Electrophilic Amination of Carbanions

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Contents

I. Introduction

The development of the electrophilic amination reaction has made it possible to transfer amino or substituted amino groups from various aminating agents into all kinds of nucleophiles (eq 1). The most interesting structural feature of electrophilic aminating agents of the type $R^1R^2N{-}Z$ is the attachment of a good leaving group Z to the NR^1R^2 group. The leaving group Z is displaced by a nucleophile during the amination process. Electrophilic reagents of the above type usually contain halogens or oxygen functions as the leaving group and have been the subject of considerable interest since they are able to react not only with nucleophiles but also with electrophiles such as ketones, Schiff bases, alkylating agents, and acylating agents to produce aminated products (eq 2). Reagents of this type have been used extensively for the amination of N, S, and P nucleophiles such as amines, sulfides, and phosphines.

$$Nu^- + R^1R^2N{-}Z \rightarrow Nu{-}NR^1R^2 + Z^- \qquad (1)$$

$$R^1, R^2 = \text{alkyl, H}$$

$$NuNH_2 \xleftarrow[-Z]{Nu^-} H_2N{-}Z \xrightarrow[-H^+]{E^+} E{-}HN{-}Z \qquad (2)$$

Although the electrophilic amination of carbanions, i.e., the conversion of organometallic compounds to amines (aminodemetalation, eq 3) has been known for a long time,[1] only isolated reports of preparations of amines from organometallic compounds have been published.

$$RM + H_2N{-}Z \rightarrow RNH_2 + MZ \qquad (3)$$

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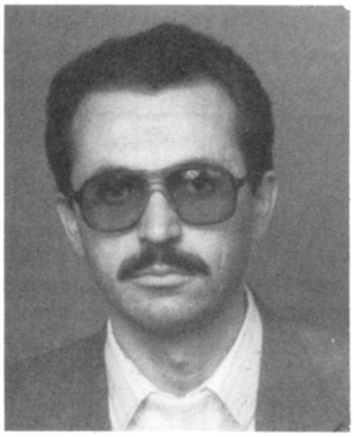

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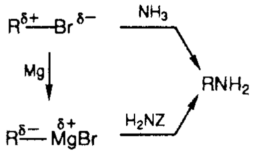
The introduction of an amino group into organometallic compounds constitutes an example for the "umpolung" methodology for the direct formation of C–N bonds and is gaining significance as a consequence of the rapidly increasing accessibility of diverse organometallic reagents. Thus, alternative approaches to amination that involve inversion of polarity are the reactions of an electrophilic alkyl halide with ammonia or amines and the conversion of the halide into a nucleophilic species, namely the corresponding Grignard or organolithium reagent, and its subsequent reaction with the H_2N-Z derivative (eq 4). The species R–Br



(4)

and R–MgBr may be considered as suppliers of $[R^{\delta+}]$ and $[R^{\delta-}]$, respectively, whereas NH_3 and H_2N-Z are $[^{\delta-}NH_2]$ and $[^{\delta+}NH_2]$ synthons, respectively. Methods of reactivity umpolung[2] and developments in the use of electrophilic reagents[3] have been the subjects of comprehensive reviews.

The increasing application of direct metalation methods[4-8] and the importance of primary amines, both as synthetic intermediates and as entries into nitrogen-containing heterocyclic systems, have created a need for electrophilic aminating reagents capable of direct combination with organometallic reagents in reactions requiring only subsequent hydrolytic workup. This interest in the direct amination of organometallic reagents is reflected in the continuing development of a variety of electrophilic aminating reagents as well as the several improvements that have been made to overcome the drawbacks associated with the syntheses of amines from Grignard and organolithium reagents. However, the electrophilic amination of organometallic reagents has not yet been the subject of a review, with the exception of two lists of key references that have appeared.[9,10] Detailed reviews on the chemistry of electrophilic aminating agents[11-19] have also briefly mentioned the amination of carbanions and included N, S, and P nucleophiles.

In continuation of our long-term interest in electrophilic amination methods for Grignard and organolithium reagents, we now survey electrophilic aminating agents for carbanions with the major emphasis being placed on the scope and limitations of synthetic methods for amines and, when possible, mechanistic aspects (literature coverage through 1988). In the discussion of the reagents **1–12**, methods for their preparations are not included but key references are cited.

H_2NX **1** H_2NOR **2** H_2NOSO_2OH **3** H_2NOAr **4** $H_2NOCOAr$ **5**

H_2NOSO_2Ar **6** $H_2NOP(O)Ar_2$ **7** RN_3 **8** $R_2C{=}NOR$ **9**

ArN_2X **10** $ROOCN{=}NCOOR$ **11** $ArNH_2, RNH_2$ **12**

N-Haloamines (**1**), *O*-alkyl-, (**2**), *O*-aryl- (**4**), *O*-acyl- (**5**), *O*-sulfonyl- (**6**), and *O*-phosphinylhydroxylamines (**7**), and hydroxylamine-*O*-sulfonic acid (**3**) are able to react with C nucleophiles directly; i.e., the reactions require nothing more than hydrolytic workup. Deprotonation of the amino group will occur competitively while electrophilic attack of the H_2N^+ group on the carbanion will be influenced by the leaving group ability of Z. Reagents **8–11** can also function as amino cation equivalents. Azides (**8**) react with Grignard and organolithium reagents to form triazene salts which are converted to the respective amines by either reductive or hydrolytic workup. Oximes (**9**) react with Grignard and organolithium reagents to produce imines which are hydrolyzed to amines. Reactions of enolates with arenediazonium salts (**10**) or dialkyl azodicarboxylates (**11**) furnish α-hydrazono or α-hydrazido compounds, respectively, which are hydrogenated to α-amino compounds. Aromatic and aliphatic amines (**12**) are N-alkylated or N-phenylated by lithium dialkyl- or diphenylcuprates; N-phenylation also occurs with tri- and pentavalent phenylbismuth compounds or tetravalent phenyllead compounds under metallic copper or copper(II) ion catalysis.

TABLE 1. Amination of Carbanions with *N*-Haloamines (1a–g)

N-haloamine	RM	scheme	ref
1a	R(Ar)MgCl	1	20, 21
	R(Ar)Li	7, eq 6	30, 31
	RCHLiCOOLi	eq 7	32, 33
	$RCNa(COOR)_2$	8	35
	R_2Zn	9	30
1b	RMgCl	2	24
1c	RMgCl	3	25
1d	RMgCl	4	26
	R_2Zn	9	30
1e	RMgCl	5	27
1f	RMgCl, C_6H_5MgBr	5, 6	27, 29
	R_2Zn	9	36
1g	RMgCl	5	27
	R_2Zn	9	36

The intention here has not been to provide an exhaustive tabulation of all aminations of each reagent but to illustrate the reported methods. However, comprehensive lists of the organomagnesium, -lithium, -zinc, and -copper compounds as well as alkali metal and silicon enolates that have been metalated by various reagents together with comparable amination conditions and yields are given at the end of this review.

II. Electrophilic Amination of Carbanions

A. With *N*-Haloamines

Monochloroamine (**1a**), monobromoamine (**1b**), dibromoamine (**1c**), nitrogen trichloride (**1d**), and mono- or dialkyl-substituted chloroamines (**1e–g**) have been employed for the electrophilic amination of Grignard, organolithium, and organozinc reagents and lithium enolates (Table 1).

H_2NCl **1a** H_2NBr **1b** $HNBr_2$ **1c** NCl_3 **1d** RNHCl **1e** R_2NCl **1f** $RNCl_2$ **1g**

The preparations and synthetic applications as aminating agents of chloro- and bromoamines have been reviewed.[11] The reactions of Grignard reagents with *N*-haloamines (**1a–g**) were comprehensively studied by Coleman and co-workers.[20-27] Depending on the Grignard reagent and haloamine chosen, primary, secondary, or tertiary amines were obtained from these reactions.

The reactions of various Grignard reagents with monochloroamine (**1a**) lead to the formation of primary amines in addition to ammonia as a byproduct (Scheme 1).[20,21]

The yield of ammonia was found to increase as the yield of the amine decreased. Highest yields of amine were found with alkylmagnesium chlorides, followed by bromides and iodides. Aminations of methyl- and

SCHEME 1

$$\mathrm{RMgCl} \xrightarrow[\text{2. } H_2O]{\text{1. } H_2NCl,\ Et_2O,\ 0\ ^\circ C} \underset{57\text{–}85\%}{RNH_2} + \underset{4\text{–}41\%}{NH_3}$$

R = C_2–C_5 alkyls, $C_6H_5CH_2$, $C_6H_5(CH_2)_2$

SCHEME 2

$$\mathrm{RMgCl} \xrightarrow[\text{2. } H_2O]{\text{1. } H_2NBr,\ Et_2O,\ -60\ ^\circ C} \underset{29\text{–}63\%}{RNH_2} + \underset{22\text{–}64\%}{NH_3} + \underset{5\text{–}15\%}{N_2}$$

R = C_4 alkyls, $C_6H_5CH_2$, $C_6H_5(CH_2)_2$

SCHEME 3

$$\mathrm{RMgCl} \xrightarrow[\text{2. } H_2O]{\text{1. } HNBr_2,\ Et_2O,\ 0\ ^\circ C} \underset{15\text{–}24\%}{RNH_2} + \underset{\sim 5\%}{R_2NH} + \underset{53\text{–}73\%}{NH_3} + \underset{1\text{–}7\%}{N_2}$$

R = C_4 alkyls, $C_6H_5CH_2$, $C_6H_5(CH_2)_2$

SCHEME 4

$$\mathrm{RMgCl} \xrightarrow[\text{2. } H_2O]{\text{1. } NCl_3,\ Et_2O,\ 0\ ^\circ C} \underset{21\text{–}32\%}{RNH_2} + \underset{2\text{–}7\%}{R_2NH} + \underset{8\text{–}27\%}{NH_3}$$

R = C_2–C_5 alkyls, $C_6H_5CH_2$, $C_6H_5(CH_2)_2$

phenylmagnesium bromides gave rise to a 26% yield of the respective amine. The reactions were carried out by adding a diethyl ether solution of **1a** to an excess of the Grignard reagent solution at 0 °C and subsequent hydrolysis. No evidence for the formation of rearrangement products was found in the reactions of **1a** with benzyl-, (α-naphthylmethyl)-, and cinnamylmagnesium chlorides; the corresponding amines were obtained in 92%, 47%, and 14% yields, respectively.[22]

The aminations of dialkylmagnesium compounds with **1a** resulted in higher yields of the amines[23] than those obtained with the alkylmagnesium chlorides. *n*-Butylamine was prepared in 82% and 97% yields by the reaction of di-*n*-butylmagnesium with **1a** in diethyl ether at 0 °C or in diethyl ether/dioxane at −60 °C, respectively, whereas use of *n*-butylmagnesium chloride produced the amine in 57% yield.

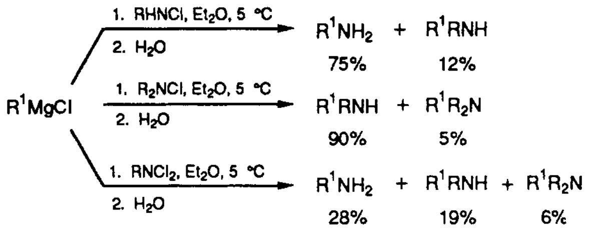
Monobromoamine reacted with Grignard reagents to form primary amines, ammonia, and nitrogen (Scheme 2).[24] The reaction of phenylmagnesium chloride with **1b** resulted in a 4% yield of aniline, an 85% yield of ammonia, and an 11% yield of nitrogen when a solution of **1b** at −60 °C (unstable at 0 °C) was added to the Grignard reagent solution at 0 °C in a specially designed apparatus.

Dibromoamine (**1c**) was reported to convert Grignard reagents into primary and secondary amines as well as ammonia and nitrogen (Scheme 3).[25]

Amination of Grignard reagents with nitrogen trichloride (**1d**) gave rise to both primary and secondary amines and ammonia (Scheme 4).[26] For these amination reactions, a diethyl ether solution of **1d** was added to a 4 molar excess of the Grignard reagent solution at 0 °C; phenylmagnesium chloride reacted thus to give a 5% total yield of amines and a 38% yield of ammonia.

Coleman has extended the aminations of Grignard reagents with **1a** to include the use of *N*-chloroalkylamines **1e–f** and *N*,*N*-dichloroalkylamines **1g** (Scheme 5).[27] The use of **1e** gave rise to primary amines together with secondary amines as side products, the use of **1f** gave secondary amines, and the use of **1g** gave primary and secondary amines together with small amounts of tertiary amines. The amination reactions were carried out in diethyl ether at 5 °C and variations in the temperature had very little effect on the outcome of the reaction.

SCHEME 5

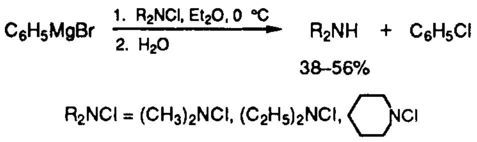


R = CH_3, C_2H_5, *n*-C_4H_9

R^1 = n-C_3–C_5 alkyls, $C_6H_5CH_2$

(for reported yields R = C_2H_5, R^1 = $C_6H_5CH_2$)

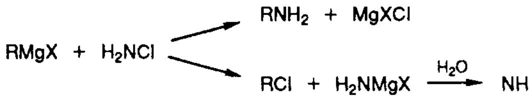
SCHEME 6



The reaction of di-*tert*-butylmagnesium with monochloro-*tert*-butylamine (**1e**) was reported to yield di-*tert*-butylamine.[28]

The amination of phenylmagnesium bromide was investigated using a number of monochlorodialkylamines (**1f**) (Scheme 6); chlorobenzene and the parent secondary amines but no alkylaniline were obtained.[29]

These observations on the aminations of Grignard reagents by haloamines are of interest as they demonstrate the ambident character of "NH_2". Coleman proposed reactions 5a and 5b to explain the formation of amines and ammonia in amination reactions with **1a**. According to reaction 5a, in which amines are formed, H_2N^+ acts as an electrophile and X as a leaving group, whereas according to reaction 5b, in which ammonia is produced, H_2N^- appears to serve as a leaving group. If this were the case, formation of an alkyl halide as well as ammonia would be expected and, in fact, in the amination of phenylmagnesium iodide with **1a**,[20] in which the yield of ammonia is the highest, an equivalent amount of chlorobenzene was isolated. The use of chloroamines also resulted in the formation of chlorobenzene without any trace of the expected amine.[29] Ammonia production was also found to be inversely proportional to amine formation, thus demonstrating that reactions 5a and 5b are occurring interdependently. The decrease in the amination yield found after substitution of bromine for chlorine in the haloamine H_2NX can be rationalized by the resultant increased basicity of nitrogen and, hence, the decreased electrophilic character of H_2N^+. The lower amination yields obtained when phenylmagnesium halides are allowed to react with **1a** than when alkyl Grignard reagents are used are possibly the result of steric factors. The yields of the amine from RMgX were found to decrease in the order X = Cl > Br > I, reflecting both steric factors and carbanionic character.



(5a)

(5b)

SCHEME 7

$$\mathrm{RLi} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. H}_2\text{NCl, Et}_2\text{O, }-50\ ^\circ\text{C}} \underset{\substack{33\%\ (\mathrm{R} = \mathrm{C_6H_5})\\ 39\%\ (\mathrm{R} = n\text{-}\mathrm{C_4H_9})}}{\mathrm{RNH_2}} + \mathrm{NH_3}$$

$$\mathrm{RLi/H_2NCl}\ \text{molar ratio} = 3/1$$

SCHEME 8

$$\mathrm{RCH(COOC_2H_5)_2} \xrightarrow[\text{benzene}]{\text{NaH}} \mathrm{RCNa(COOC_2H_5)_2} \xrightarrow[\text{2. morpholine}]{\text{1. H}_2\text{NCl, Et}_2\text{O}} \underset{70\text{–}92\%}{\mathrm{RC(NH_2)(COOC_2H_5)_2}}$$

$$\mathrm{R} = \mathrm{H, CH_3, C_2H_5}, i\text{-}\mathrm{C_3H_7}, sec\text{-}\mathrm{C_4H_9}, \mathrm{C_6H_5, C_6H_5CH_2}$$

Coleman and co-workers have found that **1a** reacts with alkyl- and phenyllithium reagents to form primary amines and ammonia (Scheme 7), but the yields are not higher than those obtained from the corresponding Grignard reagents.[30] The highest yields of amines are obtained when 3 equiv of an organolithium reagent is added to 1 equiv of **1a** at −50 °C in diethyl ether or benzene. The use of equimolar quantities of RLi and H_2NCl at 0 °C resulted in 3% and 7% yields of aniline and *n*-butylamine, respectively.

The lithium reagent derived from phenylacetylene reacted with monochlorodiethylamine (**1f**); however, about 40% of phenylacetylene was recovered (eq 6).[31]

$$\begin{tikzcd}[column sep=small] \mathrm{C_6H_5C{\equiv}CLi} \arrow[r, "\text{1. (C}_2\text{H}_5\text{)}_2\text{NCl}", "\text{2. H}_2\text{O}"'] & \underset{3\%}{\mathrm{C_6H_5C{\equiv}CN(C_2H_5)_2}} \arrow[d, "\mathrm{H_2O}"] & + & \underset{15\%}{\mathrm{C_6H_5C{\equiv}CCl}} \arrow[d, "\mathrm{C_6H_5C{\equiv}CLi}"] & (6) \\ & \underset{\text{trace}}{\mathrm{C_6H_5CH_2CON(C_2H_5)_2}} & & \underset{34\%}{\mathrm{C_6H_5C{\equiv}C{-}C{\equiv}CC_6H_5}} & \end{tikzcd}$$

The reaction of an α-lithiated carboxylic acid with **1a** resulted in a very low yield of the corresponding α-amino carboxylic acid (eq 7).[32,33]

$$\mathrm{(CH_3)_2CHCH_2COOH} \xrightarrow{\text{1. LDA, THF, 5 °C}} \mathrm{(CH_3)_2CHCHLiCOOLi} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. H}_2\text{NCl, }-50\ ^\circ\text{C}} \underset{8\%}{\mathrm{(CH_3)_2CHCH(NH_2)COOH}} \quad (7)$$

The amination of isopropylpotassium with diisopropylchloramine must be considered as unsuccessful since triisopropylamine was formed in only 3% yield.[34]

The synthesis of substituted malonates in satisfactory yields by the one-step reaction of **1a** with malonate anions has been reported (Scheme 8).[35] The carbanion of diethyl alkylmalonate (1 equiv) in diethyl ether was mixed with an ether solution of **1a** (2 equiv), and morpholine (1 equiv) was added. The reaction mixture was kept overnight at room temperature, heated under reflux for 5 h, and subjected to fractional distillation to furnish diethyl (aminoalkyl)malonate.

Coleman and co-workers also subjected dialkylzinc reagents to amination reactions with monochloroamine (**1a**),[30] nitrogen trichloride (**1d**),[30] and chloroalkylamines (**1f,g**)[36] (Scheme 9) by adding a cold solution of the chloroamine to a cold solution of an excess of the alkylzinc reagent in diethyl ether or petroleum ether.

TABLE 2. Amination of Carbanions with *O*-Alkylhydroxylamines (2a–i)

O-hydroxyl-amine	RM	scheme	ref
2a	R(Ar)MgX	10	44a
	RMgBr	11	45
	ArLi		46–51
	R(Ar)MgBr, R(Ar)Li	16, eq 12	43, 58
	RCHLiCOOLi	12, 13	32, 33
	$C_6H_5CHLiCONR_2$	eq 11	56
	$R_2CLiCONR_2$	14	57
2b	R(Ar)MgX	10	44b
	RCHLiCOOLi	12	33
2c–e	RCHLiCOOLi	12	33
2f	$C_6H_5CHLiCOOLi$	eq 10	33
2g	R(Ar)Li	17, eq 13	61
2h	R(Ar)Li	18	61
2i	C_6H_5Li	eq 14	61

SCHEME 9

$$\mathrm{R^1{}_2Zn} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. H}_2\text{NCl, petroleum ether, }-50\ ^\circ\text{C}} \underset{46\text{–}58\%}{\mathrm{R^1NH_2}} + \underset{37\text{–}47\%}{\mathrm{NH_3}}$$

$$\mathrm{R^1{}_2Zn} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. NCl}_3\text{, petroleum ether, }-30\ ^\circ\text{C}} \underset{8\text{–}37\%}{\mathrm{R^1NH_2}} + \underset{5\text{–}8\%}{\mathrm{R^1{}_2\,NH}} + \underset{15\text{–}38\%}{\mathrm{NH_3}}$$

$$\mathrm{(C_2H_5)_2Zn} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. R}_2\text{NCl, Et}_2\text{O, 0 °C}} \underset{70\%}{\mathrm{(C_2H_5)_2NH}} + \underset{2\%}{\mathrm{R_2NC_2H_5}}$$

$$\mathrm{R^1{}_2Zn} \xrightarrow[\text{2.H}_2\text{O}]{\text{1. RNCl}_2\text{, Et}_2\text{O, 0 °C}} \underset{61\text{–}78\%}{\mathrm{R^1NH_2}} + \underset{17\text{–}24\%}{\mathrm{R^1RNH}}$$

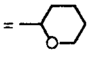
$$\mathrm{R} = \mathrm{CH_3, C_2H_5}, n\text{-}\mathrm{C_4H_9}, i\text{-}\mathrm{C_5H_{11}}$$
$$\mathrm{R^1} = \mathrm{C_2H_5}, n\text{-}\mathrm{C_3H_7}, n\text{-}\mathrm{C_4H_9}$$

For carbanion amination, organolithium and organozinc reagents have proved to be less useful than Grignard reagents. The use of mono- and dibromoamines (**1b,c**) chloroalkylamines (**1e–g**), and nitrogen trichloride (**1d**) does not seem to offer any advantages for the amination of Grignard reagents as compared to monochloroamine (**1a**). Furthermore, amination reactions of **1a** have not been utilized much in synthetic procedures because of the following major problems. (i) The preparation of **1a**[20,37] is cumbersome and the yields are not precisely reproducible; thus, the ether solutions of **1a** have to be analyzed for their H_2NCl contents before utilization in the reactions. (ii) Compound **2a** is unstable and cannot be stored; thus, the reagent must be freshly prepared before each reaction. (iii) Only alkyl Grignard reagents can be aminated with **1a** and an excess of the Grignard reagent is consumed in the reaction.

B. With *O*-Alkylhydroxylamines

O-Alkylhydroxylamines (**2a–f**; alkoxyamines) and *N*,*O*-dialkylhydroxylamines (**2g,h**) have been tested as aminating reagents for carbanions, and **2a** has been used extensively (Table 2).

H_2NOR
2a, $R = CH_3$
b, $R = CH_2C_6H_5$
c, $R = C_2H_5$
d, $R = CH(CH_3)_2$
e, $R = C(CH_3)_3$
f, R =



$RNHOCH_3$
2g, $R = CH_3$
h, $R = CH(C_6H_5)CH_3$

R_2NOCH_3
2i, $R = CH_3$

Several methods for the synthesis of *O*-alkylhydroxylamines[38,39] and *O*- and *N*-alkyl derivatives of hydroxylamine have been reported.[40,41] Numerous

SCHEME 10

$$\mathrm{RMgX} \xrightarrow[\text{2.} H_2O]{\text{1. } H_2NOCH_3,\ Et_2O,\ -15\ ^\circ C} \underset{67\text{–}80\%}{\mathrm{RNH_2}}$$

X = Cl, Br

$RMgX/H_2NOCH_3$ molar ratio = 2/1

R = C_2H_5, *sec*-C_4H_9, *t*-C_4H_9, *i*-C_5H_{11}, c-C_6H_{11}, C_6H_5, 4-BrC_6H_4, 2,4,6-$(CH_3)_3C_6H_2$, α-naphthyl

SCHEME 11

$$\mathrm{RMgBr} \xrightarrow[\text{2. } H_2O]{\text{1. } H_2NOCH_3,\ Et_2O,\ -10\ ^\circ C} \underset{40\text{–}90\%}{\mathrm{RNH_2}}$$

$RMgBr/H_2NOCH_3$ molar ratio = 2/1

R = C_2–C_5 alkyls, $CH_2{=}CHCH_2$, $C_6H_5CH_2$, $C_6H_5(CH_2)_2$, $BrMg(CH_2)_n$ (*n* = 5, 6, 10)

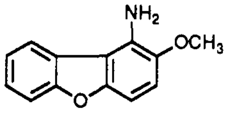
procedures are available for methoxyamine (**2a**), and a simplified, one-step preparation comprises sequential methylation of sodium hydroxylaminedisulfonate and hydrolysis.[42] The amine **2a** can also be obtained[43] by fractional distillation of a mixture of its commercially available hydrochloride salt and aqueous sodium hydroxide or sodium hydroxide in DMF. A recently published procedure consists of treatment of the hydrochloride salt with sodium hexyl oxide and subsequent fractional distillation.[10]

The amination of a carbanion with methoxyamine (**2a**) is known as the Schverdina–Kotscheschkow amination since these authors first reported the use of **2a** to convert a Grignard reagent into the corresponding amine in good yield (Scheme 10).[44a] The reaction sequence comprises treatment of 1 equiv of **1a** with 2 equiv of the Grignard reagent at −10 to −15 °C, hydrolysis, and isolation of the amines as their hydrochloride salts. Phenyllithium was also aminated in this way in 63% yield. The amination yields of alkylmagnesium halides decrease in the order Cl > Br > I.

Schverdina and Kotscheschkow also used *o*-benzylhydroxylamine (**2b**) for the amination of Grignard reagents. The yields obtained were somewhat lower than those obtained with **2a** whereas phenyllithium was aminated by **2b** in 71% yield.[44b]

Brown and Jones obtained various primary amines in 40–90% yields by reactions of 1 equiv of **2a** with 2 equiv of the alkylmagnesium bromide (Scheme 11).[45]

In contrast to the results reported by Coleman and co-workers[20,21] for aminations with **1a**, the amination yields from the reactions of alkylmagnesium bromides with **2a** were slightly higher than those obtained when the corresponding chlorides were used; however, the use of the iodides should be avoided. The reaction sequence comprises successive addition of a solution of **2a** in diethyl ether to the Grignard reagent at −15 °C, stirring for 30 min at −15 °C, warming to room temperature, heating under reflux for 2 h, and an acid quenching. The amines were isolated as the hydrochloride salts and generated in the free form by standard methods.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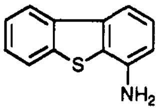
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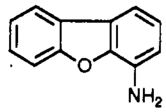
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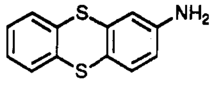
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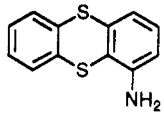
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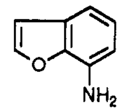
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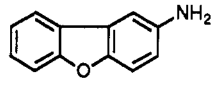
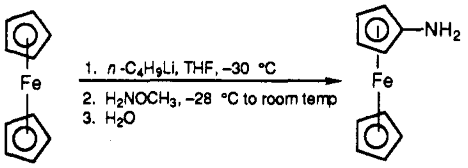

19

Gilman and co-workers used **2a** for the synthesis of 1-amino-2-methoxydibenzofuran (**13**) from the corresponding Grignard reagent[46a] as well as 4-aminodibenzothiophene (**14**),[46b] 4-aminodibenzofuran (**15**),[47] 2-aminothianthrene (**16**),[48] and 1-aminothianthrene (**17**)[49,50] from the corresponding organolithium reagents, the latter being prepared either by lithiation[46b,47,49,50] or by lithium/bromine exchange.[49] The amination reactions were performed by allowing 1 equiv of **2a** to react with 3,[46a,b,48] 2,[47] or 1 equiv[49,50] of the organometallic reagent in diethyl ether at 0 °C. The preparations of 4-aminobenzofuran (**18**) from **2a** and the respective organolithium compound and of 2-aminodibenzofuran (**19**) from **2a** and the corresponding Grignard reagent were also reported.[51] The amines **13–19** were prepared in 68, 64, 53, 63, 75, 78, and 33% yields, respectively.

Both lithiation of ferrocene and treatment of the resultant ferrocenyllithium with **2b**[52] as well as the use of 3 equiv of **2a** for the amination of ferrocenyllithium[53] resulted in poor yields of the amine (eq 8).

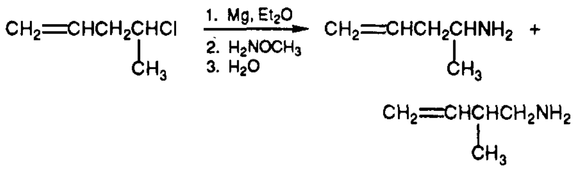


28%

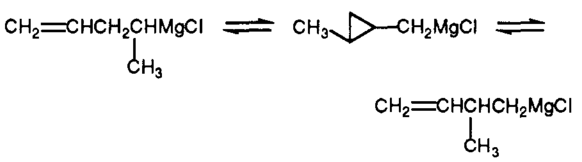
(8)

ferrocenyllithium/H_2NOCH_3 molar ratio = 1/3

A rearrangement process was reported to take place[54] in the attempted preparation of 4-penten-2-ylamine by the reaction of the Grignard reagent derived from 4-penten-2-yl chloride with **2a** (eq 9). A possible mechanism involves the rearrangement of a secondary Grignard reagent to a primary Grignard reagent by way of a three-membered ring (eq 9a).[55]



$$CH_2{=}CHCH_2\underset{CH_3}{\underset{|}{C}}HCl \xrightarrow[\substack{\text{2. } H_2NOCH_3\\ \text{3. } H_2O}]{\text{1. Mg, } Et_2O} CH_2{=}CHCH_2\underset{CH_3}{\underset{|}{C}}HNH_2 + CH_2{=}CH\underset{CH_3}{\underset{|}{C}}HCH_2NH_2 \qquad (9)$$



(9a)

The amination of α-lithiated carboxylic acids was investigated in detail by using 3-methylbutanoic acid and a number of *O*-alkylhydroxylamines (**2a–e**) (Scheme 12).[32,33] 3-Methylbutanoic acid was lithiated in the α-position by lithium diisopropylamide (LDA) in THF–HMPA at −15 °C. Amination of 1 equiv of the lithiated acid with 3 equiv of the aminating agent **2a–e** at either −15 or −70 °C furnished valine in low yield.

SCHEME 12

$$(CH_3)_2CHCH_2COOH \xrightarrow[\text{THF-HMPA}]{\text{LDA, -15 °C}} (CH_3)_2CHCHLiCOOLi \xrightarrow[\text{2. } H_2O]{\text{1. } H_2NOR\text{, -15 °C}} (CH_3)_2CHCH(NH_2)COOH$$

H_2NOR	**2a**	**2b**	**2c**	**2d**	**2e**
R	CH_3	$CH_2C_6H_5$	C_2H_5	i-C_3H_7	t-C_4H_9
valine, %	33	trace	22	25	18

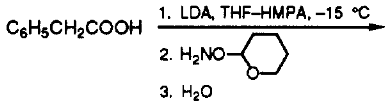
$(CH_3)_2CHCHLiCOOLi/H_2NOR$ molar ratio = 1/3

SCHEME 13

$$RCH_2COOH \xrightarrow[\substack{\text{2.}H_2NOCH_3\text{, -15 °C} \\ \text{3. } H_2O}]{\text{1. LDA, THF-HMPA}} RCH(NH_2)COOH$$

R	$(CH_3)_2CHCH_2$	$CH_3S(CH_3)_2$	$C_6H_5CH_2$	C_6H_5
amino acid, %	11	9	7	56

The maximum yield was achieved by using **2a** at −15 °C. As expected, the amination yield was found to decrease with increasing electron-donating character of the *O*-alkyl groups. This method for the conversion of carboxylic acids to α-amino acids using LDA and **2a** was then applied to the syntheses of leucine, methionine, phenylalanine, and α-phenylglycine (Scheme 13). *O*-2-Tetrahydropyranylhydroxylamine (**2f**) was employed in the analogous conversion of phenylacetic acid to α-phenylglycine (eq 10). Phenylacetamide, its N-substituted derivatives, and *tert*-butyl phenylacetate were α-lithiated, and attempts were made to aminate these lithiated derivatives with **2a** to obtain the corresponding α-amino amides and esters (eq 11).[56] No traces of the aminated products of phenylacetamide and *tert*-butyl phenylacetate were detected while the N-substituted derivatives were aminated in low yields.



(10)

$$C_6H_5CH_2COX \xrightarrow[\substack{\text{2. } H_2NOCH_3\text{, -15 °C} \\ \text{3. } H_2O}]{\text{1. LDA, THF-HMPA, -15 °C}} C_6H_5CH(NH_2)COX \quad (11)$$

X	NH(n-C_4H_9)	$N(C_2H_5)_2$	NH_2	O-t-C_4H_9
$C_6H_5CH(NH_2)COX$, %	30	15	—	—

In a further application of the amination method using **2a**, several *N*-alkyl-α-aminocarboxamides and their salts were prepared (Scheme 14).[57]

We have investigated the amination of phenyllithium and phenylmagnesium bromide with **2a**.[58] The maximum yield of aniline was obtained by addition of a diethyl ether solution of **2a** (1 equiv) to a diethyl ether solution of the organometallic compound (3 equiv) at −15 °C (eq 12).

$$C_6H_5M \xrightarrow[\text{2. } H_2O]{\text{1. } H_2NOCH_3\text{, } Et_2O\text{, -15 °C}} \underset{53\%}{C_6H_5NH_2} \qquad (12)$$

SCHEME 14

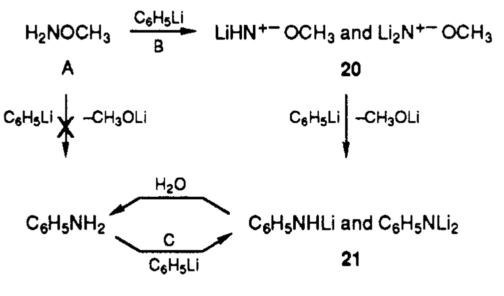
$$R^1R^2CHCONR^3R^4 \xrightarrow[\substack{\text{2. } H_2NOCH_3 \\ \text{3. } H_2O}]{\text{1. LDA, THF, -10 °C}} R^1R^2C(NH_2)CONR^3R^4$$

R^1, R^2, R^3, R^4 = H, $C_6H_5CH_2$, H, C_6H_5; H, C_6H_5, H, c-C_6H_{11}; C_6H_5, C_6H_5, H, C_6H_5; C_6H_5, C_6H_5, C_6H_5, H; H, C_6H_5, C_2H_5, C_2H_5

M = MgBr, Li

C_6H_5M/H_2NOCH_3 molar ratio = 3/1

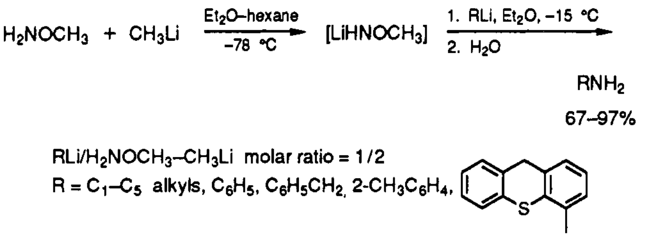
SCHEME 15



It is apparent that 3 equiv of C_6H_5M is required for the reaction with **2a**; 2 equiv is consumed for the deprotonation of the amino hydrogen atoms and 1 equiv is used up in the amination. Schverdina and Kotscheschkow[44] as well as Brown and Jones[45] reported alkyl Grignard reagent:**2a** ratios of 2:1 whereas Gilman and co-workers[46,47,49] reported that the amination of the lithium derivatives of some heterocyclic compounds occurred with a 3:1 molar ratio of the organolithium reagent:**2a**. On the other hand, there are numerous reports[59] indicating that the Grignard reagent can abstract one hydrogen atom from the NH_2 group at room temperature or lower while the lithium reagent may well react[60a] with both protons depending on the reaction conditions. These results on the deprotonation of amino groups seem to be in accord with those found in amination studies. However, the maximum yield of aniline dropped from 53% to 30% when the phenyllithium:**2a** ratio was reduced from 3:1 to 2.1.

Attempts have been made to overcome the difficulty of using at least 2 equiv of the organometallic reagent to be aminated.[58] First, it was found that the amination of phenyllithium with **2a** even at −78 °C again required a 3:1 molar ratio of phenyllithium:**2a** and that the yield was the same as that obtained at −15 °C. As suggested by Wakefield,[60b] an attempt was made to treat **2a** first with an expendable lithium reagent at low temperature and then with the lithium reagent to be aminated. However, the reaction of **2a** with n-butyllithium in a 2:1 molar ratio followed by reaction with phenyllithium or phenylmagnesium bromide gave rise to lower yields of aniline, i.e., 6% and 15%, respectively. Also, attempts to deprotonate **2a** with a base that does not normally act as a nucleophile were again unsuccessful since **2a** decomposes in the presence of bases. For aminations with **2a**, a mechanism has been proposed involving the formation of mono- and dilithium methoxy amides (**20**) as intermediates (Scheme 15). In order to prove that the amination is not a direct displacement by the carbanion at the free amino group (pathway A), experiments to trap the anions of *N*-mono- and *N*,*N*-dilithioaniline (**21**) with ethyl bromide were performed. The results indicated that phenyllithium abstracts just one proton from aniline but can abstract two protons from **2a** under the reaction conditions. This result seems to require the formation of n-lithioanilines (**21**) by the reaction of phenyllithium with mono- and dilithium methoxides (**20**) and provides evidence for pathway B or, at least, suggests that pathways A and C are not involved.

SCHEME 16



SCHEME 17

$$\mathrm{RLi}\xrightarrow[\text{2. }H_2O]{\text{1. }CH_3NHOCH_3\text{–}CH_3Li,\ Et_2O,\ -15\ ^\circ C}\mathrm{RNHCH_3}$$

R	n-C_4H_9	sec-C_4H_9	t-C_4H_9	C_6H_5
$RNHCH_3$, %	63	62	30	67

RLi/CH_3NHOCH_3–CH_3Li molar ratio = 1/1

SCHEME 18

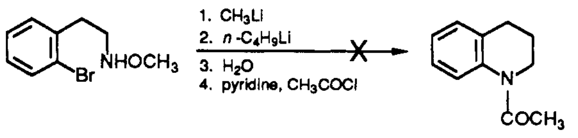
$$\mathrm{RLi}\xrightarrow[\text{2. }H_2O]{\text{1. }CH_3CH(C_6H_5)NHOCH_3\text{–}CH_3Li,\ Et_2O,\ 40\ ^\circ C}\mathrm{RNHCH(C_6H_5)CH_3}$$

R = n-C_4H_9, 68%
R = C_6H_5, 44%

Later, Beak and Kokko[43] treated **2a** with methyllithium in diethyl ether and allowed the resultant organolithium derivative to react with organolithium reagents to produce amines after hydrolysis (Scheme 16). The optimum reaction conditions were found to comprise addition of 2 equiv of **2a** in hexane to a stirred solution of 2 equiv of methyllithium in diethyl ether at −78 °C, subsequent addition of 1 equiv of an organolithium reagent, stirring at −15 °C for 2 h, and an aqueous quench to give the corresponding amines which were isolated as benzamides. Aryllithium reagents gave higher yields than alkyllithium reagents. Grignard reagents and heteroaryllithium compounds were less effectively aminated; n-butyl- and phenylmagnesium bromides were aminated in 16% and 37% yields. The absence of methyllithium or the use of phenyl- or n-butyllithium in the first step or the use of a different solvent system resulted in lower yields of the amine.

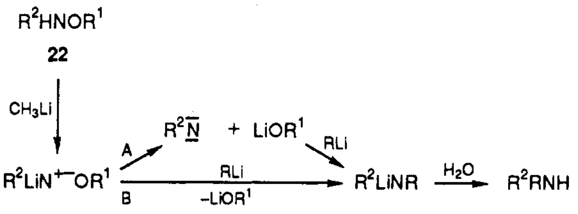
Beak and Kokko[61] have additionally reported that some N-alkyl-O-methylhydroxylamines (**2g**,**h**) are also effective as electrophilic reagents for converting organolithium derivatives to secondary amines. The reactions of N,O-dimethylhydroxylamine (**2g**)/methyllithium with butyllithium and phenyllithium gave rise to butyl- and phenylmethylamines in good yields (Scheme 17). Reactions of **2g**/methyllithium were performed as described above for **2a**/methyllithium with a 1:1 molar ratio of complex:organolithium reagent and with 2 equiv of the complex. The last method resulted in a 15% increase in the yield. Aminations with N-(1-phenylethyl)-O-methylhydroxylamine (**2h**)/methyllithium (Scheme 18) were also carried out at 40 °C since the increased temperature resulted in an increased extent of amination.

Attempts to aminate 2-lithiothiophene and 2-lithio-N,N-diisopropylbenzamide with **2g** were unsuccessful, as was also an intramolecular amination (eq 13).

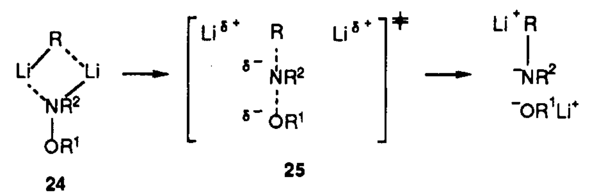


(13)

SCHEME 19



SCHEME 20



The tertiary amine N,N-dimethylaniline could not be isolated from the reaction of phenyllithium with N,N,O-trimethylhydroxylamine (**2i**); instead N-methylbenzamide was obtained (eq 14).

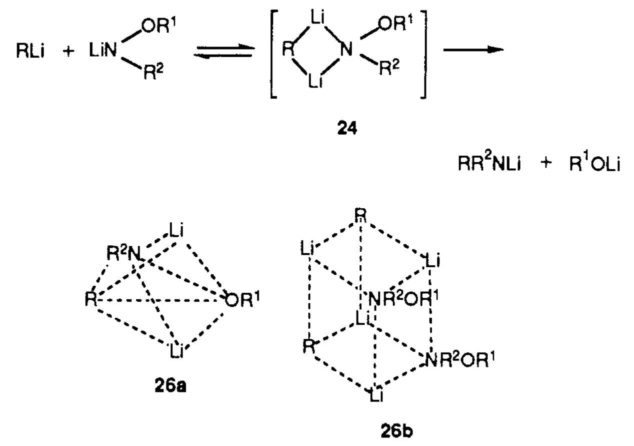
$$C_6H_5Li \xrightarrow{(CH_3)_2NOCH_3} \underset{52\%}{C_6H_5CH_2NHCH_3} \qquad (14)$$

These results suggest that alkoxyamine derivatives bearing at least one proton on nitrogen can be activated by methyllithium to provide species that are able to react with organolithium reagents and so form amines in synthetically useful yields. The **2a**/methyllithium complex is an efficient and convenient reagent for converting organolithium derivatives to primary amines since the preparation of **2a** from its commercially available hydrochloride salt[10,42,43] is easy and the amination procedures as well as the amine isolation are simple. However, use of 2 equiv of the alkoxyamine/methyllithium complex per equivalent of the organolithium reagent to be aminated is essential.

The mechanism of the electrophilic amination of organolithium derivatives by alkoxyamines has also been studied by Beak and co-workers:[10,62] two possible mechanisms were outlined (Scheme 19). The lithium alkoxyamide (**23**), formed by deprotonation of the alkoxyamine (**22**), can react either by loss of lithium methoxide to produce a nitrenoid which subsequently undergoes addition with the organolithium reagent to give the lithium amide (pathway A) or by direct displacement in the lithium alkoxyamide by the organolithium reagent to furnish the lithium amide (pathway B). Subsequent hydrolysis of the lithium amide then produces the amine end product. The observations of the authors confirmed the formation of the lithium alkoxyamide and supported pathway B for the electrophilic amination. Formally, this displacement involves the reaction of two anionic species and should thus be repulsive. However, a feasible mechanism (Scheme 20) involving an initial complex **24**, in which the entering carbon atom is disposed on the backside of the nitrogen and the nitrogen–oxygen bond is polarized, thus leading to the transition state **25**, was proposed in order to rationalize the facility of the reaction.

A theoretical study by Boche and co-workers[63] indicated that the lithium alkoxyamides **23**, and not the alkoxyamines **22** themselves, actually react with the organolithium derivatives. The facile substitution of

SCHEME 21



R^1O^- in **23** was due to the formation of (i) the $R^2LiNOR^1 \cdot RLi$ complex (**24**), (ii) the long N–O bond in **23**, and (iii) the high stability of LiR^2N^+ (R^2 = H, alkyl) in comparison to R^2NH^+. Hence, the separation of **23** into the ion pairs LiR^2N^+ and R^1O^- was a rather favored reaction, which is in agreement with the high electrophilicity of **23**.

Later, ab initio and SCF–MO calculations by Armstrong and co-workers[64] showed that the reaction of lithium alkoxyamide (**23**) with an organolithium reagent proceeds via an intermediate in which the N–O bond has a lithium bridge, thus leading to R^1OLi elimination and $R–NR^2$ bond formation.

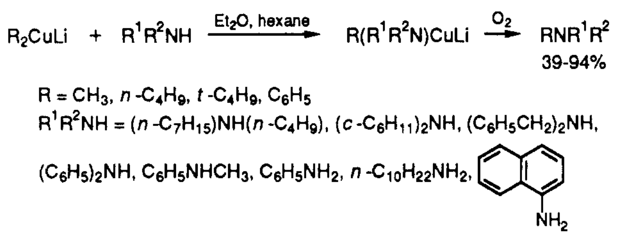
McKee[65] used the MNDO method to derive a plausible mechanism for the amination of organolithium compounds by lithium alkoxyamides. In this mechanism (Scheme 21), an initial lithium complex **24** having two lithium atom bridges between nitrogen and carbon passes through a transition state (**26a**), which is assumed to be a trigonal bipyramid with two axial lithium cations and equatorial alkoxy-, alkyl-, and alkylnitrene substituents.

Recently, Beak and co-workers[10] reported the details of their methodology and analysis of the reaction mechanism and provided evidence that this formal displacement proceeds through a transition state in which the entering and leaving groups prefer a specific geometry, presumed to be that on an S_N2 process. For the initial complex, the cubic structure **26b** appears to have an advantage over **24** in that the developing alkoxide is nearer to a formally positively charged lithium atom.

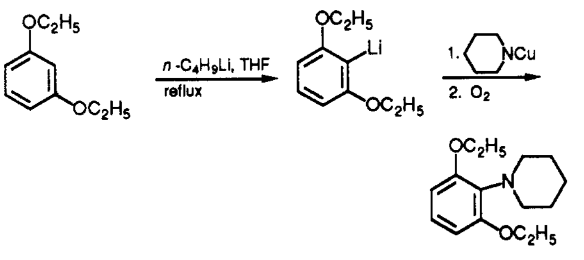
The amination of a polymeric organolithium compound has also been achieved in 92% yield.[66] Methoxyamine (**2a**)/methyllithium in THF–diethyl ether–hexane at −78 °C was added to polystyryllithium (number-average relative molecular mass 2000) in THF, and the reaction mixture was allowed to warm slowly to −15 °C and then quenched with water.

Syntheses of secondary and tertiary amines based on the oxidative coupling of lithium alkylcopper amides have been described.[67] The lithium alkylcopper amides were generated in situ from lithium dialkylcuprates and primary or secondary amines (Scheme 22). This method seems to be especially efficient for the oxidative coupling of amines with primary alkyl and aryl groups. A typical experimental procedure comprises addition of the amine (1 equiv) in diethyl ether to the lithium dialkylcuprate (5 equiv) in diethyl ether–hexane and then stirring of the reaction mixture while bubbling oxygen through it. The reactions are carried out at different temperatures depending on the reactants. The introduction of an amino group was also realized by the oxidative coupling of a lithium arylcopper amide generated from an aryllithium reagent and a copper amide.

SCHEME 22



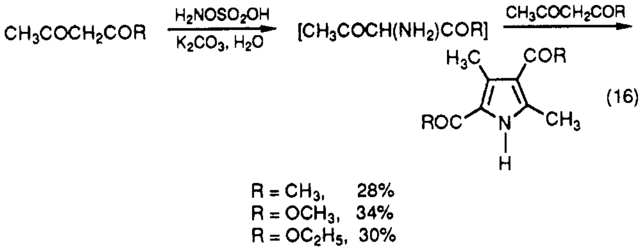
Treatment of (2,6-diethoxyphenyl)lithium (1 equiv) with copper piperidide [5 equiv; prepared from lithium piperidide and copper(I) iodide] gave *N*-(2,6-diethoxyphenyl)piperidine (eq 15).



(15)

C. With Hydroxylamine-*O*-sulfonic Acid

Hydroxylamine-*O*-sulfonic acid (HOSA, **3**) is not suitable for carbanion amination. However, its use in organic synthesis, resulting from the ability of the nitrogen center to act both as a nucleophile and as an electrophile as well as being able to provide an in situ source of other chemical entities such as diimide, have been comprehensively reviewed.[15,16] One of the two published reports on carbanion aminations with HOSA[68] concerns its reaction with some β-diketo compounds in 10% aqueous K_2CO_3 solution at room temperature overnight to furnish symmetrically substituted pyrroles (eq 16).

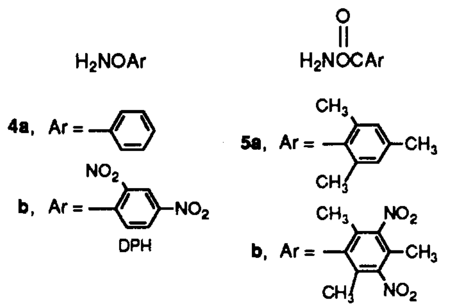


(16)

The other attempted amination with HOSA[33] yielded a trace amount of an amino acid from an α-lithiated carboxylic acid (Scheme 12).

D. With *O*-Arylhydroxylamines and *O*-Acylhydroxylamines

O-Phenylhydroxylamine (**4a**), *O*-(2,4-dinitrophenyl)hydroxylamine (DPH; **4b**), *O*-mesitoylhydroxylamine (**5a**), and *O*-(3,5-dinitromesitoyl)hydroxylamine (**5b**)

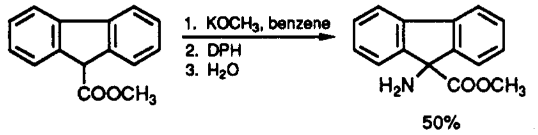


have been used for carbanion amination (Table 3).

Sheradsky and co-workers have reported methods for the preparation of *O*-(nitrophenyl)hydroxylamines and have investigated their synthetic applications.[69-71] The syntheses of various *O*-(nitrophenyl)-[72] and *O*-acylhydroxylamines[73-75] have also been reported. The preparations and amination reactions of *O*-(nitroaryl)- and *O*-acylhydroxylamines were reviewed by Tamura et al.[17] *O*-(Nitrophenyl)hydroxylamines are stable reagents[72] and are now commercially available. In general, *O*-acylhydroxylamines are too unstable for use as reagents but **5a** and **5b** were reported to be stable at room temperature.[73]

The reaction of *O*-phenylhydroxylamine (**4a**) with phenylmagnesium bromide was reported to afford aniline in 79% yield but no experimental details were given.[76]

Sheradsky and co-workers found that DPH (**4b**)[69,77] in particular is highly suitable for the amination of carbanions to give the corresponding amines and reported the synthesis of methyl 9-amino-9-fluorenecarboxylate (eq 17) and diethyl α-amino-α-phenylmalonate (eq 18).



(17)

$$C_6H_5CH(COOC_2H_5)_2 \xrightarrow[\text{2. DPH; 3. } H_2O]{\text{1. NaH, DMF}} \underset{53\%}{C_6H_5C(NH_2)(COOC_2H_5)_2} \quad (18)$$

Radhakrishna, Loudon, and Miller investigated[78] the suitability of DPH for the amination of a variety of ester enolates. Sodium enolates derived from diethyl malonate and its 2-substituted analogues are aminated with DPH, and the 2-aminomalonates thus produced are readily converted to the corresponding amino acids in good yields by hydrolysis and decarboxylation (Scheme 23). For the amination, the substituted diethyl malonate (1 equiv) was added to sodium hydride in THF, and the mixture was stirred at room temperature followed by addition of DPH (1 equiv) in THF. The mixture was stirred at room temperature overnight. Following an acidic quench, the product amino acids were recovered by standard procedures.

The same authors also considered the generality of the amination of various ester enolates of differing basicity (Scheme 24) and found that less amino group is transferred as the ester enolates become more basic. Amination of the lithium enolate of phenylacetonitrile gave the corresponding product in 7% yield. Amination of the Reformatsky reagent derived from ethyl α-bromoacetate was not successful, and 2,4-dinitrophenol was isolated in 85% yield. The reaction of the trimethylsilyl enol ether of ethyl phenylacetate with DPH in refluxing THF yielded no aminated product, and ethyl phenylacetate was recovered in 84% yield, together with the recovery of DPH in 50% yield and 2,4-dinitrophenol in 31% yield. The authors pointed out that the yield of the aminated product reflects the competition between amination and decomposition of DPH. The direct reaction of DPH with sodium hydride was shown to lead to destruction of DPH and formation of 2,4-dinitrophenol. When accompanying the amination of the more basic enolates, decomposition of DPH partly involves the formation of diimide. A possible mechanism for the base-catalyzed formation of these species is shown in eq 19.

TABLE 3. Amination of Carbanions with *O*-Aryl- and *O*-Acylhydroxylamines (4a,b and 5a,b)

hydroxylamine	RM	scheme	ref
4a	C_6H_5Li	—	76
4b	$RCNa(COOR)_2$	eq 18, 23	77, 78
	$R_2CNaCOOR$	24	78
5a,b	$RCHLiCOOLi$	12	33

SCHEME 23

$$RCH(COOC_2H_5)_2 \xrightarrow[\text{2. DPH}]{\text{1. NaH, THF}} RC(NH_2)(COOC_2H_5)_2 \xrightarrow{HCl} RCH(NH_2)COOH$$

R	CH_3	C_2H_5	$n\text{-}C_4H_9$	$C_6H_5CH_2$	$CH_2COOC_2H_5$
$RCH(NH_2)COOH$, %	84	74	46–57	73	61

SCHEME 24

$$R^1R^2CHCOOC_2H_5 \xrightarrow[\text{2. DPH; 3. } H_2O]{\text{1. MB}} R^1R^2C(NH_2)COOC_2H_5$$

$$MB = NaH \text{ or } (i\text{-}C_3H_7)NH(c\text{-}C_6H_{11})$$

R^1	C_6H_5	H	C_6H_5	CH_3	H
R^2	$COOC_2H_5$	$COOC_2H_5$	CN	C_6H_5	C_6H_5
$R^1R^2C(NH_2)COOC_2H_5$, %	65	55	54	35	12

$$B^- + ArONH_2 \rightleftharpoons BH + ArONH^- \quad (19a)$$

$$ArONH^- + ArONH_2 \rightarrow ArONHNH_2 + ArO^- \quad (19b)$$

$$B^- \text{ (or } ArO^-) + ArONHNH_2 \rightarrow HN{=}NH + BH \text{ (or ArOH)} + ArO^- \quad (19c)$$

$$2HN{=}NH \rightarrow N_2 + H_2NNH_2 \quad (19d)$$

$$H_2NNH_2 + ArONH_2 \rightarrow HN{=}NH + ArOH + NH_3 \quad (19e)$$

$$Ar = 2,4\text{-}(NO_2)_2C_6H_3$$

Radhakrishna, Loudon, and Miller also reported that there is no evidence to suggest that the mechanism of the amination reactions with DPH (**4b**) is other than a direct displacement by the nucleophilic carbanion on the electrophilic amino nitrogen. Attempts to transfer a methylamino group by using *N*-methyl-*O*-(2,4-dinitrophenyl)hydroxylamine under these amination conditions with DPH failed completely.

TABLE 4. Amination of Carbanions with *O*-Sulfonylhydroxylamines (6a–h)

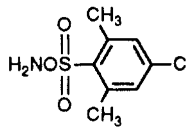
hydroxylamine	RM	scheme	ref
6a	$CHNa(CN)_2$	eq 21	80, 83
6b	R(Ar)Li	25	81
6c	R(Ar)Li	25, eq 22	81, 82
6d,e	R(Ar)Li	25	81
6f	C_6H_5MgBr		84
6h	RLi, $(RC{\equiv}C)_2LiCu$	eq 23, 26	85, 86

The use of DPH in the amination of carbanions derived from β-diketones resulted in 1–2% yield of the amine products (eq 16).[33] Reaction of α-lithiated 3-methylbutanoic acid with DPH did not lead to amination, and the use of **5a** or **5b** gave only traces of valine (Scheme 12).[33]

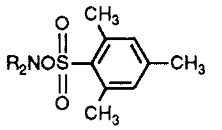
Thus, the amination of enolates derived from malonates and other enolates of comparable basicity are the only synthetically useful processes using DPH as an aminating reagent.

E. With *O*-Sulfonylhydroxylamines

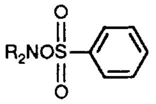
For carbanion amination, *O*-(mesitylsulfonyl)hydroxylamine (MSH; **6a**), *N*,*N*-dialkyl-*O*-(mesitylsulfonyl)hydroxylamines (**6b,c**), *N*,*N*-dialkyl-*O*-(phenylsulfonyl)hydroxylamines (**6d,e**), *N*,*N*-dialkyl-*O*-(*p*-tolylsulfonyl)hydroxylamines (**6f,g**), *N*,*N*-dimethyl-*O*-(methylsulfonyl)hydroxylamine (**6h**), and *N*-(tosyloxy)phthalimide (**6i**) have been tried (Table 4).



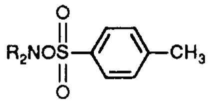
6a (MSH)



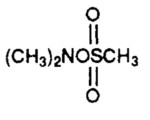
6b, R = CH_3
c, R = C_2H_5



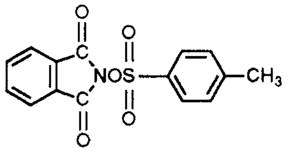
6d, R = CH_3
e, R = C_2H_5



6f, R = CH_3
g, R = $CH_2C_6H_5$



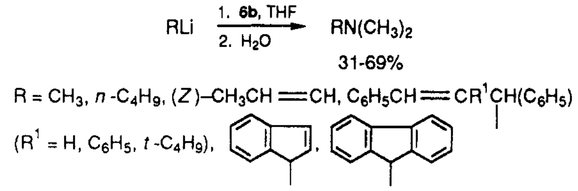
6h



6i

Methods for the syntheses of various *O*-sulfonylhydroxylamines have been published.[72,74,75] Tamura and co-workers have summarized the synthesis and properties of MSH and other *O*-sulfonylhydroxylamines and discussed their synthetic applications in reactions with various types of nucleophiles and electrophiles in detail.[17] MSH can be stored below 0 °C for a month without noticeable change. However, owing to reported explosions,[79,80] it is strongly recommended that it be prepared immediately prior to use and not stored. Compounds **6b** and **6c**, after recrystallization from diethyl ether, can be kept indefinitely and **6d** and **6e** for several weeks in a refrigerator.[81] Compound **6c** was reported to decompose[82] on standing at room temperature; however, when kept in a freezer, a sample in a plastic bag containing Drierite showed no change in its decomposition point after 6 weeks.

SCHEME 25



MSH (**6a**) was used for enolate amination to achieve a short and simple preparation of methyl α-aminodiethylphosphonoacetate.[83] The amination was carried out by treatment of methyl diethylphosphonoacetate (1 equiv) with sodium hydride in DME, followed by the addition of MSH (1 equiv) at a temperature below 30 °C (eq 20).

$$(C_2H_5O)_2POCH_2COOCH_3 \xrightarrow[\substack{2.\ MSH \\ 3.\ H_2O}]{1.\ NaH,\ DME} \underset{39\text{–}47\%}{(C_2H_5O)_2POCH(NH_2)COOCH_3} \quad (20)$$

Aminomalonitrile tosylate, a key starting material in the synthesis of a number of heterocyclic compounds, has been synthesized from malonodinitrile by using MSH[80] (eq 21) under mild conditions with a simple workup procedure. Amination followed by addition of *p*-toluenesulfonic acid led directly to a mixture of aminomalononitrile tosylate and ammonium tosylate. The latter was formed from the decomposition of MSH, presumably in the same manner as suggested for DPH (**4b**). The use of DPH did not result in expected amination.

$$NaCH(CN)_2 \xrightarrow[2.\ TosOH]{1.\ MSH,\ THF,\ 0\ ^\circ C} \underset{42\%}{H_3N^+CH(CN)_2Tos^-} + \underset{14\%}{NH_4{}^+Tos^-}$$

$$Tos = 4\text{-}CH_3C_6H_4SO_2 \quad (21)$$

Boche and co-workers converted alkyl-, alkenyl-, and aryllithium compounds into tertiary amines in good yields by using the *N*,*N*-dialkyl-*O*-(arylsulfonyl)hydroxylamines **6b–e**, and the scope of the amination with *N*,*N*-dimethyl-*O*-(mesitylsulfonyl)hydroxylamine (**6b**) was investigated systematically (Scheme 25).[81] α-Naphthyllithium and α-naphthylmagnesium bromide were aminated with **6b** or **6d** in 9% and 69% yields, respectively. Aminations of phenylmagnesium bromide with **6c** and *cis*- or *trans*-(2,3-diphenylcyclopropyl)magnesium bromide with **6b** both resulted in 47% yields. The lithium enolate derived from ethyl phenylcyanoacetate was aminated with **6b** in 95% yield. Aminations with **6b–e** were achieved by addition of the organolithium reagent in diethyl ether solution to a suspension of the aminating reagent of THF at −10 °C and stirring the mixture at room temperature. Amines were isolated after the usual workup.

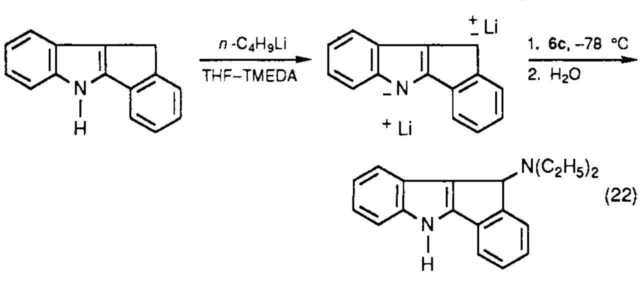
Treatment of phenylmagnesium bromide or cyclohexylmagnesium bromide with **6f** was reported to give a 54% yield of *N*,*N*-dimethylaniline or 14% yield of *N*,*N*-dimethylcyclohexylamine.[84]

SCHEME 26

$$2RC{\equiv}CLi + RC{\equiv}CCu \rightarrow (RC{\equiv}C)_3CuLi_2 \xrightarrow[Et_2O,\ -20\ ^\circ C]{2(CH_3)_2NOSO_2CH_3} 2RC{\equiv}CN(CH_3)_2 + RC{\equiv}CCu + 2LiOSO_2CH_3$$

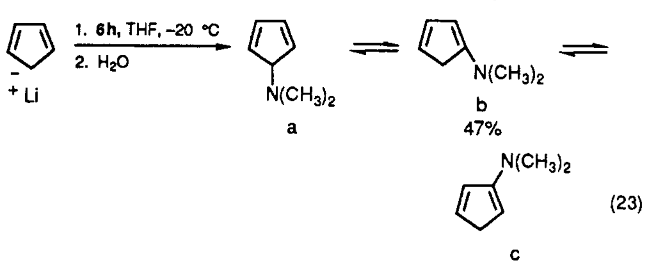
R	n-C_3H_7	n-C_4H_9	C_6H_5
$RC{\equiv}CN(CH_3)_2$, %	69	60	83

Amination of dibenzo[*b*,*f*]-1-azapentalene dianion with **6c** resulted in the formation of 10-(diethylamino)-5,10-dihydroindeno[1,2-*b*]indole (eq 22).[82]



(22)

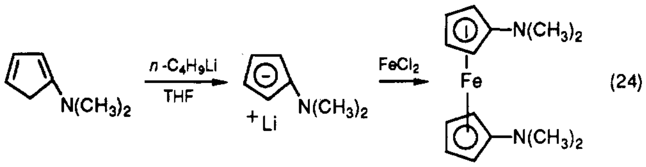
Boche and co-workers used **6h** for the electrophilic amination of cyclopentadienyllithium (eq 23).[85] The



(23)

reaction of cyclopentadienyllithium with **6h** in THF at −20 °C afforded *N*,*N*-dimethyl-1,3-cyclopentadienylamine (b isomer).

(Pentamethylcyclopentadienyl)lithium was aminated in the same way with a 40% yield. When a solution of *N*,*N*-dimethyl-1,3-cyclopentadienylamine in THF was allowed to react with *n*-butyllithium in hexane at −30 °C, the colorless [(dimethylamino)cyclopentadienyl]-lithium precipitated out almost quantitatively and its reaction with $FeCl_2$ in THF gave the dark orange bis(dimethylamino)ferrocene (eq 24).

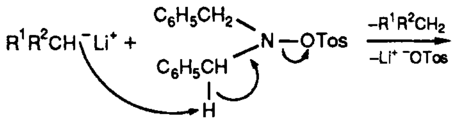


(24)

1-Alkynylcuprates, prepared from 1-alkynyllithiums, could be electrophilically aminated with **6h** in good yields (Scheme 26).[86] When 1-alkynyllithium reagents and 1-alkynylmagnesium bromides were allowed to react with **6h**, they gave no aminated products or only traces thereof, respectively. For the maximum yield of amination, 2 equiv of **6h** was used per equivalent of cuprate and even the use of excess aminating reagent also resulted in amination of only two of the three alkyne groups of the cuprate.

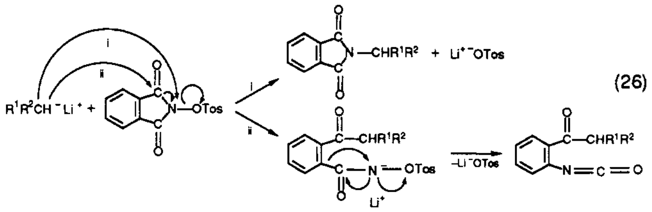
Finally, dialkylamination of alkyl- and alkenyllithium derivatives can be carried out effectively by using **6b** as the aminating reagent, and 1-alkynyllithiums can also be dialkylaminated by using **6h** via organocopper intermediates.

Dibenzylaminations of a series of carbanions with *N*,*N*-dibenzyl(*p*-tolylsulfonyl)hydroxylamine (**6g**) were recently attempted by Sheradsky.[87] It was found that, unlike the reactions of the corresponding dimethyl and diethyl derivatives of *O*-(mesitylsulfonyl)hydroxylamine (**6b**,**c**), which result in dialkylamination,[81] the reaction of **6g** with a series of carbanions led always to the Schiff base via elimination (eq 25). These reactions produced the starting carbon acids, benzaldehyde, and benzylamine formed by hydrolysis during workup.

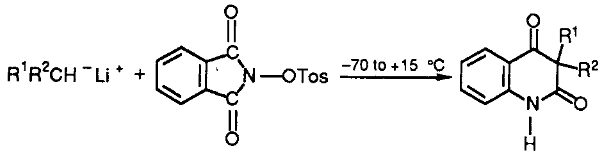


$$C_6H_5CH{=}NCH_2C_6H_5 \xrightarrow{H_2O} C_6H_5CHO + C_6H_5CH_2NH_2 \quad (25)$$

In order to avoid the problem of the competing elimination, the authors employed the reactions of the carbanions with *N*-(tosyloxy)phthalimide (**6i**) to produce the N-substituted phthalimides, which can be easily transformed to primary amines (eq 26, path i); the reaction, however, was also expected to lead to *o*-isocyanato ketones (eq 26, path ii). The reactions of aryl carbanions and enolate anions with **6g** gave 3,3-disubstituted quinoline-2,4-diones (eq 27) in moderate yields. The proposed mechanism involves the possible product from eq 26, path ii, which is attacked by the carbanion to form another carbanion which then undergoes intramolecular attack at the carbonyl group, leading to cyclization to form the dione (eq 28).

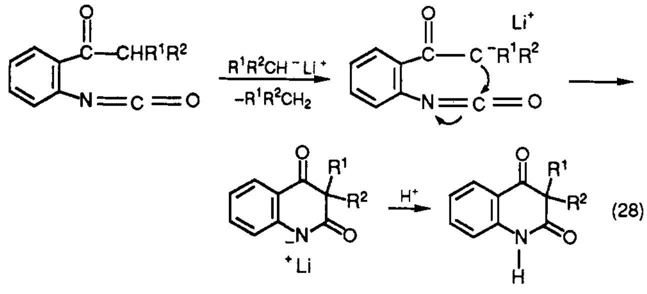


(26)



(27)

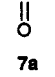
38–63%



(28)

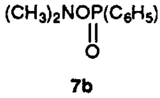
F. With *O*-Phosphinylhydroxylamines

Recently, *O*-(diphenylphosphinyl)hydroxylamine (**7a**) and its *N*,*N*-dialkyl derivatives, e.g., *N*,*N*-dimethyl-*O*-(diphenylphosphinyl)hydroxylamine (**7b**), have been used for amination of carbanions as well as N, S, and P nucleophiles (Table 5). Preparative methods for **7a**



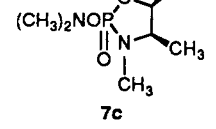
$H_2NO\underset{\underset{O}{\|}}{P}(C_6H_5)_2$

7a



$(CH_3)_2NO\underset{\underset{O}{\|}}{P}(C_6H_5)_2$

7b



7c

TABLE 5. Amination of Carbanions with *O*-Phosphinylhydroxylamines (7a–c)

hydroxylamine	RM	scheme	ref
7a	R(Ar)MgBr, R(Ar)Li	eq 31, 27	85, 90, 91
	$RCNa(COOR)_2$	eq 30	90
7b	R(Ar)MgBr, R(Ar)Li	27	91
	$(RC{\equiv}C)_2LiCu$	28	86
	$RC(CN)Li(OSi(CH_3)_3)$	29	92
7c	RMgX, RLi	eq 32	93
	RCHLiCOOR	30	93

have been discussed in detail[88] and, recently, a direct method for the preparation of *N*,*N*-dialkyl-*O*-(diphenylphosphinyl)hydroxylamines has been developed.[89] Reagents **7a** and **7b** are stable compounds and can be stored indefinitely at −20 °C.

The preparation of primary amines from carbanions by using **7a** has been described by two groups. Colvin and co-workers[90] found that **7a** acts as a good aminating reagent toward some stabilized carbanions and Grignard reagents. Reaction of the sodium salt of benzyl diethylphosphonoacetate (1 equiv) with **7a** (1 equiv) in THF at −78 °C led to the α-aminophosphonoacetate (eq 29) in one simple operation. The sodium salts of di-

$$(C_2H_5O)_2POCH_2COOCH_2C_6H_5 \xrightarrow[\substack{2.\ H_2NOPO(C_6H_5)_2\\ 3.\ H_2O}]{1.\ NaH,\ THF} (C_2H_5O)_2POCH(NH_2)COOCH_2C_6H_5 \quad 60\% \tag{29}$$

ethyl malonate and malononitrile (1 equiv) were aminated with **7a** (1 equiv) in good yields (eq 30). Ami-

$$CH_2(COOC_2H_5)_2 \text{ or } CH_2(CN)_2 \xrightarrow[2.\ H_2NOPO(C_6H_5)_2]{1.\ NaH,\ THF} CH(NH_2)(COOC_2H_5)_2\ (57\%) \text{ or } CH(NH_2)(CN)_2\ (50\%) \tag{30}$$

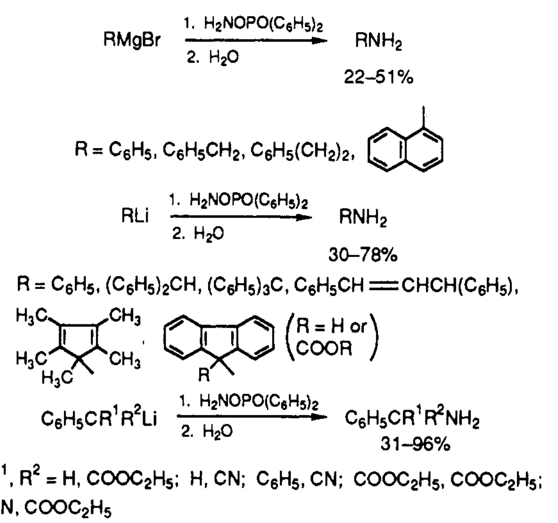
nations using the corresponding lithium salts were considerably less effective. For the amination of Grignard reagents, phenyl- and hexylmagnesium bromides were allowed to react with **7a** in THF at −78 °C. The use of phenyllithium produced only traces of aniline (eq 31).

$$RMgBr \xrightarrow[2.\ H_2O]{1.\ H_2NOPO(C_2H_5)_2} RNH_2 \qquad \begin{array}{l} R = C_6H_5,\ 67\% \\ R = n\text{-}C_6H_{13},\ 27\% \end{array}$$

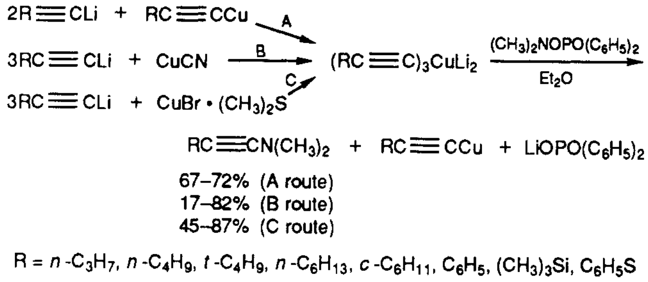
$$RMgBr/H_2NOPO(C_6H_5)_2 \text{ molar ratio} = 2/1 \tag{31}$$

Boche and co-workers used[91] **7a** and **7b** for the amination of a series of Grignard reagents, organolithium derivatives, and lithium enolates (Scheme 27). With alkyl and aryl Grignard and organolithium reagents, moderate yields of the corresponding amines were obtained. The amination yield was found to decrease in the order RMgCl > RMgBr, which is similar to that found with monochloroamine (**1a**).[20,21] Benzylmagnesium bromide and benzylmagnesium chloride were aminated with 51% and 70% yields, respectively. For the amination reaction, **7a** at −20 °C was added to the Grignard reagent or organolithium compound (1 equiv; prepared by metalation in THF at −15 °C), and the mixture was stirred at room temperature for 12 h. After hydrolysis, the amines were recovered by the usual acid–base treatment.

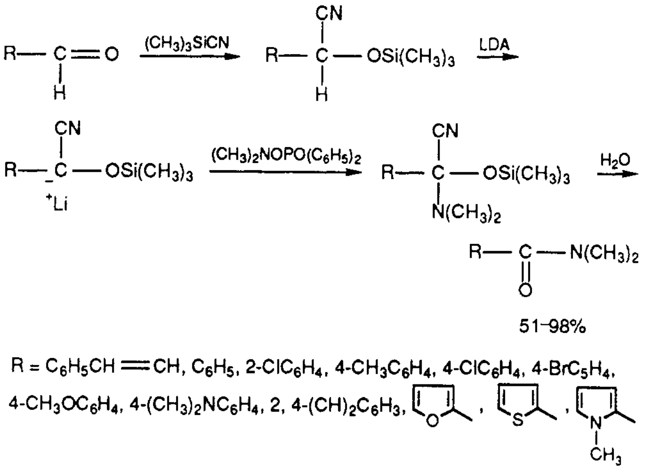
SCHEME 27



SCHEME 28



SCHEME 29



The use of **7b** generally resulted in higher yields, suggesting protonation of the carbon nucleophiles by the amino group of **7a**.

It was reported[86] that **7b** instead of **6h** could also be successfully used in the amination of cyclopentadienyllithium;[85] **7b** was also used to convert 1-alkynyllithium cuprates derived from 1-alkynyllithiums into 1-alkynylamines, and these reactions were reported to give yields comparable to those obtained with **6h** (Scheme 28).[86]

The electrophilic amination of *O*-(trimethylsilyl)cyanohydrin anions derived from aldehydes succeeded in high yields using **7b** (Scheme 29).[92] Aromatic, heteroaromatic, and α,β-unsaturated aldehydes were converted into *O*-(trimethylsilyl)cyanohydrins with trimethylsilyl cyanide. This was followed by treatment

TABLE 6. Amination of Carbanions with Azides (8a–k)

azide	RM	scheme	ref
8a	ArMgBr	31	103
	ArLi	32–34, eq 36, eq 37	104, 106, 108, 109
	$C_6H_5CH_2CH_2MgBr$		103
8b	C_6H_5MgBr	eq 38	110
8c	R(Ar)MgBr	36, 37, eq 39	101, 111, 112
8d–h	C_6H_5MgBr, $C_6H_5CH_2CH_2MgBr$	36, 37	111
8i	ArMgBr, ArLi	38, eq 40	113, 114
8j	ArLi	40, 41	115, 116
8k	ArMgBr, ArLi	42	117

SCHEME 30

$$C_6H_5CR^1R^2Li \xrightarrow[2.\ H_2O]{1.\ \mathbf{7c},\ THF} \underset{\substack{50\text{–}62\% \\ (8\text{–}23\%\ ee)}}{C_6H_5CR^1R^2N(CH_3)_2}$$

R^1, R^2 = H, $COOC_2H_5$; CH_3, $COOC_2H_5$; H, CN

with lithium diisopropylamide, the amination was carried out at −78 to +20 °C for 5 h, and the amines were hydrolyzed to the *N,N*-dimethylamides. Lithium compounds of *O*-(trimethylsilyl)cyanohydrins are synthetically important owing to their easy preparation from aldehydes and simple workup in their reactions with electrophiles. The amination of cyanohydrin anions corresponds to an extraordinarily mild and specific oxidation of aldehydes to amides.

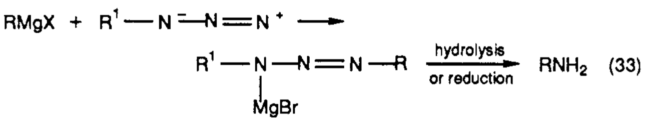
The chiral amination reagent (2*R*,4*S*,5*R*)-2-[*O*-(*N,N*-dimethylhydroxylamino)]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**7c**) was prepared and reacted with a number of lithium enolates and Grignard reagents in THF at −15 °C to yield chiral tertiary amines (Scheme 30 and eq 32, respectively).[93]

$$C_6H_5CH(CH_3)MgX \xrightarrow[2.\ H_2O]{1.\ \mathbf{7c},\ THF} \underset{\substack{63\%,\ ee\ 30\%\ (X{:}Cl) \\ 40\%,\ ee\ 44\%\ (X{:}Br)}}{C_6H_5CH(CH_3)N(CH_3)_2} \qquad (32)$$

As outlined, the introduction of amino and dimethylamino groups via **7a** and **7b**, respectively, provides an easy synthetic method for the amination of a variety of Grignard reagents, organolithium reagents, and lithium enolates. Even in those cases where only moderate to fair yields are obtained, the reaction may prove useful due to the easy access and stability of the reagents as well as their low tendency to undergo side reactions.

G. With Azides

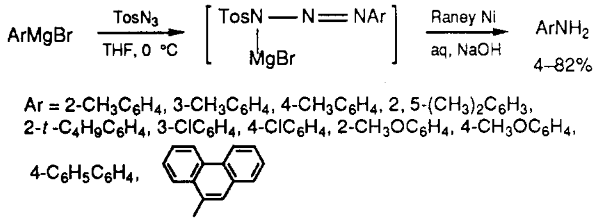
Organic azides can react with carbon nucleophiles to provide azido or diazo compounds.[19,94] However, it has been well established that azides can also react with Grignard reagents and organolithium compounds to give 1,3-disubstituted triazenes (eq 33).[18,19,94–99] Conversion into the respective amine can be brought about by either reductive or hydrolytic workup.



$$RMgX + R^1{-}N^{-}{=}N{\equiv}N^{+} \longrightarrow \underset{\substack{| \\ MgBr}}{R^1{-}N}{-}N{=}N{-}R \xrightarrow[\text{or reduction}]{\text{hydrolysis}} RNH_2 \qquad (33)$$

8a–k

SCHEME 31



$$ArMgBr \xrightarrow[THF,\ 0\ °C]{TosN_3} \left[\underset{\substack{| \\ MgBr}}{TosN}{-}N{=}NAr\right] \xrightarrow[aq,\ NaOH]{Raney\ Ni} \underset{4\text{–}82\%}{ArNH_2}$$

Ar = 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 2, 5-$(CH_3)_2C_6H_3$, 2-*t*-$C_4H_9C_6H_4$, 3-ClC_6H_4, 4-ClC_6H_4, 2-$CH_3OC_6H_4$, 4-$CH_3OC_6H_4$, 4-$C_6H_5C_6H_4$,

So far, azides **8a–k** have been used for the preparation of primary amines (Table 6). The uses of *p*-

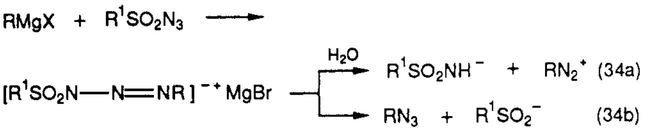
RN_3

8a, R = 4-$CH_3C_6H_4SO_2$ (Tos)
b, R = $(C_6H_5)_3Si$
c, R = $C_6H_5SCH_2$
d, R = 4-$CH_3OC_6H_4SCH_2$
e, R = $C_6H_5OCH_2$
f, R = CH_3SCH_2
g, R = CH_3OCH_2
h, R = $(CH_3)_3SiOC(i\text{-}C_3H_7)$
i, R = $(CH_3)_3SiCH_2$ (TMSMA)
j, R = $R^1CH{=}CR^2$
k, R = $(C_2H_5O)_2PO$ (DPPA)

toluenesulfonyl azide (**8a**), (phenylthio)methyl azide (**8c**), (trimethylsilyl)methyl azide (TMSMA; **8i**), and diphenyl phosphorazidate (DPPA, **8k**) have been extensively investigated. The azide **8a** is a shock-sensitive reagent;[100] **8c** was reported to be stable and could not be detonated by shock.[101] However, great caution is advisable in the handling of the azides, especially in large-scale synthetic work.

The use of azides in organometallic chemistry has been discussed,[18] and preparative methods and synthetic uses of azides have been surveyed in an excellent review.[19]

The reaction of Grignard reagents with sulfonyl azides was reported[97] to give sulfonyltriazenes, which are prone to fragmentation in two ways: cleavage to a sulfonamide and a diazo compound (eq 34a) and cleavage to a sulfinic acid and an azide (eq 34b).

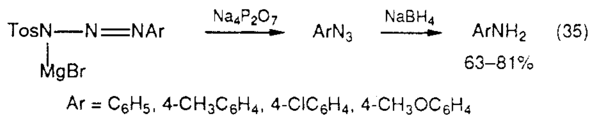


$$RMgX + R^1SO_2N_3 \longrightarrow$$

$$[R^1SO_2N{-}N{=}NR]^{-+}MgBr \xrightarrow{H_2O} R^1SO_2NH^- + RN_2^+ \qquad (34a)$$

$$[R^1SO_2N{-}N{=}NR]^{-+}MgBr \longrightarrow RN_3 + R^1SO_2^- \qquad (34b)$$

p-Toluenesulfonyl azide (**8a**) was found[102] to give only *p*-toluenesulfonamide and a diazo compound on reaction with carbanions. However, the reaction of **8a** with aryl Grignard reagents followed by reductive workup led to the isolation of arylamines in good yields in a one-pot procedure (Scheme 31).[103] The reductions of the tosyltriazene salts were carried out with Raney nickel and an aqueous base. The experimental procedure is as follows: To the Grignard reagent prepared from aryl bromide (1 equiv) and magnesium in THF is added **8a** (1 equiv). The reaction mixture is stirred and poured into a mixture of aqueous sodium hydroxide and ice. Raney nickel is added in portions with vigorous stirring. The mixture is steam-distilled and the product amines are isolated by diethyl ether extraction of the steam distillate. Attempts to prepare aliphatic amines were unsuccessful due to the instability of the triazene salts; β-phenylethylamine gave at best only a 25% yield. Anilines could also be prepared by the reduction of azides, which, in turn, were synthesized by fragmentation of tosyltriazene salts (eq 35). Yields of the azides were moderate; however, the overall conversions to amines were reported to compare favorably with those

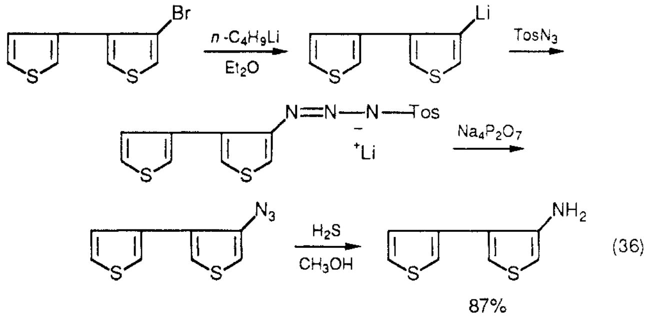

$$\mathrm{TosN{-}N{=}NAr}\ (\mathrm{MgBr}) \xrightarrow{\mathrm{Na_4P_2O_7}} \mathrm{ArN_3} \xrightarrow{\mathrm{NaBH_4}} \mathrm{ArNH_2} \quad (35)$$

63–81%

Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-$CH_3OC_6H_4$

obtained by in situ reduction of the triazene salts with Raney nickel.

p-Toluenesulfonyl azide (**8a**) was used in the facile transformation of ortho-substituted lithiobithienyls into amine derivatives.[104] Preparation of tosyltriazene salts from lithiobithienyls and **8a**, followed by fragmentation to azidobithienyls and reduction to aminobithienyls, gave aminobithienyls in 71–95% yields. The procedure for the synthesis of 2-amino-3,3′-dithienyl is shown in eq 36. Lithiobithienyls were prepared from the six isomeric ortho-substituted bromothienyls with *n*-butyllithium in diethyl ether at −70 °C, and a diethyl ether solution of 1 equiv of **8a** was added at the same temperature. The mixture was stirred for 5 h at −70 °C. When the temperature had reached −10 °C, the resulting triazene salt was filtered, the salt was suspended in diethyl ether, and tetrasodium pyrophosphate in water was added. The mixture was stirred overnight at 5 °C, and azidobithienyls were isolated from the organic layer. Reductions of azidobithienyls were carried out by bubbling hydrogen sulfide at 0 °C through a methanolic solution. After removal of the solvent and sulfur, the product amines were isolated.



(36)

87%

The utility of **8a** for introducing amino groups into ortho-lithiated aromatic compounds[105] has been reported (Scheme 32).[106] A one-pot procedure for the preparation of ortho-substituted anilines in good yields was similar to that used for the amination of arylmagnesium bromides.[103]

Ortho-amination of lithiated tertiary benzamides[107] with **8a** provided a short route for the synthesis of diversely substituted anthranilamides in modest to good yields (Scheme 33).[108] Substituted *N*,*N*-diethylbenzamides (1 equiv) were lithiated with *sec*-butyllithium in THF–TMEDA at −78 °C for 1 h and then treated with **8a** (1 equiv) according to the procedure used for lithiobithienyls.[104] Although the intermediate tosyltriazene lithium salts could be isolated, the best overall yields were achieved by their direct reduction with sodium borohydride under phase-transfer conditions to give the anthranilamides. Transmetalation of the lithiated species into the corresponding Grignard reagents using $MgBr_2{\cdot}2Et_2O$ leads to insignificant improvement in the yield of the anthranilamide.

The directed, lithiation-mediated ortho-amination procedure was extended to reactions of phenyloxazoline, methoxymethoxy, and carbamate systems to give ortho-substituted arylamines in good yields (Scheme 34).

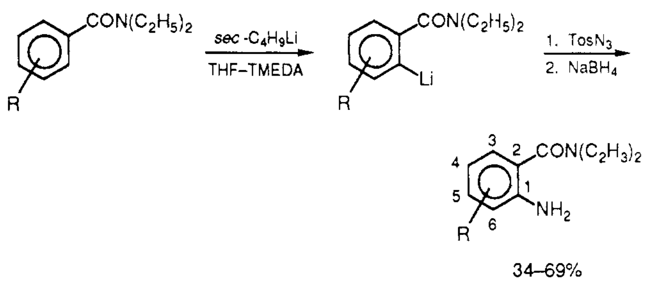
SCHEME 32

$$\mathrm{ArLi} \xrightarrow[\text{2. Raney Ni}]{\text{1. TosN}_3} \mathrm{ArNH_2}$$

37–85%

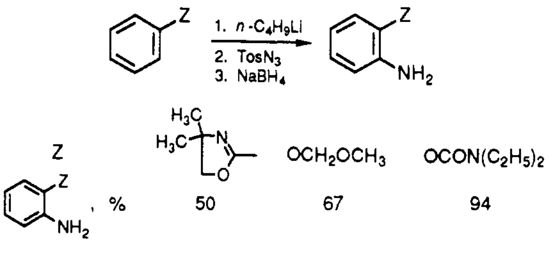
Ar = C_6H_5, 2-$CH_3OC_6H_4$, 2-$(CH_3)_2NCH_2C_6H_4$, 2-$CH_3NHCOC_6H_4$, 2-CH_3O-6-$CH_3NHCOC_6H_4$

SCHEME 33



R = H, 5-CH_3, 3-CH_3O, 4-CH_3O, 5-CH_3O, 6-CH_3O, 6-Cl, 3-$(CH_3)_3Si$-4-CH_3O, 3-$CH(Si(CH_3)_3)_2$-4-CH_3O, 5-CH_3-6-CH_3O

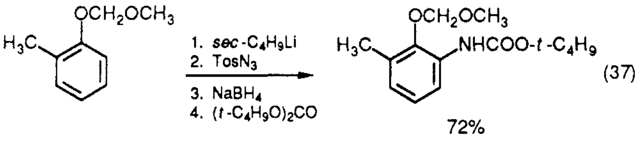
SCHEME 34



Z	oxazolinyl	OCH_2OCH_3	$OCON(C_2H_5)_2$
%, 2-Z-aniline	50	67	94

The procedure followed was identical with that used for diethylbenzamides, whereas the methoxymethoxy case required metalation with *tert*-butyllithium at 0 °C in diethyl ether.

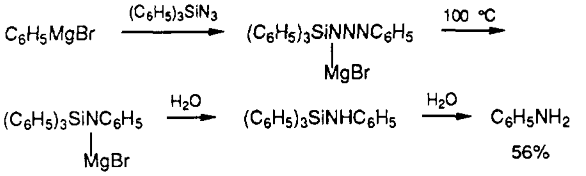
This approach was recently utilized in the regiospecific transformation of *o*-methyl(methoxymethoxy)benzene to the carbamate (eq 37).[109]



(37)

The oxidative coupling reaction of methoxy-substituted, ortho-lithiated benzamides with anilidochloro- or anilidocyanocuprates was reported to yield *N*-arylanthranilamides in moderate yields. This class of compounds was further converted into acridones. This work represents the second example[67] of substituted amino ligand transfer from heterocuprates (Scheme 35). The ortho-lithiated tertiary benzamide was heated with the anilido cuprates, generated from the lithioanilide and CuCl or CuCN in THF at −78 °C. The best results were obtained by treating the lithiated benzamide (1 equiv) with anilidocyanocuprate (5 equiv) at −10 °C. Subsequent oxygenation gave the anthranilamide.

Triphenylsilyl azide (**8b**) was reported[110] to aminate Grignard reagents. The triazene salt formed from the reaction of phenylmagnesium bromide with **8b** decomposed at 100–120 °C by elimination of nitrogen to give *N*-(triphenylsilyl)amide (eq 38a); subsequent hydrolysis led to aniline. Substitution of the azide group by the aryl group was also observed as a parallel reaction (eq 38b).



$$C_6H_5MgBr \xrightarrow{(C_6H_5)_3SiN_3} (C_6H_5)_3Si\underset{MgBr}{N}NNC_6H_5 \xrightarrow{100\ °C} (C_6H_5)_3Si\underset{MgBr}{N}C_6H_5 \xrightarrow{H_2O} (C_6H_5)_3SiNHC_6H_5 \xrightarrow{H_2O} \underset{56\%}{C_6H_5NH_2} \quad (38a)$$

$$C_6H_5MgBr + (C_6H_5)_3SiN_3 \rightarrow (C_6H_5)_3SiC_6H_5 \quad (38b)$$

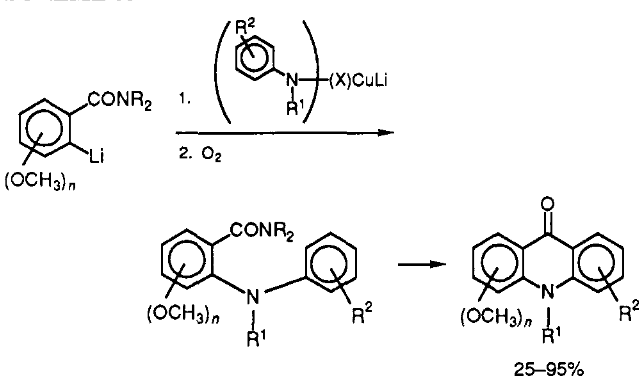
(Phenylthio)methyl azide (**8c**)[101,111] was used successfully for the amination of aryl- and alkylmagnesium bromides by Trost and Pearson. Direct utilization of organolithium compounds failed because of the lower acidity of the lithium salts. Addition of 1 equiv of $MgBr_2$ in THF to 1 equiv of aryllithium in diethyl ether or THF and subsequent addition of the resultant solution to **8c** (1.1 or 1.2 equiv) in THF at −78 to 0 °C followed by quenching with ammonium chloride at 0 °C gave the triazene salts (Scheme 36). Direct utilization of the aryl Grignard reagent precluded the need to add $MgBr_2$. For the purposes of amination, the triazene salts were not isolated, but dissolved in THF and hydrolyzed with methanol–aqueous potassium hydroxide to give the anilines.[101] In the case of the preparation of primary alkylamines,[111] the addition of the alkyl Grignard reagent to **8c** was followed by quenching with acetic anhydride, and resulting *N*-acyltriazenes were hydrolyzed (Scheme 37).

Trost and Pearson also undertook a systematic comparison[111] of various heteroatom-substituted methyl azides, ZCH_2N_3 (**8c**–**h**). The experiments established the order **c** ~ **d** > **f** > **g** ≫ **e** ~ **h**, since **8c** and **8d** react smoothly with phenylmagnesium bromide at −78 to 0 °C to give an 88% yield of triazene whereas **8e** and **8h** led only to the recovery of unchanged azide. A direct competition between **8f** and **8g** for phenethylmagnesium bromide at −78 to 0 °C led to the corresponding triazenes in a molar ratio of 7:1. This order does not correspond to either the Lewis basicity toward magnesium salts or the electron density, but clearly demonstrates the activating influence of sulfur compared to oxygen and of the arylthio group compared to the alkylthio group.

ZCH_2N_3
8c, Z = C_6H_5S
d, Z = p-$H_3COC_6H_4S$
e, Z = C_6H_5O
f, Z = CH_3S
g, Z = CH_3O
h, Z = $(CH_3)_3SiOCH(i\text{-}C_3H_7)$

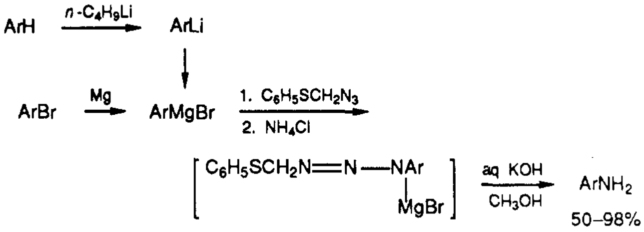
The structure of the initial addition product, **27a** or **27b**, was investigated[111] by quenching it with acetic anhydride to produce the acylated triazenes, **28a** or **28b** (Scheme 38). The adduct(s) formed in the reaction of phenethylmagnesium bromide with **8c** were quenched and a single product was obtained in 83% yield, which was chemically verified as **28a** by hydrolyzing it to the acetamide (**29a**). Cyclohexylmagnesium bromide gave only the acylated triazene (**28a**) in 76% yield but if the initial product, **27a** and/or **27b**, was warmed to 0 °C before quenching with acetic anhydride, only the regioisomer, **28b**, was isolated in 65% yield. On the assumption that the acyl group is transferred with allylic inversion, Trost and Pearson suggested that two different triazene salts, **27a** and **27b**, were formed under the above conditions; **27a** and **27b** are stabilized by internal ligation of sulfur to magnesium salts leading to four- and six-membered-ring chelates, respectively. An explanation depending upon the mechanism of attack of carbon onto an azide function was given for the exclusive kinetic formation of the thermodynamically less stable magnesium salt. Thus, treating phenethylmagnesium bromide with **8c**, quenching the initial adduct at a temperature between −78 and 0 °C to give a mixture of acylated triazenes, **28a** and **28b**, and subsequent reaction of this mixture with a number of nucleophiles led to the acetamide, **29a**, and recovered **28b**. Apparently, the attack on **28b** is less favorable, thus showing the ability of the lone pair of electrons at sulfur to stabilize an S_N2 transition state. This study revealed that the addition of a Grignard reagent to azides proceeds by a stereochemically controlled pathway.

SCHEME 35



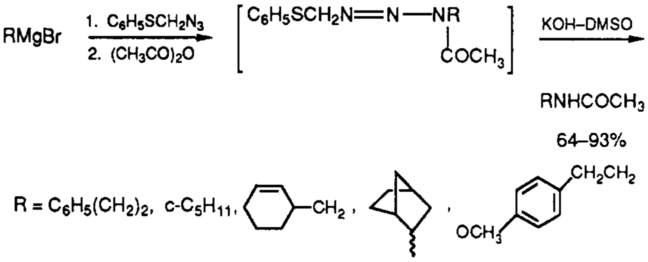
R = CH_3, C_2H_5; R^1 = H, CH_3
R^1 = H, OCH_3; X = Cl, CN

SCHEME 36

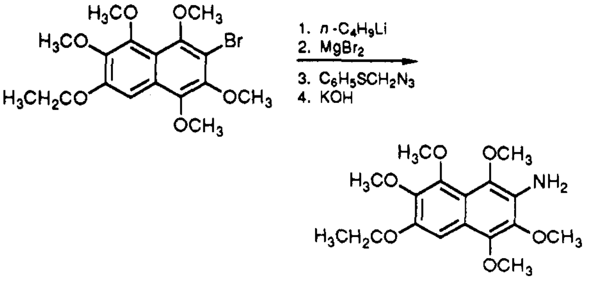


Ar = C_6H_5, 2-$CH_3OC_6H_4$, 4-$CH_3OC_6H_4$, 2-$(CH_3)_2NCH_2C_6H_4$, 2,6-$(CH_3O)_2C_6H_3$, 2-(CH_3O)-5-$C_6H_5C_6H_3$, 2-(t-C_4H_9CONH)-5-Cl

SCHEME 37

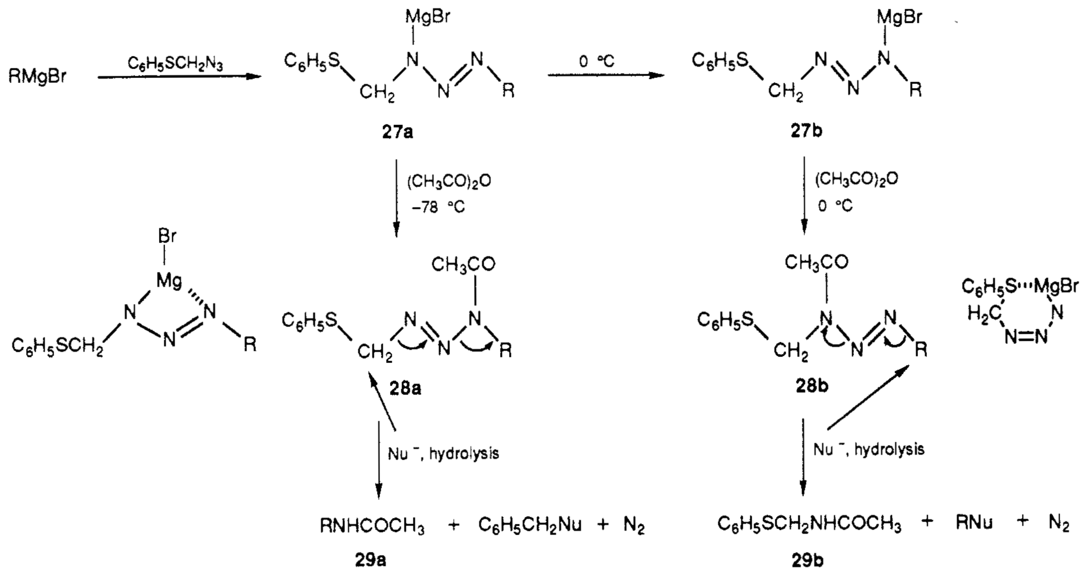


In a five-step synthesis of the naphthalene nucleus of Streptovaricin D in 33% overall yield, **8c** was used for introduction of the amino group (eq 39).[112]

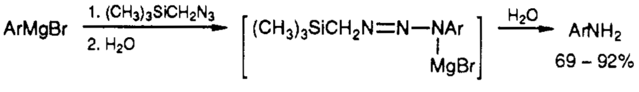


(39)

SCHEME 38



SCHEME 39

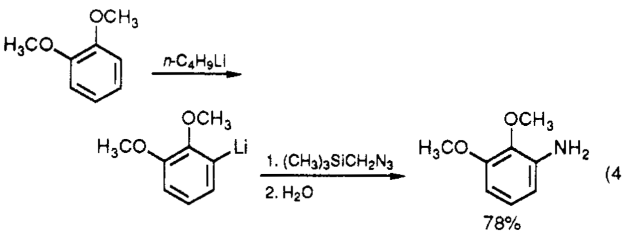


$$\mathrm{ArMgBr} \xrightarrow[2.\ H_2O]{1.\ (CH_3)_3SiCH_2N_3} \left[\begin{matrix}(CH_3)_3SiCH_2N{=}N{-}\underset{\displaystyle MgBr}{\underset{|}{N}}Ar\end{matrix}\right] \xrightarrow{H_2O} \underset{69-92\%}{ArNH_2}$$

Ar = C_6H_5, 2-$CH_3OC_6H_4$, 4-$CH_3OC_6H_4$, 4-ClC_6H_4, 2,6-$(CH_3)_2C_6H_3$

Another heteroatom-substituted methyl azide, (trimethylsilyl)methyl azide (TMSMA; **8i**), was used by Nishiyama and Tanaka for the amination of aryl Grignard and aryllithium compounds (Scheme 39).[113] This process required merely a neutral hydrolysis to decompose the intermediate triazenes. In a typical procedure, TMSMA (1.2 equiv) in diethyl ether was added to a diethyl ether solution of the Grignard reagent or lithium compound (1 equiv) at room temperature, and the mixture was stirred for 3 h. After removal of low-boiling substances under reduced pressure, the product amines were recovered from the residue. The authors suggested the formation of triazenes on the basis of Trost and Pearson's study[101,111] but did not report any details on the mechanisms of formation and decomposition of [(trimethylsilyl)methyl]triazene salts. The yields of amines from aryllithium reagents were found to be lower when compared with those from aryl Grignard reagents.

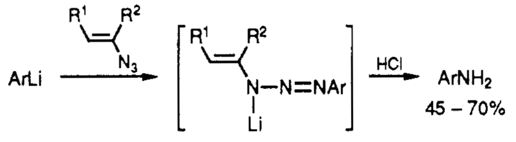
In a five-step synthesis of the alkaloid aaptamine, veratrol was ortho-lithiated and then aminated with TMSMA (**8i**) (eq 40).[114]



(40)

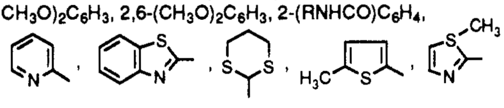
Hassner and co-workers found that[115,116] vinyl azides (**8j**) can act as H_2N^+ equivalents upon reaction with aryl- and heteroaryllithium reagents and produce arylamines in good yields (Scheme 40). In a typical procedure, **8j** (1 equiv) is added to an organolithium reagent (1 equiv) in THF at −78 °C. The mixture is allowed to warm to room temperature and is worked up with aqueous acid or base to recover the amines. Unlike (phenylthio)methyl azide (**8c**), vinyl azides can be used in the preparation of heterocyclic amines, and even benzyllithium can be transformed into benzylamine in 60% yield. Furthermore, Grignard reagents are more effective than organolithium reagents in reactions with **8c**, whereas the opposite is true for **8j**.

SCHEME 40



R^1, R^2 = H, C_6H_5; t-C_4H_9, H

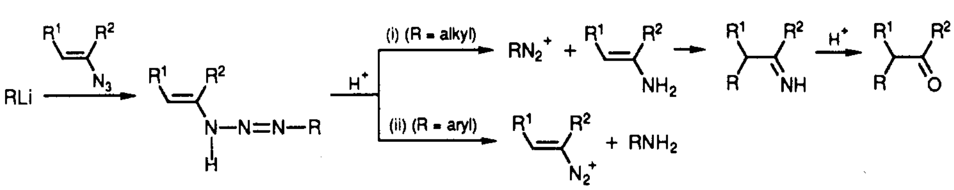
Ar = C_6H_5, 2,3-$(CH_3O)_2C_6H_3$, 2,6-$(CH_3O)_2C_6H_3$, 2-$(RNHCO)C_6H_4$,



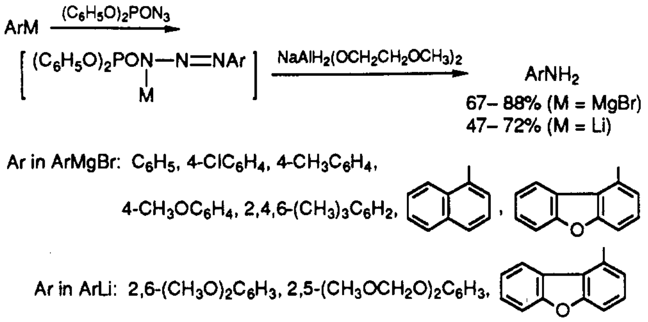
The attack of organolithium reagents on vinyl azides (**8j**) was reported[115,116] to proceed via formation of triazene intermediates, which were isolated. In the case of the hydrolysis of triazenes obtained from alkyllithium reagents, alkyl group transfer to carbon takes place via a diazonium compound and vinylamines, which hydrolyze to ketones (Scheme 41, path i). Treatment of aryltriazenes with dilute acid leads to the formation of amines and vinyldiazonium salts (Scheme 41, path ii); a vinyldiazonium salt is presumably transformed into an aldehyde or ketone.

Diphenyl phosphorazidate (DPPA; **8k**) was found[117] to react easily with aryl- and heteroaryllithium and Grignard reagents to give phosphoryltriazenes, which were treated with sodium bis(2-methoxyethoxy)aluminum hydride to give amino compounds in modest to good yields in a one-pot procedure (Scheme 42). Phosphoryltriazene intermediates can be isolated although they are labile; however, better results are obtained by their direct reduction in the same reaction vessel. A typical experimental procedure is as follows:

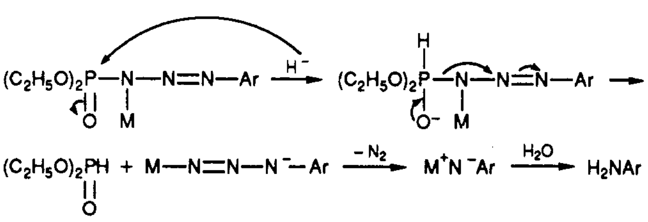
SCHEME 41



SCHEME 42



SCHEME 43



The arylmagnesium bromide or aryllithium reagent (1.1 equiv) is added to DPPA (**8k**; 1 equiv) in diethyl ether or in THF, respectively, at −72 °C. The mixture is stirred at that temperature for 2 h and then warmed to −20 °C (not necessary in the case of an organolithium compound). Again at −70 °C, sodium bis(2-methoxyethoxy)aluminum hydride in toluene (4.4 equiv) is added, followed by stirring at 0 °C for 1 h. After an aqueous quench, the product amines are isolated by the usual procedure. Methanolic hydrogen chloride or potassium hydroxide may also be used for the reductive decomposition of triazenes.

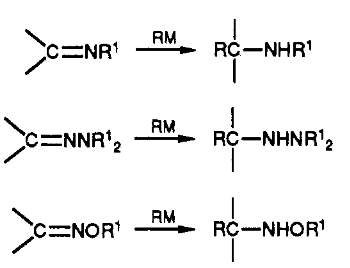
The efficiency of this method is either superior or comparable to that of the others. A number of arylmagnesium bromides were converted to the corresponding amines in good yields. Ortho-lithiated aromatic compounds afforded the corresponding amines in modest to good yields. Extension of the method to lithiated heteroaromatic compounds produced amino heteroaromatic compounds smoothly.

A plausible mechanism for the reductive decomposition of phosphoryltriazenes with hydrides is given in Scheme 43.

Amination reactions using azides require their reaction with Grignard reagents or organolithium compounds in a 1:1 molar ratio to form triazenes, which are then reduced or hydrolyzed to produce amines in a one-pot procedure. The uses of **8a**,[103] **8c**,[101] **8i**,[113] and **8k**[117] for the amination of arylmagnesium bromides have been reported. For the amination of aryllithium reagents, **8a**,[106,108] **8i**,[113] **8j**,[115] and **8k**[117] have been used, and for heteroaryllithium reagents, **8j**[115] and **8k**[117] have been used. Alkyl Grignard reagents and lithium compounds have not been reported to be aminated by use of azides—except in a few cases with **8a**[103] and **8c**[111]—in useful yields. Since aromatic and heteroaromatic lithium compounds are readily accessible by direct lithiation or lithium–halogen exchange, the use of azides represents a useful method for the synthesis of aromatic and heteroaromatic amines not readily synthesized by other methods.

H. With Oximes

The addition of organometallic compounds to imines, oximes, and hydrazones has become a useful process for the synthesis of amines and other compounds of interest (eq 41).[118]



(41)

It was found that ketoximes can also serve as electrophilic aminating reagents for Grignard reagents and organolithium reagents (eq 42).

(42)

Before surveying the amination processes with ketoximes, we include, due to its relevance to the present discussion, a very brief summary of the various scattered reports of reactions of Grignard reagents and organolithium reagents with oximes that furnish amines, amino acids, aziridines, β-amino alcohols, and other products.

The addition of organometallic reagents to oximes[118] has found limited applicability since oximes are often less electrophilic and less easily activated than the corresponding imines. In addition, the synthesis of the addition products requires the use of a considerable excess of organolithium reagents. α-Deprotonation of oximes and their *O*-alkyl derivatives with alkyllithium compounds is a facile reaction resulting in the formation of dianions, which can alkylated[119–122] or acylated[123] with high regioselectivity.

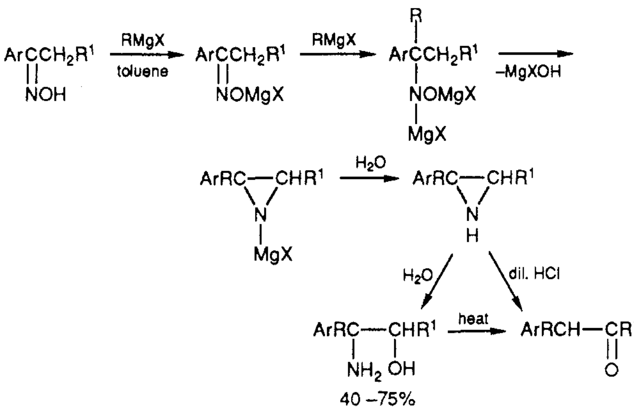
The reaction of benzaldoxime or its *O*-alkyl derivatives with phenylmagnesium bromide was reported to yield *N*-benzhydrylaniline (eq 43).[124]

$$C_6H_7CH{=}NOR^1 \xrightarrow[Et_2O,\ 35\ ^\circ C]{C_6H_5MgBr} \underset{49\%}{(C_6H_5)_2CHNHC_6H_5}$$

$$R^1 = H,\ CH_3,\ C_6H_5CH_2 \qquad (43)$$

The reactions of aromatic aldoximes with alkyl Grignard reagents gave *N*-alkylanilines, as well as ke-

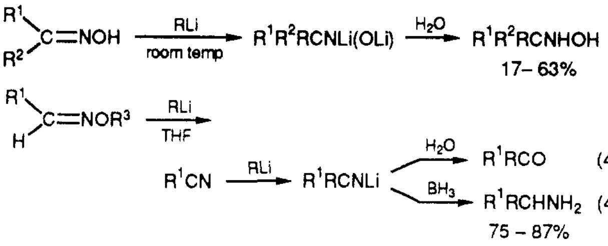
SCHEME 44



timines as side products (eq 44),[125] and *N*-arylformamide and aryl cyanide were isolated as intermediates.

$$ArCH{=}NOH \xrightarrow{RMgX} HCONHAr + ArCN \xrightarrow{RMgX} ArNHCHR_2 + Ar(R)C{=}NH \quad (44)$$

The reaction of aldoximes or dialkyl and diaryl ketoximes with a large excess of an organolithium compound yielded hydroxylamines (eq 45);[126] however, *O*-alkyl aldoximes were converted into ketones in high yield when they were treated with Grignard reagents or alkyllithium compounds (eq 46a).[127] Amines were also obtained as the reductive alkylation products after BH_3 reduction before the hydrolysis (eq 46b).



$$R^1R^2C{=}NOH \xrightarrow[\text{room temp}]{RLi} R^1R^2RCNLi(OLi) \xrightarrow{H_2O} R^1R^2RCNHOH \quad (45)$$

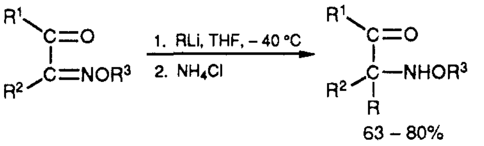
17–63%

$$R^1HC{=}NOR^3 \xrightarrow[THF]{RLi} R^1CN \xrightarrow{RLi} R^1RCNLi \xrightarrow{H_2O} R^1RCO \quad (46a)$$

$$R^1RCNLi \xrightarrow{BH_3} R^1RCHNH_2 \quad (46b)$$

75–87%

Organolithium reagents have been recently reported[128] to react with glyoxylate- and pyruvate-derived oximes to provide an efficient and direct route for the synthesis of unusual α-*N*-hydroxyamino acids (eq 47).



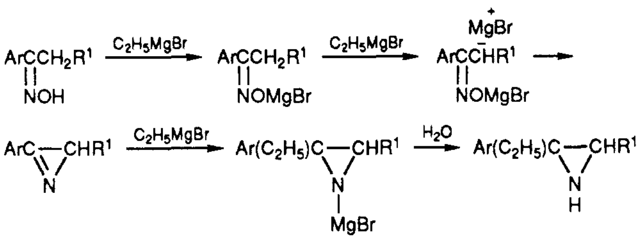
$$R^1C(=O)C(=NOR^3)R^2 \xrightarrow[2.\ NH_4Cl]{1.\ RLi,\ THF,\ -40\ ^\circ C} R^1C(=O)C(R)(R^2)NHOR^3 \quad (47)$$

63–80%

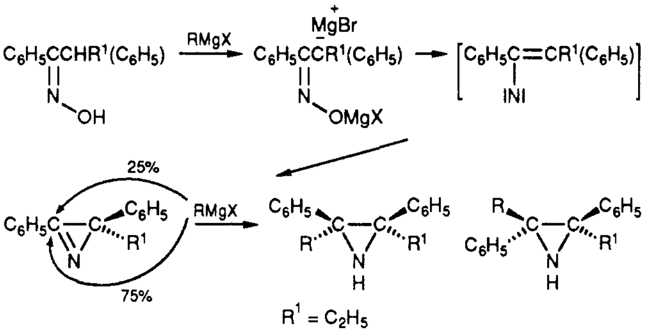
The formation of ethylenimines (aziridines) from alkyl or aryl ketoximes and Grignard reagents was first reported by Hoch and co-workers.[129–131] Subsequently, Campbell and co-workers showed that aryl Grignard reagents react with alkylaryl or dialkyl ketoximes to yield either ethylenimines or β-amino alcohols, the product obtained depending on the conditions used in the hydrolysis of the addition complex, and they suggested[132–136] a sequence of intermediates to account for the products (Scheme 44).

The reaction of alkyl ketoximes was also investigated and the results, in general, supported Campbell's proposals about the reaction sequence.[137–139] Later, a reaction process including the formation of azirines was proposed[140,141] for reactions of arylalkyl ketoximes with alkyl Grignard reagents (Scheme 45).

SCHEME 45



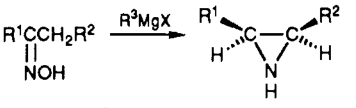
SCHEME 46



The reactions of cyclooctanone oxime tosylates with organolithium reagents were also investigated.[142] Reactions of oximes with Grignard reagents leading to aziridines were briefly reviewed.[143]

Alvernhe, Laurent, and co-workers investigated the mechanism and stereochemistry of the reaction of Grignard reagents with various ketoximes systematically[144–155] and prepared a number of aziridines in synthetically useful yields.[145,148,151,154,155] They reported that[150,152] the reaction proceeds through a vinyl nitrene intermediate leading to an azirine, that azirine formation is regiospecific since ring formation occurs with the group syn to the oxime hydroxy group,[144–148] and that the addition takes place on the less hindered side of the azirine leading to the diastereomeric aziridines[144,146,149,152] (Scheme 46).

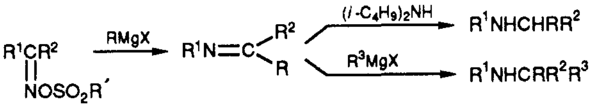
Ketoximes were also reported to undergo reduction to aziridines in their reactions with cyclohexyl- or isobutylmagnesium chloride rather than conversion to Hoch–Campbell products (eq 48).[156]



(48)

R^3 = *i*-C_4H_9, c-C_6H_{11}

The Beckmann rearrangement of oxime sulfonates by Grignard reagents provides an efficient and general entry to α-alkyl- and α,α-dialkylamines in good yields, since treatment of oxime sulfonates with Grignard reagents furnished the imines which were converted to α-alkylamines with diisobutylaluminum hydride (eq 49a) or further alkylated with allylic and propargylic Grignard reagents to give α,α-dialkylamines (eq 49b).[157]



$$R^1C(=NOSO_2R')R^2 \xrightarrow{RMgX} R^1N{=}C(R^2)R \xrightarrow{(i\text{-}C_4H_9)_2NH} R^1NHCHRR^2 \quad (49a)$$

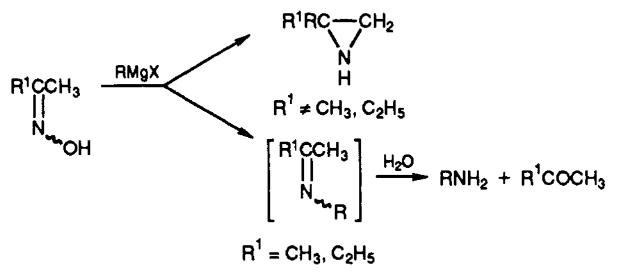
$$R^1N{=}C(R^2)R \xrightarrow{R^3MgX} R^1NHCRR^2R^3 \quad (49b)$$

So far, oximes **9a–e** and *O*-substituted derivatives **9f–k** have been used for preparation of primary amines (Table 7).

TABLE 7. Amination of Carbanions with Oximes (9a–k)

oxime	RM	scheme	ref
9a	α-$C_{10}H_7MgBr$	eq 50	154
9b	C_6H_5MgBr	eq 51	136
9c	R(Ar)MgX, C_6H_5Li	47, 48	154, 158
9d	C_6H_5Li	49	154
9e	C_6H_5MgBr	50	147
9f	ArMgBr, ArLi	51	159
9g–k	ArMgBr	eq 53	160

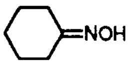
SCHEME 47



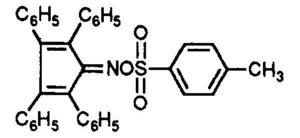
The first example of the use of oximes for the amination of a Grignard reagent was the reaction of benzaldoxime (**9a**) with α-naphthylmagnesium bromide,

$R^1R^2C{=}NOH$

9a, $R^1 = H; R^2 = C_6H_5$
b, $R^1 = CH(CH_3)_2, R^2 = C_6H_5$
c, $R^1 = CH_3, R^2 = CH_3$
d, $R^1 = CH_3, R^2 = C_2H_5$



9e

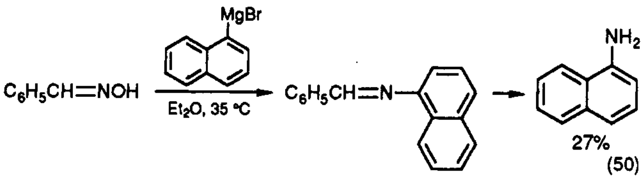


9f

$R^1R^2C{=}NOX$

9g, $R^1 = CH_3, R^2 = CH_3, X = 2,4,6\text{-}(CH_3)_3C_6H_2SO_2$
h, $R^1 = CH_3, R^2 = C_6H_5, X = 2,4,6\text{-}(CH_3)_3C_6H_2SO_2$
i, $R^1 = CH_3, R^2 = CH_3, X = 4\text{-}CH_3C_6H_4SO_2$
j, $R^1 = C_6H_5, R^2 = C_6H_5, X = CH_3$
k, $R^1 = C_6H_5, R^2 = C_6H_5, X = Si(CH_3)_3$

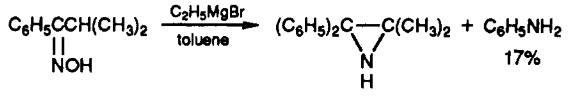
which was reported to yield α-naphthylamine, in contrast to the reaction of phenylmagnesium bromide (eq 50).[124]



(50)

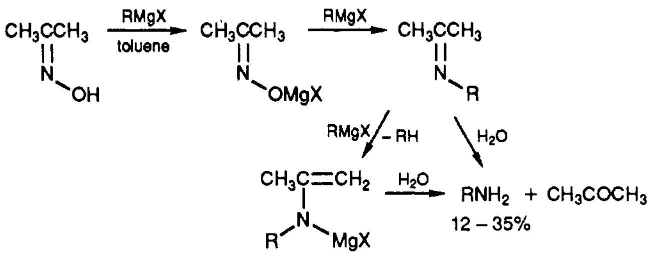
Grignard reagent/oxime molar ratio = 3/1

Isobutyrophenone oxime (**9b**) produced aniline as well as the Hoch–Campbell product in its reaction with phenylmagnesium bromide (eq 51).[136]



(51)

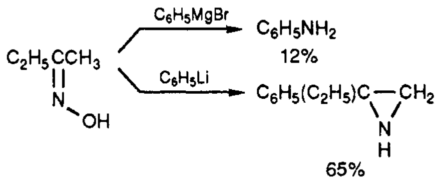
SCHEME 48



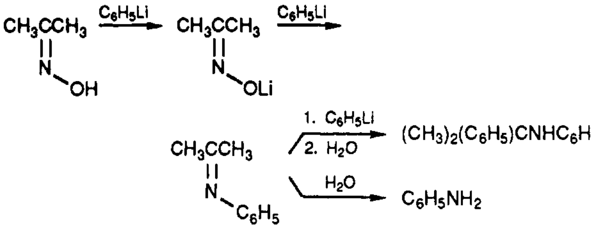
RMgX/oxime molar ratio = 1/1

R = n-C_4H_9, $C_6H_5(CH_2)_2$, C_6H_5, 4-ClC_6H_4, 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$, 2-$CH_3OC_6H_4$

SCHEME 49



Alvernhe, Laurent, and co-workers have reported that the reactions of acetone and butanone oximes with Grignard reagents do not yield aziridines, but primary amines, and that the ketone can be isolated (Scheme 47).[154,158] The reaction of acetone oxime (**9c**) with aryl and alkyl Grignard reagents gave primary amines in good yields;[158] however, 2 or 3 equiv of the Grignard reagent appears to be required for amination, since by increasing the ratio of RMgX:oxime from 1:1 to 2:1, the yield of amines almost doubled. Using a ratio of 3:1 was reported not to change the yield of amine, but the reaction of 2 or 3 mol of n-butylmagnesium bromide with 1 mol of acetone oxime resulted in the formation of 1.1 or 2 mol of butane, respectively. This result could be explained by the isomerization of the imine to the enamine (Scheme 48). In the case of phenyllithium, a 1:4 mixture of aniline and the addition product of phenyllithium to the imine was obtained (eq 52). However,

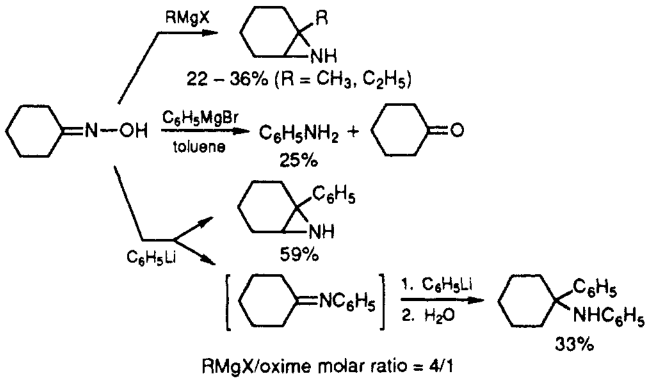


(52)

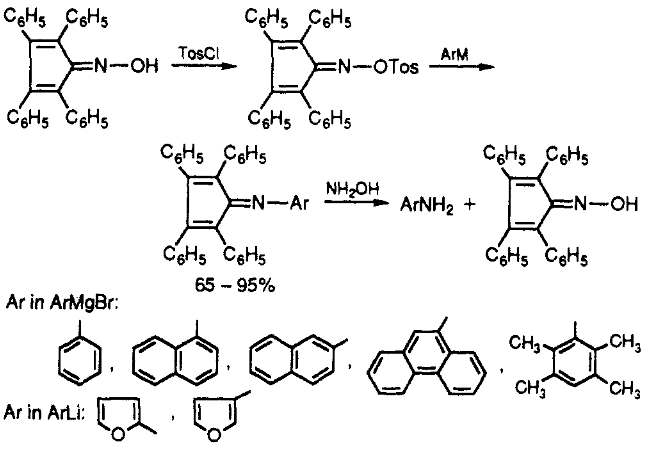
the reaction of butanone oxime (**9d**) with phenyllithium was reported to result in the isolation of an aziridine (Scheme 49).[154] Cyclohexanone oxime (**9e**) reacted with alkyl Grignard reagents and phenylmagnesium bromide to produce aziridines and aniline, respectively; however, the reaction with phenyllithium gave an aziridine as well as the addition product of phenyllithium to the imine (Scheme 50).[147]

Murdoch and co-workers reported[159] reactions of aryllithium and Grignard reagents with tetracyclone oxime O-tosylate (**9f**) to give the corresponding imines, which are then converted to arylamines by reaction with excess hydroxylamine (Scheme 51). A typical experimental procedure is as follows: Oxime tosylate **9f** (1 equiv) is added to phenylmagnesium bromide (7 equiv) in THF at −78 °C and stirred for 45 min. The imine is extracted with benzene, purified by liquid chromatography and crystallization, and then stirred at room temperature for 2 h with excess hydroxylamine in aqueous pyridine. The oxime is precipitated on acidification and, following base treatment, aniline is isolated as benzanilide (90% yield).

SCHEME 50



SCHEME 51



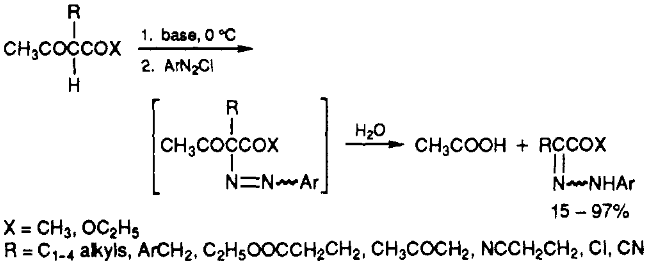
We have used a number of O-substituted ketoximes, $R_2C{=}NOX$, for the amination of phenylmagnesium bromide and found acetoxime *O*-mesitylenesulfonate (**9g**) to be a good amino-transfer reagent.[160] The amination yield decreases in the order **9g** > **9h** > **9i** ≫ **9j** > **9k**. The conditions for the amination of aryl Grignard reagents have been optimized as follows: Treatment of 1.3 equiv of arylmagnesium bromide with 1 equiv of **9g** in diethyl ether–toluene, stirring at 75 °C for 40 h, and acid hydrolysis give the corresponding amines, which are isolated by chromatography. The yields of aniline and *p*-toluidine are 58% and 36%, respectively. Amination of cyclohexylmagnesium bromide has been carried out at 0 °C for 2 h and led to a 40% yield of cyclohexylamine. The use of copper(I) iodide or magnesium chloride as a catalyst decreased the reaction time remarkably and/or increased the amine yield. On addition of 6% of copper(I) iodide, the yield of aniline has been found to be 54% after 2 h (eq 53). The use of phenyllithium and phenylzinc chloride resulted in a lower yield. Use of diphenylcopper(I) magnesium bromide at −20 °C gave aniline in 25% yield. Further work to reduce the reaction time still more and to improve the amination yield is in progress.

$R_2C{=}NOX$

9g, $R = CH_3$; $X = 2,4,6\text{-}(CH_3)_3C_6H_2SO_2$
h, $R = C_6H_5$; $X = 2,4,6\text{-}(CH_3)_3C_6H_2SO_2$
i, $R = CH_3$; $X = 4\text{-}CH_3C_6H_4SO_2$
j, $R = C_6H_5$; $X = CH_3$
k, $R = C_6H_5$; $X = Si(CH_3)_3$

$$C_6H_5MgBr \xrightarrow[2.\ H_2O]{1.\ \mathbf{9g},\ \text{ether–toluene, CuI, 75 °C}} \underset{54\%}{C_6H_5NH_2} \tag{53}$$

SCHEME 52



SCHEME 53

$$RZnCl + ArBF_4 \xrightarrow[Et_2O,\ 0\ °C]{} \underset{0\text{–}35\%}{RN{=}NAr}$$

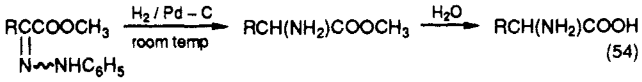
$R = t\text{-}C_4H_9,\ C_6H_5CH_2,\ C_6H_5,\ 4\text{-}ClC_6H_4,\ 4\text{-}CH_3CC_6H_4,\ 2,4,6\text{-}(CH_3)_3C_6H_2$
$Ar = C_6H_5,\ 4\text{-}ClC_6H_4,\ 4\text{-}CH_3OC_6H_4,\ 2,4,6\text{-}(CH_3)_3C_6H_2$

I. With Arenediazonium Salts

Arenediazonium salts act as amino cation equivalents as well as aryl cation equivalents, and the coupling of active methylene compounds with arenediazonium salts in protic media to give hydrazono compounds is known as the Japp–Klingemann reaction.[161] The Japp–Klingemann reaction is a special case of the coupling of diazonium salts with aliphatic compounds, distinguished by the fact that the intermediate azo compound ordinarily undergoes solvolysis to the corresponding hydrazono compound as rapidly as it is formed (Scheme 52). Acetoacetic acid esters have been extensively used in the Japp–Klingemann reaction.

For the preparation of α-hydrazono esters, equivalent amounts of the active methylene compound and the diazonium salt are allowed to react in acetate-buffered aqueous solution (or in the presence of a base, e.g., potassium hydroxide or sodium ethoxide) at 0 °C. The time required for the separation of the products varies with the activity of the methinyl group. Azo compounds are sometimes encountered as intermediates. (*E*)- and (*Z*)-α-hydrazono compounds were usually crystallized from ethanol or benzene.

The α-hydrazono or α-azo esters formed are easily reduced to α-amino acid esters in nearly quantitative yields when treated with hydrogen in the presence of palladium on carbon[162] and can then be hydrolyzed to the α-amino acids (eq 54).

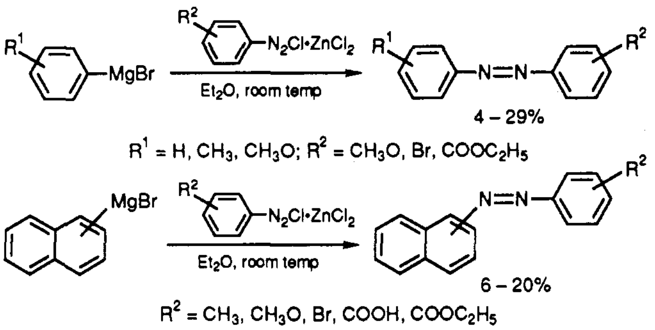


$$\underset{\|\atop N\sim NHC_6H_5}{RCCOOCH_3} \xrightarrow[\text{room temp}]{H_2/Pd-C} RCH(NH_2)COOCH_3 \xrightarrow{H_2O} RCH(NH_2)COOH \tag{54}$$

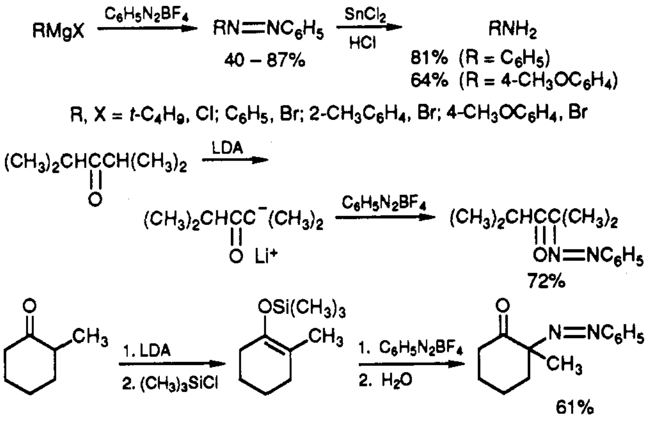
Simple esters do not work in the Japp–Klingemann reaction; in addition the reaction is not applicable to α-disubstituted acetoacetates, which are possible starting materials for α-disubstituted amino acids, since the success of the reaction requires the presence of an acidic hydrogen.

Organomagnesium, -lithium, -zinc, -cadmium, and -mercury compounds were subjected to the Japp–Klingemann reaction.[163-165] It was found[163] that alkyl- and arylzinc chlorides react with aryldiazonium tetrafluoroborates suspended in diethyl ether at 0 °C to give azo compounds in low yields (Scheme 53). Use of organomagnesium, -lithium, -cadmium, and -mercury compounds gave greatly reduced yields as do attempts

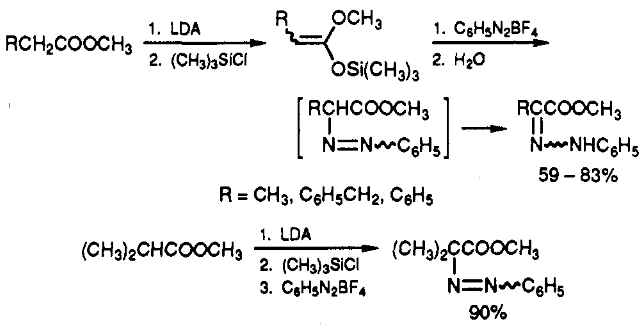
SCHEME 54



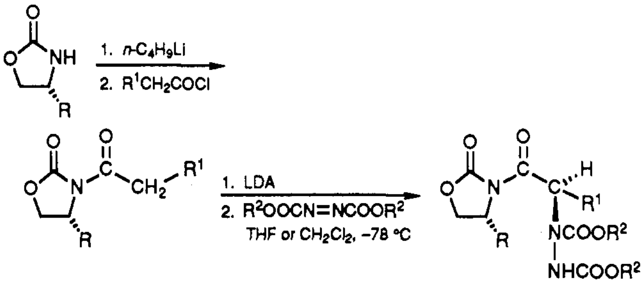
SCHEME 55



SCHEME 56



SCHEME 57



R	R^1	R^2	yield, %	ref
$C_6H_5CH_2$	CH_3, i-C_3H_7, t-C_4H_9, $CH_2{=}CHCH_2$, $C_6H_5CH_2$, C_6H_5	t-C_4H_9	91 – 96	168
i-C_3H_7	CH_3, i-C_3H_7, $C_6H_5CH_2$	CH_3, C_2H_5, t-C_4H_9, $C_6H_5CH_2$	83 – 91	169

to carry out the reaction as a homogeneous reaction in pyridine.

Arylmagnesium bromides were reacted with substituted benzenediazonium chloride–zinc chloride double salts[164] in diethyl ether at 0 °C or at room temperature to yield azo compounds in low yields (Scheme 54).

Later, it was reported that[165] coordinating solvents (such as THF) and lower temperatures (−78 °C) increase the yield of reaction between Grignard reagents and benzenediazonium tetrafluoroborate (**10a**) (Scheme 55). Use of organolithium reagents and lithium cuprates gave lower yields; lithium and silicon enolates of ketones were also employed. A typical experimental procedure is as follows: The organometallic reagent was added to 1.1 equiv of benzenediazonium tetrafluoroborate[166] suspended in THF at −78 °C. The reaction mixture was hydrolyzed to give the phenylazo compound, which was reduced with tin(II) chloride to give the amine in excellent yield.

Recently, it was observed[167] that the silicon enolates of esters (i.e., silyl ketene acetals) also react with benzenediazonium tetrafluoroborate (**10b**) to give α-azo or α-hydrazono esters, which are converted to α-amino esters upon hydrogenolysis (Scheme 56). Disubstituted silyl ketene acetals afforded the α-azo esters owing to the lack of an α-hydrogen atom. The silyl ketene acetal, which was prepared by deprotonation of an α-substituted acetic acid ester with LDA followed by quenching with chlorotrimethylsilane, was dissolved in pyridine and treated with solid benzenediazonium tetrafluoroborate (**10a**; 1.3 equiv) at 0 °C for 2 h. The resulting mixture was hydrolyzed to give (*E*)- and (*Z*)-hydrazono esters.

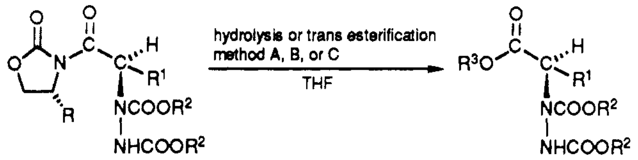
Electrophilic amination of silicon enolates with the aminating reagent **10a** constitutes a new methodology for introducing an amino group onto the α-carbon atom of simple esters.

J. With Dialkyl Azodicarboxylates

It has been recently reported[168–170] that α-amino acids are readily obtained by hydrogenolysis of α-hydrazino compounds, which are easily accessible in good yields and high optical purity through amination of chiral enolates by dialkyl azodicarboxylates.

Dialkyl azodicarboxylates (DAAD) react with the lithium enolates derived from the *N*-acyloxazolidones[168,169] to provide the hydrazide adducts in excellent yields (Scheme 57). In a typical experimental procedure, *N*-acyloxazolidones, obtained by N-acylation of oxazolidinones, were converted to their lithium enolates[170–173] (1.1 equiv of LDA, THF, −78 °C), and a solution of the DAAD (1.2 equiv, CH_2Cl_2, −78 °C[168] or 1.1 equiv, THF, −78 °C[169]) was added. The reactions were then immediately quenched with glacial acetic acid[168] or ammonium chloride solution.[169] A conventional isolation procedure afforded the diastereomerically pure hydrazides[168] or a mixture of diastereomers.[169] The diastereomeric ratios indicated that the substitution of both the dialkyl azodicarboxylate and the acyl side chain of the oxazolidinone influences the selectivity.[169] As the size of the R^2 group on the aminating reagent increases, the ratio improves (CH_3 < C_2H_5 < $CH_2C_6H_5$ < t-C_4H_9). Similarly, a greater bulk of the acyl side chain also increases the stereoselectivity (CH_3 < $CH_2C_6H_5$ < i-C_3H_7). Since the diastereomers are generally difficult to separate, the use of the more hindered di-*tert*-butyl azodicarboxylate (DBAD) (**11a**) or dibenzyl azodicarboxylate (**11b**) was found to be

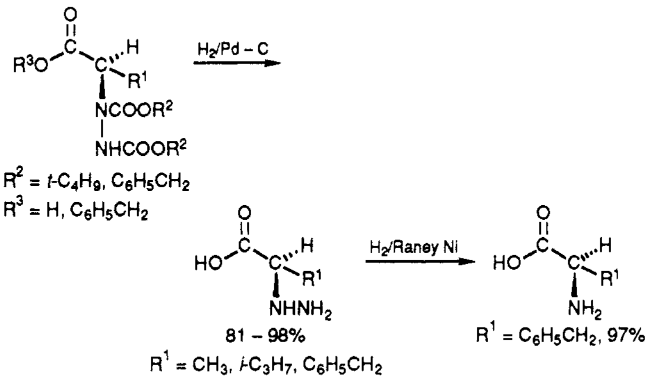
SCHEME 58



$R^1 = CH_3$, $i\text{-}C_3H_7$, $t\text{-}C_4H_9$, $C_6H_5CH_2$, C_6H_5
$R^2 = t\text{-}C_4H_9$, $C_6H_5CH_2$

method (reagent and conditions)	R^3	yield, %	ref
A (LiOH, 2:1 THF – H_2O, 3 h, 0 °C)	H	82 – 85	168, 169
B (CH_3OMgBr, CH_3OH, 30 min, 0 °C)	CH_3	71 – 89	168
C ($C_6H_5CH_2OLi$, THF, 2 h, – 50 °C)	$C_6H_5CH_2$	51 – 96	168, 169

SCHEME 59



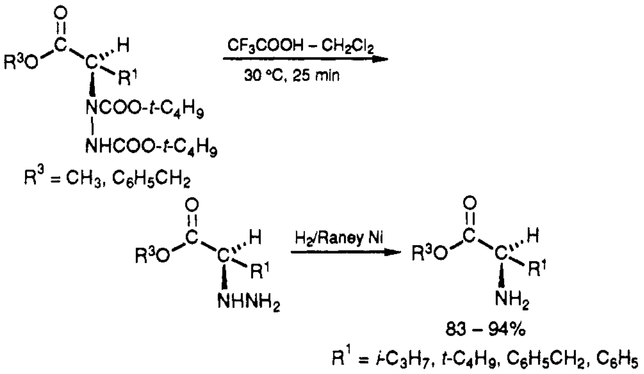
synthetically advantageous.[169] Dialkyl azodicarboxylates (DAAD) are commercially available reagents. Procedures have been published for preparation of DBAD.[174,175]

For removal of the chiral oxazolidinone moiety, hydrazide adducts were subjected to three types of reactions (Scheme 58): hydrolysis (method A),[168] methanolysis (method B),[168] and benzyl alcohol transesterification (method C).[168,169] Lithium benzyl oxide was found[169] to be the reagent of choice for carrying out the desired transesterification without concomitant racemization.

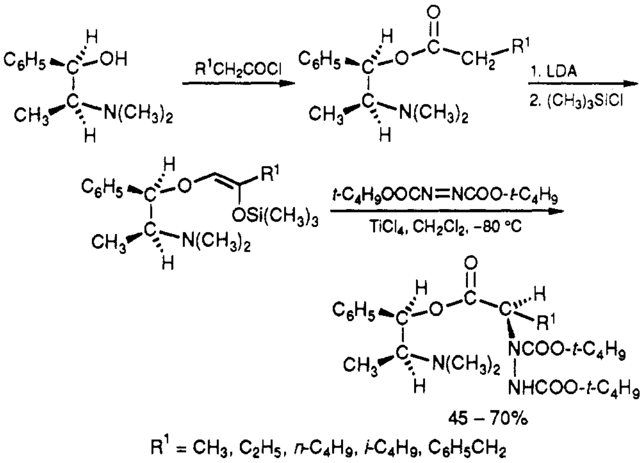
α-Hydrazides were hydrogenolyzed on palladium–carbon to the free α-hydrazino acids, and Raney nickel was used[169] to hydrogenolyze α-hydrazino acids[176,177] to the parent α-amino acids without detectable racemization (Scheme 59). In an alternative method for the conversion of α-hydrazido derivatives to α-amino esters,[168] an α-hydrazido ester was first deprotected to an α-hydrazino ester with trifluoroacetic acid in dichloromethane (1:1), and the resulting solution was then directly hydrogenated over Raney nickel to obtain the α-amino ester, accompanied only by a negligible loss in enantiomeric purity (Scheme 60).

For the stereoselective preparation of α-hydrazino and α-amino acids, the reaction of the DAAD–$TiCl_4$ complex with silicon enolates derived from *O*-acyl-*N*-methylephedrine has been shown to be a practical method[170] (Scheme 61). (1*R*,2*S*)-*N*-Methylephedrine was treated with an acyl chloride to obtain the corresponding acyl derivatives. LDA enolization, (THF, −78 °C) and chlorotrimethylsilane trapping (−78 °C) gave the silyl ketene acetals, which were worked up without aqueous quenching. Addition of silyl ketene acetals to the di-*tert*-butyl azodicarboxylate (**11a**)–$TiCl_4$ complex (1 equiv, CH_2Cl_2, -80 °C) gave the hydrazides in good yield and with high stereoselectivity.

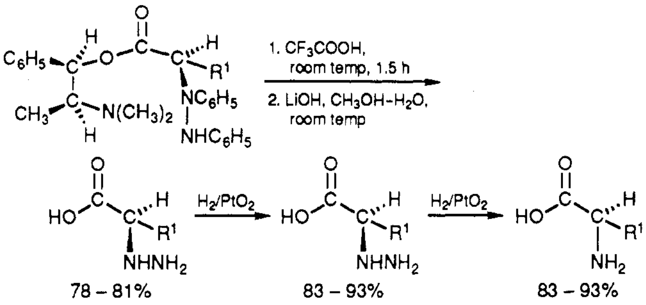
SCHEME 60



SCHEME 61



SCHEME 62



For removal of the *N*-methylephedrine moiety, the hydrazide adducts were converted to α-hydrazino esters, which were hydrolyzed to give α-hydrazino acids. Reduction with hydrogen over platinum oxide gave the corresponding α-amino acids in high yields and optical purity (Scheme 62).

K. With Amines

In a new development, Barton and co-workers have found that pentavalent and trivalent phenylbismuth compounds[178,179] and tetravalent phenyllead compounds[180] are able to N-arylate amines in the presence of catalytic amounts of copper or stoichiometric amounts of copper(II) diacylates.

Aliphatic and aromatic primary and secondary amines are mono- or di-N-phenylated by triphenylbismuth diacylates $[(C_6H_5)_3Bi(OCOR)_2]$ under copper catalysis[178,181] or by triphenylbismuth $[(C_6H_5)_3Bi]$ in the presence of copper(II) diacylate[179] in mild, selective, and high-yielding reactions.

SCHEME 63

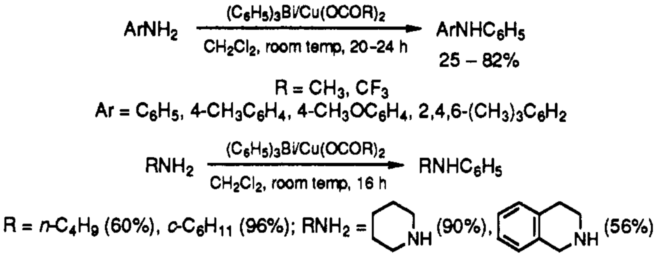
$$\mathrm{ArNH_2} \xrightarrow[\mathrm{CH_2Cl_2,\ room\ temp,\ 15\ min\ to\ 72\ h}]{\mathrm{(C_6H_5)_3Bi(OCOCH_3)_2/Cu}} \underset{90\text{–}97\%}{\mathrm{ArNHC_6H_5}}$$

$\mathrm{Ar} = \mathrm{C_6H_5},\ 4\text{-}\mathrm{CH_3C_6H_4},\ 4\text{-}\mathrm{CH_3OC_6H_4},\ 2,4,6\text{-}(\mathrm{CH_3})_3\mathrm{C_6H_2},\ 2\text{-}\mathrm{O_2NC_6H_4},\ 4\text{-}\mathrm{O_2NC_6H_4}$

$$\mathrm{RNH_2} \xrightarrow[\mathrm{CH_2Cl_2,\ room\ temp,\ 4\text{–}24\ h}]{\mathrm{(C_6H_5)_3Bi(OCOCH_3)_2/Cu}} \mathrm{RNHC_6H_5}$$

$\mathrm{R^1} = n\text{-}\mathrm{C_4H_9}\ (60\%),\ \text{c-}\mathrm{C_6H_{11}}\ (90\%),\ \mathrm{C_6H_5CH_2CH(COOC_2H_5)}\ (70\%)$

SCHEME 64



Reactions of substituted anilines and aliphatic amines with $(C_6H_5)_3Bi(OCOCH_3)_2$ (1.1 equiv) in dichloromethane in the presence of copper (0.1 equiv) at room temperature afforded[178] the corresponding N-mono- or N,N-diphenylated amines in high yields (Scheme 63). Phenylation of diphenylamine and bis(4-methoxyphenyl)amine with 2.2 equiv of the reagent gave the respective products in 23% and 78% yields, respectively. *n*-Butylamine was diphenylated in 70% yield. Aliphatic and heterocyclic secondary amines were not phenylated. Various pentavalent phenylbismuth derivatives were tried as N-phenylating agents, and the bis(trifluoroacetate) derivative, $(C_6H_5)_3Bi(OCOCF_3)_2$, was found to be the most efficient since its use decreased the reaction time remarkably.

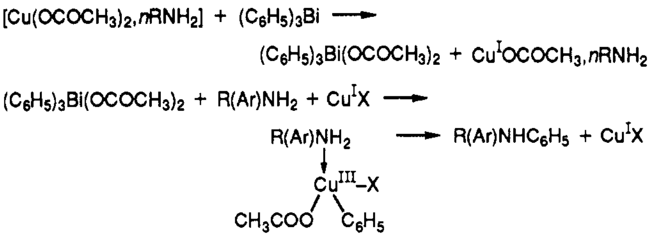
The N-phenylation of amines by triphenylbismuth diacetate catalyzed by copper diacetate was reported;[181] however, the reaction required a large excess of the amine.

Amines react with $(C_6H_5)_3Bi$ in the presence of copper diacylate (0.5 equiv) to give good yields of the monophenylated derivatives[179] (Scheme 64). Stoichiometric use of the copper(II) salt gave the best yields, in contrast to the catalytic amount required in the $(C_6H_5)_3Bi(OCOR)_2$ + Cu species system. Whereas in the $(C_6H_5)_3Bi(OCOR)_2$ + Cu or Cu(II) systems the yields are mostly related to the steric hindrance of the amine, the $(C_6H_5)_3Bi$ + $Cu(OCOR)_2$ system shows also a dependence on the basicity of the amine.

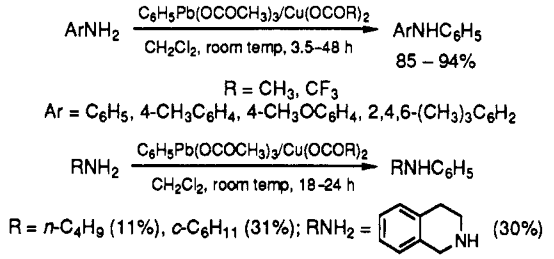
The proposed mechanism[179] for the phenylation with phenylbismuth reagents involves an in situ oxidation of $(C_6H_5)_3Bi$ by the $Cu(OCOCH_3)_2$–amine complex to give $(C_6H_5)_3Bi(OCOCH_3)_2$, which subsequently reacts with a copper(I) species to give a phenylcopper(III) species which, in turn, phenylates the amine (Scheme 65). The reaction of amines with lithium dialkyl- or diarylcuprates was already stated to yield N-alkylated or N-arylated amines[67] (Scheme 22).

Lastly, the copper-catalyzed phenylkation of aromatic and aliphatic amines using $(C_6H_5)_xPb(OCOCH)_{4-x}$ and $Cu(OCOR)_2$ (0.1 equiv) has been reported.[180] Phenyllead triacetate (x = 1) was the most efficient of the lead reagents (Scheme 66). Reactions of $C_6H_5Pb(OCOCH_3)_3$ with aliphatic or alicyclic amines gave the corresponding *N*-phenyl derivatives in poor to modest yields. Thus, the $(C_6H_5)_3Bi(OCOR)_2$ + Cu system is much superior. At present, one limitation of the procedure is when an expensive aryl halide has to be used to prepare the bismuth derivative, since at least 2 equiv of C_6H_5 is lost from $(C_6H_5)_3Bi(OCOR)_2$, with only one being used in the reaction.

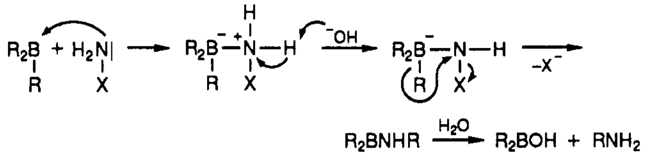
SCHEME 65



SCHEME 66



SCHEME 67



Arylations using organobismuth and organolead reagents have been recently reviewed.[182]

L. Miscellaneous Reactions

The reaction between phenylmagnesium bromide and nitrosyl chloride was investigated[183-185] and the product was found to be diphenylamine and not nitrosobenzene as reported in the earlier literature.[186] Nitrosobenzene and diphenylnitric oxide were, however, detected as reaction intermediates.[187] Symmetrical diarylamines were prepared by reacting aryl Grignard reagents with nitrosyl chloride (eq 55).[188] The reaction of phenyllithium with nitrosyl chloride also yielded diphenylamine.[189]

$$\mathrm{ArMgX} \xrightarrow[-78\ ^\circ\mathrm{C,\ Et_2O}]{\mathrm{NOCl}} \underset{11\text{–}28\%}{\mathrm{Ar_2NH}}$$

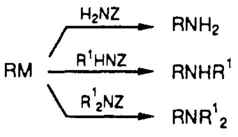
$$\mathrm{Ar} = \mathrm{C_6H_5},\ \mathrm{CH_3C_6H_4} \tag{55}$$

Molecular nitrogen was found to react with aryllithium compounds in the presence of some transition-metal compounds to give primary amines after hydrolysis (eq 56).[190]

$$\mathrm{ArLi} + \mathrm{N_2} \xrightarrow[2.\ \mathrm{H_2O}]{1.\ \mathrm{TiCl_4}} \mathrm{ArNH_2} + \mathrm{NH_3} \tag{56}$$

After reviewing electrophilic amination methods for organomagnesium, -lithium, -zinc, and -copper com-

TABLE VIII. Amination of Carbanions[a,b]



M = Li, Na, K, MgX, Cu, Zn

entry	RM	aminating reagent	yield,[c] %	ref	scheme
		R = Alkyl			
1	CH_3MgBr	1a-1	26	20	1
2	CH_3Li	1a-2	7	30	7
3	CH_3Li	2a–CH_3Li	80	43	16
4	CH_3Li	6b	45	81	25
5	CH_3Li	6e	39	81	25
6	C_2H_5MgCl	1a-1	57	20	1
7	C_2H_5MgCl	1d-1	29	26	4
8	C_2H_5MgBr	1a-1	28	20	1
9	C_2H_5MgBr	2a-1	67	44a	10
10	C_2H_5MgBr	2a-2	81	45	11
11	C_2H_5MgBr	2b-1	46	44b	10
12	C_2H_5Li	2a–CH_3Li	78	43	16
13	$(C_2H_5)_2Zn$	1a-3	46	30	9
14	$(C_2H_5)_2Zn$	1a-2	17	30	9
15	$(C_2H_5)_2Zn$	1f[d]	70	36	9
16	$(C_2H_5)_2Zn$	1g	78	36	9
17	$(C_2H_5)_2Zn$	1g	71	36	9
18	$C_6H_5(CH_2)_2MgCl$	1a-1	74	20	1
19	$C_6H_5(CH_2)_2MgCl$	1b	34	24	2
20	$C_6H_5(CH_2)_2MgCl$	1c	18	25	3
21	$C_6H_5(CH_2)_2MgCl$	1d-1	30	26	4
22	$C_6H_5(CH_2)_2MgCl$	2a-2	68	45	11
23	$C_6H_5(CH_2)_2MgBr$	8a-1	25	103	31
24	$C_6H_5(CH_2)_2MgBr$	8c	80	111	37
25	$C_6H_5(CH_2)_2MgBr$	9c-2	48	158	48
26	$4\text{-}CH_3OC_6H_4(CH_2)_2MgBr$	8c	75	111	37
27	$n\text{-}C_3H_7MgCl$	1a-1	58	20	1
28	$n\text{-}C_3H_7MgCl$	1g	52	27	5
29	$n\text{-}C_3H_7MgBr$	1a-1	27	20	1
30	$n\text{-}C_3H_7MgBr$	2a-2	85	45	11
31	$(n\text{-}C_3H_7)_2Zn$	1d-2	17	30	9
32	$i\text{-}C_3H_7MgCl$	1a-1	65	21	1
33	$i\text{-}C_3H_7MgCl$	1d-1	23	26	4
34	$i\text{-}C_3H_7MgBr$	1a-1	37	21	1
35	$n\text{-}C_4H_9MgCl$	1a-1	59	20	1
36	$n\text{-}C_4H_9MgCl$	1b	29	24	2
37	$n\text{-}C_4H_9MgCl$	1c	15	25	3
38	$n\text{-}C_4H_9MgCl$	1d-1	59	26	4
39	$n\text{-}C_4H_9MgCl$	1e	72	27	5
40	$n\text{-}C_4H_9MgCl$	1f[e]	85	27	5
41	$n\text{-}C_4H_9MgCl$	1g	36	27	5
42	$n\text{-}C_4H_9MgCl$	1g	43	27	5
43	$n\text{-}C_4H_9MgCl$	2a-2	58	45	11
44	$n\text{-}C_4H_9MgBr$	1a-1	27	20	1
45	$n\text{-}C_4H_9MgBr$	2a-2	63	45	11
46	$n\text{-}C_4H_9MgBr$	2a-CH_3Li	16	43	16
47	$n\text{-}C_4H_9MgBr$	9c-1	15	158	48
48	$(n\text{-}C_4H_9)_2Mg$	1a-4	97	23	—
49	$n\text{-}C_4H_9Li$	1d-3	39	30	7
50	$n\text{-}C_4H_9Li$	2a–CH_3Li	77	43	16
51	$n\text{-}C_4H_9Li$	2g–CH_3Li	63	61	17
52	$n\text{-}C_4H_9Li$	2h–CH_3Li	68	61	18
53	$n\text{-}C_4H_9Li$	6b, 6d	47	81	25
54	$sec\text{-}C_4H_9MgCl$	1a-1	70	21	1
55	$sec\text{-}C_4H_9MgCl$	1b	46	24	2
56	$sec\text{-}C_4H_9MgCl$	1c	21	25	3
57	$sec\text{-}C_4H_9MgCl$	1d-2	23	26	4
58	$sec\text{-}C_4H_9MgCl$	2a-1	73	44a	10
59	$sec\text{-}C_4H_9MgCl$	2a–CH_3Li	67	43	16
60	$sec\text{-}C_4H_9MgCl$	2g-CH_3Li	62	61	17
61	$i\text{-}C_4H_9MgBr$	2a-2	90	45	11
62	$t\text{-}C_4H_9MgCl$	1a-1	60	20	1
63	$t\text{-}C_4H_9MgCl$	1b	45	24	2
64	$t\text{-}C_4H_9MgCl$	1c	24	25	3
65	$t\text{-}C_4H_9MgCl$	1d-1	30	26	4
66	$t\text{-}C_4H_9MgCl$	2a-1	74	44a	10

TABLE VIII (Continued)

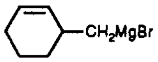
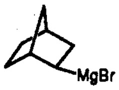
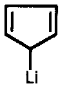
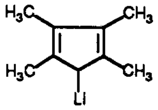
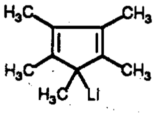
entry	RM	aminating reagent	yield,[c] %	ref	scheme
67	t-C_4H_9MgCl	**2a**-2	70	45	11
68	t-C_4H_9MgCl	**10a**	40[f]	165	55
69	t-C_4H_9MgBr	**1a**-1	20	21	1
70	t-C_4H_9Li	**2a**–CH_3Li	80	43	16
71	t-C_4H_9Li	**2g**–CH_3Li	30	61	17
72	n-$C_5H_{11}MgCl$	**1d**-1	21	26	4
73	n-$C_5H_{11}MgCl$	**1g**	34	27	5
74	n-$C_5H_{11}MgCl$	**2a**-2	46	45	11
75	n-$C_5H_{11}MgBr$	**2a**-2	65	45	11
76	sec-$C_5H_{11}MgCl$	**1a**-1	72	21	1
77	sec-$C_5H_{11}MgBr$	**1a**-1	32	21	1
78	i-$C_5H_{11}MgCl$	**1a**-1	55	20	1
79	i-$C_5H_{11}MgCl$	**2a**-1	80	44a	10
80	i-$C_5H_{11}MgCl$	**2a**-2	60	45	11
81	i-$C_5H_{11}MgBr$	**1a**	27	20	1
82	i-$C_5H_{11}MgCl$	**2a**-1	71	44a	10
83	i-$C_5H_{11}MgBr$	**2a**-2	65	45	11
84	i-$C_5H_{11}MgBr$	**1b**-1	62	44b	10
85	t-$C_5H_{11}MgCl$	**1a**-1	66	21	1
86	t-$C_5H_{11}MgCl$	**2a**-2	49	45	11
87	n-$C_6H_{13}MgBr$	**7a**-1	27	90	eq 31
88	$BrMg(CH_2)_5MgBr$	**2a**-2	63	45	11
89	$BrMg(CH_2)_6MgBr$	**2a**-2	51	45	11
90	$BrMg(CH_2)_{10}MgBr$	**2a**-2	53	45	11
91		**6b**	47	81	25
92	c-$C_6H_{11}MgBr$	**2b**-1	62	44b	10
93	c-$C_6H_{11}MgBr$	**6f**	14	84	——
94	c-$C_6H_{11}MgBr$	**8c**	93	111	37
95		**8c**	64	111	37
96		**8c**	70	111	37
	R = Allylic, Benzylic				
97	$CH_2{=}CHCH_2MgBr$	**2a**-2	40	45	11
98	$C_6H_5CH{=}CHCH(C_6H_5)Li$	**6b**	37	81	25
99	$C_6H_5CH{=}C(t\text{-}C_4H_9)CH(C_6H_5)Li$	**6b**	31	81	25
100	$C_6H_5CH{=}C(C_6H_5)CH(C_6H_5)Li$	**6b**	38	81	25
101	$C_6H_5CH{=}C(C_6H_5)CH(C_6H_5)Li$	**6c**	39	81	25
102	$C_6H_5CH{=}CHCH_2MgCl$	**1a**-1	14	22	——
103	$C_6H_5CH{=}CHCH_2MgCl$	**2a**-2	5	45	11
104		**6h**	47	85	eq 23
105		**6h**	40	85	eq 23
106		**7a**-2	37	91	27
107	$C_6H_5CH_2MgCl$	**1a**-1	85	20	1
108	$C_6H_5CH_2MgCl$	**1b**	63	24	2
109	$C_6H_5CH_2MgCl$	**1c**	34	25	3
110	$C_6H_5CH_2MgCl$	**1d**-1	32	26	4
111	$C_6H_5CH_2MgCl$	**1e**	75	27	5
112	$C_6H_5CH_2MgCl$	**1e**	70	27	5
113	$C_6H_5CH_2MgCl$	**1f**[g]	95	27	5
114	$C_6H_5CH_2MgCl$	**1f**[h]	90	27	5
115	$C_6H_5CH_2MgCl$	**1f**[i]	78	27	5
116	$C_6H_5CH_2MgCl$	**1g**	28	27	5
117	$C_6H_5CH_2MgCl$	**1g**	43	27	5
118	$C_6H_5CH_2MgCl$	**2a**-2	57	45	11
119	$C_6H_5CH_2MgCl$	**2b**-1	79	44b	10
120	$C_6H_5CH_2MgCl$	**7a**-2	70	91	27

TABLE VIII (Continued)

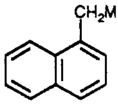
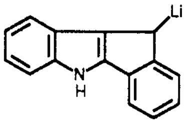
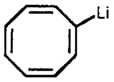
entry	RM	aminating reagent	yield,[c] %	ref	scheme
121	$C_6H_5CH_2MgBr$	**7a**-2	51	91	27
122	$C_6H_5CH_2Li$	**2a**–CH_3Li	97	43	16
123	$C_6H_5CH_2Li$	**7a**-2	30	91	27
124	$C_6H_5CH_2Li$	**8j**	60	115	40
125	$C_6H_5CH(CH_3)MgCl$	**7c**	63	93	eq 32
126	$C_6H_5CH(CH_3)MgBr$	**7c**	40	93	eq 32
127		**1a**-1	47	22	——
128		**6c**	43	82	eq 22
129	$(C_6H_5)_2CHLi$	**7a**-2	41	91	27
130	$(C_6H_5)_3Li$	**7a**-2	30	91	27
		R = Alkenyl, Alkynyl			
131	$(Z)\text{-}CH_3CH{=}CHLi$	**6c**	28	81	25
132		**6b**	69	82	eq 22
133	$(n\text{-}C_3H_7C{\equiv}C)_3CuLi_2$	**6h**	69	86	26
134	$(n\text{-}C_3H_7C{\equiv}C)_3CuLi_2$	**7b**	87	86	28
135	$(n\text{-}C_4H_9C{\equiv}C)_3CuLi_2$	**6h**	60	86	26
136	$(n\text{-}C_4H_9C{\equiv}C)_3CuLi_2$	**7b**	78	86	28
137	$(t\text{-}C_4H_9C{\equiv}C)_3CuLi_2$	**7b**	71	86	28
138	$(n\text{-}C_6H_{13}C{\equiv}C)_3CuLi_2$	**7b**	82	86	28
139	$C_6H_5C{\equiv}CLi$	**1f**[j]	3	31	eq 6
140	$(C_6H_5C{\equiv}C)_3CuLi_2$	**6h**	83	86	26
141	$(C_6H_5C{\equiv}C)_3CuLi_2$	**7b**	70	86	28
142	$((CH_3)_3SiC{\equiv}C)_3CuLi_2$	**7b**	67	86	28
143	$(C_6H_5SC{\equiv}C)_3CuLi_2$	**7b**	45	86	28
144	$(c\text{-}C_6H_{11}C{\equiv}C)_3CuLi_2$	**7b**	75	86	28
		R = Aryl, Heteroaryl			
145	C_6H_5MgCl	**1a**-1	27	20	1
146	C_6H_5MgCl	**1b**	35	24	2
147	C_6H_5MgCl	**1d**-1	5	26	4
148	C_6H_5MgBr	**1a**-1	15	20	1
149	C_6H_5MgBr	**2a**-1	67	44a	10
150	C_6H_5MgBr	**2a**–CH_3Li	37	43	16
151	C_6H_5MgBr	**2b**-1	57	44b	10
152	C_6H_5MgBr	**4a**	79	76	——
153	C_6H_5MgBr	**6c**	47	81	25
154	C_6H_5MgBr	**6f**	54	84	——
155	C_6H_5MgBr	**7a**-1	67	90	eq 31
156	C_6H_5MgBr	**7a**-2	22	91	27
157	C_6H_5MgBr	**8a**-2	81	103	eq 35
158	C_6H_5MgBr	**8b**	56	110	eq 38
159	C_6H_5MgBr	**8c**	88	101	36
160	C_6H_5MgBr	**8i**	72	113	39
161	C_6H_5MgBr	**8j**	68	115	40
162	C_6H_5MgBr	**8k**	73	117	42
163	C_6H_5MgBr	**9b**	17	136	eq 51
164	C_6H_5MgBr	**9c**-2	62	158	48
165	C_6H_5MgBr	**9d**	12	154	49
166	C_6H_5MgBr	**9e**	25	147	50
167	C_6H_5MgBr	**9f**	90	159	51
168	C_6H_5MgBr	**10a**	81	165	55
169	C_6H_5Li	**1a**-2	33	30	7
170	C_6H_5Li	**2a**-1	63	44a	10
171	C_6H_5Li	**2a**-2	71	45	11
172	C_6H_5Li	**2a**-4	53	58	eq 12
173	C_6H_5Li	**2a**–CH_3Li	90	43	16
174	C_6H_5Li	**2b**-1	71	44b	10
175	C_6H_5Li	**2g**–CH_3Li	67	61	17
176	C_6H_5Li	**2h**–CH_3Li	44	61	18
177	C_6H_5Li	**8a**-1	80	106	32
178	C_6H_5Li	**8j**	68	115	40
179	$2\text{-}CH_3C_6H_4MgBr$	**8a**-1	82	103	31
180	$2\text{-}CH_3C_6H_4MgBr$	**10a**	87[f]	165	55
181	$2\text{-}(CH_3)_2NCH_2MgBr$	**8c**	71	101	36

TABLE VIII (Continued)

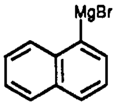
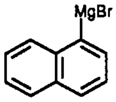
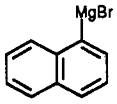
entry	RM	aminating reagent	yield,[c] %	ref	scheme
182	$2\text{-}CH_3OC_6H_4MgBr$	**8a**-1	63	103	31
183	$2\text{-}CH_3OC_6H_4MgBr$	**8c**	98	101	36
184	$2\text{-}CH_3OC_6H_4MgBr$	**8i**	73	113	39
185	$2\text{-}CH_3O_6H_4MgBr$	**9c**-1	18	158	48
186	$2\text{-}(CH_3)_2NCH_2C_6H_4Li$	**8a**-1	52	106	32
187	$2\text{-}(CH_3)_2NCH_2C_6H_4Li$	**8i**	41	113	39
188	$2\text{-}t\text{-}C_4H_9C_6H_5MgBr$	**8a**-1	19	103	31
189	$2\text{-}CH_3OC_6H_4Li$	**2a**–CH_3Li	96	43	16
190	$2\text{-}CH_3OC_6H_4Li$	**8a**-1	75	106	32
191	$2\text{-}CH_3OC_6H_4Li$	**8i**	35	113	39
192	$2\text{-}C_6H_5CH_2C_6H_4MgBr$	**8a**-1	71	103	31
193	$2\text{-}CH_3OCH_2OC_6H_4Li$	**8a**-4	67	108	34
194	$2\text{-}(C_2H_5)_2NCOOC_6H_4Li$	**8a**-4	94	108	34
195	$2\text{-}CH_3NHCOC_6H_4Li$	**8a**-1	37	106	32
196	$2\text{-}(C_2H_5)_2NCOC_6H_4Li$	**8a**-4	40	108	33
197	$2\text{-}(C_2H_5)_2NCOC_6H_4Li$	**8j**	52	115	40
198	$3\text{-}CH_3C_6H_4MgBr$	**8a**-1	79	103	31
199	$3\text{-}ClC_6H_4MgBr$	**8a**-1	41	103	31
200	$4\text{-}CH_3C_6H_4MgBr$	**8a**-1	66	103	31
201	$4\text{-}CH_3C_6H_4MgBr$	**8a**-2	67	103	eq 35
202	$4\text{-}CH_3C_6H_4MgBr$	**8k**	88	117	42
203	$4\text{-}CH_3C_6H_4MgBr$	**9c**-2	70	158	48
204	$4\text{-}CH_3C_6H_4Li$	**1a**-2	16	30	7
205	$4\text{-}C_6H_5C_6H_4MgBr$	**8a**-1	62	103	31
206	$4\text{-}CH_3OC_6H_4MgBr$	**8a**-1	51	103	31
207	$4\text{-}CH_3OC_6H_4MgBr$	**8a**-2	77	103	eq 35
208	$4\text{-}CH_3OC_6H_4MgBr$	**8c**	72	101	36
209	$4\text{-}CH_3OC_6H_4MgBr$	**8i**	69	113	39
210	$4\text{-}CH_3OC_6H_4MgBr$	**8k**	84	117	42
211	$4\text{-}CH_3OC_6H_4MgBr$	**9c**-1	12	158	48
212	$4\text{-}CH_3OC_6H_4MgBr$	**10a**	64	165	55
213	$4\text{-}ClC_6H_4MgBr$	**8a**-1	49	103	31
214	$4\text{-}ClC_6H_4MgBr$	**8a**-2	63	103	eq 35
215	$4\text{-}ClC_6H_4MgBr$	**8i**	92	113	39
216	$4\text{-}ClC_6H_4MgBr$	**8k**	79	116	42
217	$4\text{-}ClC_6H_4MgBr$	**9c**-1	20	158	48
218	$4\text{-}BrC_6H_4MgBr$	**2b**-1	58	44b	10
219	$2,5\text{-}(CH_3)_2C_6H_3MgBr$	**8a**-1	76	103	31
220	$2,6\text{-}(CH_3)_2C_6H_3MgBr$	**8i**	79	113	39
221	$2\text{-}((C_2H_5)_2NCO)\text{-}5\text{-}CH_3C_6H_3Li$	**8a**-4	82	108	33
222	$2\text{-}(CH_3OCH_2O)\text{-}3\text{-}CH_3C_6H_3Li$	**8a**-4	72	109	eq 37
223	$2\text{-}CH_3O\text{-}5\text{-}C_6H_5C_6H_3MgBr$	**8c**	91	101	36
224	$2,3\text{-}(CH_3O)_2C_6H_3Li$	**8i**	78	114	eq 40
225	$2,6\text{-}(CH_3O)_2C_6H_3Li$	**8c**	50	101	36
226	$2,6\text{-}(CH_3O)_2C_6H_3Li$	**8j**	70	115	40
227	$2,6\text{-}(CH_3O)_2C_6H_3Li$	**8k**	72	117	42
228	$2,5\text{-}(CH_3OCH_2O)_2C_6H_3Li$	**8k**	47	117	42
229	$2\text{-}CH_3NHCO\text{-}6\text{-}CH_3OC_6H_3Li$	**8a**-1	34	106	32
230	$2\text{-}(C_2H_5)_2NCO\text{-}3\text{-}CH_3OC_6H_3MgBr$	**8a**-4	71	108	33
231	$2\text{-}(C_2H_5)_2NCO\text{-}3\text{-}CH_3OC_6H_3Li$	**8a**-4	66	108	33
232	$2\text{-}(C_2H_5)_2NCO\text{-}5\text{-}CH_3OC_6H_3Li$	**8a**-4	34	108	33
233	$2\text{-}(C_2H_5)_2NCO\text{-}6\text{-}CH_3OC_6H_3Li$	**8a**-4	55	108	33
234	$2\text{-}t\text{-}C_4H_9CONH\text{-}5\text{-}ClC_6H_3MgBr$	**8c**	88	101	36
235	$2\text{-}(C_2H_5)_2NCO\text{-}6\text{-}ClC_6H_3MgBr$	**8a**-1	36	108	33
236	$2,4,6\text{-}(CH_3)_3C_6H_2MgBr$	**2b**-1	25	44b	10
237	$2,4,6\text{-}(CH_3)_3C_6H_2MgBr$	**8b**	26	110	eq 38
238	$2,4,6\text{-}(CH_3)_3C_6H_2MgBr$	**8k**	67	117	42
239	$2\text{-}(C_2H_5)_2NCO\text{-}5\text{-}CH_3\text{-}6\text{-}CH_3OC_6H_2Li$	**8a**-4	69	108	33
240	$2\text{-}(C_2H_5)_2NCO\text{-}3\text{-}(CH_3)_3Si\text{-}4\text{-}CH_3OC_6H_2Li$	**8a**-4	69	108	33
241	$4\text{-}(C_2H_5)_2NCO\text{-}3\text{-}CH(Si(CH_3)_3)_2\text{-}4\text{-}CH_3OC_6H_2Li$	**8a**-4	47	108	33
242	$2,3,5,6\text{-}(CH_3)_4C_6HMgBr$	**9f**[k]	65	159	51
243		**2a**-2	38	45	11
244		**6b**, **6d**	69	81	25
245		**7a**-2	31	91	27

TABLE VIII (Continued)

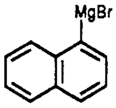
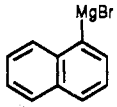
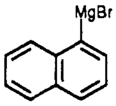
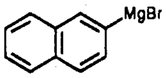
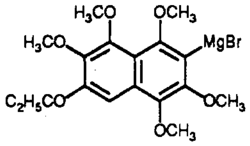
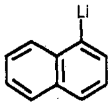
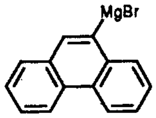
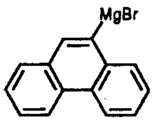
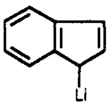
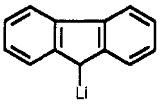
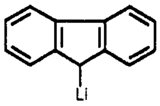
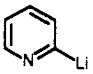
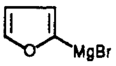
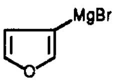
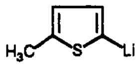
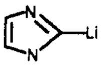
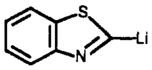
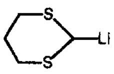
entry	RM	aminating reagent	yield,^{c} %	ref	scheme
246		**8k**	89	116	42
247		**9a**	27	124	eq 50
248		**9f**^{k}	83	159	51
249		**9f**^{k}	70	159	51
250		**8c**	71	112	eq 39
251		**6b**, **6d**	9	81	25
252		**8a**-1	54	103	31
253		**9f**^{k}	83	159	51
254		**6b**	57	81	25
255		**6b**	61	81	25
256		**7a**-2	30	91	27
257		**8j**	45	115	40
258		**9f**^{k}	78	159	51
259		**9f**^{k}	81	159	51
260		**8j**	58	115	40
261		**8j**	45	115	40
262		**8j**	53	115	40
263		**8j**	60	115	40

TABLE VIII (Continued)

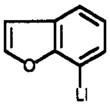
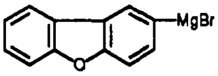
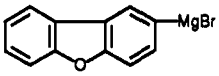
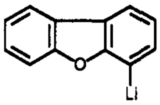
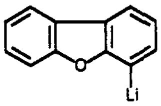
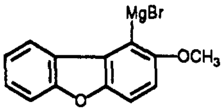
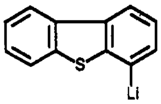
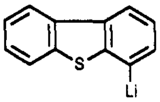
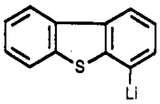
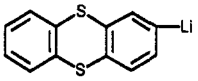
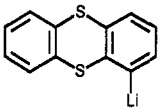
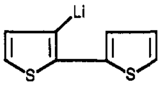
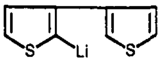
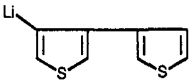
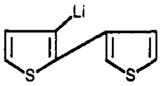
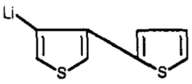
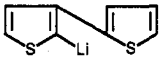
entry	RM	aminating reagent	yield,[c] %	ref	scheme
264		**2a**	78	51	—
265		**2a**	33	51	—
266		**8k**	71	117	42
267		**2a**-1	53	47	—
268		**8k**	58	117	42
269		**2a**-4	68	46a	—
270		**2a**-4	64	46b	—
271		**2a**–CH_3Li	55	43	16
272		**8k**	62	117	42
273		**2a**-4	63	48	—
274		**2a**-5	75	49, 50	—
275		**8a**-3	92	104	36
276		**8a**-3	87	104	36
277		**8a**-3	91	104	36
278		**8a**-3	93	104	36
279		**8a**-3	95	104	36
280		**8a**-3	71	104	36
		R = Enolic			
281	$CH_3CHLiCOY$ (Y = $OH^{l,m}$)	**11a**–$TiCl_4$	92	170	61, 62
282	$CH_3CHLiCOY$ (Y = OH^{n})	**11a**	83^{o}	169	57–59
283	$C_6H_5CHLiCOY$ (Y = $OH^{l,m}$)	**11a**–$TiCl_4$	93	170	61, 62
284	$CH_3SCH_2CHLiCOOLi$	**2a**-3	9	33	13
285	$C_6H_5CH_2CHLiCOOLi$	**2a**-3	7	33	13
286	$C_6H_5CH_2CHLiCOY$ (Y = $OH^{l,m}$)	**11a**–$TiCl_4$	89	170	61, 62

TABLE VIII (Continued)

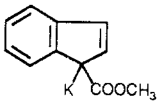
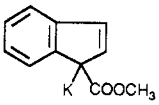
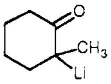
entry	RM	aminating reagent	yield,[c] %	ref	scheme
287	$C_6H_5CH_2CHLiCOY$ (Y = OH[n])	**11b**	97	169	57–59
288	*i*-$C_3H_7CHLiCOOLi$	**1a**-1	8	33	12
289	*i*-$C_3H_7CHLiCOOLi$	**2a**-3	33	33	12
290	*i*-$C_3H_7CHLiCOOLi$	**2b**-2	5	33	12
291	*i*-$C_3H_7CHLiCOOLi$	**2c**	22	33	12
292	*i*-$C_3H_7CHLiCOOLi$	**2d**	25	33	12
293	*i*-$C_3H_7CHLiCOOLi$	**2e**	18	33	12
294	*i*-$C_3H_7CHLiCOOLi$	**3**	5	33	12
295	*i*-$C_3H_7CHLiCOOLi$	**5a**	4	33	12
296	*i*-$C_3H_7CHLiCOOLi$	**5b**	5	33	12
297	*i*-$C_3H_7CHLiCOY$ (Y = OH[n])	**11b**	98[o]	169	57–59
298	*n*-$C_4H_9CHLiCOY$ (Y = OH[l,m])	**11a**–$TiCl_4$	90	170	61, 62
299	*i*-$C_4H_9CHLiCOOLi$	**2a**-3	11	33	13
300	*i*-$C_4H_9CHLiCOY$ (Y = OH[l,m])	**11a**–$TiCl_4$	91	170	61, 62
301	$C_6H_5CHLiCOOLi$	**2a**-3	56	33	13
302	$C_6H_5CHLiCOOLi$	**2f**	46	33	eq 10
303	$(C_2H_5)_2POCHNaCOOCH_3$	**6a**-2	47	83	20
304	$(C_2H_5)_2POCHNaCOOCH_3$	**7a**-1	60	90	29
305	$CH_3CHLiCOOCH_3$[l]	**10a**	59[f]	167	56
306	$C_6H_5CHLiCOY$ (Y = $OCH_2C_6H_5$[p])	**11a**	83–94[q]	168	57, 58, 60
307	$C_6H_5CH_2CHLiCOOCH_3$[l]	**10a**	76[f]	167	56
308	$C_6H_5CH_2CHLiCOY$ (Y = $OCH_2C_6H_5$[p])	**11a**	83–94[q]	168	57, 58, 60
309	*i*-$C_4H_9CHLiCOY$ (Y = $OCH_2C_6H_5$[p])	**11a**	83–94[q]	168	57, 58, 60
310	*t*-$C_4H_9CHLiCOY$ (Y = $OCH_2C_6H_5$[p])	**11a**	83–94[q]	168	57, 58, 60
311	$C_6H_5CHLiCOOCH_3$[l]	**10a**	83[f]	167	56
312	$C_6H_5CHLiCOOC_2H_5$	**7a**-2	45	91	27
313	$C_6H_5CHLiCOOC_2H_5$	**7c**	50	93	30
314	$C_6H_5CHNaCOOC_2H_5$	**4b**-3	12	78	24
315	$(CH_3)_2CLiCOOCH_3$[l]	**10a**	90[f]	167	56
316	$C_6H_5C(CH_3)LiCOOC_2H_5$	**4b**-3	35	78	24
317	$C_6H_5C(CH_3)LiCOOC_2H_5$	**7c**	56	93	30
318	$CH_3COCHKCOOCH_3$	**3**	34	68	eq 16
319	$CH_3COCHKCOOC_2H_5$	**3**	30	68	eq 16
320	$CH_3COCHKCOOC_2H_5$	**4b**-1	2	17	eq 16
321	$CH_3COCHKCOOC_2H_5$	**6a**	2	17	eq 16
322		**4b**-1	50	69, 77	eq 17
323		**7a**	47	91	27
324	$CH_3COCHKCOCH_3$	**3a**	28	68	eq 16
325	$CH_3COCHKCOCH_3$	**4b**-1	2	17	eq 16
326	$(CH_3)_2CHCOCLi(CH_3)_2$	**10a**	72[f]	165	55
327		**10a**	61[f]	165	55
328	$C_6H_5CHLiCON($*n*-$C_4H_9)Li$	**2a**-3	30	56	eq 11
329	$C_6H_5CHLiCON(C_2H_5)_2$	**2a**-3	15	56	eq 16
330	$C_6H_5CHLiCN$	**7a**-2	37	91	27
331	$C_6H_5CHLiCN$	**7c**	62	93	30
332	$(C_6H_5)_2CLiCN$	**7a**-2	67	91	27
333	$CHNa(COOC_2H_5)_2$	**1a**-5	92	35	8
334	$CHNa(COOC_2H_5)_2$	**4b**-3	55	78	24
335	$CHNa(COOC_2H_5)_2$	**7a**	57	90	eq 30
336	$CH_3CNa(COOC_2H_5)_2$	**1a**-5	85	35	8
337	$CH_3CNa(COOC_2H_5)_2$	**4b**-3	84	78	23
338	$C_2H_5CNa(COOC_2H_5)_2$	**1a**-5	89	35	8
339	$C_2H_5CNa(COOC_2H_5)_2$	**4b**-3	74	78	23
340	*i*-$C_3H_7CNa(COOC_2H_5)_2$	**1a**-5	71	35	8
341	*n*-$C_4H_9CNa(COOC_2H_5)_2$	**4b**-3	73	78	23
342	*sec*-$C_4H_9CNa(COOC_2H_5)_2$	**1a**-5	83	35	8
343	$C_6H_5CH_2CNa(COOC_2H_5)_2$	**1a**-5	72	35	8
344	$C_6H_5CH_2CNa(COOC_2H_5)_2$	**4b**-3	73	78	23
345	$C_6H_5CLi(COOC_2H_5)_2$	**7a**	31	91	27
346	$C_6H_5CNa(COOC_2H_5)_2$	**1a**-5	70	35	8
347	$C_6H_5CNa(COOC_2H_5)$	**4b**-2	53	69, 77	eq 18
348	$C_6H_5CNa(COOC_2H_5)$	**4b**-3	65	78	24
349	$(CH_2COOC_2H_5)CNa(COOC_2H_5)_2$	**4b**-3	61	78	23
350	$CN(C_6H_5)CLiCOOC_2H_5$	**6b**	95	81	25
351	$CN(C_6H_5)CLiCOOC_2H_5$	**7a**-2	96	91	27

TABLE VIII (Continued)

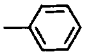
entry	RM	aminating reagent	yield,[c] %	ref	scheme
352	$CN(C_6H_5)CNaCOOC_2H_5$	**4b**-3	54	78	24
353	$CHNa(CN)_2$	**4b**	—	80	eq 21
354	$CHNa(CN)_2$	**6a**-2	42	80	eq 21
355	$CHNa(CN)_2$	**7a**	50	90	eq 30

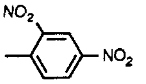
[a] Reagents: H_2NZ, **1a–g**, **2a–e**, **3**, **4a,b**, **5a,b**, **6a**, **7a**, **8a–c**, **8i–k**, **9a–f**, **10a**, **11a,b**; R^1HNZ, **2g,h**; R^1_2NZ, **6b–f,h**, **7b,c**.

H_2NCl
1a
H_2NBr
1b
$HNBr_2$
1c
NCl_3
1d

H_2NOR
2a, $R = CH_3$
b, $R = CH_2C_6H_5$
c, $R = C_2H_5$
d, $R = CH(CH_3)_2$
e, $R = C(CH_3)_3$
$RNHOCH_3$
2g, $R = CH_3$
h, $R = CH(C_6H_5)CH_3$

H_2NOSO_2OH
3 (HOSA)

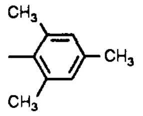
H_2NOAr
4a, Ar =


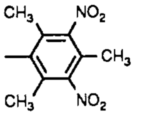
4b, Ar =


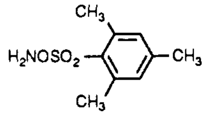
(DPH)

$RHNCl$
1e
R_2NCl
1f
$RNCl_2$
1g

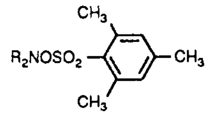
$H_2NOCOAr$

5a, Ar =


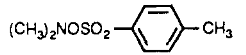
5b, Ar =




6a (MSH)

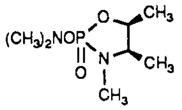


6b, $R = CH_3$
c, $R = C_2H_5$
$R_2NOSO_2C_6H_5$
6d, $R = CH_3$
e, $R = C_2H_5$



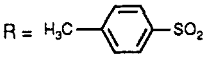
6f
$(CH_3)_2NOSO_2CH_3$
6h

$H_2NOPO(C_6H_5)_2$
7a
$(CH_3)_2NOPO(C_6H_5)_2$
7b



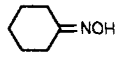
7c

RN_3

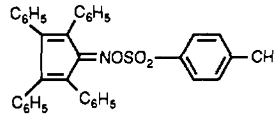
8a, R =


b, $R = (C_6H_5)_3Si$
c, $R = C_6H_5SCH_2$
i, $R = (CH_3)_3SiCH_2$ (TMSMA)
j, $R = R^1CH{=}CR^2$
(R^1, R^2 = H, C_6H_5, $t\text{-}C_4H_9$, H)
k, $R = ((C_2H_5O)_2PO$ (DPPA)

$R^1R^2C{=}NOH$
9a, $R^1 = H$, $R^2 = C_6H_5$
b, $R^1 = CH(CH_3)_2$, $R^2 = C_6H_5$
c, $R^1 = CH_3$, $R^2 = CH_3$
d, $R^1 = CH_3$, $R^2 = C_2H_5$



9e



9f

$C_6H_5N_2BF_4$
10a

$ROOCN{=}NCOOR$ (DAAD)
11a, $R = C(CH_3)_3$ (DBAD)
b, $R = CH_2C_6H_5$

[b] Key: Experimental conditions for the aminating reagents (solvent, RM/reagent molar ratio, reaction temperature, reaction time): **1a**-1: Et_2O, excess, 0 °C; **1a**-2: Et_2O, 3/1, −5 °C, overnight; **1a**-3: petroleum ether, excess, −30 °C, overnight; **1a**-4: Et_2O/dioxane, 3/1, −60 °C, 1 h; **1a**-5: Et_2O, 1/2, room temperature, overnight; **1b**, **1c**: Et_2O, excess, −5 °C; **1d**-1: Et_2O, 4/1, 0 °C; **1d**-2: same as **1a**-3; **1d**-3: Et_2O, 3/1, −5 °C, overnight; **1e**, **1f**, **1g**: Et_2O, excess, 0–5 °C; **2a**-1: Et_2O, 2/1, −15 °C; **2a**-2: Et_2O, 2/1, −15 °C, 0.5 h, reflux, 2 h; **2a**-3: THF, 1/3, −15 °C, 2 h, room temperature, overnight; **2a**-4: Et_2O, 3/1, −15 °C; **2a**-5: Et_2O, 1/1, −15 °C; **2b**-1: same as **2a**-1; **2b**-2, **2c**, **2d**, **2e**: same as **2a**-3; **2a**–CH_3Li: Et_2O, 1/2, −15 °C, 2 h; **2g**–CH_3Li: Et_2O, 1/1, −15 °C, 2 h; **2h**–CH_3Li: Et_2O, 1/1, 40 °C; **3**: H_2O, 2/1, room temperature, overnight; **4a**-1: not reported; **4b**-1: benzene, 1/1, room temperature, overnight; **4b**-2: DMF, 1/1, room temperature, overnight; **4b**-3: THF, 1/1, room temperature, overnight; **5a**, **5b**: same as **2a**-3; **6a**: DME, 1/1, <30 °C, 0.5 h; **6b**, **6c**, **6d**, **6e**, **6f**: THF, 1/1, −10 °C to room temperature, 15 h; **6h**: Et_2O, 1/2, −20 °C; **7a**-1: 1/1, −78 °C, 2 h, room temperature, overnight; **7a**-2: THF, 1/1, −20 °C to room temperature, 12 h; **7b**: Et_2O, 1/2, −20 °C, 1 h; **7c**: THF, 1/1, −15 °C; **8a**-1: THF, 1/1, 0 °C, reduction of triazene salt; **8a**-2: THF, 1/1, 0 °C, fragmentation of triazene salt; **8a**-3: Et_2O, 1/1, −70 °C, 5 h, reduction of triazene salt; **8a**-4: THF, 1/1, −78 °C, 1 h, reduction of triazene salt; **8b**: Et_2O, 1/1, 100 °C, decomposition of triazene salt; **8c**: THF, 1/1.2, −78 to 0 °C, hydration of triazene salt; **8i**: Et_2O, 1/1.2, room temperature, 3 h, hydration of triazene salt; **8j**: THF, 1/1, −78 °C to room temperature, hydration of triazene salt; **8k**: Et_2O, 1/1, −72 °C, 2 h, −20 °C, reduction of triazene salt; **9a**: Et_2O, 3/1, reflux; **9b**: not reported; **9c**-1: toluene, 1/1; **9c**-2: toluene, 2/1, hydration of imine; **9d**, **9e**: same as **9c**; **9f**: THF, 7/1, −78 °C, hydration of imine; **10b**: pyridine, 1/1.3, 0 °C, 2 h, hydrogenolysis of α-hydrazono compound; **11a,b**: THF or CH_2Cl_2, 1/1.1 or 1/1.2, −78 °C, removal of Y (oxazolidinone or *N*-methylephedrine moiety) by hydrolysis or esterification, hydrogenolysis of α-hydrazino compound. [c] Yields of free amines or hydrochloride salts, *N*-benzoyl or *N*-acetyl derivatives. Free amines were isolated with reagents **2a**-2,3,4,5,6,7, **8a**-3, **8i**, **8j**, **8k**, and **9**; hydrochloride salts were obtained with reagents **1**, **2a**-1, **2b**, and **8a**-1; *N*-benzoyl derivatives with **2a**–CH_3Li, **2g**–CH_3Li, and **2h**–CH_3Li; and *N*-acetyl derivatives with **8a**-2 and **8c**. [d] Product amine, $(C_2H_5)_2NH$. [e] Product amine, $(n\text{-}C_4H_9)_2NH$. [f] Yield of α-hydrazono or α-azo compound. [g] Product amine, $(C_6H_5CH_2)NHCH_3$. [h] Product amine, $(C_6H_5CH_2)NHC_2H_5$. [i] Product amine, $(C_6H_5CH_2)NH(i\text{-}C_3H_7)$. [j] Product amine, $C_6H_5C{\equiv}CN(C_2H_5)_2$. [k] Yield of imine. [l] Converted into silyl ketene acetal. [m] Y = *N*-methylephedrine auxiliary, hydrolyzed to acid. [n] Y = oxazolidinone moiety, hydrolyzed to acid. [o] Yield of α-hydrazino acid. [p] Y = oxazolidinone moiety, hydrolyzed to benzyl ester. [q] Yield of MTPA derivative of α-amino acid.

pounds and arylbismuth and aryllead reagents, we will now give a brief summary of the use of aminating reagents for the conversion of boranes into amines. Amination of organoboranes provides a useful method for introducing an amino functionality in a regio- and stereospecific manner. Methods for the convenient synthesis of primary amines from the reaction of trialkylboranes, R_3B, with monochloroamine (**1a**) were developed by Brown and co-workers (eq 57).[191-193]

$$R_3B + H_2NCl \xrightarrow{NaOH} RB(NHR)_2 \xrightarrow{H_2O} 2RNH_2 + RB(OH)_2 \quad (57)$$

However, only two of the three alkyl groups in R_3B could be utilized since, following hydrolysis, one of the reaction products is the monoalkylboronic acid, $RB(OH)_2$, which reacts with **1a** very slowly and thus the maximum possible yield of the amine is limited to 67%. Kabalka and co-workers aminated trialkylboranes in good yields with **1a** generated in situ[194,195] and used monochloroalkylamines, **1e**, to achieve the synthesis of secondary amines (eq 58).[196] The reaction of tri-

$$R_3B \xrightarrow[2.\ H_2O]{1.\ R^1HNCl} RR^1NH \qquad (58)$$

alkylboranes with monochlorodialkylamines, **1f**, was also reported.[197,198] Amination methods of organoboranes with HOSA (**3**) (eq 59) have been devel-

$$R_3B + 2H_2NOSO_2OH \xrightarrow[\text{diglyme}]{\text{THF or}} RB(NHR)_2 \xrightarrow{H_2O} 2RNH_2 + RB(OH)_2 \qquad (59)$$

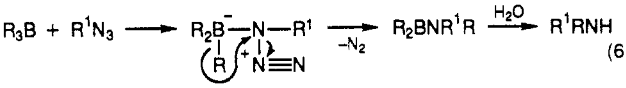
oped[191,198-200] and well summarized by Brown and coworkers.[193] They overcame the limitation to quantitative utilization of the alkyl groups by preparing a mixed organoborane, RR^1_2B, in which R shows a significantly greater migratory aptitude than R^1. For this purpose, organodimethylboranes, prepared by hydroboration of alkenes with dimethylborane, were reacted[193] with HOSA to afford the corresponding primary amines in almost quantitative yields (eq 60).

$$R(CH_3)_2B \xrightarrow[2.\ H_2O]{1.\ \text{HOSA, THF}} RNH_2 \qquad (60)$$

Triphenylborane, prepared from phenylmagnesium bromide and boron trifluoride, was found to react with HOSA to give aniline in 35% yield.[201] The use of MSH (**6a**),[202] *N*-chloro(2,4-dinitrophenyl)hydroxylamine,[203] and chloramine-T[204] in the amination of organoboranes was reported.

The suggested mechanism for the amination of organoboranes[193] is anionotropic rearrangement of the organoborate complex involving the migration of an alkyl group from the electron-rich boron to the neighboring, electron-deficient nitrogen (Scheme 67).

Brown and co-workers have reported[205] that the reaction of trialkylboranes with azides followed by hydrolysis gives rise to good yields of secondary amines (eq 61). Dialkylchloroboranes ($RBCl_2$) and alkyldichloroboranes ($RBCl_2$) provide even better yields. Kabalka and co-workers[206] have used hydrazoic acid generated in situ to prepare amines in good yields (eq 62).

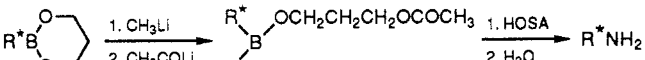


$$R_3B + R^1N_3 \longrightarrow \underset{\substack{| \\ R}}{R_2\overset{-}{B}}-\underset{\substack{| \\ \overset{+}{N}\equiv N}}{N}-R^1 \xrightarrow[-N_2]{} R_2BNR^1R \xrightarrow{H_2O} R^1RNH$$

(61)

$$R_3B \xrightarrow[2.\ H_2O]{1.\ HN_3} R_2BNHR \xrightarrow{H_2O} RNH_2 \qquad (62)$$

Primary amines of very high optical purity can be obtained[207] from the chiral boronic esters through the intermediate formation of alkylmethylborinic esters (eq 63). The preparation and use of chiral organoboranes[208] and boronic esters[209] in asymmetric synthesis have been recently reviewed.



(63)

A list of organomagnesium, -lithium, -zinc, and -copper compounds and alkali metal and silicon enolates aminated with reagents **1–11**, comparable amination conditions, and yields are given in Table 8.

III. Concluding Remarks

The increasing accessibility of diverse organometallic reagents coupled with the importance of primary amines renders the electrophilic aminating reagents an important class of organic compounds.

The present review has tried to classify the reagents for the electrophilic amination of carbanions and to show the preparative advantages and scope of the methods. Electrophilic amination of carbanions has recently gained renewed attention as a result of the growing utility of direct metalation methods and also the search for an umpolung methodology for the direct formation of C–N bonds. It is hoped that this review will reflect the current rapid increase of the interest in the area. However, much further work is needed to extend the scope of the synthetic methods and to find milder conditions.

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