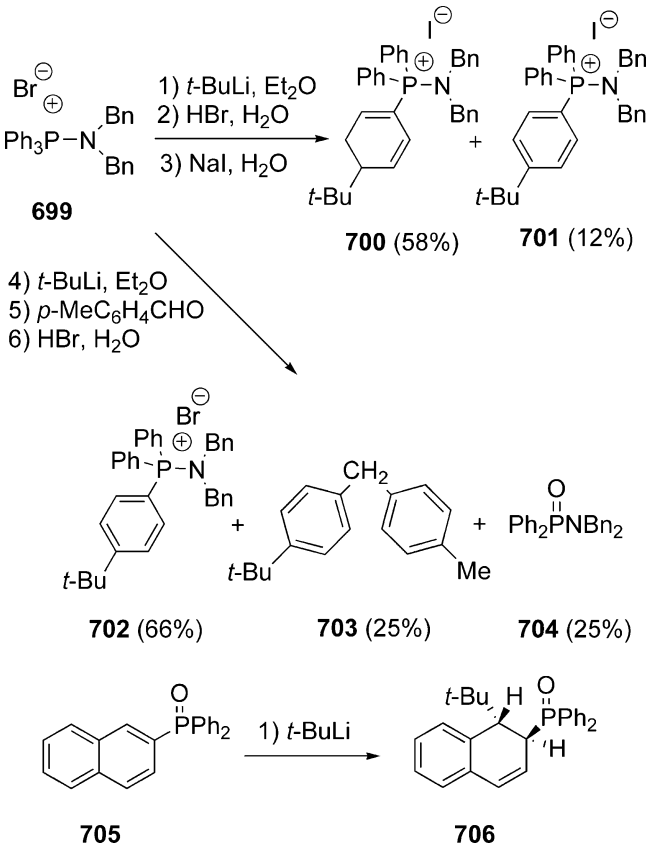

**Table 43. Dearomatizing Anionic Cyclization of Triazenes 695 ($R^2$ = Me)[a]**

| entry | $R^1$ | $R^3$ | yield (%) |
|---|---|---|---|
| 1 | H | H | **697a** (73) |
| 2 | Me | H | **697b** (64)[b] |
| 3 | $-(CH_2)_2-$ | H | **697c** (75) |
| 4 | $-(CH_2)_3-$ | H | **697d** (58) |
| 5 | H | Me | **697e** (65) |
| 6 | Me | Me | **697f** (52)[c] |
| 7 | $-(CH_2)_2-$ | Me | **697g** (85) |
| 8 | $-(CH_2)_3-$ | Me | **697h** (63) |

[a] Data taken from ref 359. [b] Diastereomeric ratio of 26:74. [c] Diastereomeric ratio of 17:83.

butanol, phenol, 2-*tert*-butyl-4-methylphenol, 2,6-di-*tert*-butyl-4-methylphenol, trifluoroacetic acid, and *p*-toluenesulfonic acid. The series of products formed in the protonation study are shown in Scheme 98.[377] Methanol was found to be the best acid for obtaining tetrahydrobenzo[*c*]-1-aza-2$\lambda^5$-phospholes **718** containing a [1,3]-cyclohexadiene system with a cis-fusion of the rings in good yields. Compound **719**, representing the preferred trans ring systems, was observed only in the anionic dearomatizing reaction of **717a** and subsequent protonation with *p*-toluenesulfonic acid. The protonation with 2,6-di-*tert*-butyl-4-methylphenol (DTBMP) was very significant, for it gave exclusively products of

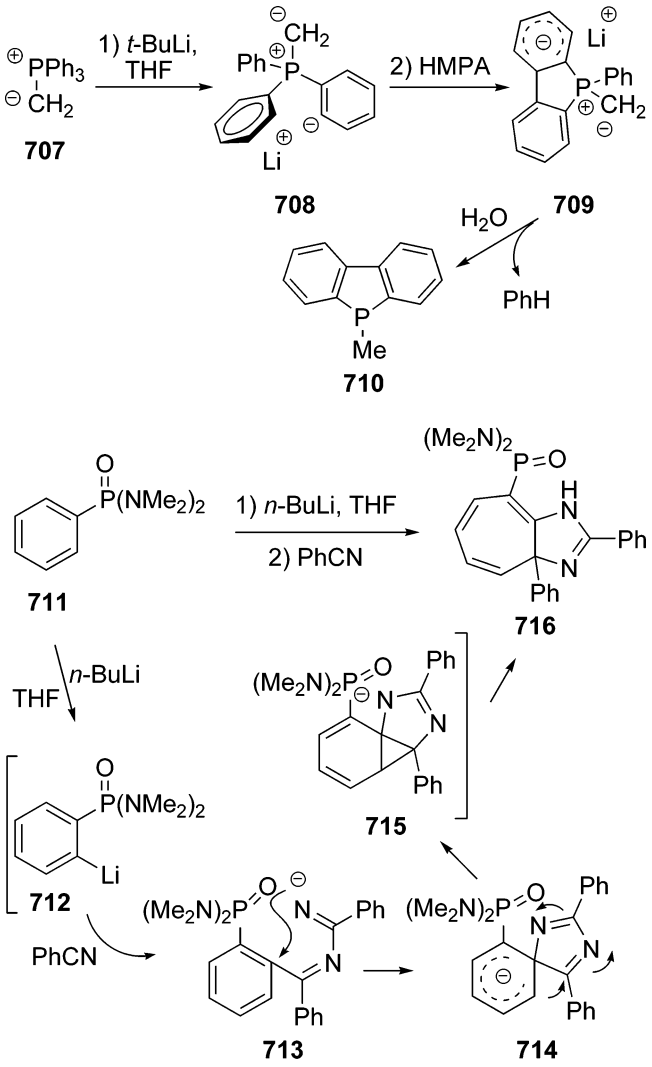
**Scheme 96**




$\gamma$-protonation **722** in excellent yields. Compounds **722** were obtained as single stereoisomers except when phosphinamide **717c** was used as starting material. In this case, the bulkiness of the *tert*-butyl group linked to the nitrogen reduced the stereoselectivity of the anionic cyclization, leading to the formation of small amounts of **724a** ($R^1$ = *t*-Bu, $R^2$ = H), an epimer of **722c** at the stereogenic center adjacent to the nitrogen atom. The distribution of products obtained is indicated in Table 44.

The trapping reaction with MeI suffered from several competing reactions [rearomatization, ortho-methylation, and base-induced formation of the methylated phosphine oxide $Ph_2P(O)C(Me)_2CH_2CH_3$], which eroded the yield of the dearomatization−methylation products. The process was significantly improved through the systematic study of the variables controlling the sequence of reactions: metalation and quench times, use of lithium-coordinating additives (none, HMPA, DMPU, TMEDA), nature of the electrophile (MeI, $CF_3SO_3Me$, $Me_3O^+BF_4^-$), and size of the substituents linked to the nitrogen.[378] The best results were obtained by treating phosphinamides **717** with 2.5 equiv of *s*-BuLi at −90 °C in THF in the presence of 6 equiv of DMPU during 12 h and then reaction with MeI for 2 h. Under these conditions, a mixture of azaphospholes **718e**:**719d**:**722e** was obtained in a ratio 6:16:78, in 89% total yield (Scheme 98; Table 44, entry 10). The use of allyl bromide, methyl 2-bromoacetate, and benzyl bromide as alkylating reagents afforded exclusively products of $\gamma$-addition in high yields. Allyl bromide and methyl 2-bromoacetate provide products resulting from the attack of the cyclohexadienyl anion at both faces (Table 44, entries 17−19). However, benzyl bromide underwent reaction only through the *re* face of the delocalized anionic system to give **722h**,**i** quantitatively (Table 44, entries 15 and 16). In the case of phosphinamide **717c** with

**Scheme 97**




a bulky *t*-Bu group linked to the nitrogen, the successive anionic cyclization−alkylation with alkyl halides progressed at a lower rate and with a significant decrease in the regio- and stereoselectivity. The highest conversion (86%) was observed when the time of the metalation step was increased from 30 min to 12 h in the presence of DMPU. Nevertheless, the regio- and stereoselectivity remained almost unaffected. Significantly, the methylation with methyl triflate led to the predominant formation of products of attack α to the phosphorus (Table 44, entry 14). The same behavior was observed in the case of phosphinamide **717a** (Table 44, entry 11).

Aldehydes proved to be excellent electrophiles for trapping the dearomatized species formed in the anionic cyclization of **717**. Addition of the cyclohexadienyl anion to the carbonyl group occurred exclusively through the γ position with respect to the phosphorus of the *re* face. Only two products, **722m**−**t** and **727a**−**h**, were obtained, which correspond to the diastereoisomers resulting from the attack of the nucleophile at both faces of the carbonyl moiety. This means that only 2 of 16 possible diastereoisomers were formed. On the basis of X-ray data, the major diastereoisomer was identified as the product arising from the attack of *like* topicity **722m**−**t**. Moreover, the use of DMPU as cosolvent instead of HMPA allowed the time of the metalation and electrophilic quench steps to be reduced to 15 min each without affecting the high regio- and stereoselectivity of the process. Either aromatic or aliphatic aldehydes participated in this reaction. Yields were very high except for phosphinamide **717c**. The bulky *t*-Bu group produced the expected diminution in the yield and stereoselectivity of the reaction. For short times of metalation and reaction with the electrophile a 1:1 mixture of γ-substituted azaphospholes **722t**/**727h** and **724c**/**728** was obtained. However, the ratio of **722t**/**727h**:**724c**/**728** rose to 83:17 with increased reaction time to 4 h. This result indicates that the anionic cyclization reaction must be reversible and that the dearomatized anion precursor of **722t**/**727h** is thermodynamically more stable than the epimeric species, which produces derivatives **724c**/**728**. The diastereoselectivity of the reactions of phosphinamides **717a**,**b** ranged from 74:26 to 85:15. The two reaction periods of dearomatization of **717a** and subsequent trapping with benzaldehyde produced a decrease in the diastereoselectivity without affecting the yield (entry 21). This study shows that the addition reaction to the carbonyl group is also reversible and that **722m** and **727a** are, respectively, the products of kinetic and thermodynamic control.

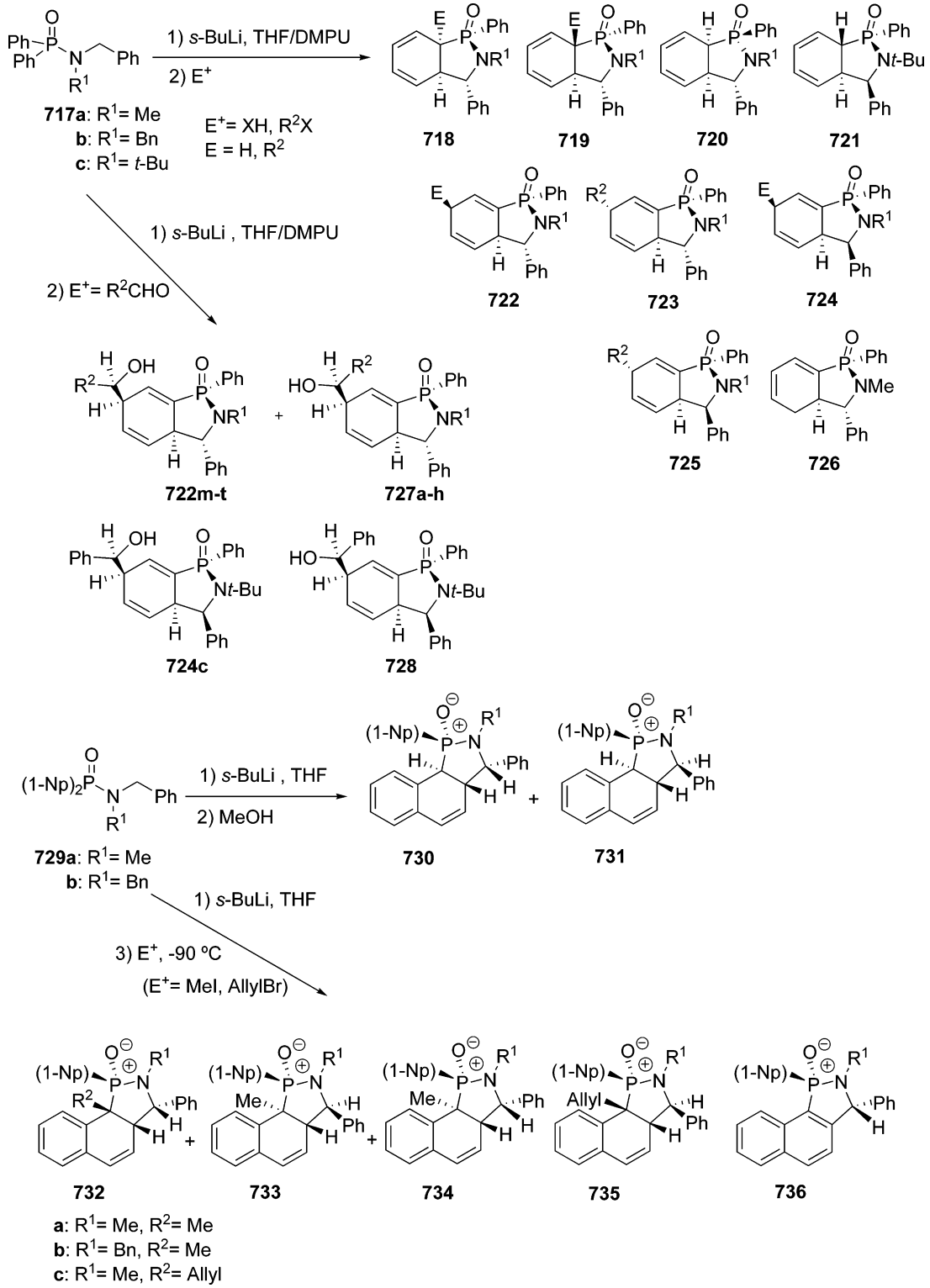
As expected, anionic cyclization of naphthylphosphinamides **729** occurs more easily, for example, no additives are required. The intermediate lithium dihydronaphthalenes were trapped with MeOH, MeI, and allyl bromide leading to benzophosphaisoindoles. Protonation and methylation afforded heterocycles **730a**,**b** and **732a**,**b**, respectively, in high yield and with high stereoselectivity. Allylation was less efficient, leading to derivative **732c** in 41% yield, together with epimer **735** (11%) and the rearomatized product **736** (28%) (Scheme 98, bottom).[379]

### *15.3.4. Mechanism of the Dearomatizing Anionic Cyclization*

In the optimization of the dearomatizing anionic cyclization−alkylation with aldehydes of phosphinamides **717**, it was observed that, for short reaction times, and particularly when the reactions were performed in the absence of strong co-ordinating cosolvents, products derived from the presence of anions ortho to the phosphorus as well as benzylic anions were isolated. In the presence of HMPA or DMPU the reaction furnished the pair of azaphosphole epimers **722**/**727** quantitatively.[378] Using $D_2O$ as quenching reagent led to similar results. These facts suggest that co-ordinating cosolvents either favor the exclusive lithiation at the benzylic position or accelerate the translocation of the anion ortho into the benzylic one. This dichotomy was solved by performing the dearomatization−protonation of the phosphinamide **717a**-$d_2$ dideuterated at the benzylic carbon. The bulky phenol DTBMP was used as proton source. The reaction afforded a statistical distribution of azaphospholes **722u**−**w** (ratio 1:1:2, Scheme 99), indicating that HMPA or DMPU catalyzes the conversion of the ortho-lithiated *N*-benzylphosphinamide, **737**, into the corresponding benzylic anion, **738**.[380] The possible dearomatized product **722x**, resulting from deprotonation at the benzylic position in intermediate **739** (Scheme 99), was not observed. A kinetic isotopic effect probably inhibited the direct lithiation at this position.

NMR monitoring of the reaction allowed the mechanism of the dearomatizing anionic cyclization of phosphinamides **717** to be disentangled.[380] First, in the absence of co-ordinating solvents, two *s*-BuLi−phosphinamide precomplexes **740** and **741** are formed in a ratio of 1:3 (Scheme 100). These intermediates were identified as diastereomeric

**Scheme 98**




dimers constructed around a $(LiO)_2$ core based on the multiplicity shown by the lithium signals in the $^7$Li NMR spectrum measured at −110 °C. The $^7$Li signal of **740** is a triplet [$\delta(^7\text{Li})$ 2.43 ppm, $^2J_{\text{PLi}} = 5.0$ Hz], consistent with a dimer in which the *s*-Bu moieties are of *like* configuration, whereas **741** is the isomer of *unlike* configuration, showing a double doublet for the $^7$Li signal [$\delta(^7\text{Li})$ 2.36 ppm, $^2J_{\text{PLi}} =$ 4.0 and 5.5 Hz]. The two diastereotopic $^{31}$P nuclei of this complex exhibit different $^{31}$P,$^7$Li couplings. The splitting of the $^7$Li signals of **740** and **741** at very low temperature is indicative of a slow rate of inversion at the carbanion center of *s*-BuLi on the NMR time scale, a situation rarely observed experimentally. In complexes **740** and **741**, the pairs of substituents in relative positions 1 and 3 are cis oriented. Precomplexes **742** and **743** with a trans orientation of these substituents were not detected. Most probably steric repulsions between substituents at adjacent positions make them too unstable to allow detection.

Precomplexes **740** and **741** undergo benzylic deprotonation to give the monomeric lithium derivative **745** $\delta(^7\text{Li})$ 0.01 ppm, doublet, $^2J_{\text{PLi}} = 4.5$ Hz]. This anion has a relatively short lifetime (<90 min) and evolves through intramolecular

**Table 44. Dearomatizing Anionic Cyclization of Phosphinamides 717 and 729**

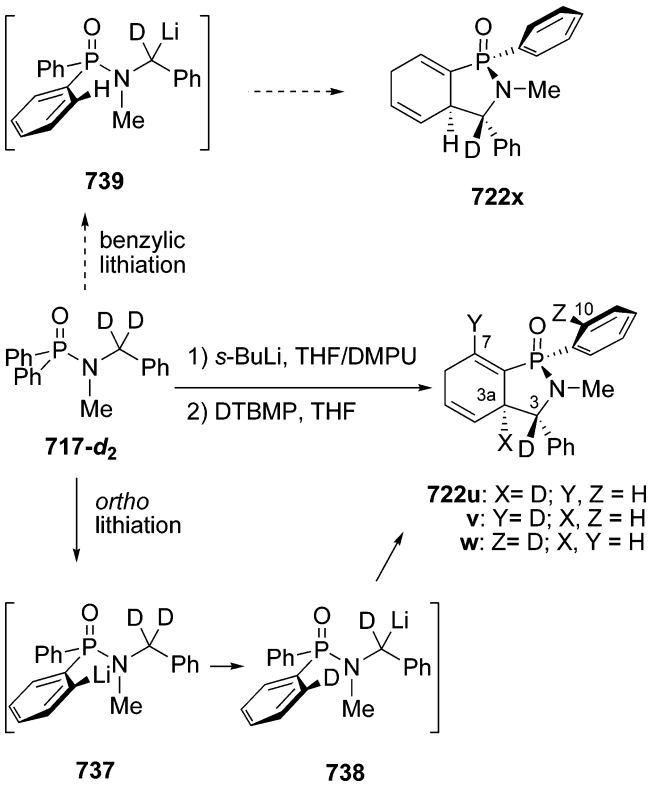
| | | | | yield (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| entry | SM | $R^1$ | $R^2$ | **718** | **719** | **722** | **727** | **730** | **732** |
| 1 | **717a**[a,b] | Me | H | **a** (65) | | **a** (18) | | | |
| 2 | **717b**[a,b] | Bn | H | **b** (52) | | **b** (18) | | | |
| 3 | **717c**[a,b] | *t*-Bu | H | **c** (28) | | **c** (12) | | | |
| 4 | **717a**[a,c] | Me | H | **a** (13) | **a** (42) | **a** (20) | | | |
| 5 | **717c**[a,c] | *t*-Bu | H | **c** (21) | **b** (22) | **c** (17) | | | |
| 6 | **717a**[a,d] | Me | H | | | **a** (97) | | | |
| 7 | **717b**[a,d] | Bn | H | | | **b** (94) | | | |
| 8 | **717c**[a,d] | *t*-Bu | H | | | **c** (69)[e] | | | |
| 9 | **717a**[f] | Me | D | **d** (19) | **c** (24) | **d** (35) | | | |
| 10 | **717a**[g,h] | Me | Me | **e** (5) | **d** (14) | **e** (69) | | | |
| 11 | **717a**[g,i] | Me | Me | **e** (16) | **d** (30) | **e** (37) | | | |
| 12 | **717b**[g,h] | Bn | Me | **f** (8) | **e** (27) | **f** (53) | | | |
| 13 | **717c**[g,h] | *t*-Bu | Me | **g** (11) | **f** (13) | **g** (40)[j] | | | |
| 14 | **717c**[g,i] | *t*-Bu | Me | **g** (18) | **f** (37) | **g** (8)[k] | | | |
| 15 | **717a**[g,l] | Me | Bn | | | **h** (86) | | | |
| 16 | **717b**[g,l] | Bn | Bn | | | **i** (84) | | | |
| 17 | **717a**[g,m] | Me | Allyl | | | **j** (48)[n] | | | |
| 18 | **717a**[g,o] | Me | $CH_2CO_2Me$ | | | **k** (79)[p] | | | |
| 19 | **717b**[g,o] | Bn | $CH_2CO_2Me$ | | | **l** (66)[q] | | | |
| 20 | **717a**[g,r] | Me | Ph | | | **m** (76) | **a** (17) | | |
| 21 | **717a**[g,r] | Me | Ph | | | **m** (54)[s] | **a** (31) | | |
| 22 | **717a**[g,r] | Me | 4-Cl-$C_6H_4$ | | | **n** (69) | **b** (19) | | |
| 23 | **717a**[g,r] | Me | 4-MeO-$C_6H_4$ | | | **o** (75) | **c** (14) | | |
| 24 | **717a**[g,r] | Me | *i*-Pr | | | **p** (74) | **d** (19) | | |
| 25 | **717b**[g,r] | Bn | Ph | | | **q** (67) | **e** (23) | | |
| 26 | **717b**[g,r] | Bn | 4-Cl-$C_6H_4$ | | | **r** (63) | **f** (27) | | |
| 27 | **717b**[g,r] | Bn | 4-MeO-$C_6H_4$ | | | **s** (77) | **g** (13) | | |
| 28 | **717c**[g,r] | *t*-Bu | Ph | | | **t** (24) | **h** (9)[t] | | |
| 29 | **717c**[g,r] | *t*-Bu | Ph | | | **t** (40) | **h** (7)[u] | | |
| 30 | **729a**[v,w] | Me | | | | | | **a** (94) | |
| 31 | **729b**[v,w] | Bn | | | | | | **b** (96) | |
| 32 | **729a**[v,x] | Me | Me | | | | | | **a** (76) |
| 33 | **729b**[v,x] | Bn | Me | | | | | | **b** (78) |
| 34 | **729a**[v,y] | Me | allyl | | | | | | **c** (41) |

[a] Data taken from ref 377. [b] Protonation with MeOH. [c] Protonation with *p*-toluenesulfonic acid. [d] Protonation with DTBMP. [e] Compound **724a** ($R^1$ = *t*-Bu, $R^2$ = H) was also formed in a yield of 16%. [f] Quench with $D_2O$; data taken from ref 376. [g] Data taken from ref 378. [h] Quench with MeI. [i] Quench with methyl trifluoromethanesulfonate. [j] Compounds **724b** (15%, $R^1$ = *t*-Bu, $R^2$ = Me) and **725a** (6%, $R^1$ = *t*-Bu, $R^2$ = Me) were also obtained. [k] Compounds **724b** (5%) and **725a** (2%) were also obtained. [l] Quench with BnBr. [m] Quench with allylBr. [n] Compound **723a** ($R^1$ = Me, $R^2$ = Allyl) was also formed in a yield of 37%. [o] Quench with $BrCH_2CO_2Me$. [p] Compound **723b** ($R^1$ = Me, $R^2$ = $CH_2CO_2Me$) was also formed in a yield of 14%. [q] Compound **723c** ($R^1$ = Bn, $R^2$ = $CH_2CO_2Me$) was also formed in a yield of 18%. [r] Quench with aldehydes $R^2CHO$. [s] Time for metalation and electrophilic quench of about 12 h. [t] Compounds **724c** (29%, $R^1$ = *t*-Bu, $R^2$ = Ph) and **728** (5%) were also obtained. [u] Reaction time with PhCHO of 4 h. Compounds **724c** (8%, $R^1$ = *t*-Bu, $R^2$ = Ph) and **728** (2%) were also obtained. [v] Data taken from ref 379. [w] Quench with MeOH. [x] Quench with MeI. [y] Quench with allylBr.

conjugate addition to each *P*-phenyl ring leading to all four possible stereosiomers of the dearomatized species **748**−**751**. These anions were identified as monomers on the basis of the appearance of each lithium nucleus as a doublet in the $^7$Li NMR spectrum. As the reaction progresses, only species **748** and **749** remain in solution, thus confirming the reversibility of the anionic cyclization reaction. At −90 °C, the ratio of anions **748**:**749** is 1:0.1. This ratio changed to 1:0.17 when the reaction temperature was raised to −70 °C. Regarding ortho-lithiated anion **744**, its presence is detected by NMR from the first moment and its concentration is not time dependent. In the early stages of the reaction, the $^{31}$P NMR spectrum shows at least two broad signals for this anion, probably due to the existence of mixed aggregates. When the reaction reaches the steady state, the $^{31}$P signal of **744** sharpens. Most importantly, the $^7$Li signal can be resolved into a triplet ($^2J_{PLi}$ = 7.0 Hz).[381] This fact revealed the coupling of the lithium nucleus to two phosphorus nuclei and allows **744** to be identified as a dimer. It was assumed that ortho lithiation occurred through the intermediation of precomplexes **742** and **743**, which were too reactive to be detected. Trapping reactions with electrophiles at short times of metalation and electrophilic quench allowed the products corresponding to the existence of ortho, benzylic, and dearomatized anions **746**, **747**, and **722**, respectively, to be obtained. Figure 1 shows the 2D $^7$Li,$^{31}$P HMQC spectrum of a sample corresponding to the initial moments of the reaction of **717a** with *s*-BuLi. The $^7$Li,$^{31}$P correlations of all species formed can be distinguished, except those arising from the ortho anions. The large signal width of these species implies that the transverse magnetization created at the beginning of the experiment is lost via very rapid transverse relaxation during the time period required for $^2J_{PLi}$ evolution. The NMR study afforded the first evidence of complex induced proximity effects (CIPE model)[200] in the ortho- and benzylic-directed lithiation of a phosphinamide. The structure of a mixed aggregate formed between phosphinamide **717a** and the lithium salt of DTBMP has been recently described.[382]

The analogous NMR study on a sample containing an excess of HMPA showed in the first set of spectra exclusively the presence of dearomatized species **748** and **749** in a ratio of 1:0.6. The lithium cation is coordinated to HMPA as evidenced by the correlations observed in the 2D ROESY spectrum (measured at −70 °C) between the methyl protons of the complexed HMPA and the protons of the cyclohexa-

**Scheme 99**




dienyl system of the lithium azaphospholes **748** and **749**. These results demonstrate the accelerating effect of HMPA in promoting the translocation of the ortho anion **744** to the benzylic species **745** and the subsequent anionic cyclization reaction. When the sample was warmed to −10 °C, the ratio of **748** to **749** changed to 55:45, indicating that these two species are the precursors of the kinetic and thermodynamic control products, respectively. Performing the process in bulky quantities and quenching the reaction with DTBMP

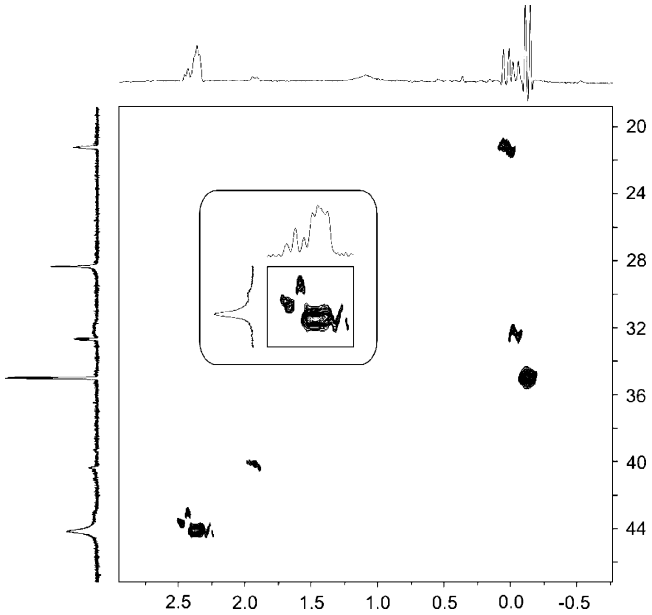



**Figure 1.** 2D $^{7}$Li,$^{31}$P{$^{1}$H} HMQC NMR (194.37 MHz) of the earlier stages in the lithiation of **717a** with *s*-BuLi at −110 °C in THF-$d_8$. (Inset) Correlation detected for the species **740** and **741**. Experiment started at a metalation time of 2 min. Total measuring time = 2 h and 40 min. Reproduced with permission from ref 380. Copyright 2004 American Chemical Society.

furnished a mixture of **722a** and its epimer at the phosphorus center **752** in a ratio of 55:45 in 88% yield (Scheme 100).

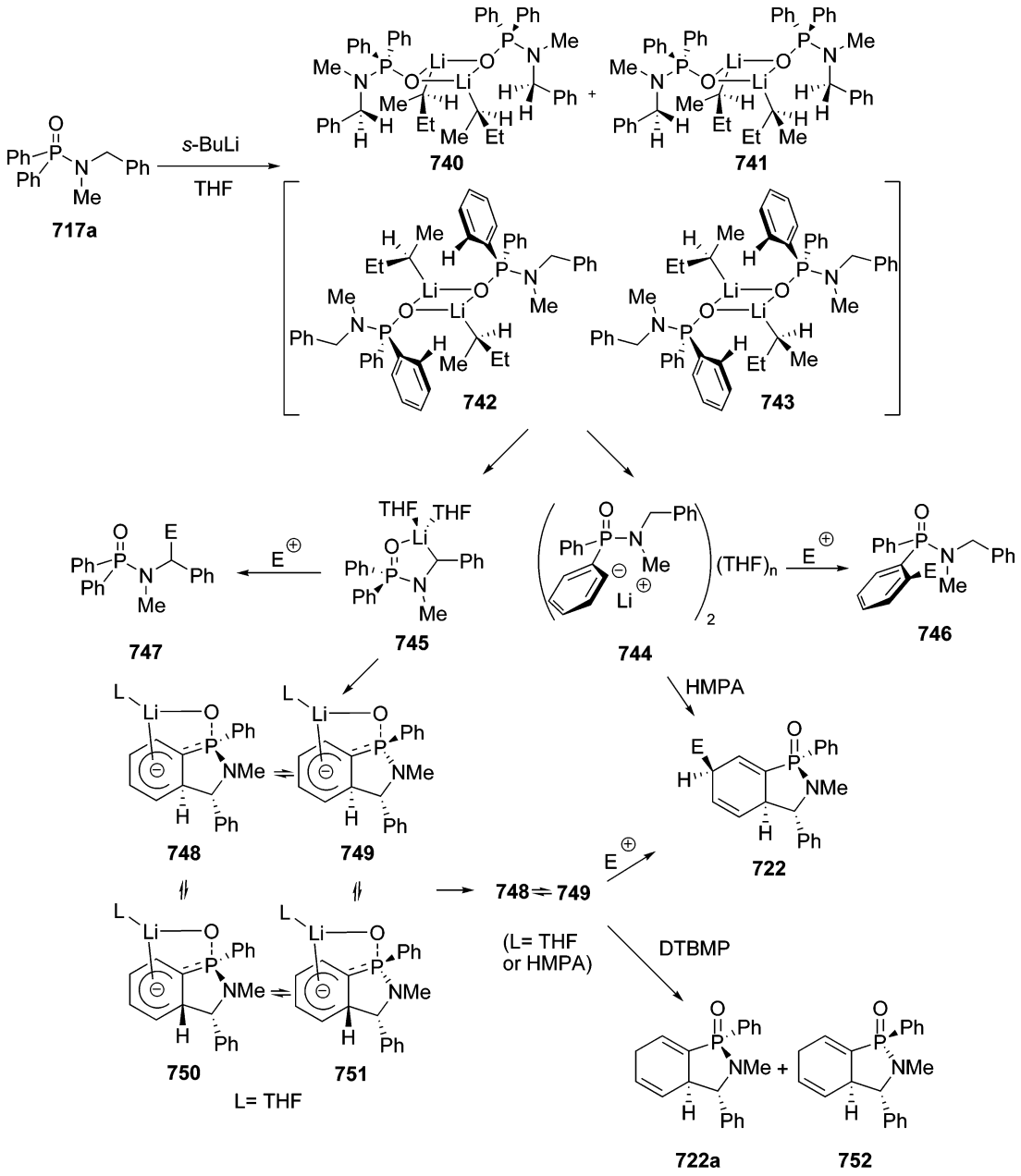
The NMR study discussed provided, for the first time, a detailed picture of the steps involved in a dearomatizing anionic cyclization reaction. The cyclization stage can be described by two different mechanisms: a *5-endo-trig* Michael-type addition of the benzylic anion to the ortho position of an electron-deficient phenyl ring or a disrotatory electrocyclic ring closure, as proposed by Clayden and co-workers for the analogous reaction of *N*-benzylcarboxamides lithiated at the benzylic position.[152] To gain insight into this reaction mechanism, González and co-workers performed an ab initio (MP2/6-31+G*) and density functional theory (DFT) (Becke3LYP/6-31+G*) study of the cyclization of the series of model anions **753**−**761** shown in Scheme 101.[383] Anions **754** and **755** were selected as prototypical examples of six-electron disrotatory ring closure reactions, whereas the cyclization of anions **753**, **758**, and **759** were considered to proceed through an essentially ionic mechanism.

The transition states of all cyclizations were located. The cyclization of dicarboxamide **757** may produce either pyrroline derivative **763** or *β*-lactam **764**. The calculations showed that the latter, arising from an ionic *4-exo-trig* ring closure, is strongly favored over the electrocyclic reaction, a result which is in good agreement with experimental results.[384] The analysis of the transition structures of the cyclization of **754**, **755**, and acrylamide **756** indicated some pericyclic character for the cyclization of **756**. However, the bond-forming lengths and the degree of pyramidalization of the carbons being connected through the new bond in the transition structures **TS-760** and **TS-761** for the cyclization of benzamide **760** and phenylphosphinamide **761**, respectively, were very similar to those calculated for the cyclization of **753**, **758**, and **759** (cf. **TS-759** in Scheme 101). On the basis of these results, it was concluded that the anionic cyclization of acrylamides, benzamides, and phosphinamides is best described as an ionic conjugate addition and not through an electrocyclic ring closure. Including the lithium cation in the calculated model reactions produced a significant increase of the activation energies of the process without affecting the reaction pathway. This increase was attributed to a greater stabilization of the starting ions than the transition state structures. Figure 2 shows the stationary points of the potential energy surface of lithium phosphinamide **765** calculated by DFT methods.

## *16. Aromatic Rings Linked to a Silicon Atom*

Magnesium-anthracene is a valuable magnesium source for the preparation of Grignard reagents. When 1,8-bis-(chloromethyl)naphthalene **766** is allowed to react with magnesium-anthracene derivative **767** in THF, a deep brown solution results, which upon reaction with chlorotrimethylsilane during 12 h affords 1,8-bis[(trimethylsilyl)methyl]-naphthalene **770** as the only product. The uniqueness of **770** implies that the precursor bis(organomagnesium) **768** is generated quantitatively, with the concomitant formation of 9-trimethylsilylanthracene **769** as byproduct. However, if the reaction mixture of organomagnesium **768** and anthracene **769** is left for 3 days, nucleophilic addition of **768** to the 10-position of **769** takes place. After quenching of the reaction with hydrochloric acid, compound **771** is obtained in 43% yield as a single isomer possessing $C_2$ symmetry (Scheme 102).[385]

**Scheme 100**




## *17. Aromatic Rings Linked to a Sulfur Atom*

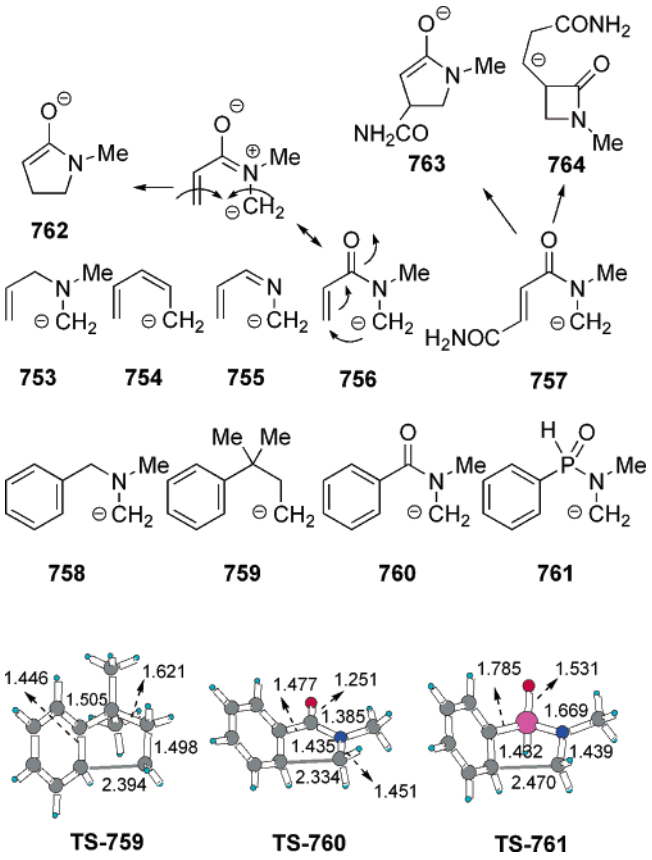
$D_NAr$ reactions of electron-deficient aromatic rings due to the presence of sulfur-containing functional groups have been observed for only aryl sulfones and sulfonamides.

### 17.1. Sulfones

Early attempts to assess the intermolecular addition of an organometallic reagent to an aromatic ring activated by a sulfone moiety were disappointing. The lack of reactivity observed may be attributed mostly to the nucleophiles essayed [$(EtO_2C)_2CH^-$, $NH_2^-$, $MeS(O)CH_2^-$, etc.].[386] Stoyanovich and co-workers provided the only example of an intermolecular conjugate addition of a nucleophile to an aryl sulfone leading to isolable dearomatized products. In the search for a method of ortho-lithiation of *tert*-butyl naphthyl sulfone **772**, it was treated with *n*-BuLi in refluxing diethyl ether for 5 h. After quenching of the reaction mixture with $CO_2$, acid **196** was obtained. Its formation involved a [1,4] conjugate addition of the base to the aromatic ring to give adduct **773**. Quenching the reaction with either $H_2O$ or $D_2O$ allowed the isolation of dihydronaphthalenes **774** in acceptable yields. Ortho-lithiation was achieved by performing the metalation at −70 °C (Scheme 103).[387]

Dearomatization of sulfones via anionic cyclization reactions proved to be much more fruitful. The starting point of this chemistry was the discovery by Truce and co-workers in 1958 of a new rearrangement with the pattern of a Smiles rearrangement.[388] The treatment of phenyl mesityl sulfone **776b** with *n*-BuLi in ether produced a dark solution, which, upon refluxing for 2 h and subsequent acidification, afforded 2-benzyl-4,6-dimethylbenzenesulfinic acid **777** (Scheme 104). Soon after, Drozd found that by metalation of **776**, 5,7-dimethyl-4a,9a-dihydrothioxanthene 10,10-dioxide **778** could be isolated by carrying out the reaction at 0 °C for 6 min followed by carboxylation−decarboxylation.[389] The rearrangement leading to the sulfinic acid **777** represents an intramolecular nucleophilic substitution involving a Meisen-

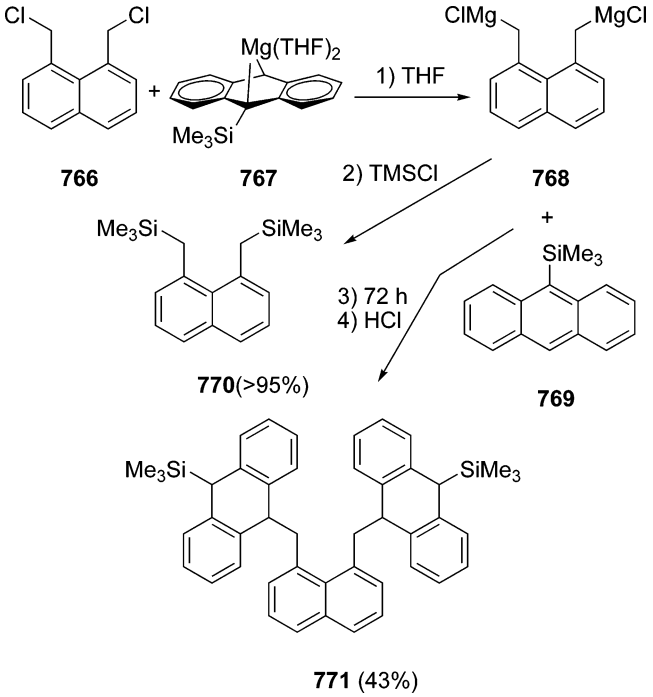
**Scheme 101**




heimer-type intermediate or a similar intermediate complex, whereas **778** is the result of an intramolecular conjugate addition. The role of compounds **778** in the Truce−Smiles rearrangement has been extensively investigated, mostly by Drozd and co-workers, and the topic has been covered in excellent reviews.[390−392] In the following, we will summarize the main conclusions of those studies. The dihydrothioxanthene 10,10-dioxides described are shown in Schemes 104 and 105, and the yields are given in Table 45.[393−404]

Anionic cyclization of diaryl sulfones through lithiation at a benzylic position is a general process provided that short reaction times (2.5−12 min) are used. Dearomatized products **778** and **779** are obtained in moderate to low yield by

**Scheme 102**




trapping the resulting anions with water or $D_2O$ and via carboxylation−decarboxylation. Long reaction times allow the rearrangement to proceed furnishing sulfinic acids. Protonation with water occurs at the α position to the sulfone moiety, except for *p*-chlorophenyl mesityl sulfone **776g**. In this case, dihydrothioxanthene 10,10-dioxide **780** derived from γ-protonation of the anionic cycloadduct was exclusively obtained,[403] albeit in very low yield (Scheme 104). Dihydrothioxanthene dioxides **778**−**779** are, chronologically, the first examples of the formation of dearomatized compounds via anionic cyclization reactions reported. A remarkable feature of the anionic cyclization of lithiated sulfones **776** is the formation of six-membered rings, whereas in the analogous processes previously described, five-membered heterocycles are obtained.

The regioselectivity of the cyclization and the relative configuration of the ring fusion depend on the susbtitution pattern of the aromatic ring undergoing the nucleophilic attack. For diaryl sulfones **776** with a para substituent, only

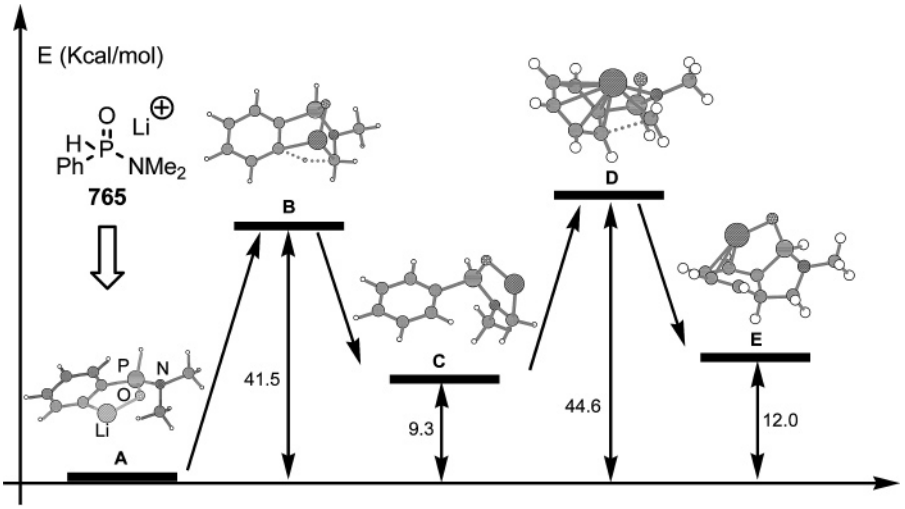
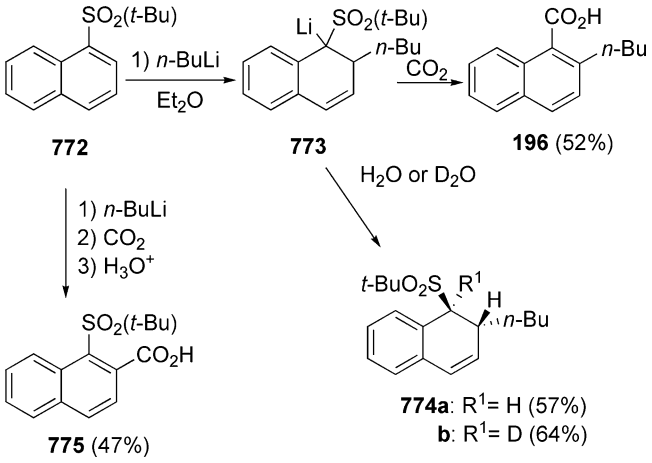



**Figure 2.** Selected geometrical parameters and diagram of relative energies of the stationary points corresponding to the cyclization reaction of the model lithium phosphinamide **765**, at the Becke3LYP/6-31+G* level of theory.

**Scheme 103**




one product is possible. When the substituent occupies an ortho or meta position, two products may be formed. Electron-donating substituents in the meta position direct the cyclization to the adjacent ortho position, leading generally to *cis*-dihydrothioxanthene 10,10-dioxides **779**. The bulky *m*-*tert*-butyl-substituted derivative is the exception, affording products of attack at ortho and para positions of the substituent, the latter being a mixture of cis and trans stereoisomers. *m*-Anisyl mesityl sulfone fails to give the respective dihydrothioxanthene dioxide. The orientation effect of ortho substituents on the ring being attacked depends on their nature and, in part, their size. Alkyl (+I) and phenyl (moderate −I) groups exclusively direct the addition of the nucleophile to position 6, yielding *cis*-dihydrothioxanthene dioxides. However, strongly electronegative substituents such as chlorine undergo substitution, affording thioxanthene 10,-10-dioxides. The *o*-methoxy substituent, possessing negative

**Scheme 104**

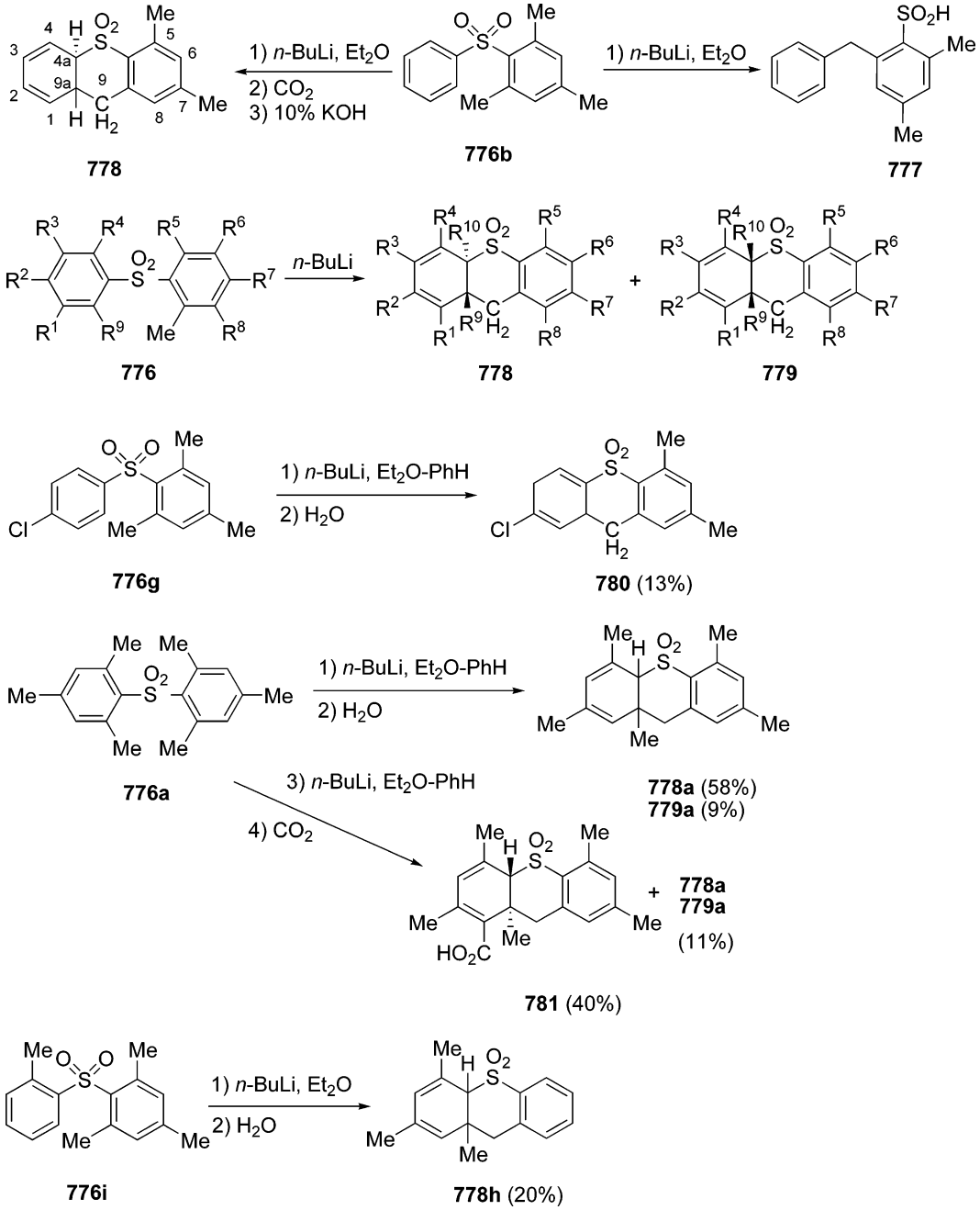


**Table 45. Dearomatizing Anionic Cyclization of Sulfones 776; Electrophilic Trapping with $H_2O$ or $D_2O$, unless Otherwise Stated**

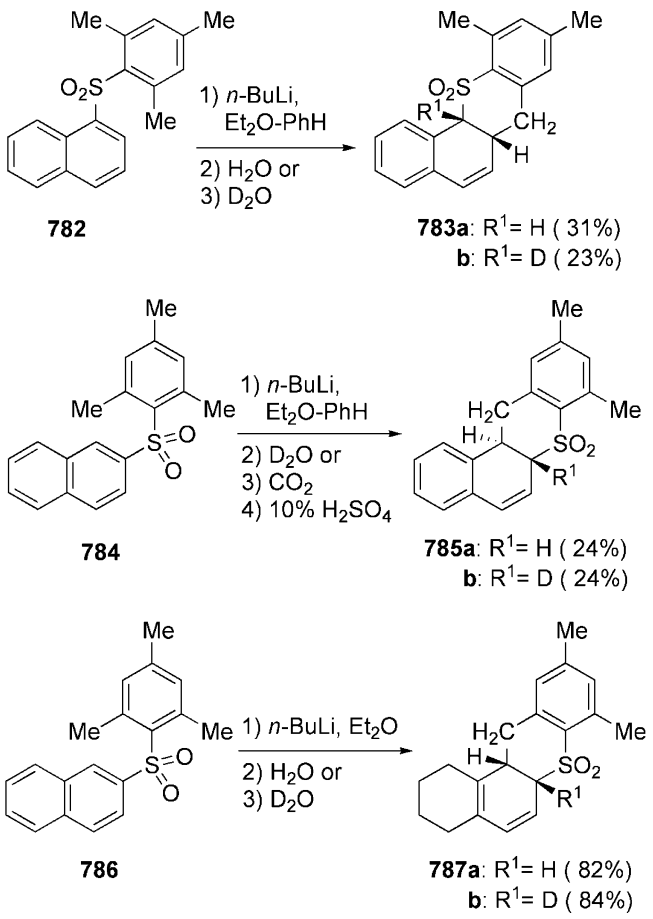
| entry | 776 | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | $R^7$ | $R^8$ | $R^9$ | $R^{10}$ | yield (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | **a** | H | Me | H | Me | Me | H | Me | H | Me | H | **778a** (58) | **779a** (9) |
| 2[b] | **a** | H | Me | H | Me | Me | H | Me | H | Me | D | **778b** (55) | **779b** (6) |
| 3[b] | **b** | H | H | H | H | Me | H | Me | H | H | D | **778c** (42) | |
| 4[b] | **c** | H | Me | H | H | Me | H | Me | H | H | D | **778d** (45) | |
| 5[c] | **d** | Me | Me | H | H | Me | H | Me | H | H | H | | **779c** (63) |
| 6[c] | **d** | Me | Me | H | H | Me | H | Me | H | H | D | | **779d** (63) |
| 7[d] | **e** | Me | H | H | H | Me | H | Me | H | H | H | | **779e** (40) |
| 8[d] | **e** | Me | H | H | H | Me | H | Me | H | H | D | | **779f** (33) |
| 9[d] | **e** | Me | H | H | H | Me | H | Me | H | H | H | **778e** (36)[e] | |
| 10[f] | **f** | H | MeO | H | H | Me | H | Me | H | H | H | **778f** (44)[e] | |
| 11[g] | **g** | H | Cl | H | H | Me | H | Me | H | H | H | | **780** (13) |
| 12[h] | **h** | Me | H | H | Me | H | Me | H | H | H | H | | **779g** (46) |
| 13[i] | **i** | H | Me | H | Me | H | H | H | H | Me | H | | **779h** (20)[j] |
| 14[k] | **j** | H | H | H | Ph | Me | H | Me | H | H | H | | **779i** (25) |
| 15[k] | **j** | H | Ph | H | H | Me | H | Me | H | H | H | **778g** (17)[e] | |
| 16[l] | **k** | H | H | H | Et | Me | H | Me | H | H | H | | **779j** (39) |
| 17[m] | **l** | H | H | H | Et | H | Me | H | H | H | H | | **779k** (22) |
| 18[m] | **m** | H | H | H | H | Me | Me | H | Me | H | H | **778h** (30)[e] | |
| 19[m] | **n** | H | H | H | H | H | Me | H | H | H | H | **778i** (12)[e] | |
| 20[m] | **o** | H | H | H | H | H | H | Me | H | H | H | **778j** (15)[e] | |
| 21[m] | **p** | H | H | H | H | H | H | H | Me | H | H | **778k** (22)[e] | |
| 22[m] | **q** | H | H | H | H | H | Me | Me | H | H | H | **778l** (15)[e] | |
| 23[m] | **r** | Me | H | H | H | H | Me | H | H | H | H | **778m** (11)[e] | |
| 24[m] | **s** | H | Me | H | H | H | Me | H | H | H | H | **778n** (16)[e] | |
| 25[n] | **t** | Et | H | H | H | Me | H | Me | H | H | H | | **779l** (58)[e] |
| 26[n] | **u** | H | Et | H | H | Me | H | Me | H | H | H | **778o** (52)[e] | |
| 27[n] | **v** | H | H | H | Et | Me | H | Me | H | H | H | | **779m**[o] |
| 28[p] | **w** | H | *i*-Pr | H | H | Me | H | Me | H | H | H | **778p** (56)[e] | |
| 29[p] | **x** | H | *t*-Bu | H | H | Me | H | Me | H | H | H | **778q** (52)[e] | |
| 30[p] | **y** | *i*-Pr | H | H | H | Me | H | Me | H | H | H | | **779n** (50)[e] |

[a] Data taken from ref 404. [b] Data taken from ref 393. [c] Data taken from ref 394. [d] Data taken from ref 395. [e] Isolated by carboxylation−decarboxylation of the dearomatized cyclic anion. [f] Data taken from ref 396. [g] Data taken from ref 403. [h] Data taken from ref 397. [i] Data taken from ref 405. [j] Relative configuration not given. [k] Data taken from ref 398. [l] Data taken from ref 399. [m] Data taken from ref 400. [n] Data taken from ref 401. [o] Yield not given. [p] Data taken from ref 402.

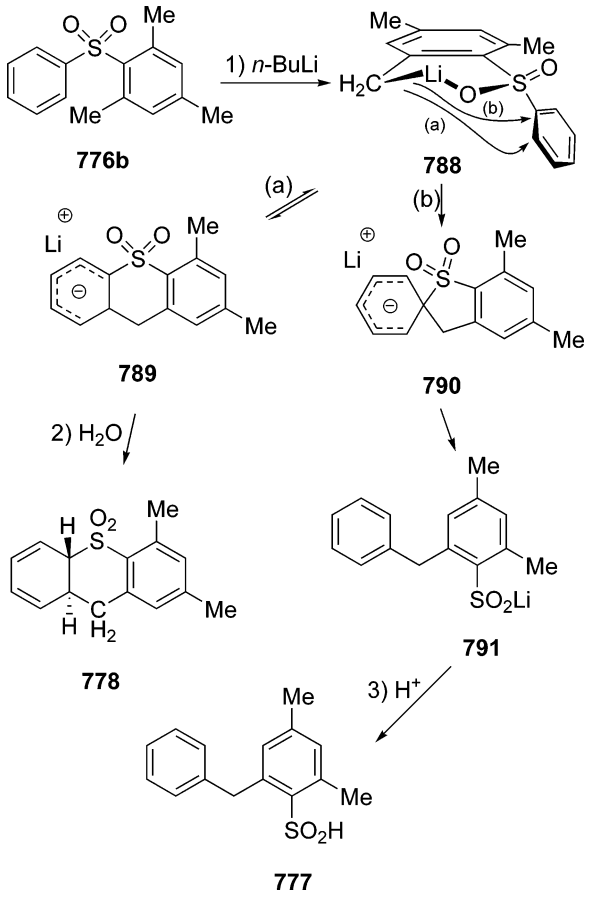
inductive and positive mesomeric effects, represents the borderline situation giving rise to products of both displacement of the OMe group and dearomatization. Anionic cyclization by attack onto a quaternary carbon has been observed in dimesityl sulfone **776a**. Quenching the reaction with water afforded a mixture of *trans*- and *cis*-2,4,5,7,9a-pentamethyl-4a,9a-dihydrothioxanthene 10,10-dioxides **778a** and **779a**, respectively.[404] However, trapping the dearomatized anions with $CO_2$ gave carboxylic acid **781** together with small amounts of compounds **778a** and **779a**. Interestingly, lithiation of *o*-tolyl mesityl sulfone **776i** occurs at the tolyl methyl group to give 2,4,9a-trimethyl-4a,9a-dihydrothioxanthene 10,10-dioxides **778h** (unspecified configuration) rather than the possible products derived from the lithiation of a mesityl methyl group.[405] On the other hand, lithiation of *o*- and *p*-trifluoromethylphenyl mesityl sulfones with butyl-lithium takes place initially at the ortho position of the $SO_2$ group as evidenced by carboxylation of the corresponding anions. It has been suggested that these ortho anions may translocate to a benzylic one, which then rearranges to the corresponding sulfinic acid.[406] Dearomatization of 1-naphthyl-,[407,408] 2-naphthyl-,[408] and 6-tetrallyl[409] rings can also be effected through anionic cyclization of the corresponding aryl mesityl sulfones **782**, **784**, and **786** upon reaction with *n*-butyl-lithium for a short period of time. Protonation, deuteration, or carboxylation−decarboxylation allowed the isolation of the tetracyclic compounds **783**, **785**, and **787** (Scheme 105).

Dihydrothioxanthene 10,10-dioxides **778**−**779** have been shown to isomerize to the open-chain precursors **776** upon reaction with *n*-BuLi, thus demonstrating that the anionic cyclization reaction of sulfones **776** is a reversible process. The position of the equilibrium depends on the reaction conditions used (solvent, temperature, presence of coordinating cosolvents), conformational preferences, acceptor capability of the aromatic ring suffering the nucleophilic attack, and nucleophilicity of the benzylic anion. The mechanism

**Scheme 105**



**Scheme 106**

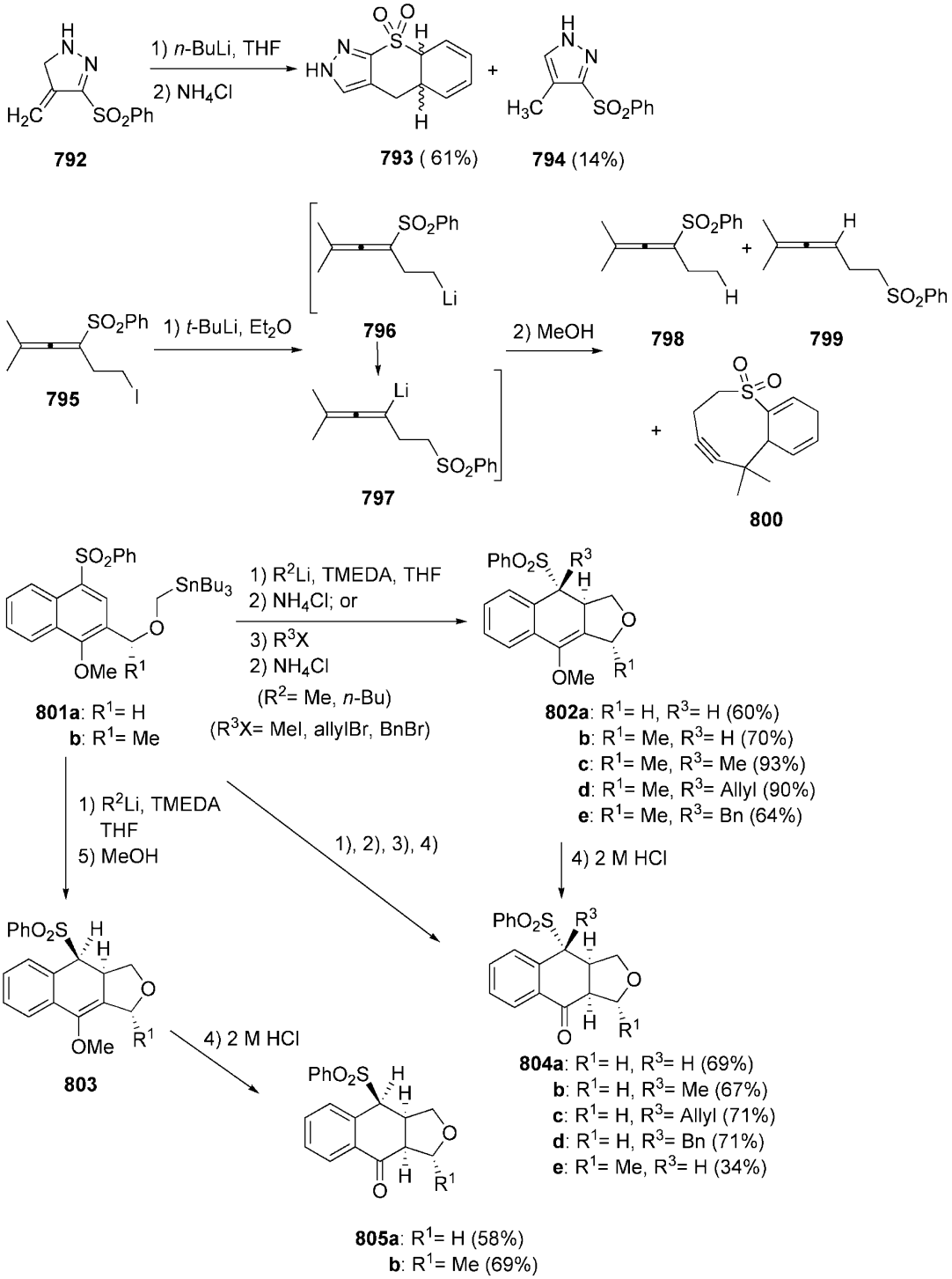



proposed for the conversion of diaryl sulfones **776** into sulfinic acids **777** or dearomatized heterocycles **778**−**779** by treatment with *n*-BuLi begins with the formation of the benzylic anion **788** (Scheme 106). This anion may proceed by intramolecular attack to the unperturbed *S*-phenyl ring at the ortho position (route a) or at the ipso carbon (route b), leading to the dearomatized species **789** and **790**, respectively. The Michael-type adduct **789** exists in equilibrium with the open-chain precursor **788**, whereas the spiro intermediate **790** undergoes rearrangement to the lithium sulfinate **791**. Cycloadducts **789** have a short lifetime and are, therefore, products of kinetic control. They may be trapped by electrophilic quench of the reaction as soon as the lithiation is completed to give dihydrothioxanthene 10,10-dioxides **778**−**779**. Increasing the reaction time to a few hours favors the formation of the rearranged product, isolated as the corresponding sulfinic acid **777** after acidic workup.

The equilibrium is shifted toward the benzylic anion **788** with increasing (i) temperature of the reaction, (ii) ability of the solvent to coordinate the lithium cation (PhH < $Et_2O$ < THF), and (iii) steric demand of the benzylic carbanion, as well as the use of strongly coordinating cosolvents such as TMEDA or HMPA.[410,411] Methyl groups at the ortho position of the ring undergoing nucleophilic attack hinder the formation of cyclic anions **789** due to steric interactions with the $SO_2$ moiety. Similarly, a decrease of the nucleophilicity of the benzylic anion by charge delocalization through binding to phenyl rings suppresses the intramolecular addition reaction, without affecting appreciably the rearrangement process.[412] The composition of the equilibrium has been investigated by UV spectroscopy. Anions **788** and **789** show their absorption maxima at about $\lambda_{max}$ 320 nm and 350−370 nm, respectively.[413,414] Moreover, lithiation of either sulfones **776** or the dihydrothioxanthene 10,10-dioxides **778**−**779** led to the same UV spectrum, thus confirming the existence of an equilibrium between the benzylic anion and the cyclic one. The results obtained are rather of qualitative nature due to the existence of anions **788** and **789** together with the sulfinic salt **791** and, in some cases, rearomatized products. Nevertheless, these studies represent the first spectroscopic investigation of the structure of the intermediate species formed in a dearomatizing anionic cyclization reaction. The study of the Truce−Smiles rearrangement of aryl mesityl sulfones revealed two characteristics also found in the anionic cyclization of *N*-benzylphosphinamides: the cyclization is reversible, and ortho-to-benzylic translocation may occur. Translocation from an ortho anion to a benzylic species has been also observed in the lithiation of *N*-benzylcarboxamides.[151] Although a rather limited number of dearomatizing conjugate additions have been described, these features appear to be a common pattern of reactivity in such reactions.

Padwa and co-workers reported an additional example of the Truce−Smiles rearrangement involving, in this case, a heterocyclic system. The treatment of sulfone **792** with *n*-BuLi and subsequent aqueous workup gave tricycles **793** (61% yield, 1:1 mixture of cis:trans isomers) as the major products (Scheme 107). The negative charge generated on the nitrogen by metalation is attached to the phenyl ring in a [1,4] manner through the exo-methylene moiety. The pyrazole expected **794** was formed as a byproduct.[415] Crandall and Ayers, in a study devoted to the application of allenes in anionic cyclization processes, found that the reaction of allenylsulfone **795** with *t*-BuLi at −100 °C afforded a 1:4:5 mixture of deiodinated allene **798**, rearranged sulfone **799**, and the dearomatized sulfone **800**. The bicyclic product obtained is the result of an intramolecular cyclization of an organometallic reagent, although completely different from that expected. The reaction pathway suggested for the formation of **798**−**800** assumed that lithium−iodine exchange on **795** affords the anion **796**, which undergoes [1,3] transfer of the phenylsulfonyl group to give allenyl anion **797**. Protonation of these species provides the corresponding allene derivatives **798** and **799**. Alternatively, anion **797** undergoes intramolecular attack at the ortho position of the sulfonyl-activated phenyl ring, furnishing **800** after quenching of the reaction with methanol.[416] It is of interest to note that the eight-membered ring formed in the dearomatizing cyclization leading to **800** represents the largest ring ever reported for this type of processes. Recently, Clayden et al. extended the anionic cyclization of diaryl sulfones to substrates containing an organolithium sidearm. Lithiation of naphthyl phenyl sulfones **801** by tin−lithium exchange with methyl-lithium is followed, even at −78 °C, by intramolecular attack to the naphthyl ring. The resulting dearomatized species were protonated and alkylated to give tetrahydronaphthofurans **802** with excellent diastereoselectivities (Scheme 107).[417] The methoxyvinyl moiety of these heterocycles was readily hydrolyzed with dilute hydrochloric acid, affording ketones **804**. The conversion of sulfones **801** into ketones **804** was performed in a one-pot manner. Products of electrophilic trapping **802** were isolated only by quenching the reaction at low temperature with $NH_4Cl$. Using methanol as a proton source and allowing the reaction to warm to room temperature afforded a crude reaction mixture

**Scheme 107**

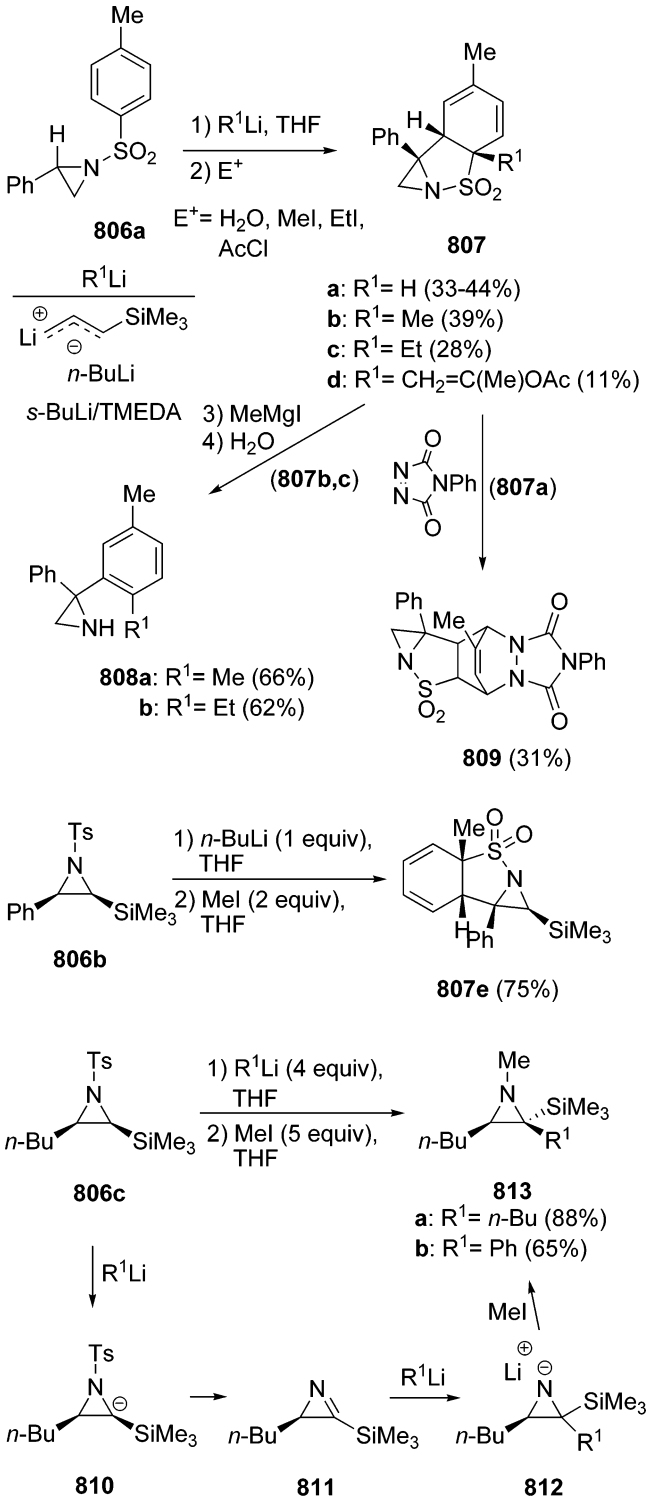



consisting presumably of epimers **803**, which were hydrolyzed to ketones **805a**,**b** by treatment with dilute HCl.

## 17.2. Sulfonamides

Arylsulfonamides, another electron-deficient aryl system owing to the conjugation with a sulfur-containing electron-withdrawing group, also undergo dearomatizing anionic cyclization reactions. While searching for a method of preparing homoallylamines via ring opening of an aziridine with an arylsulfonyl nitrogen substituent, Schaumann and co-workers found that exposure of aziridinyl *p*-tolyl sulfonamides **806a** to lithium allyltrimethylsilane afforded, after aqueous workup, dearomatized compound **807a** as the major product in 33% yield (Scheme 108).[418] Hence, benzylic deprotonation position was preferred over ring opening. The initial anion formed undergoes cyclization by attack at the ortho position of the phenyl nucleus bound to the sulfonamide linkage. This unexpected chemical behavior proved to be rather general. The deprotonation was also performed with more common organolithium bases such as *n*-BuLi and *s*-BuLi/TMEDA. The dearomatized anions were trapped with $H_2O$, MeI, EtI, and $CH_3COCl$. In all cases, electrophilic attack α to the sulfur was observed, giving tricyclic compounds **807a**−**d** containing a [1,3] cyclohexadienyl

**Scheme 108**




system, apparently as single stereoisomers. The treatment of **807b**,**c** with a Grignard reagent effected the rearomatization via deprotonation and subsequent elimination of the $SO_2$ group to give α,α-disubstituted aziridines **808**. Additionally, the reaction of **807a** with 4-phenyl-4*H*-1,2,4-triazole-3,5-dione furnished the Diels−Alder cycloadduct **809** in a yield of 31%.

Aggarwal and Ferrera applied this chemistry to *C*-silyl-*N*-tosylaziridines **806b**,**c**. For aziridine **806b** containing a phenyl substituent, deprotonation occurs at the benzylic position. Quenching the reaction with MeI produces tricyclic aziridine **807e** as a single diastereomer (Scheme 108).[419] Lithiation at the ring carbon atom α to the silicon became feasible on *N*-tosylaziridine **806c** in which the phenyl substituent is absent. However, the *C*-silyl-stabilized anions **810** underwent *β*-elimination of the tosyl moiety, yielding azirines **811**. Addition of the base to the imine group of **811**, followed by capture of the resulting anion **812** with methyl iodide, led to trisubstituted aziridines **813**.[420]

Recently, Florio and co-workers showed the stereochemical constraints involved in the anionic cyclization of *N*-sulfonylaziridines. They prepared diastereomeric aziridines **814** and **815**, which were then lithiated by treatment with *s*-BuLi/TMEDA at −98 °C. Only anion **816** derived from **814** underwent intramolecular ortho attack to the phenyl ring to some extent. On exposure of **816** to $D_2O$, a mixture of aziridines **817** and **818** was obtained, with the latter being formed in 28% yield. Addition of MeI to **816** afforded a mixture of four products **819**−**822** in which the dimethylated aziridine **819** predominated. The tricyclic aziridine **821** was formed only in 8% yield (Scheme 109).[421] Azirine **822** was synthesized in high yields by simply warming the reaction to room temperature after the deprotonation was completed. This product was obtained quantitatively in the lithiation of **815** at −78 °C and subsequent addition of MeI. The presence of an alkylating agent was unnecessary. Apparently, at this temperature the anion generated is unstable and undergoes *β*-elimination of the benzenesulfonyl group. Performing the lithiation at −98 °C followed by electrophilic quench with $D_2O$ furnished the dideuterated aziridine **823** in high yield. The relative configuration of the aziridines obtained showed that anions arising from **814** and **815** are configurationally stable.

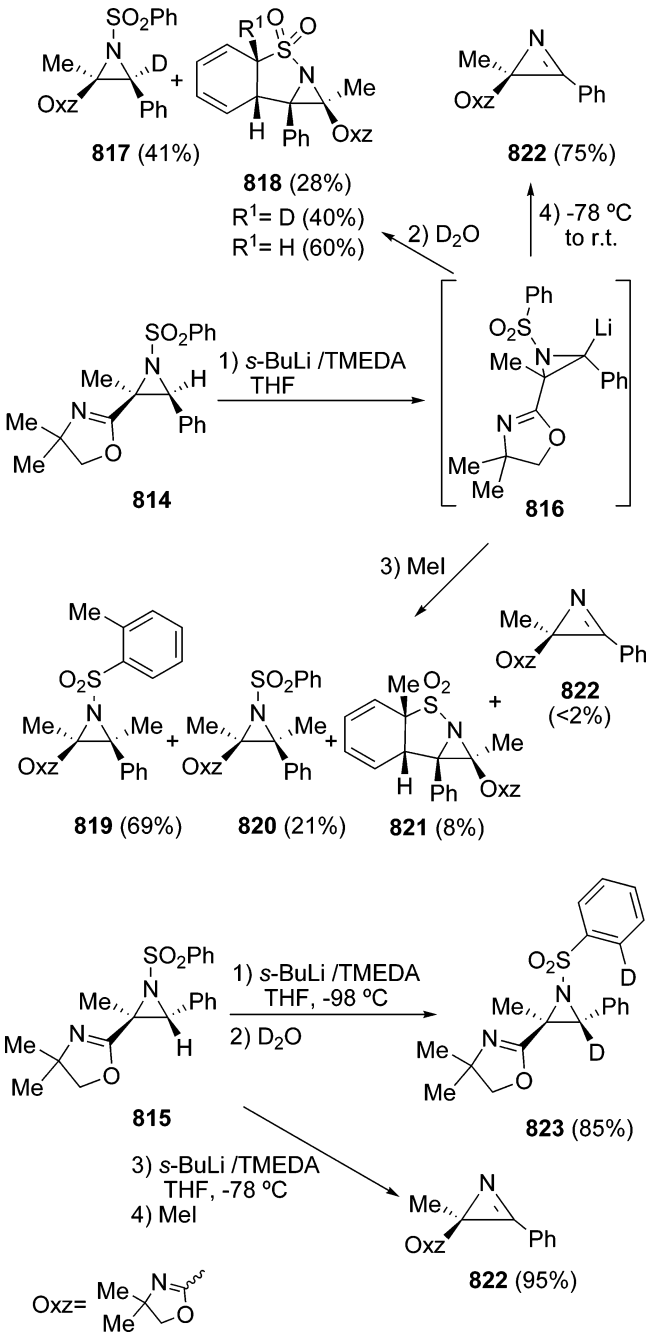
## *18. Miscellaneous Nucleophilic Dearomatizing Reactions*

A number of $D_NAr$ reactions have been described in which the electron deficiency of the aryl system is due to the presence of functional groups less common than those previously discussed or the use of some particular reaction conditions.

The strong electron-withdrawing nature of the pentacarbonyl metal moiety of Fischer carbene complexes has been shown to activate an adjacent phenyl ring toward nucleophilic addition. *s*-BuLi or *t*-BuLi undergoes reaction with Fischer arylcarbene complexes **824** at −78 °C in THF to give [1,6] adducts. Once the addition of the nucleophile was completed, the quench of the reaction with MeOTf provided dearomatized 1,4-dialkylated complexes **825** in moderate yields and with low stereoselectivity (Scheme 110, mixtures of Z/E diastereoiomers; Table 46 entries 1−3).[422] The bulky alkoxy group prevents the [1,2] attack at the carbene carbon. Introducing a methoxy group at the para position of the phenyl ring promotes the exclusive [1,4] addition of the nucleophile. Thus, the reaction of complex **824c** with *t*-BuLi for 5 min at −78 °C and subsequent addition of MeOTf gave the dearomatized complex **827**, albeit in low yield (Table 46, entry 4). The reaction proceeds stereospecifically starting with enantiomerically pure **824c** (Table 46, entries 5 and 6). Removal of the $Cr(CO)_5$ moiety was readily accomplished by oxidation with pyridine *N*-oxide, yielding esters **826**.

Hirotani and Zen reported the one-step formation of spiroisoxazolines **832** from the reaction of nitroarenes **828** with $TiCl_4$ in toluene (Scheme 110; Table 46).[423] The formation of heterocycles **832** may be explained by the initial coordination of the Lewis acid to one oxygen atom of the

**Scheme 109**




nitro group of **828**. The complex **829** thus obtained undergoes cyclization to give the spiro intermediate **830**, which is converted into **831** by conjugate addition of chloride ion followed by $\beta$-elimination of $TiOCl_2$. Chloride ion addition to the cationic species **831** or Friedel−Craft reaction with the solvent leads to products **832**−**834**. The feasibility of the latter process has been demonstrated by transforming **834b** into **832c** upon treatment with $TiCl_4$ in toluene. Apparently, the nucleophilicity of the solvent plays an important role in the efficiency of the reaction. In benzene the reaction proceeds in very low yield (Table 46, entry 8), and in chlorobenzene the formation of the corresponding chlorophenylated spiroisoxazoline was completely inhibited.

1,2-Dialkyl-1,2-dihydronaphthalenes **836** have been obtained by treatment of borate anion **835** with a series of alkylating reagents ($CH_3CH{=}CHCH_2Br$, $Me_2C{=}CHCH_2Br$, $R^1OTs$, $R^1{}_2SO_4$, $R^1OSO_2F$, $R^1I$, where $R^1$ = Me, Et) and subsequent dehydroboration with aqueous NaOH (Scheme 110).[424] It has been suggested[425] that the formation of the disubstituted products occurs by direct carbon−boron bond formation with the alkylating agents rather than through predissociation of borates **835** into aryl-lithiums and boranes.

A variety of nucleophiles (e.g., sodium borohydride,[426] sodium cyanide,[427,428] amines,[429−431] trialkyl phosphites,[432]) have been directly introduced to aromatic hydrocarbons through photochemical electron-transfer reactions.[433] Irradiation of solutions of the nucleophile and the aromatic compound in the presence of 1,3-dicyanobenzene (*m*DCNB) or 1,4-dicyanobenzene (*p*DCNB) in mixtures of acetonitrile/water 9:1 or DMF/$H_2O$ 3:1 afforded dihydroaromatic derivatives among other products. Some examples are given in Scheme 111. Nucleophilic addition to the aromatic system is accomplished by attack at the anion radical generated by electron transfer from the excited singlet state of the aromatic hydrocarbon to *p*DCNB. A detailed discussion of this topic is outside the scope of this review.

## *19. Synthetic Applications of Nucleophilic Dearomatizing Reactions*

In the previous sections it has been shown that a large number of methods are available for dearomatization of myriad aromatic substrates, leading to dihydroaromatic compounds incorporating different degrees of functionality and with good regio- and stereocontrol. Hydroaromatic systems constitute part of the ring skeleton of numerous natural products.[434−438] However, the application of $D_NAr$ reactions to the preparation of natural products or some mimetic analogues has been explored only in aromatic rings activated by carboxamide, oxazoline, oxazolidine, nitro, phosphinamide, and sulfone groups.

### 19.1. Synthesis of Heterocyclic Compounds

Non-natural benzomorphans such as metazocine **842a**, *N*-allyl-*N*-normetazocine **842b**, and the clinically used pentazocine **842c** are synthetic analogues of the natural opium alkaloid (−)-morphine and are well-known for their opioid activity. They are important substances as analgesics owing to the lack of the undesired addicting side effects of (−)-morphine. Compounds **842b** and **842c** also showed $\sigma$ receptor activity. In the search for new $\sigma$ receptor binding ligands of enhanced activity, Carroll and co-workers prepared benzomorphans **845** and **846** in modest yield but high optical purity (overall yields of **846** of 33−53%, ee ≥ 99%) according to the method of Pridgen et al.[216] Addition of Grignard reagents to the oxazolidine **438** derived from (*R*)-phenylglycinol and naphthaldehyde followed by quenching with dilute HCl or methyl iodide gave 1,2-dihydronaphthalene-carboxaldehydes **441** and **442**, respectively (see also Scheme 69). Reduction of **441** with methanolic sodium borohydride furnished alcohols **398** (Scheme 112).[439−441] Aldehydes **441** and alcohols **398** were converted into the amine intermediates **843** by a series of conventional reactions. Applications of these transformations to compounds **442** provided the aminoalkyldihydronaphthalenes **844**. Cyclization of **843** and **844** by the action of $Hg(OAc)_2$ followed by demercuriation with $NaBH_4$ or $LiAlH_4$ led to the desired products **845** and **846**, respectively. The enantiomers of **845** were synthesized in a similar manner starting with the naphthyloxazolidine bearing (*S*)-phenylglycinol as chiral auxiliary. Binding studies revealed that compounds **845a**−**c**

**Scheme 110**

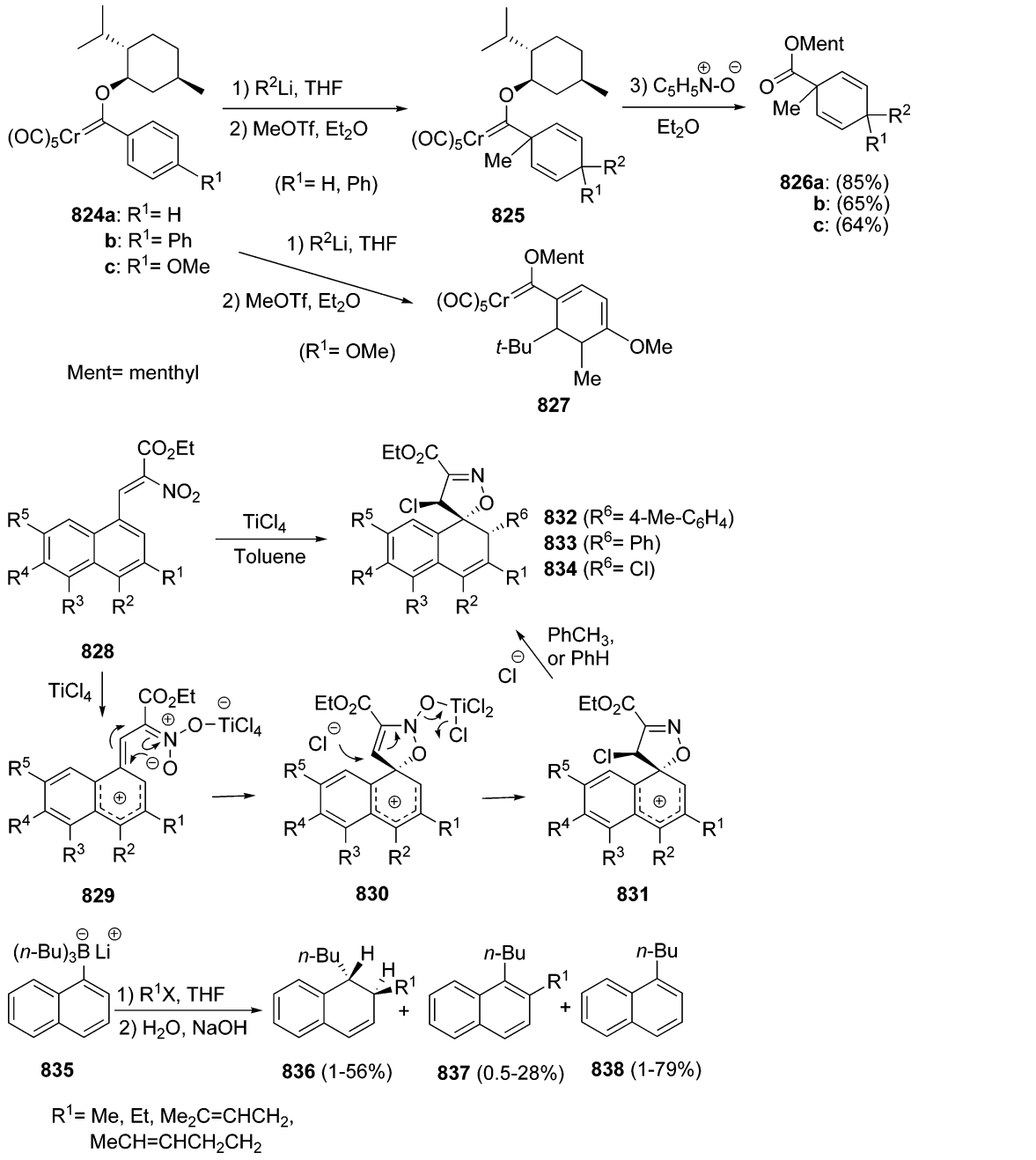


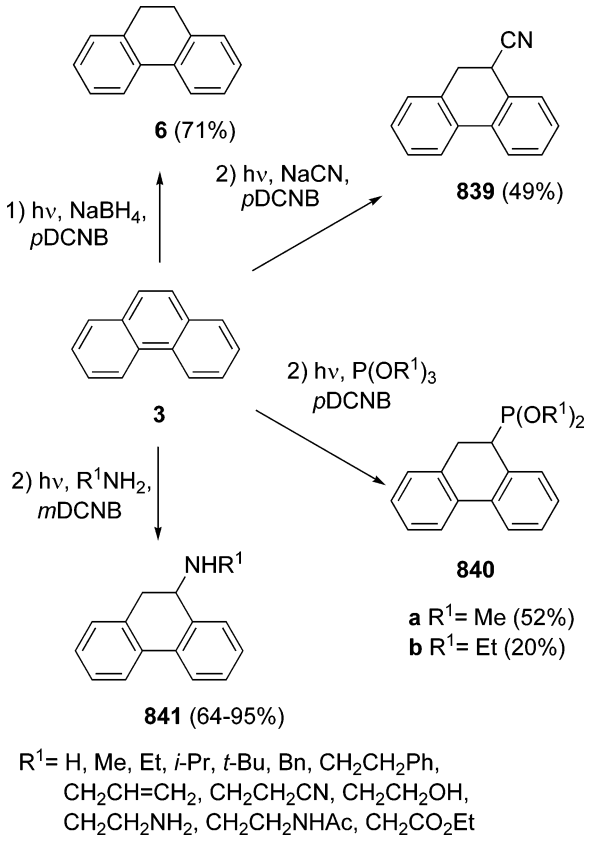

**Table 46. Dearomatizing Anionic Cyclization of Compounds 824 and 828**

| entry | SM | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | yield (%), (dr) |
|---|---|---|---|---|---|---|---|
| 1[a] | **824a** | H | *s*-Bu | | | | **825a** (45), (1.9:1) |
| 2[a] | **824a** | H | *t*-Bu | | | | **825b** (41), (1.4:1) |
| 3[a] | **824b** | Ph | *s*-Bu | | | | **825c** (68), (3:1) |
| 4[a] | **(±)-824c** | OMe | *t*-Bu | | | | (±)-**827** (27) |
| 5[a] | **(+)-824c** | OMe | *t*-Bu | | | | (+)-(6*R*,7*S*)-**827** (28) |
| 6[a] | **(−)-824c** | OMe | *t*-Bu | | | | (−)-(6*R*,7*S*)-**827** (28) |
| 7[b] | **828a** | H | H | H | H | H | **832a** (40)[c] |
| 8[b,d] | **828a** | H | H | H | H | H | **833a** (10) + **834a** (3) |
| 9[b] | **828b** | H | Me | H | H | H | **832b** (90) |
| 10[b] | **828c** | H | Cl | H | H | H | **832c** (77) + **834b** (7) |
| 11[b] | **828d** | | (−CH=CH−)$_2$ | H | H | H | **832d** (50) + **834b** (4) |
| 12[b] | **828e** | H | H | | (−CH=CH−)$_2$ | Br | **832e** (61) |

[a] Data taken from ref 422. [b] Data taken from ref 423. [c] 3-Chloro-3-(4′-chloro-1′-naphthyl)-2-hydroxyiminopropionate was also formed in 40% yield. [d] Benzene was used as solvent.

with a configuration of (1*R*,5*R*,9*R*) exhibited greater affinity for the $\sigma_1$ receptors than enantiomers (1*S*,5*S*,9*S*). This fact constitutes a reversal of the receptor enantioselectivity as compared with pentazocine and other 6,7-benzomorphans.

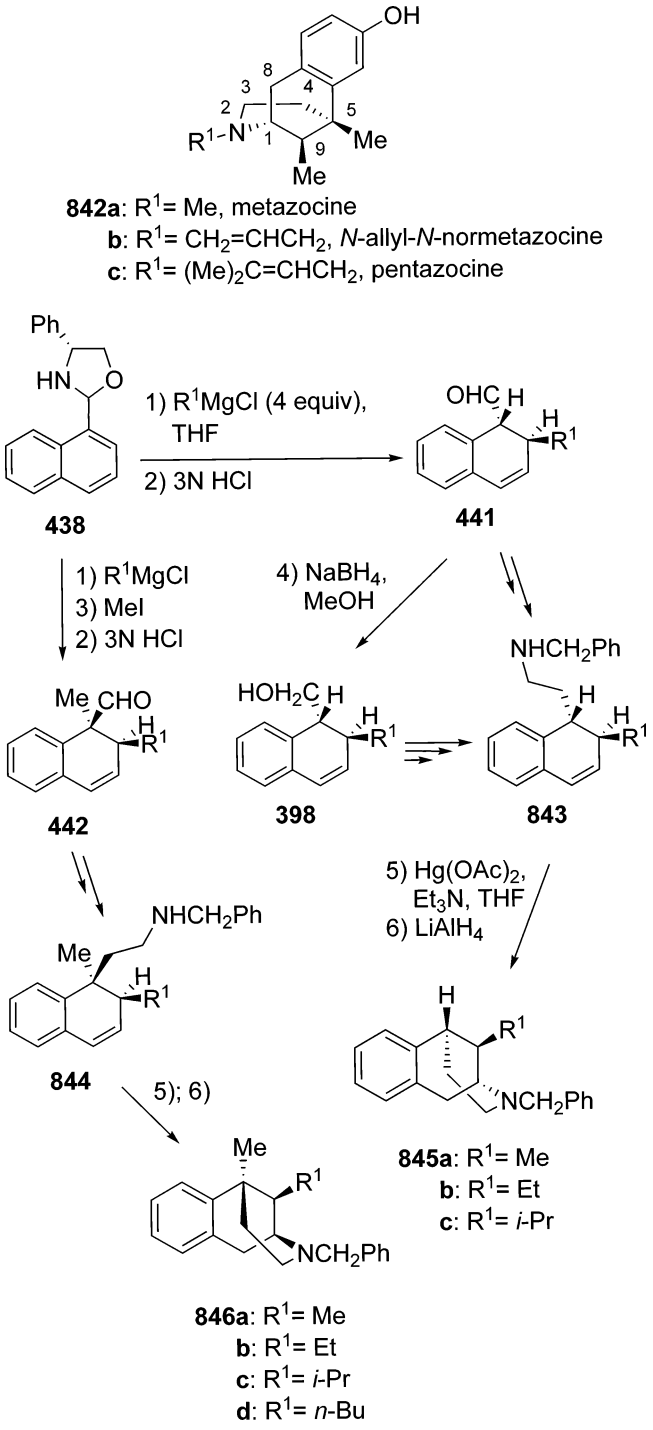
**Scheme 111**




Functionalized 3-ABNs have attracted great interest because of their pharmaceutical use.[253,442−444] As discussed in section 14.1.1.b, 3-ABNs can be prepared by successive reduction−aminoalkylation of nitroarenes. Pryce and coworkers utilized this strategy for the synthesis of benzoazocine **853** and pyridoazozine **854**. These compounds are analogues of cytisine **855**, a potent insecticide acting on acetylcholine receptors.[445] The target molecules were prepared in three steps starting from the corresponding 1,3-dinitronaphthalene derivative **460** and **847** (Scheme 113).[446] Reduction with $NaBH_4$ followed by double Mannich reaction with formaldehyde and methylamine afforded tricyclic compounds **848** and **849**. Reaction of **848** with sodium methanethiolate in DMSO at 80 °C produced sulfides **850a** and **851a** in a ratio 1:10 in 56% yield. Furthermore, the analogous reaction of **849** for 4 days at 40 °C furnished a mixture of the mononitro compound **850b**, sulfide **851b**, and bisulphide **852**. Hydrogenation of **851a** and of **851b** or **852** in the presence of Raney nickel gave cytisine analogues **853** and **854**, respectively.

The primary products of the reduction−aminoalkylation of nitroarenes have been used as synthetic intermediates for the preparation of molecules difficult to obtain by other methods. Thus, trinitroazaadamantane **492a** was transformed into azadamantane **858** in a sequence of reactions starting with the reduction of **492a** to the triamino derivative **856** by the action of hydrazine in the presence of Raney nickel. Then, bromo for amino group substitution via diazotation afforded **857**, which was debrominated upon treatment with hydrazine in the presence of Raney nickel to give **858** (Scheme 114).[263] Although this route provides azaadamantane **858** in acceptable yield, the efficiency of the process is limited by the availability of the starting material, which was obtained in only 8−15% yield.

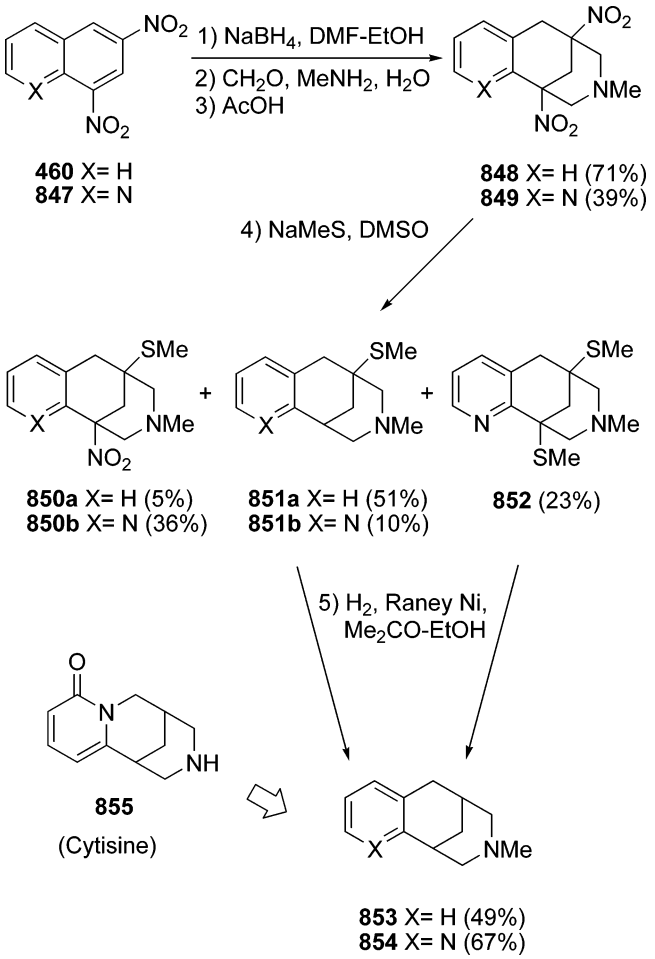
**Scheme 112**




Reduction of 3-ABNs has also been described. Exposure of dinitro compounds **485** to hydrogen in the presence of Raney nickel[447,448] or palladium on carbon[447] produced the diamino derivatives **859** resulting from the perhydrogenation of the carbon−carbon double bond and the nitro groups of the parent system (Scheme 114; Table 47). Hydrogenation of compounds **485s** and **485ba** was performed in the presence of ammonia. The ammonium salts formed showed increased solubility in methanol without affecting the catalyst. Reduction with tributyltin hydride was also attempted. However, this reaction provided a mixture of nitrohydroxylamines in low yield.[446]

Selective transformation of the carbon−carbon double bond of 3-ABNs **485** was achieved through dihydroxylation

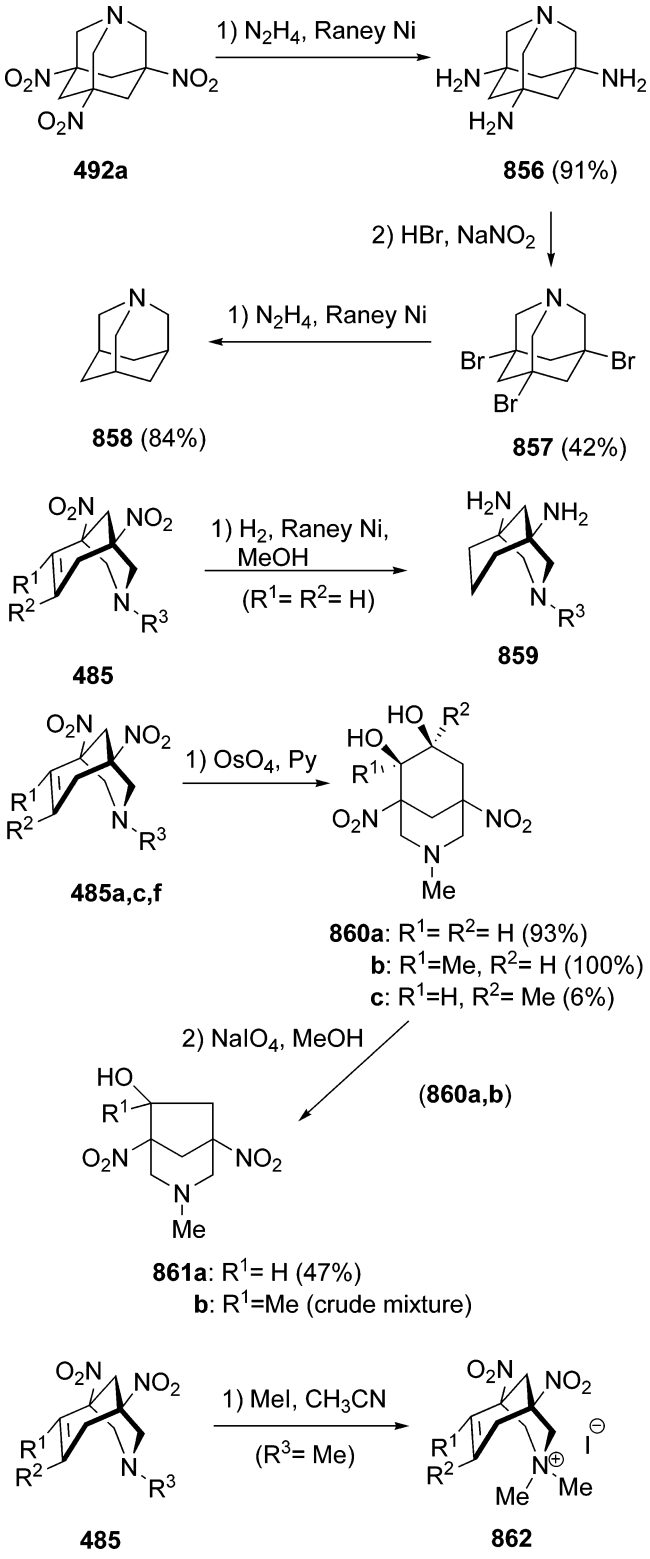
**Scheme 113**




of **485a**,**c**,**f** with osmium tetroxide. The *cis*-diols **860** thus obtained were further converted into the 3-azabicyclo[3.2.1]-octanols **861** by reaction with sodium periodate.[255] The tertiary amine moiety of 3-ABNs **485** represents an additional opportunity for the introduction of molecular diversity. Alkylation of *N*-methyl derivatives with MeI in refluxing acetonitrile led to the quaternary ammonium salts **862** (Scheme 114; Table 47).[449] Electron-withdrawing groups at positions 6 and 7 of the bicyclic system caused a decrease in the reaction yield (entries 9, 12, and 16). Alkylation of 3-ABNs with substituents at the nitrogen atom such as Et, $CH_2CH_2Br$, Bn, $CH_2CO_2H$, $CH_2CH_2OH$, and CH(Et)OH failed, which suggests that attack at the nitrogen by methyl iodide is very sensitive to steric hindrance.

$\gamma$-Amino acids have attracted recently great interest as building blocks for the preparation of $\gamma$-peptides.[210,212,213,450−453] Contrary to what could be expected due to the flexibility of the chain connecting the amino and carboxy groups in these amino acids, well-defined secondary structures were found in oligopeptides consisting of only four residues.[454] Phosphorus-containing mimetics of $\gamma$-amino acids such as $\gamma$-aminophosphinic acids are important target molecules owing to their interesting biological properties.[455−457] Phosphinothricin **863a**, an amino acid contained in the natural tripeptide bialaphos, is an important member of this family currently used as a nonselective herbicide.[458] Phosphinothricin analogues **863b,c** and cyclic derivatives **864** also showed herbicidal activity.[459] $\gamma$-Aminophosphinic acids may also act as agonists or antagonists on GABA receptors.[460−464]

**Scheme 114**




The azaphospholes resulting from the dearomatizing anionic cyclization of *N*-benzylphosphinamides (see section 15.3.3) represent a facile entry into functionalized $\gamma$-aminophosphinic acids of wide structural diversity. Hydrolysis of the phosphinamide linkage of tetrahydrobenzoazaphospholes **718** and **722** may be effected under very mild conditions. Thus, treatment of a solution of these heterocycles in acetone with 2 N HCl at room temperature gives quantitatively $\gamma$-(*N*-alkylamino)phosphinic acids **865** and **866** (Scheme 115).[376,377] The solvolysis with dry 0.6 N HCl in

**Table 47. Yield of Products 859[a] and 862[b]**

| entry | 485 | $R^1$ | $R^2$ | $R^3$ | yield (%) |
|---|---|---|---|---|---|
| 1 | **a** | H | H | Me | **859a** (65) |
| 2 | **o** | H | H | Et | **859b** (85) |
| 3 | **p** | H | H | Bn | **859c** (70) |
| 4 | **r** | H | H | $CH(Et)CH_2OH$ | **859d** (65) |
| 5 | **s** | H | H | $CH_2CO_2H$ | **859e** (72) |
| 6 | **t** | H | H | $(CH_2)_2OH$ | **859f** (75) |
| 7 | **ba** | H | H | $(CH_2)_2CO_2H$ | **859g** (82) |
| 8 | **a** | H | H | Me | **862a** (73) |
| 9 | **b** | Cl | H | Me | **862b** (45) |
| 10 | **d** | Me | H | Me | **862c** (87) |
| 11 | **e** | OMe | H | Me | **862d** (95) |
| 12 | **bj**[b] | Br | H | Me | **862e** (42) |
| 13 | **bk**[b] | $O(CH_2)_2Cl$ | H | Me | **862f** (83) |
| 14 | **bl**[b] | OPh | H | Me | **862g** (54) |
| 15 | **h** | H | OMe | Me | **862h** (87) |
| 16 | **m** | H | $CONH_2$ | Me | **862i** (46) |

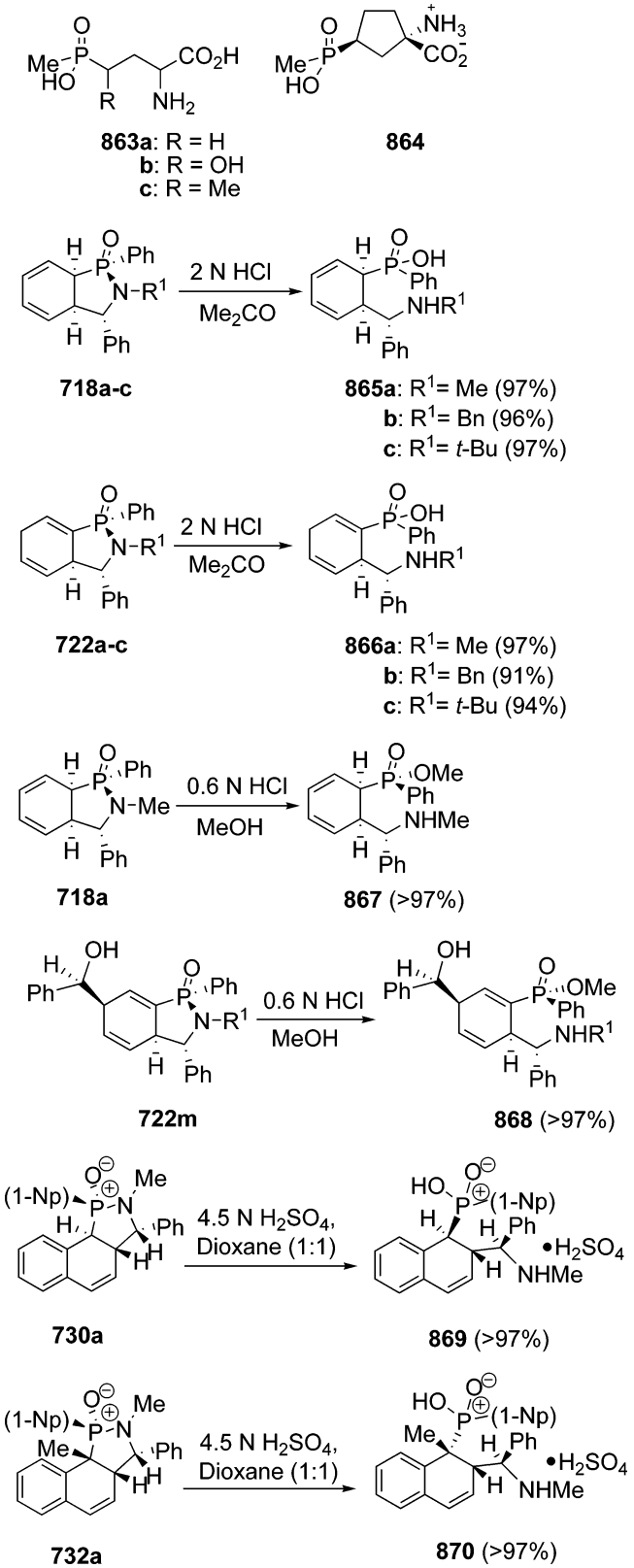
[a] Data taken from ref 448. [b] Data taken from ref 449.

methanol affords stereospecifically and in quantitative yield the corresponding methyl esters **867** and **868**, with inversion of the configuration at the phosphorus center. Cleavage of the P−N bond of benzophosphaisoindoles **730a** and **732a** requires harder conditions than the analogous heterocycles **718** and **722**. In this case, conversion into the $\gamma$-aminophosphinic acids containing a dihydronaphthalene system **869** and **870**, respectively, was achieved by refluxing a solution of **730a** and **732a** in a mixture of dioxane and 4.5 N $H_2SO_4$ (1:1) for 8 h (Scheme 115).[379] The reluctance of the phosphinamide function of **730a** and **732a** to hydrolysis was attributed to difficulties of nucleophilic attack at the phosphorus atom due to steric encumbrance. An important feature of $\gamma$-aminophosphinic acids shown in Scheme 115 is the presence of a carbocyclic system. This structural element causes a restriction to the conformational space available to the molecule, which may facilitate its recognition by a receptor.

Anionic cyclization of naphthalene rings activated by a carboxamide[157] or a sulfone[417] group constitutes a route to tricyclic systems present in some natural products. The synthetic utility of this dearomatizing reaction has been demonstrated by converting sulfone derivative **804a** into lactones **873** and **874**, two skeletal analogues of podophyllotoxin **875**. The pivotal ketone **872** was prepared in four steps starting with the stereoselective reduction of **804a** with sodium borohydride to give **871**. The resulting alcohol was protected as a silyl ether, and subsequent desulfonylation by electrophilic hydroxylation with $MoO_5$·py·DMPU (MoOPD) afforded **872** (Scheme 116). Removal of the sulfonyl moiety of the dearomatized products **804** was also effected by reduction with sodium amalgam.

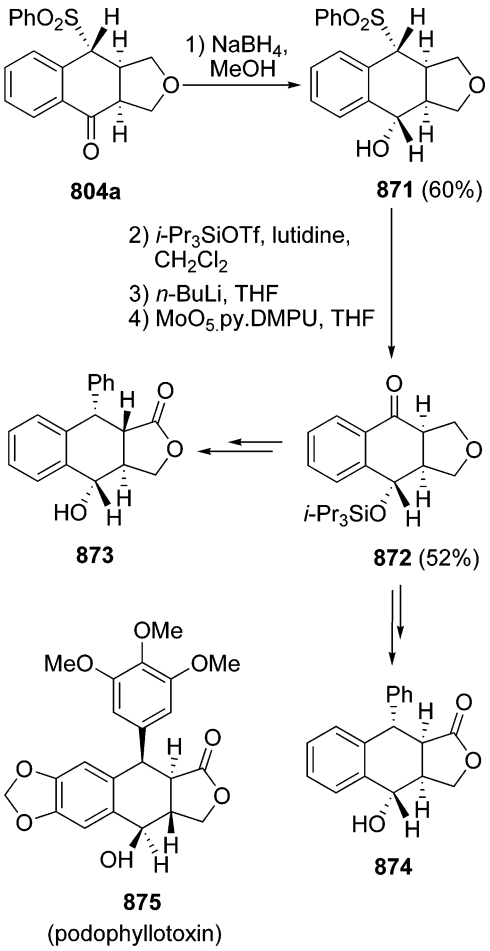
Kainoids are a family of naturally occurring, non-proteinogenic amino acids that exhibit potent neuroexcitatory and excitotoxic activities. They are pyrrolidine dicarboxylic acids of general structure **876** differing in the substituent at C4 (Scheme 117). The most representative members of this class of compounds include (−)-α-kainic acid **877**, (−)-domoic acid **879**, and acromelic acid A **880**. A common feature to all kainoids is the 2,3-trans-3,4-cis relative disposition of the substituents, except for (+)-α-*allo*-kainic acid **878**, in which the groups at C3 and C4 are trans. Considerable investigations have been devoted to the synthesis of kainoids and non-natural analogues with improved pharmacological profile. Clayden and co-workers noted that the dearomatized products **246** obtained in the anionic cyclization of naphthamides **242**

**Scheme 115**




(see section 9.2) contained a pyrrolidone system having three contiguous stereocenters about the ring with the same relative stereochemistry as the kainoid amino acids. They applied the dearomatizing cyclization of lithiated naphthamides to the synthesis of two aryl analogues of acromelic acid **886** and **887**,[158,465] the kainoid-like derivative **889**,[158] and the parent member kainic acid (see below). This chemistry has been covered in detail in two recent reviews.[149,466] Conversion

**Scheme 116**




of the tricyclic lactam system of **246** into a kainoid skeleton involved the three key steps outlined in Scheme 117: oxidation of the phenyl ring adjacent to the nitrogen atom to a carboxylic acid, ring opening of the dihydronaphthalene moiety, and reduction of the amide functional group to an amine. On the basis of this synthetic strategy, amide **242c** was selected as starting material for the synthesis of racemic acromelic acid derivative **886**. The reasons for this choice are best explained by looking at the central intermediate **246h** formed in the anionic cyclization reaction: (1) the cumyl protecting group at nitrogen is stable to strong bases, but easily removable by the action of acids; (2) the electron-donating *p*-methoxy substituent in the aryl ring at the α position with respect to the nitrogen facilitates the aryl oxidation step as compared with an unsubstituted phenyl ring; and (3) the methyl vinyl ether moiety may be readily hydrolyzed to a carbonyl group, thus allowing the requisite ring cleavage via a Baeyer−Villiger oxidation. The essential steps in the transformation of **242c** onto **886** are shown in Scheme 117. N Protection through the *tert*-butyloxycarbonyl group (Boc) was used owing to its resistence to the ruthenium-catalyzed aryl oxidation conditions. Ring opening of lactone **883** by reaction with sodium methoxide in methanol furnished pyrrolidone **884**. Further elaboration of this molecule led to **886**. On the other hand, saponification of **883** with lithium hydroxide followed by ester formation with diazomethane gave a mixture of **884** and **885** in a ratio 1:5. The latter was converted to **887** by the same route used to prepare **886**.

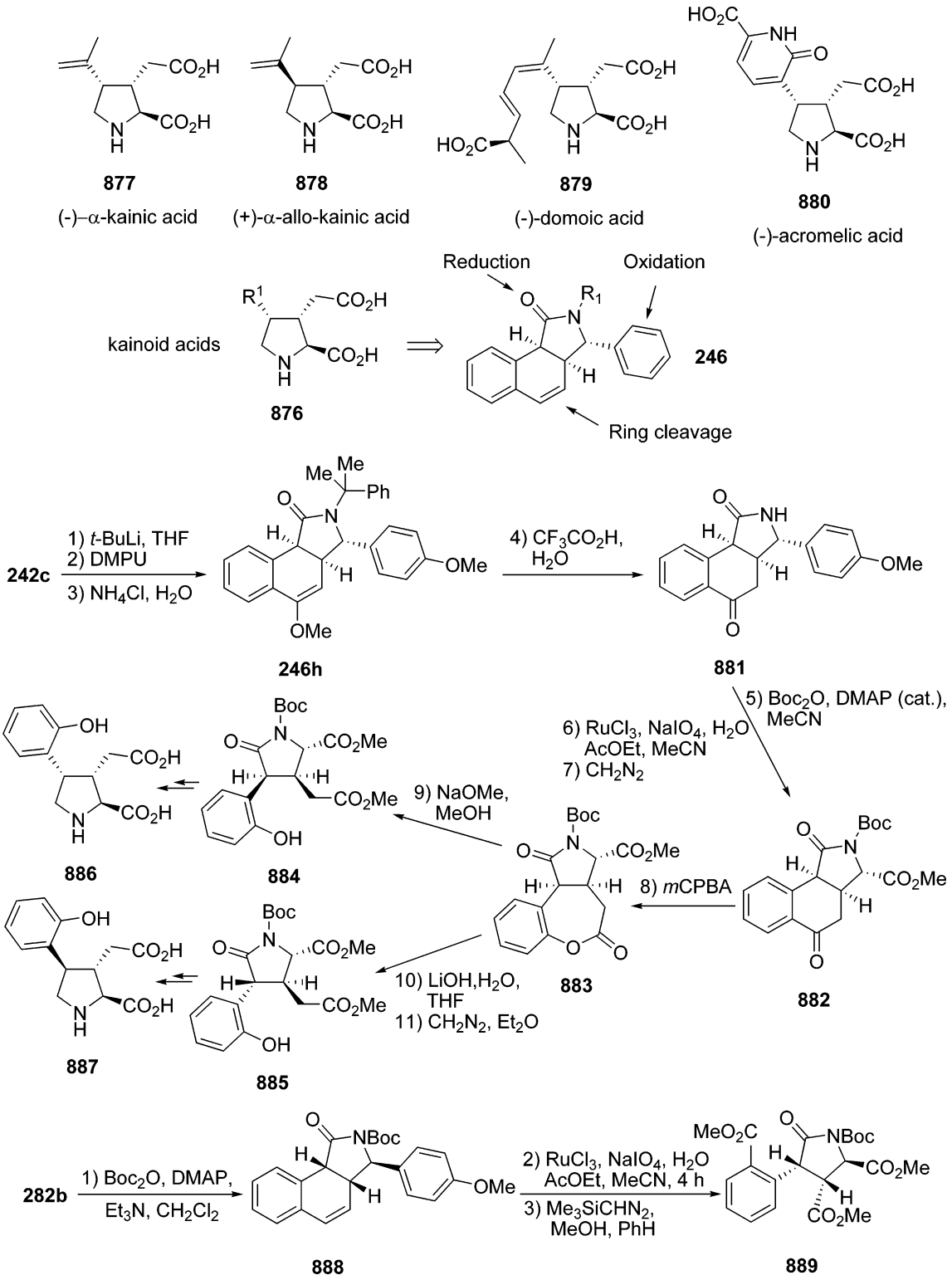
Tricyclic lactam **881** was prepared in almost enantiomerically pure form using (*S*)-phenylglycinol-derived naphthamide **278e** as starting material. The anionic cyclization of this amide was rather inefficient, affording **279e** in 32% yield (Scheme 50).[158] The asymmetric synthesis of **881** represents a formal asymmetric synthesis of the acromelic acid analogue **886**. The enantiomer of **881** was synthesized following a similar route starting from (*R*)-**278d**. Compound **282b** was further manipulated to give the pyrrolidone **889**, which is structurally related to the kainoids (Scheme 117).

Bicyclic pyrrolidone **293** (Scheme 52) proceeding from the dearomatization of chiral benzamide (*R*,*R*)-**289b** was a suitable precursor for the asymmetric synthesis of the novel α-methyl kainic acid **892**. The synthetic strategy was basically the same as that used in the dearomatized naphthalene series. Conjugate addition of $Me_2CuLi$ allowed the introduction quantitatively and stereospecifically of the methyl group of the isopropenyl susbtituent at C4 of **892** (Scheme 118). The interconversion of N-protecting groups was achieved by sequential reaction with cerium ammonium nitrate and $Boc_2O$ to yield ketolactam **890**. In this case, it proved to be advantageous to invert the order of the oxidative operations on this substrate as compared with the synthesis of **886** and **887**. Thus, the reaction of **890** with *m*CPBA to give the lactone **891** preceded the oxidative degradation of the *p*-methoxyphenyl ring catalyzed by Ru(VIII). Fortunately, the Baeyer−Villiger oxidation of ketone **890** was fully regioselective in the sense required. The lactam carbonyl group was reduced with DIBAL-H and $Et_3SiH$ at the end of the synthetic sequence prior to deprotection of the functional groups. The process constitutes the first synthesis of the α-methylated analogue of kainic acid **892**.

The synthesis of **886**, **887**, **889**, and **892** indicates that dearomatizing anionic cyclization of arylamides is an interesting strategy for the elaboration of either a phenyl or a naphthyl nucleus into functionalized pyrrolidones containing a cyclohexadiene or dihydronaphthalene system in a stereocontrolled manner. These heterocycles can be manipulated to afford kainic acid derivatives. Although the method is rather cumbersome and some synthetic steps suffer from low yields, it represents a valuable alternative to other routes to kainoids. The synthetic utility of the anionic cyclization of *N*-benzylbenzamides was extended by modifying the method to obtain aromatized products. Oxidation with dry air of the dearomatized lithiated intermediate formed upon cyclization and subsequent reaction with methanesulfonyl chloride in the presence of triethylamine provided 2,3-dihydroisoindolones **893** in moderate to good yield (Scheme 118).[467] By performing the deprotonation with a chiral base such as **306** or using chiral amide **283g** as starting material, it was possible to obtain enantiomerically enriched heterocycles **893a** and **895**, respectively. Tri- and tetrasubstituted amides **243x**−**aa** bearing an *o*-methoxy substituent furnished dihydroisoindolones **893b**,**e**−**g** via substitution of the OMe group simply by treatment with LDA. N Deprotection was smoothly achieved by heating the heterocycles with trifluoroacetic acid as exemplified by the conversion of **893a**,**b** into the corresponding de-*tert*-butylated derivatives **894**.

The dearomatizing cyclization reaction of lithiated *N*-benzylbenzamides developed by Clayden and co-workers has also been applied to the synthesis of kainic acid **877**, the parent member of the kainoid family of amino acids. Successive cyclization−protonation−acid hydrolysis of amide **243g** afforded bicyclic ketoamide **252c** (see Scheme 45), which was converted into racemic **877** by a sequence of reactions. The most significant transformations of this

**Scheme 117**

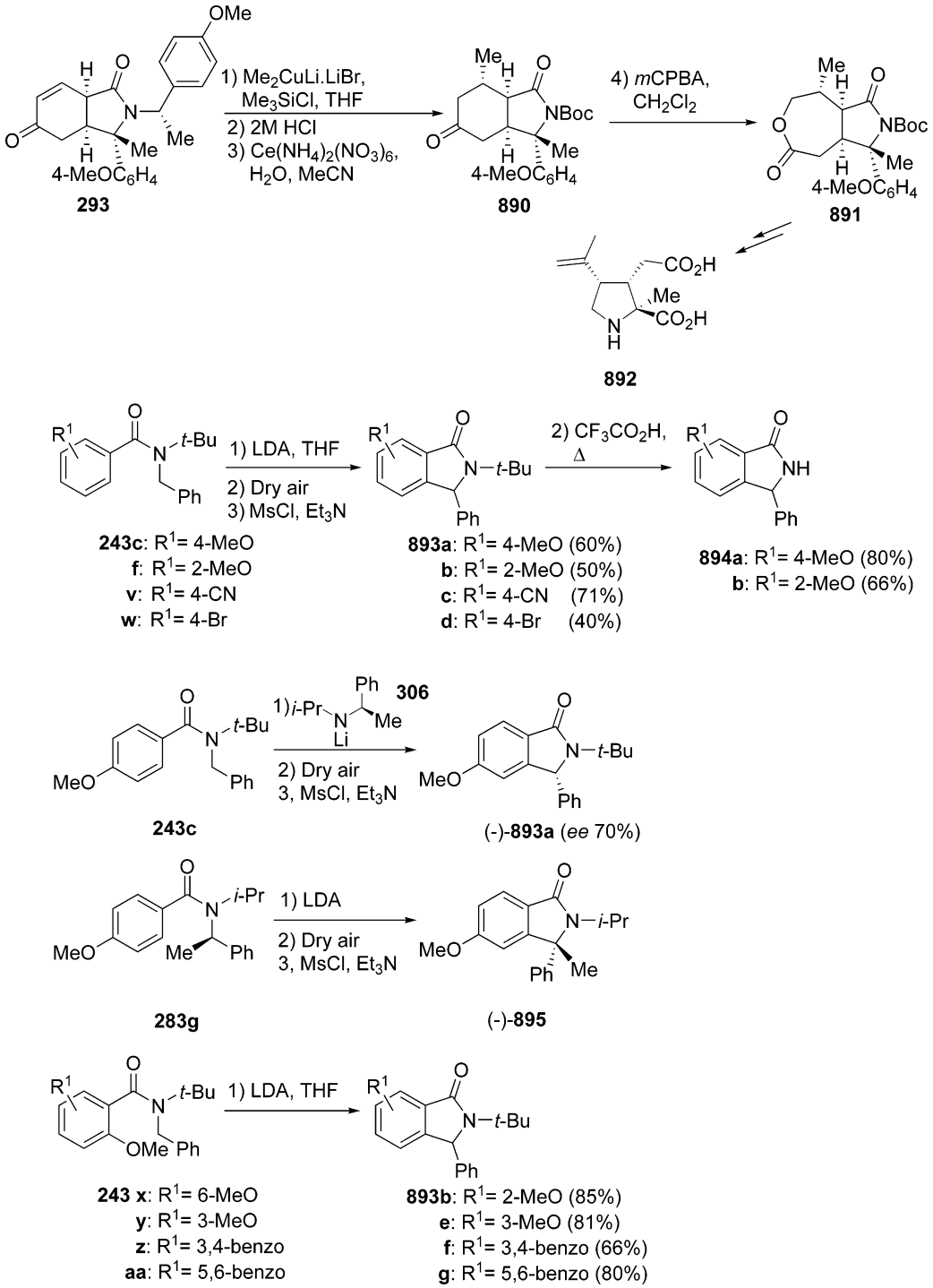



synthesis include methylation via conjugate addition, Boc protection of the nitrogen atom, Ru-catalyzed oxidation of the *m*-methoxyphenyl ring, Baeyer−Villiger oxidation of the ketone, ring opening of the resulting lactone followed by dehydration to provide the isopropenyl substituent at C4, and reduction of the CO group of the amide moiety carbonyl.[466,468] The asymmetric version of the process was accomplished by enantioselective deprotonation of **246w** with the chiral base **306** (Scheme 119).[166,469]

## 19.2. Synthetic Applications of the Dearomatization of Naphthyloxazolines

The conjugate addition of nucleophiles to oxazoline-substituted naphthalenes represents the most successful methodology that makes use of $D_NAr$ reactions for the preparation of complex molecules. Developed by Meyers and co-workers, the efficiency of this strategy has been amply demonstrated in the arena of natural products chemistry through the construction of structural fragments of some

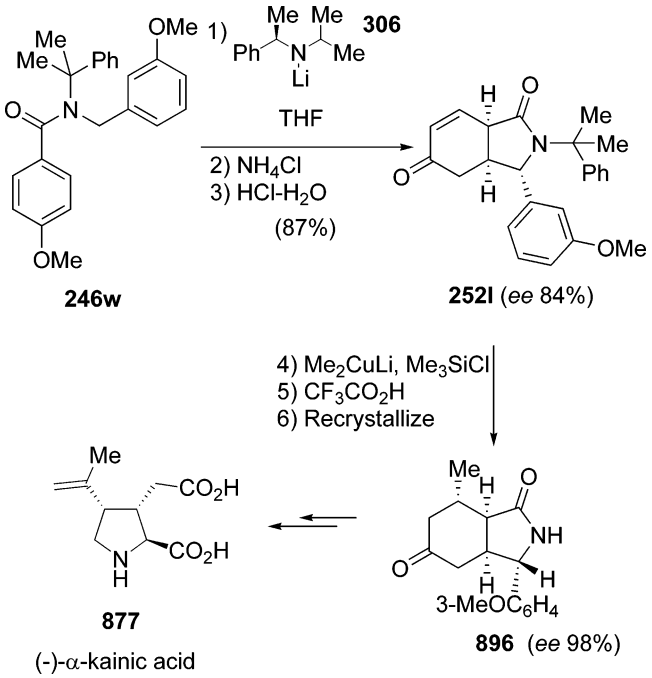
**Scheme 118**




natural products or analogues, as well as the total synthesis of a variety of natural products. The achievements made by using this synthetic tool are summarized in Chart 1. The syntheses accomplished include an analogue of the bottom half of the antibiotic (−)-chlorothricolide **898**,[470] the AB ring of aklavinone **899**,[471] the tetracyclic ring system present in aphidicolin **900**, scopadulcic acid B **901**, or kaurene **902**,[472] the total synthesis of the sesquiterpene lacinilene C7 methyl ether **903**,[198] the lignan lactones (+)-phyltetralin **904**,[195] (−)-podophyllotoxin **905**,[473] (−)-isopicropodophyllone **906**,[474] (−)-epipodophyllotoxin **907**,[475] and the key intermediates in the route to the narcotic (−)-aphanorphine **908** and the analgesic (−)-eptazocine **909**.[476] The literature covering this material has been partially reviewed.[14c] The major drawback of this methodology is the limitation to condensed aromatic hydrocarbons. In the phenyl series, the reactivity observed corresponds exclusively to aromatic substitution processes.[477−480]

Common to all target molecules shown in Chart 1 is the realization of a tandem nucleophilic addition−electrophilic quench on a suitably substituted naphthyl oxazoline at the beginning of the synthetic route (see section 12). Except for the case of a proton, the electrophile enters invariably trans to the organolithium reagent. In this way, two adjacent stereogenic centers are formed, generally with very high selectivity. When the electrophile is an alkylating or acylating agent, one center is a quaternary carbon, well-known to be more challenging to generate than a tertiary carbon one. The

**Scheme 119**




approach to the octahydronaphthalene system of (−)-chlorothricolide **898** involved the enantioselective addition of 4-pentenyl-lithium to naphthyl oxazoline **387c** followed by trapping with MeI to give dihydronaphthalene **910** (Scheme 120). Further elaboration produced **911**, an analogue of the octahydronaphthalene moiety present in **898**. The [1,6] regioselective addition of lithium allyltrimethylsilane to naphthyl oxazolines (Scheme 62) was applied to the synthesis of **912**, the crucial intermediate in the route to lacinilene C7 methyl ether **903**. Naphthalenone **912** was prepared by singlet oxidation of the [1,6] adduct formed from the reaction of naphthyl oxazoline **377** with lithium allyltrimethylsilane and subsequent quench with methyl iodide. Naphthalenone **912** and some of its derivatives showed anti-HIV-1 activity.[481]

Central to the synthesis of the chiral tetrahydronaphthalene moiety of the anthracyclinone aklavinone **899** was the asymmetric addition of vinyl-lithium to oxazoline *ent*-**387c**. Protonation of the adduct with trifluoroacetic acid followed by reduction with $LiAlH_4$ afforded the alcohol **913**. The latter is a precursor of the AB-ring substructure **914** of aklavinone (Scheme 120). The same strategy was used for the construction of the tetracyclic system present in various diterpenes. Addition of vinyl-lithium to naphthyl oxazoline **387a** followed by reaction with 2-methyl-2-(2-iodoethyl)-1,3-dioxolane furnished dihydronaphthalene **915**, which was further manipulated to provide compounds **917** and **918** showing the skeleton of aphidicolin **900** and scopadulcic acid B **901**, respectively. Similarly, oxazoline **388a** led, after elimination of the chiral auxiliary and acidic deprotection, to the keto aldehyde **919**. Once the requisite stereochemistry and functionalization into the naphthyl system had been introduced, the molecule was further transformed into ester **920**, which exhibits the tetracyclic ring system present in diterpenes of the kaurane family such as kaurene **902**.

The scope of Meyers's dearomatizing method was expanded by employing silyl reagents as nucleophiles. Dimethylphenylsilyl-lithium underwent reaction with oxazoline **387i** to give, after trapping with MeI, the trans addition product **921** as the major stereoisomer (dr > 20:1). Dihydronaphthalene **921** was converted in a straightforward manner into the alcohol **923** and the homologous aldehyde **926**. Products **923** and **926** are known precursors for alkaloids (−)-aphanorphine **908** and (−)-eptazocine **909** (Scheme 121). Formally, the use of the silylating agent is equivalent to the addition of lithium hydride to **387i**, providing the requisite high degree of stereocontrol for the quaternary center. In addition, dearomatized naphthyl oxazolines incorporating a silyl group **928** were modified to give fused tricyclic systems such as **929** and **930** in which the silicon served as surrogate for oxygen and nitrogen, respectively.[482] It must be stressed that oxygen nucleophiles do not undergo addition to naphthyl oxazolines owing to insufficient nucleophilicity.

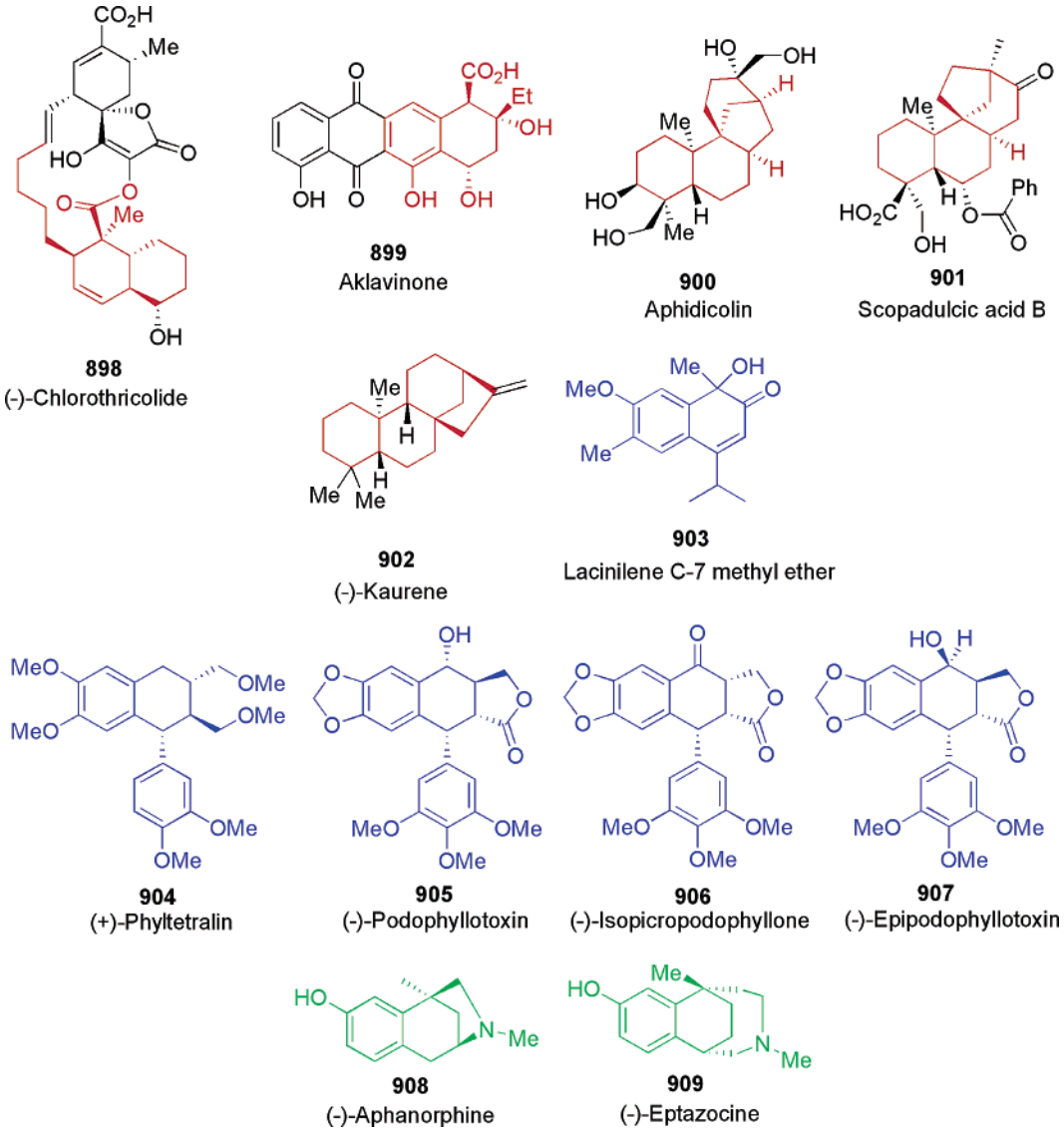
The real dimension of Meyers's methodology can be best appreciated in the elegant asymmetric total synthesis of the aryl lignans (+)-phyltetralin **904** and (−)-podophyllotoxin **905**. The crucial step in the sequence of reactions leading to these products was the preparation of the corresponding dihydronaphthalene derivatives **932** and **934**. These products were smoothly obtained in a highly diastereoselective manner by treating chiral oxazolines **931** and **933** with 3,4-dimethoxyphenyl-lithium and 3,4,5-trimethoxyphenyl-lithium (TMPHLi), respectively, followed by quenching with 2-propanol (Scheme 122). The transformation of **932** into (+)-phyltetralin **904** was achieved by removal of the oxazoline moiety, reduction of the resulting carbaldehyde group to alcohol, hydrogenation of the carbon−carbon double bond, and methylation of the alcohol previously formed. The route to (−)-podophyllotoxin **905** continued with a sequence of reactions starting with the conversion of **934** into lactone **935**. Overall, the processes constituted the first enantioselective synthesis of **905**. Fifteen years later, Sherburn and co-workers utilized a modification of Meyers's methodology for synthesizing (−)-isopicropodophyllone **906**, a natural product that can be converted into podophyllotoxin.[474] They treated the 2-naphthyl oxazoline **936** with dimethylphenylsilyl-lithium, and the azaenolate formed was acylated with allyl chloroformate, yielding ester **937** as a single diastereomer. From this point the sequence of transformations leading to **906** is markedly different from Meyers's synthesis of podophyllotoxin. A pivotal intermediate in the process was the thionocarbonate **938** (Scheme 122).

A final example of this chemistry has been provided by Linker and co-workers.[475] They reported the synthesis of (−)-epipodophyllotoxin **907** in a process starting with the addition of TMPHLi to oxazoline **939**. Quenching the reaction mixture with methanesulfonic acid in methanol instead of the 2-propanol used in Meyers's protocol afforded directly the ester **940** in a yield of 64% and ee 96%. Epoxidation of the carbon−carbon double bond of **940** followed by deprotonation gave the hydroxyl ester **941**, together with the epimer at the hydroxylic carbon (dr of 9.9:1). The latter was transformed into the natural product (−)-epipodophyllotoxin **907** in four additional steps.

## *20. Summary and Outlook*

As shown in this review, a number of methods enable the use of aromatic rings, either unsubstituted or functionalized with a large variety of electron-withdrawing groups, as a particular type of Michael acceptor for $\alpha,\beta$ and/or $\beta,\gamma$-conjugate addition reactions with a wide range of nucleophiles. The competing reaction of nucleophilic addition to the activating group is generally inhibited by steric effects. The employment of coordinating solvents to enhance the

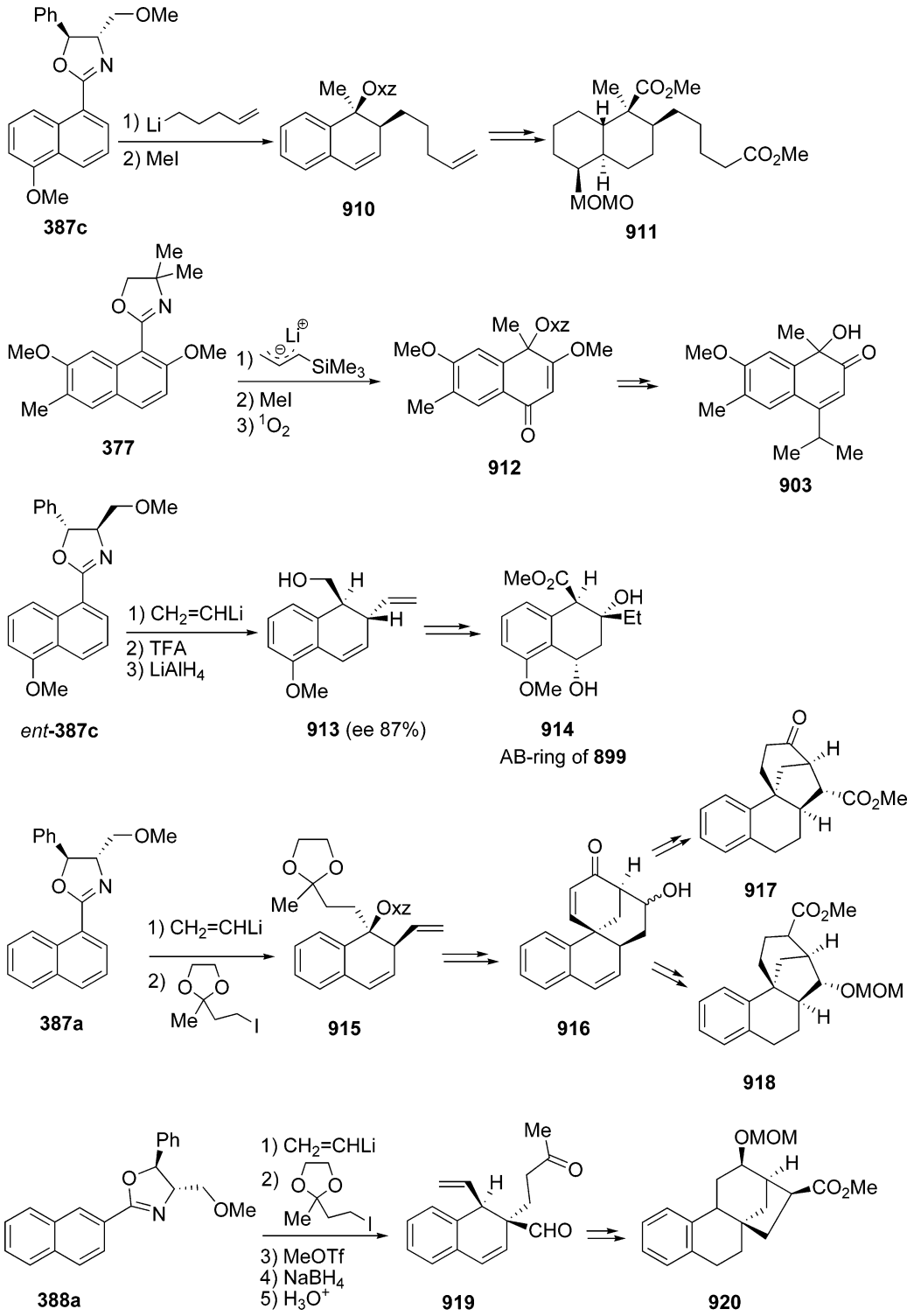
**Chart 1. Applications of $D_NAr$ Reactions of Naphthyloxazolines to the Chemistry of Natural Products**[a]




[a] The structural accessibility by this methodology is indicated by a color key. Red: partial structures or analogue systems have been prepared. Blue: total synthesis has been performed. Green: formal total synthesis via a key intermediate.

reactivity of the anions represents also a common element of controlling the reaction pathway. It is apparent that, in a number of cases, the applicability of the method has been limited to show the feasibility of the dearomatizing process through the reaction with a reduced group of simple organometallic reagents. However, it is also evident that very efficient methods are available for the inter- and intramolecular dearomatization of aryl systems via nucleophilic addition. Electrophilic quench leads to functionalized cyclohexadiene and dihydronaphthalene systems with a predictable high regio- and stereochemical outcome. The transfer of functionality to the parent aromatic ring takes place in one synthetic operation. Either the nucleophile that attacks the aromatic substrate or the electrophile used for trapping the dearomatized species can act as a source of functionality. The use of the dearomatized systems thus obtained as intermediates for the synthesis of natural products and nonnatural analogues has been demonstrated. This approach is a valuable alternative to more established dearomatization chemistry. Significant advances in this area have been made in the past decade. On the horizon, the new technologies applied to drug discovery programs may benefit from innovative synthetic methods making use of dearomatizing reactions. $D_NAr$-based methodologies may provide building blocks tailored to prepare small molecules containing specific functionalizations and stereochemistry in a cyclic skeleton. A key feature of $D_NAr$ reactions is the installation of carbon−carbon and carbon−heteroatom bonds on readily available carbocyclic starting materials in a regio- and stereoselective manner. Structural diversity associated with the substitution pattern of the aromatic system might be introduced via well-known strategies (e.g., $S_EAr$, $S_NAr$, directed ortho metalation or cross-coupling reactions). Atom efficiency is an issue that may require improvement. On many occasions, the preparation of the nucleophile consumes at least a stoichiometric amount of an alkyl-lithium reagent. The development of catalysts capable of promoting $D_NAr$ reactions would be an important contribution to extend the applicability of this chemistry in organic synthesis. The first steps in this direction have been already reported.[89] Detailed mechanistic studies will also be welcome as a means of understanding the large number of experimental results accumulated and predicting new ways for the disruption of aromaticity.

**Scheme 120**



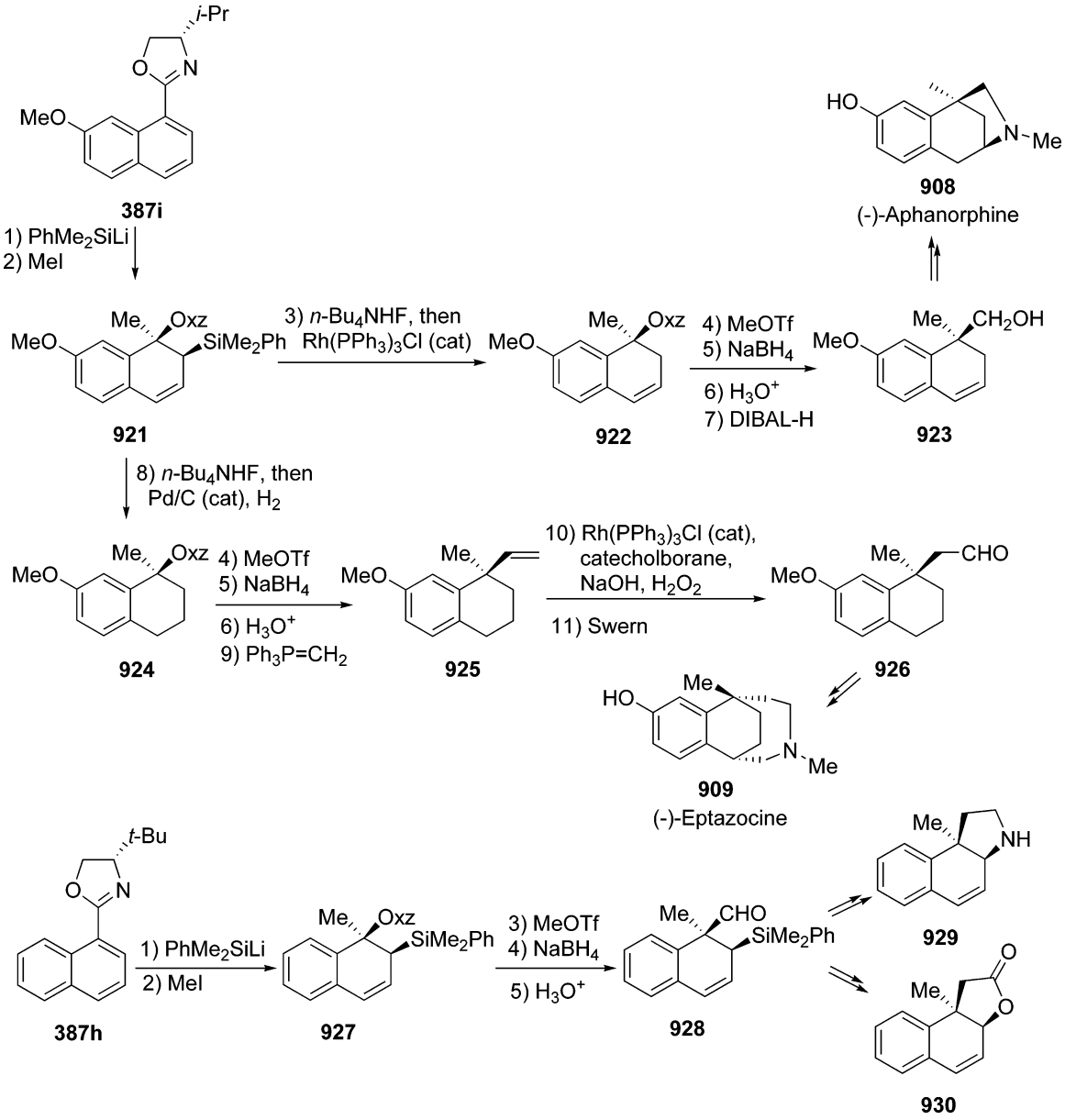

To conclude, the history of $D_NAr$ processes dates back more than a century. Although early findings in this area passed unnoticed, the investigation of $D_NAr$ reactions continued over the years without decreasing interest. The pathway taken so far has provided numerous achievements and constitutes a firm body of knowledge for further discoveries and applications.

## *21. Note Added in Proof*

During the review and revision of the manuscript new contributions to $D_NAr$ reactions appeared in the literature. This section describes briefly the work published from January 2005 to September 2006.

Atroshchenko's group has continued investigating the chemistry of Janovsky $\sigma$-complexes. They have prepared new examples of polyfunctional derivatives of 3-ABN **557b**−**j**[483] (Scheme 123) by applying to 2,4-dinitrophenol **447g** the same procedure previously described by Severin and Temme[289] for the synthesis of **557a** ($R^1 = R^2 =$ Me, see section 14.1.3, Scheme 80). Quenching the reaction with orthophosphoric acid in place of acetic acid affords a slight increase of the yield of **557a**. When the same sequence of reactions is carried

**Scheme 121**

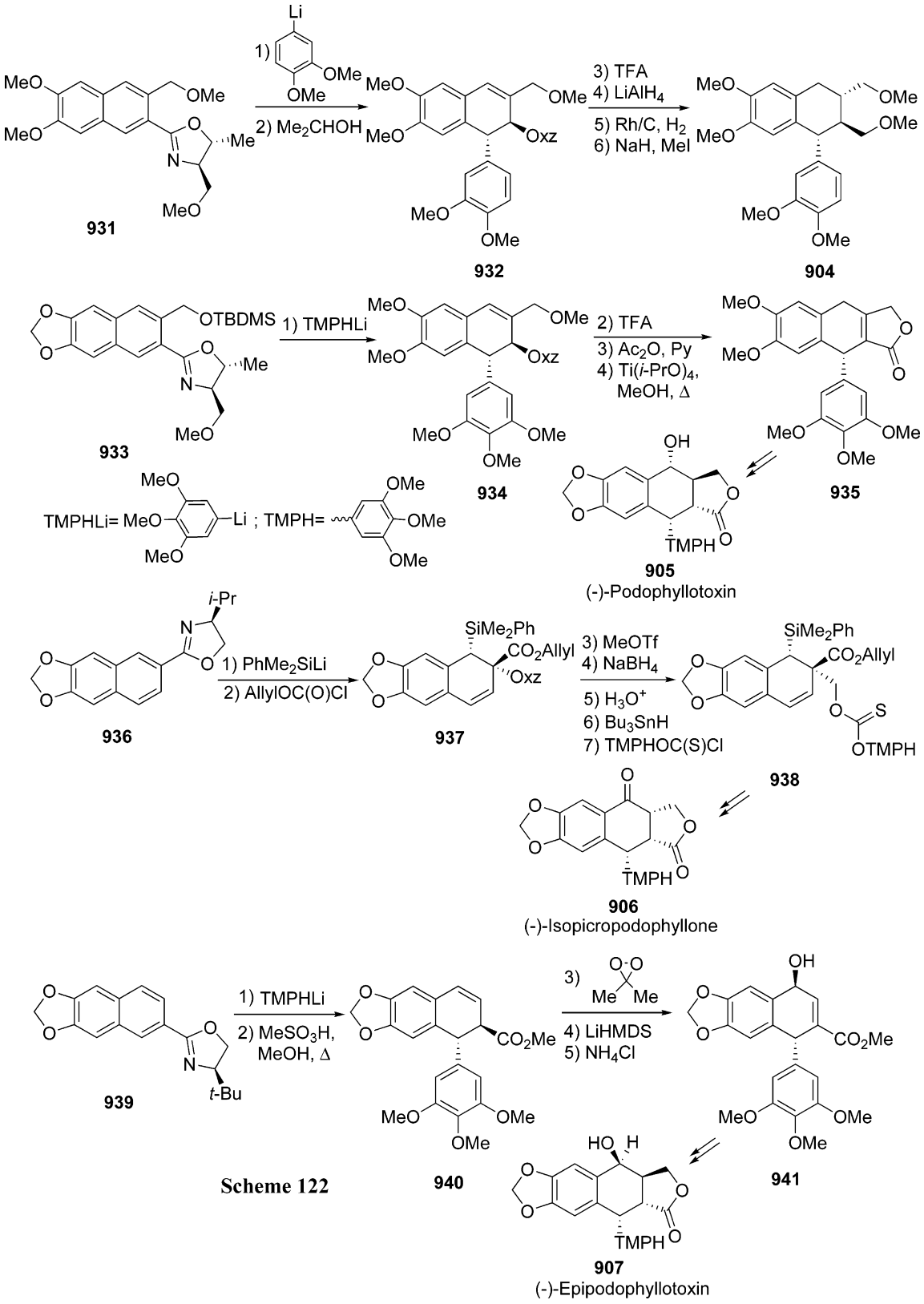



out on 5,7-dinitro-8-hydroxyquinoline **943**, the expected 3-ABN derivatives **945**, which are analogues of **561** (see Schemes 80 and 113) are obtained in moderate yield.[484] A more interesting result is the dearomatization of 1-(2-hydroxyethoxy)-2,4-dinitrobenzene **946** through reduction with sodium borohydride (Scheme 123). The trianion **947** thus generated contains a side arm that may participate in a spirocyclization reaction via ipso attack (see Scheme 88). The Mannich condensation of **947** with formaldehyde and methylamine affords a mixture of the common product **948** and the spiro isomer **949**. It must be remembered that the treatment of the spiro Meisenheimer complex **642** (see Scheme 89) derived from **946** with $MeOSO_2F$ leads solely to the product of methylation at the terminal oxygen atom **643**.[485]

Clayden and co-workers, who developed the dearomatization of arylamides through anionic cyclization into an efficient methodology (see section 19) for organic synthesis, have provided an impressive example of its applicability with the first total synthesis of (−)-isodomoic acid C **950** (Scheme 123).[486] The isodomoic acid C is a member of the family of kainoid amino acids that was synthesized using a strategy similar to that employed in the preparation of (−)-kainic acid (see Schemes 117 and 119). The key step of the process is the asymmetric anionic cyclization of *N*-benzyl benzamide **243g**. The acidic quench of the resulting dearomatized anion gives enone **252c**, which is isolated enantiomerically pure through recrystallization from ethyl acetate. The transformation of the substituents bonded to the pyrrolidone ring of **252c** into those present in isodomoic acid C is based on the ruthenium(VIII) oxidation of the phenyl ring adjacent to the nitrogen and the Baeyer−Villiger oxidation of the ketone group of **252c**. The partial skeleton of **252c** retained by isodomoic acid C is indicated in red in Scheme 123.

A detailed theoretical study of the dearomatizing anionic cyclization of phosphinamides at the Becke3LYP/6-31+G* level of theory appeared in the first quarter of 2005.[487] The investigations on model reactions of *N*-benzylphosphinamides predict a potential-energy surface that reproduces remarkably well the sequence of steps identified in a previous NMR study:[380] (i) formation of a prereactive complex between the substrate and the base, (ii) evolution to give $N-C_\alpha$ and $C_{ortho}$ anions, and (iii) cyclization of the $N-C_\alpha$ anion to yield dearomatized products. The calculations show

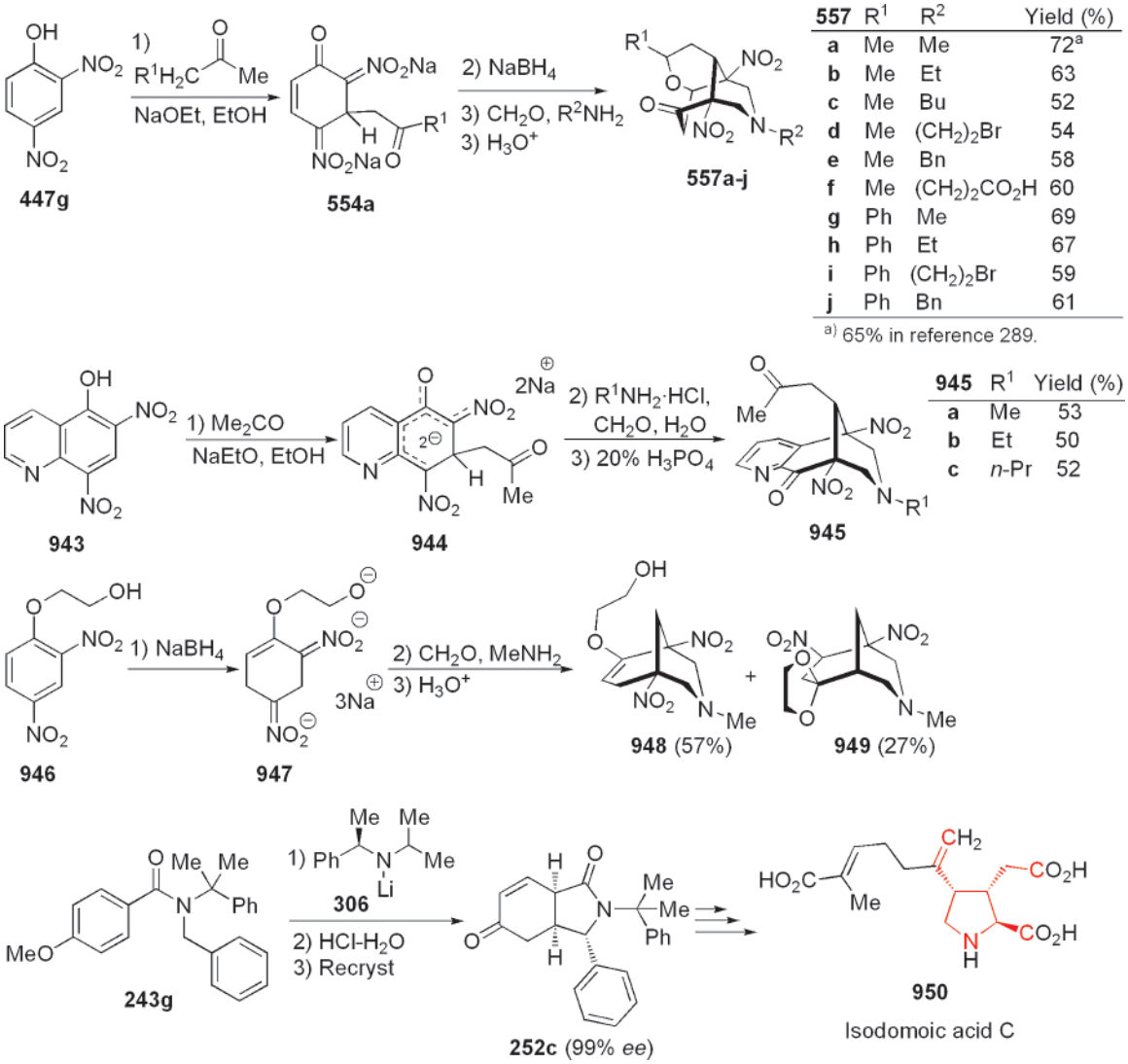
**Scheme 122**




**Scheme 122**

that N−$C_\alpha$ lithiation is thermodynamically preferred with respect to the lithiation at the ortho position, that the translocation from $C_{ortho}$ to N−$C_\alpha$ anions is feasible only under the action of coordinating solvents (HMPA or DMPU), that the cyclization takes place through a conjugate addition of the anion to the ortho position of a *P*-phenyl ring, and that the stereochemical course of the process is subjected to thermodynamic control. The anionic cyclization of *N*-allyl phosphinamides was also modeled. The calculations predict that the cyclization through the $\gamma$-carbon of the allylic system is favored with respect to the α-attack, leading to the formation of seven-membered rings. These predictions were experimentally confirmed. Thus, the dearomatization of the *N*-allyl phosphinamide **951** and subsequent protonation with

**Scheme 123**




| 557 | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|
| a | Me | Me | 72[a] |
| b | Me | Et | 63 |
| c | Me | Bu | 52 |
| d | Me | $(CH_2)_2Br$ | 54 |
| e | Me | Bn | 58 |
| f | Me | $(CH_2)_2CO_2H$ | 60 |
| g | Ph | Me | 69 |
| h | Ph | Et | 67 |
| i | Ph | $(CH_2)_2Br$ | 59 |
| j | Ph | Bn | 61 |

[a] 65% in reference 289.

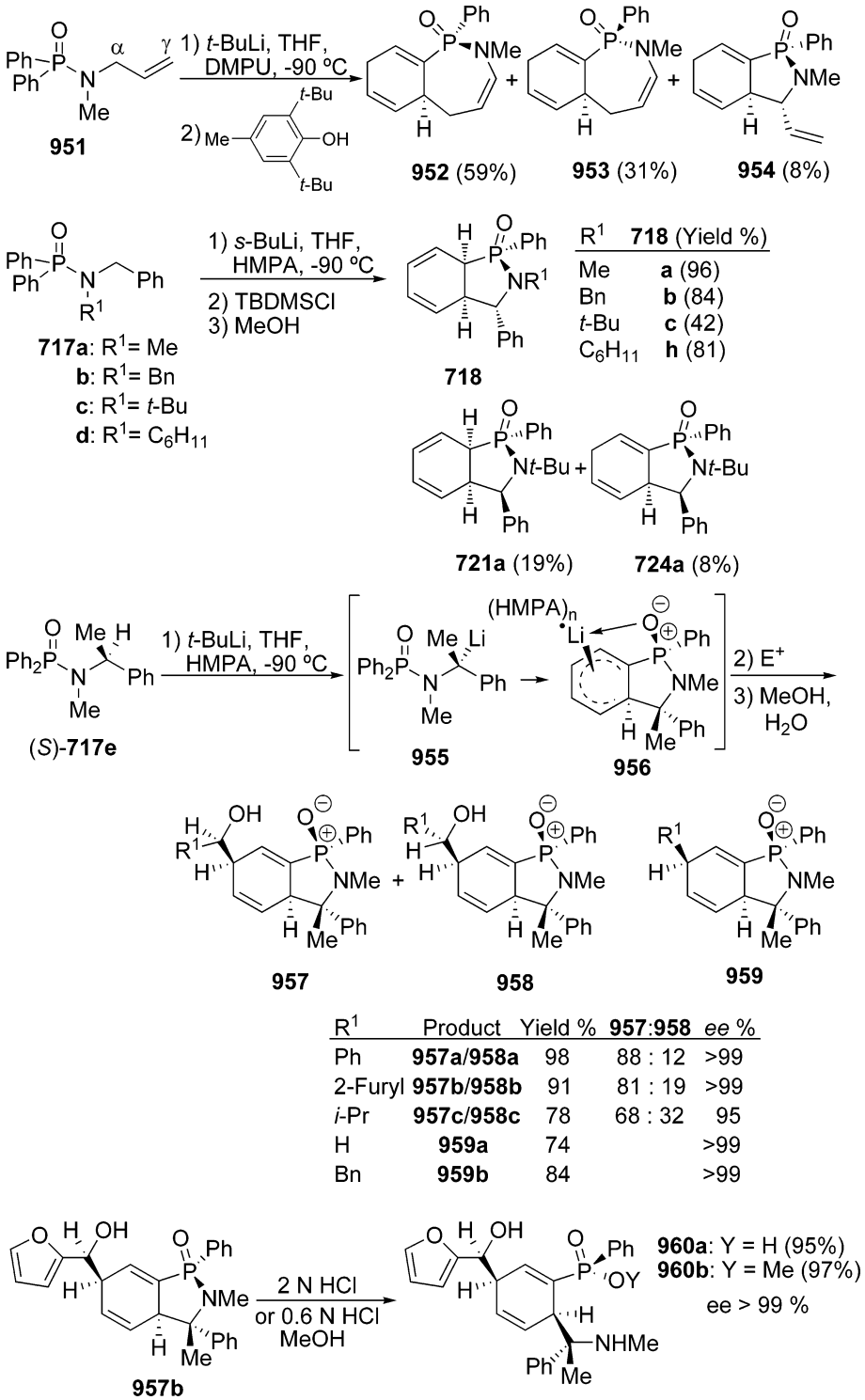
| 945 | $R^1$ | Yield (%) |
|---|---|---|
| a | Me | 53 |
| b | Et | 50 |
| c | *n*-Pr | 52 |

DTBMP affords a mixture of **952**:**953**:**954** in a ratio of 60:32:8 (Scheme 124), in good agreement with the results from the theoretical calculations.

In section 15.3.3 it was pointed out that treating the dearomatized anions arising from the anionic cyclization of phosphinamides **717** with methanol leads to products of α protonation **718** containing a [1,3]-cyclohexadienic system in moderate to good yield (see Scheme 98 and Table 44). With the aim of improving the selective formation of **718**, López-Ortiz and co-workers investigated the effect on the process of a wide range of proton sources (ethyleneglycol, ammonium chloride, aliphatic and aromatic amines, aliphatic amides, sulfonic and carboxylic acids).[488] A high α/γ protonation ratio (91:9, yield of 81%) is obtained only when the anionic cyclization reaction of phosphinamide **717a** is quenched with acetamide. For phosphinamides **717b**−**d** (Scheme 124) the ratios of α/γ products range from 71:29 to 40:60. Remarkably, the addition of *tert*-butyldimethylsilyl chloride (TBDMSCl) to the reaction mixture prior to the protonation with methanol inhibits nearly completely the formation of γ-protonated compounds (Scheme 124). The exception is phosphinamide **717c**. The presence of the bulky *tert*-butyl substituents at the nitrogen atom produces a decrease of the reaction yield and favors the appearance of byproducts **721a** (19%) and **724a** (8%). The same researchers described the first dearomatizing anionic cyclization of an enantiomerically pure phosphinamide (*S*)-**717e** (Scheme 124).[489] The dearomatized species **956** undergoes reaction with aliphatic and aromatic aldehydes, benzyl bromide, and the bulky phenol DTBMP to give tetrahydrobenzophospholes **957**, **958**, and **959** containing a [1,4]-cyclohexadiene system in high yield and with excellent diastereo- and enantioselectivities. The reaction proceeds through a chiral *N*-benzylic carbanion **955**, which is configurationally stable on the time scale of the cyclization, an unprecedented feature in the chemistry of *N*-benzylic anions dipolarly stabilized by a phosphorus-containing group. It is worth mentioning that a single chiral center controls very efficiently the configuration of up to four new stereogenic centers, one of them five bonds away from the source of chirality. Solvolysis of the P−N bond of **957b** readily affords enantiomerically pure the γ-*N*-methylamino phosphinic acid **960a** and the ester **960b** almost quantitatively. The products of dearomatization of *N*-benzyl diphenyl- and dinaphthyl-phosphinamides as well as the amino acids and esters generated in their solvolysis showed interesting antitumor activity.[490,491]

The nucleophilic dearomatization of cationic benzylic systems discussed in section 3.3 was extended by Dyker and co-workers to provide a method of accessing to *p*-quinodimethanes based on the addition of *C*- and *N*-nucleophiles

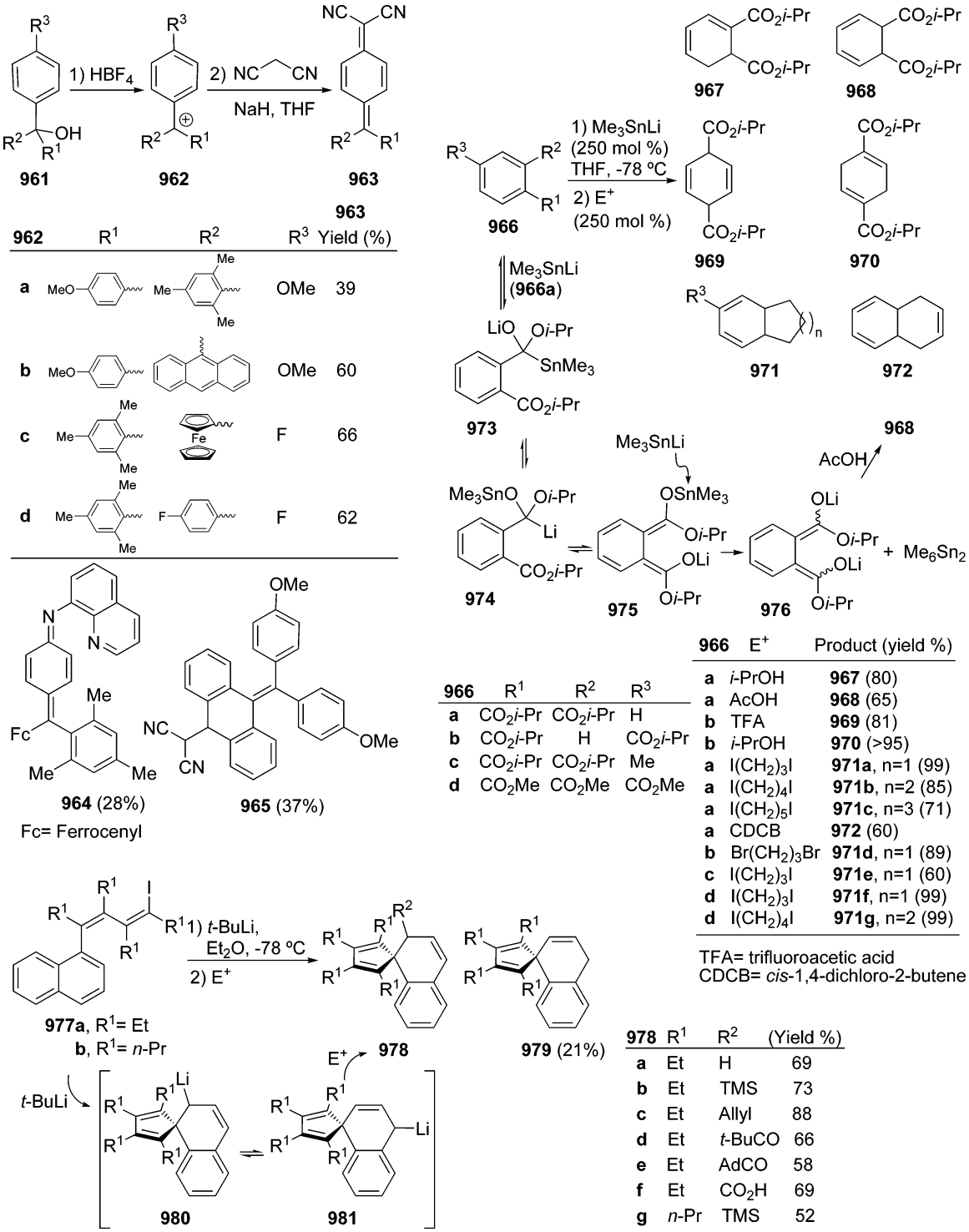
**Scheme 124**




to triarylmethyl cations. The reaction of **962** with the sodium salts of malononitrile and 8-aminoquinoline leads to the functionalized *p*-quinodimethanes **963** and **964**, respectively, in moderate to good yields (Scheme 125).[492] The formation of **963** and **964** takes place through the regioselective attack of the nucleophile at the ipso carbon of **962** bearing the $R^3$ substituent, followed by $HR^3$ ($R^3$ = F, MeO) elimination. The bulky aryl substituents $R^1$ and $R^2$ bonded to the cationic center prevent the approach of the nucleophile to this position. When $R^2$ is a 9-anthryl system, the byproduct **965** arising from addition of the nucleophile to the anthracene ring is also obtained (see section 3.3).

Sardina et al. have reported a novel $D_NAr$ alkylation process consisting of the reaction of trimethylstannyl-lithium with aromatic diesters **966** and subsequent trapping with a series of electrophiles (Scheme 125) to give compounds **967**−**972**.[493] In this case, the mechanism proposed for explaining the formation of the dearomatized products begins with the attack of the nucleophile at one of the carbonyl groups of **966**. The resulting intermediate **973** undergoes a Sn−Brook rearrangement leading to carbanion **974**, which is in equilibrium with the enolate **975**. The reaction of the latter with a second equivalent of $Me_3SnLi$ furnishes the dianion **976**. This bis-enolate **976** could be characterized

**Scheme 125**




through NMR and represents the species that is finally trapped with mono- and bis-electrophiles to yield the products **967**−**972**.

Wang and Xi found that the lithiation of the 1-iodo-4-naphthyl-1,3-butadiene derivatives **977** and subsequent treatment with a variety of electrophiles afford the spiro compounds **978** almost exclusively (Scheme 125). Only in the case of the aqueous quench is a mixture of the isomers **978a** and **979** obtained in a ratio of 77:23.[494] The isolation of products **978** and **979** indicates that the reaction proceeds through the intermediates **980** and **981** arising from ipso attack of the expected anion generated upon iodine−lithium exchange.

## 22. Abbreviations

ABN, azabicyclo[3.3.1]nonanes; ATPH, aluminum tris(2,6-diphenylphenoxide); Ar, any aromatic structural fragment; BHA, 2,6-di-*tert*-butyl-4-methoxyphenol; Boc, *tert*-butyloxycarbonyl; CHT, cycloheptatriene; CIP, contact ion pair; COD, cyclooctadienyl; *m*CPBA, 3-chloroperbenzoic acid; *m*DCNB, 1,3-dicyanobenzene; *p*DCNB, 1,4-dicyanobenzene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DHA, dihydroanthracene; DIBAL-H, di-*iso*-butylaluminum hydride; DME, dimethoxyethane; DMPU, 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one; $D_NAr$, nucleophilic dearomatization; *p*DNB, 1,4-dinitrobenzene; DTBMP, 2,6-di-*tert*-

butyl-4-methylphenol; ESR, electron spin resonance; HMPA, hexamethylphosphoramide; LAH, lithium aluminum hydride; LiDBB, lithium 4,4′-di-*tert*-butylbiphenyl; *p*MB, 4-methoxybenzyl; MoOPD, $MoO_5$·py·DMPU; NBS, *N*-bromosuccinimide; NOE, nuclear Overhauser effect; PMDETA, *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine; SET, single electron transfer; SIP, separated ion pair; SM, starting material; TASF, tris(dimethylamino)sulfonium difluorotrimethylsiliconate; TBAF, tetrabutylammonium fluoride; THF, tetrahydrofuran; THP, tetrahydropyran; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMOPD, *N*,*N*,*N*′,*N*′-tetramethyl-*o*-phenylenediamine; TMP, 2,2,6,6-tetramethylpiperidinyl; TMPH, 3,4,5-trimethoxyphenyl; TMPHLi, 3,4,5-trimethoxyphenyllithium; TNB, *sym*-trinitrobenzene; UV, ultraviolet.

## 23. Acknowledgment

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