

Electrophilic Amination of Carbanions

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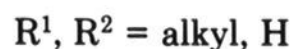
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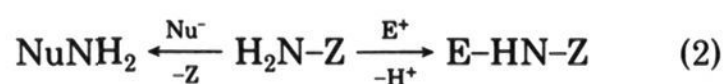
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I. Introduction

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 inter-



esting structural feature of electrophilic aminating agents of the type $\text{R}^1\text{R}^2\text{N-Z}$ 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

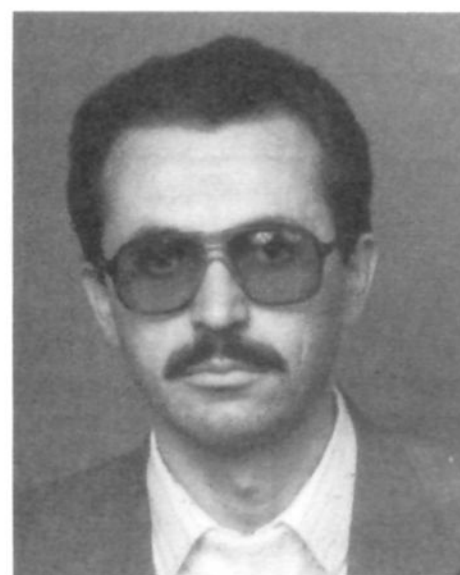


used extensively for the amination of N, S, and P nucleophiles such as amines, sulfides, and phosphines.

Although the electrophilic amination of carbanions, i.e., the conversion of organometallic compounds to amines (aminodemetalation, eq 3) has been known for



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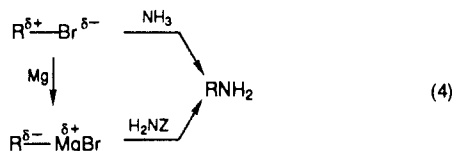


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a long time,¹ only isolated reports of preparations of amines from organometallic compounds have been published.

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

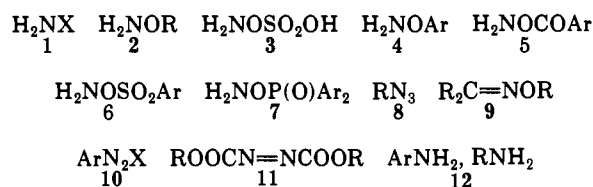
reactions of an electrophilic alkyl halide with ammonia or amines and the conversion of the halide into a nucleophilic species, namely the corresponding Grignard or organolithium reagent, and its subsequent reaction with the H_2N-Z derivative (eq 4). The species R-Br



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 umpolung² and developments in the use of electrophilic reagents³ have been the subjects of comprehensive reviews.

The increasing application of direct metalation methods⁴⁻⁸ 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 agents¹¹⁻¹⁹ 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.



N-Haloamines (1), *O*-alkyl-, (2), *O*-aryl- (4), *O*-acyl- (5), *O*-sulfonyl- (6), and *O*-phosphinyloxyamines (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

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

<i>N</i> -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 ₂ Zn	9	30
1b	RMgCl	2	24
1c	RMgCl	3	25
1d	RMgCl	4	26
	R ₂ Zn	9	30
1e	RMgCl	5	27
1f	RMgCl, C ₆ H ₅ MgBr	5, 6	27, 29
	R ₂ Zn	9	36
1g	RMgCl	5	27
	R ₂ Zn	9	36

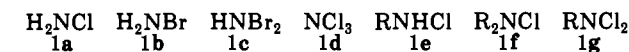
or hydrolytic workup. Oximes (9) react with Grignard and organolithium reagents to produce imines which are hydrolyzed to amines. Reactions of enolates with arenediazonium salts (10) or dialkyl azodicarboxylates (11) furnish α -hydrazono or α -hydrazido compounds, respectively, which are hydrogenated 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.

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).

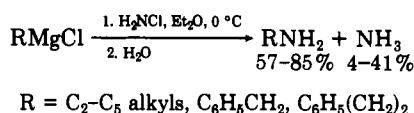


The preparations and synthetic applications as aminating agents of chloro- and bromoamines have been reviewed.¹¹ The reactions of Grignard reagents with *N*-haloamines (1a-g) were comprehensively studied by Coleman and co-workers.²⁰⁻²⁷ Depending on the Grignard reagent and haloamine chosen, primary,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

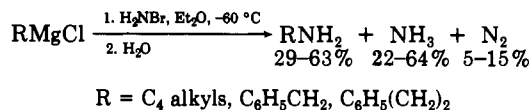
The reactions of various Grignard reagents with monochloroamine (1a) lead to the formation of primary amines in addition to ammonia as a byproduct (Scheme 1).^{20,21}

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

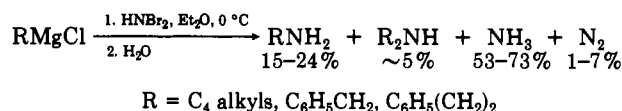
SCHEME 1



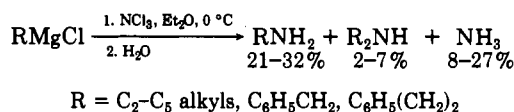
SCHEME 2



SCHEME 3



SCHEME 4



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 amines²³ 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.

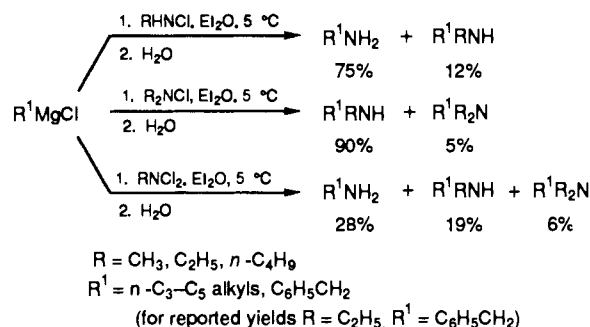
Monobromoamine reacted with Grignard reagents to form primary amines, ammonia, and nitrogen (Scheme 2).²⁴ The reaction of phenylmagnesium chloride with **1b** resulted in a 4% yield of aniline, an 85% yield of ammonia, and an 11% yield of nitrogen when a solution of **1b** at –60 °C (unstable at 0 °C)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

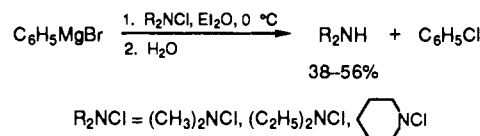
Amination of Grignard reagents with nitrogen trichloride (**1d**) gave rise to both primary and secondary amines and ammonia (Scheme 4).²⁶ For these amination reactions, a diethyl ether solution of **1d** was added to a 4 molar excess of the Grignard reagent solution at 0 °C; phenylmagnesium chloride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

SCHEME 5



SCHEME 6

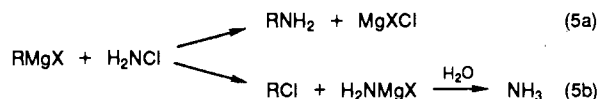


tertiary amines. The amination reactions were carried out in diethyl ether at 5 °C and variations in the temperature had very little effect on the outcome of the reaction.

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

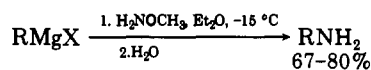
The amination of phenylmagnesium bromide was investigated using a number of monochlorodialkylamines (**1f**) (Scheme 6); chlorobenzene and the parent secondary amines but no alkyaniline were obtained.²⁹

These observations on the aminations of Grignard reagents by haloamines are of interest as they demonstrate the ambident character of “NH₂”. Coleman proposed reactions 5a and 5b to explain the formation



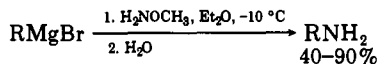
of amines and ammonia in amination reactions with **1a**. According to reaction 5a, in which amines are formed, H₂N⁺ acts as an electrophile and X as a leaving group, whereas according to reaction 5b, in which ammonia is produced, H₂N[–] appears to serve as a leaving group. If this were the case, formation 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 H₂NX can be rationalized by the resultant increased basicity of nitrogen and, hence, the decreased electrophilic character of H₂N⁺. 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.

SCHEME 10



X = Cl, Br
 RMgX/H₂NOCH₃ molar ratio = 2/1
 R = C₂H₅, *sec*-C₄H₉, *t*-C₄H₉, *i*-C₅H₁₁, *c*-C₆H₁₁, C₆H₅,
 4-BrC₆H₄, 2,4,6-(CH₃)₃C₆H₂, α -naphthyl

SCHEME 11



RMgBr/H₂NOCH₃ molar ratio = 2/1
 R = C₂–C₆ alkyls, CH₂=CHCH₂, C₆H₅CH₂,
 C₆H₅(CH₂)₂, BrMg(CH₂)_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 obtained⁴³ 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

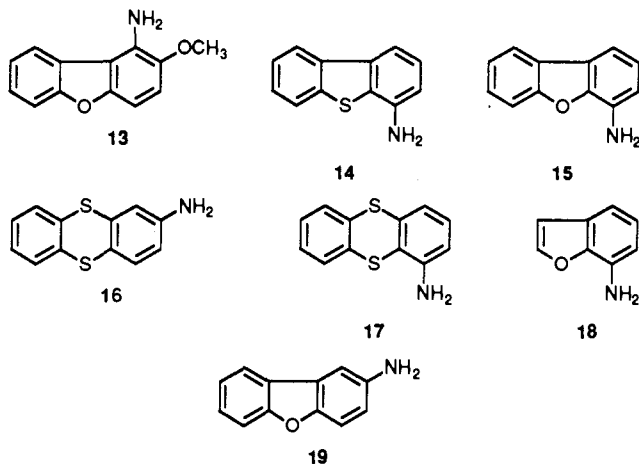
The amination of a carbanion with methoxyamine (**2a**) is known as the Schverdina–Kotscheschkow amination since these authors first reported the use of **2a** to convert a Grignard reagent into the corresponding amine in good yield (Scheme 10).^{44a} The reaction sequence comprises treatment of 1 equiv 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

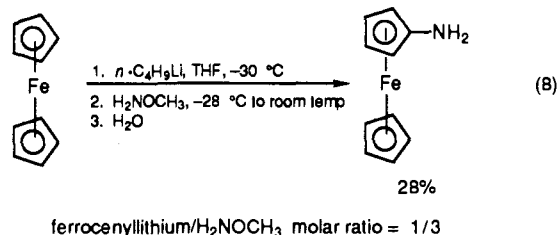
In contrast to the results reported by Coleman and co-workers^{20,21} for aminations with **1a**, the amination yields from the reactions of alkylmagnesium bromides with **2a** were slightly higher than those obtained when the corresponding chlorides were used; however, the use of the iodides should 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.

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

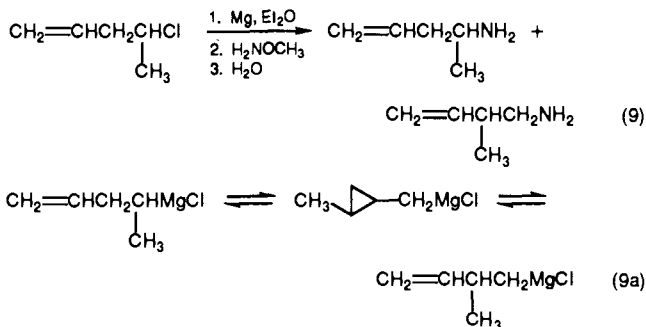


react with 3,^{46a,b,48} 2,⁴⁷ or 1 equiv^{49,50} of the organometallic reagent in diethyl ether at 0 °C. The preparations of 4-aminobenzofuran (**18**) from **2a** and the respective organolithium compound and of 2-aminodibenzofuran (**19**) from **2a** and the corresponding Grignard reagent were also 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 ferrocenyllithium⁵³ resulted in poor yields of the amine (eq 8).

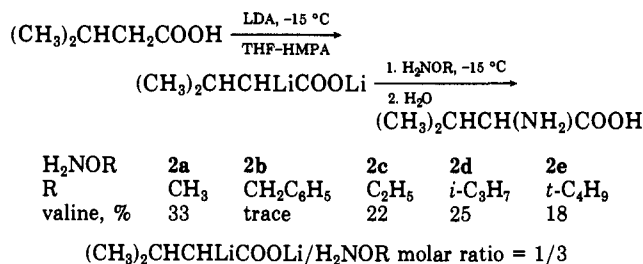


A rearrangement process was reported to take place⁵⁴ in the attempted preparation of 4-penten-2-ylamine by the reaction of the Grignard reagent derived from 4-penten-2-yl chloride with **2a** (eq 9). A possible mechanism involves the rearrangement of a secondary Grignard reagent to a primary Grignard reagent by way of a three-membered ring (eq 9a).⁵⁵

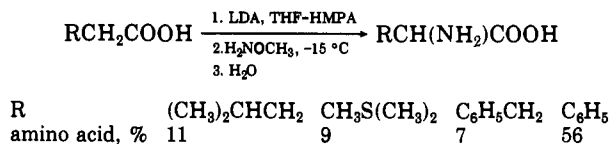


The amination of α -lithiated carboxylic acids was investigated in detail by using 3-methylbutanoic acid and a number of *O*-alkylhydroxylamines (**2a–e**) (Scheme 12).^{32,33} 3-Methylbutanoic acid was lithiated in the α -position by lithium diisopropylamide (LDA) in THF–HMPA at –15 °C. Amination of 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.

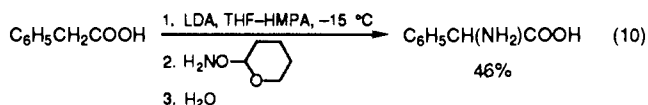
SCHEME 12



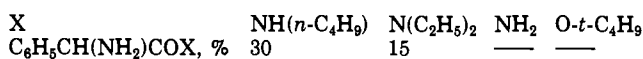
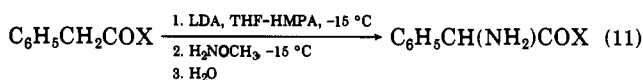
SCHEME 13



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*-



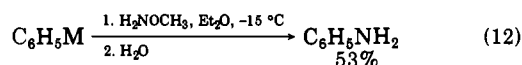
substituted derivatives, and *tert*-butyl phenylacetate were α -lithiated, and attempts were made to aminate these lithiated derivatives with **2a** to obtain the corresponding α -amino amides and esters (eq 11).⁵⁶ No



traces of the aminated products of phenylacetamide and *tert*-butyl phenylacetate were detected while the *N*-substituted derivatives were aminated in low yields.

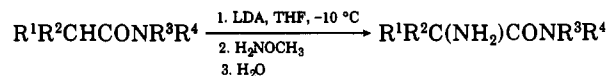
In a further application of the amination method using **2a**, several *N*-alkyl- α -aminocarboxamides and their salts were prepared (Scheme 14).⁵⁷

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).



It is apparent that 3 equiv of C₆H₅M 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 Kotscheschkow⁴⁴ as well as Brown and Jones⁴⁵ reported alkyl Grignard reagent:**2a** ratios of 2:1 whereas Gilman

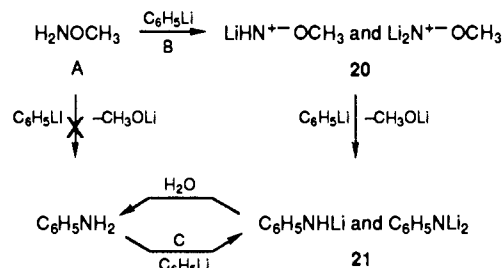
SCHEME 14



R¹, R², R³, R⁴ = H, C₆H₅CH₂, H, C₆H₅;
H, C₆H₅, H, *c*-C₆H₁₁; C₆H₅, C₆H₅, H, C₆H₅; C₆H₅, C₆H₅, C₆H₅, C₆H₅,
H; H, C₆H₅, C₂H₅, C₂H₅

M = MgBr, Li
C₆H₅M/H₂NOCH₃ molar ratio = 3/1

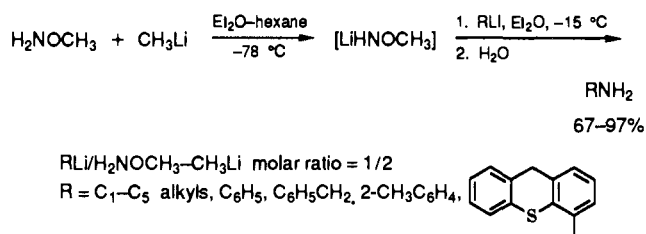
SCHEME 15



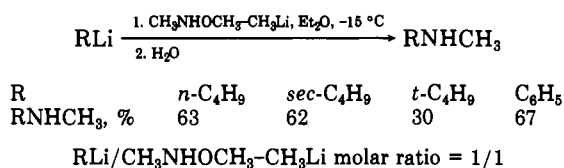
and co-workers^{46,47,49} reported that the amination of the lithium derivatives of some heterocyclic compounds occurred with a 3:1 molar ratio of the organolithium reagent:**2a**. On the other hand, there are numerous reports⁵⁹ indicating that the Grignard reagent can abstract one hydrogen atom from the NH₂ 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.

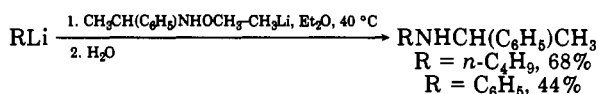
SCHEME 16



SCHEME 17



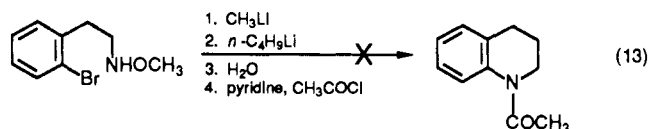
SCHEME 18



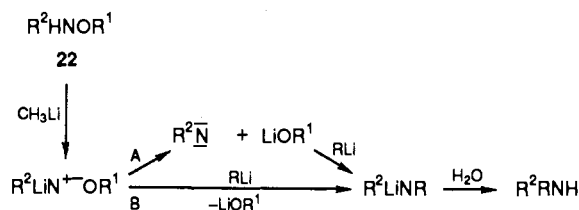
Later, Beak and Kokko⁴³ treated **2a** with methyllithium in diethyl ether and allowed the resultant organolithium derivative to react with organolithium reagents to produce amines after hydrolysis (Scheme 16). The optimum reaction conditions were found to comprise addition of 2 equiv of **2a** in hexane 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 alkylolithium reagents. Grignard reagents and heteroarylolithium 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 Kokko⁶¹ 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 phenylmethanamines 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. Amination 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.

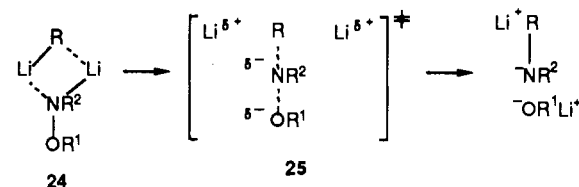
Attempts to aminate 2-lithiothiophene and 2-lithio-*N,N*-diisopropylbenzamide with **2g** were unsuccessful, as was also an intramolecular amination (eq 13).



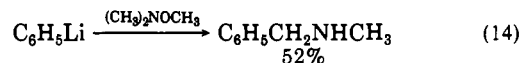
SCHEME 19



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).

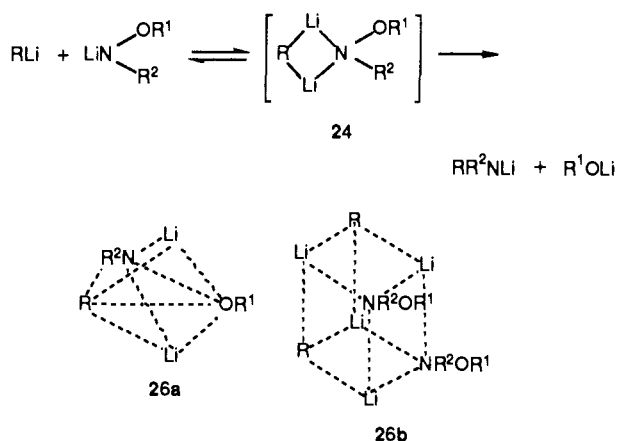


These results suggest that alkoxyamine derivatives bearing at least one proton on nitrogen can be activated by methyllithium to provide species that are able to react with organolithium reagents and so form amines in synthetically useful yields. The **2a**/methyllithium complex is an efficient and convenient 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-workers⁶³ 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 $\text{R}^2\text{LiNOR}^1\text{-RLi}$ complex (**24**), (ii) the long N–O bond in **23**, and (iii) the high stability of LiR^2N^+ ($\text{R}^2 = \text{H}$, 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-workers⁶⁴ 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.

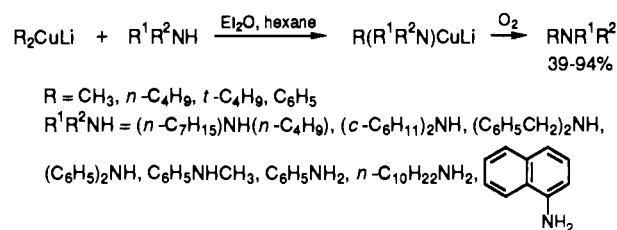
McKee⁶⁵ used the MNDO method to derive a plausible mechanism for the amination of organolithium compounds by lithium alkoxyamides. In this mechanism (Scheme 21), an initial lithium complex **24** having two lithium atom bridges between nitrogen and carbon passes through a transition state (**26a**), which is assumed to be a trigonal bipyramid with two axial lithium cations and equatorial alkoxy-, alkyl-, and alkylnitrene substituents.

Recently, Beak and co-workers¹⁰ 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 $\text{S}_{\text{N}}2$ 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.

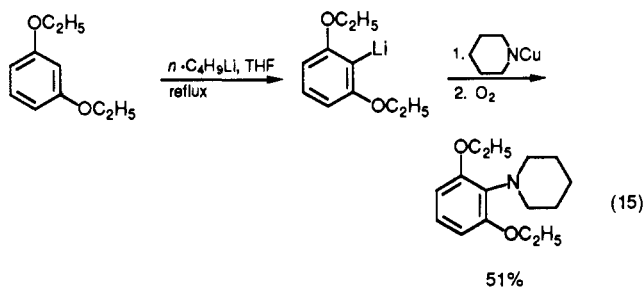
Syntheses of secondary and tertiary amines based on the oxidative coupling of lithium alkylcopper amides have been described.⁶⁷ The lithium alkylcopper amides were generated *in situ* from lithium dialkylcuprates and primary or secondary amines (Scheme 22). This method seems to be especially efficient 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

SCHEME 22



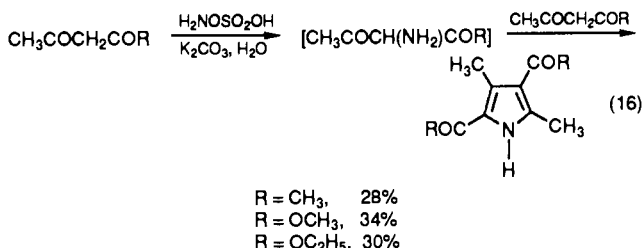
then stirring of the reaction mixture while bubbling oxygen through it. The reactions are carried out at different temperatures depending on the reactants. The introduction of an amino group was also realized by the oxidative coupling of a lithium arylcopper amide generated from an aryllithium reagent and a copper amide.

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).



C. With Hydroxylamine-*O*-sulfonic Acid

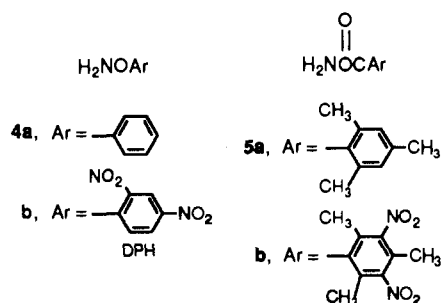
Hydroxylamine-*O*-sulfonic acid (HOSA, **3**) is not suitable for carbanion amination. However, its use in organic synthesis, resulting from the ability of the nitrogen center to act both as a nucleophile and as an electrophile as well as being able to provide an *in situ* source of other chemical entities such as diimide, have been comprehensively reviewed.^{15,16} One of the two published reports on carbanion aminations with HOSA⁶⁸ 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).



The other attempted amination with HOSA³³ yielded a trace amount of an amino acid from an α -lithiated carboxylic acid (Scheme 12).

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

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

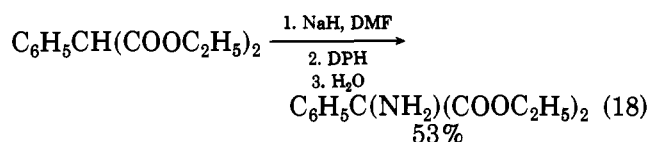
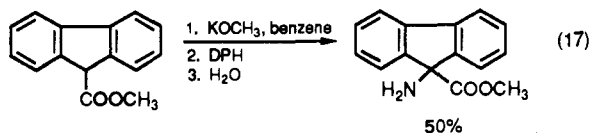


have been used for carbanion amination (Table 3).

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*-acylhydroxylamines⁷³⁻⁷⁵ 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 reagents⁷² 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-fluorene-carboxylate (eq 17) and diethyl α -amino- α -phenylmalonate (eq 18).



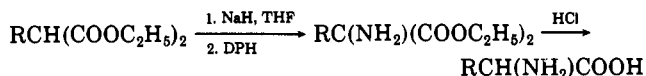
Radhakrishna, Loudon, and Miller investigated⁷⁸ the suitability of DPH for the amination of a variety of ester enolates. Sodium enolates derived from diethyl malonate and its 2-substituted analogues are aminated with DPH, and the 2-aminomalones thus produced are readily converted to the corresponding 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

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

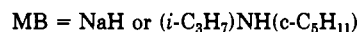
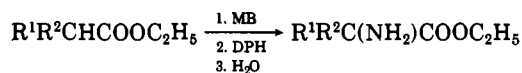
hydroxylamine	RM	scheme	ref
4a	C ₆ H ₅ Li	—	76
4b	RCNa(COOR) ₂	eq 18, 23	77, 78
	R ₂ CNaCOOR	24	78
5a,b	RCHLiCOOLi	12	33

SCHEME 23



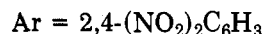
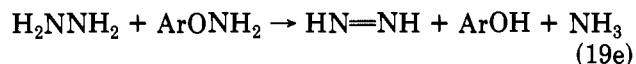
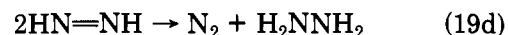
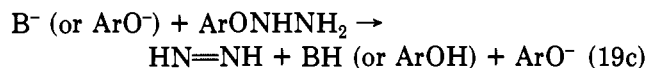
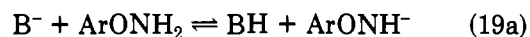
R	CH ₃	C ₂ H ₅	<i>n</i> -C ₃ H ₇	C ₆ H ₅ CH ₂	CH ₂ COOC ₂ H ₅
RCH(NH ₂)-COOH, %	84	74	46-57	73	61

SCHEME 24



R ¹	C ₆ H ₅	H	C ₆ H ₅	CH ₃	H
R ²	COOC ₂ H ₅	COOC ₂ H ₅	CN	C ₆ H ₅	C ₆ H ₅
R ¹ R ² C(NH ₂)-COOC ₂ H ₅ , %	65	55	54	35	12

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.



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)

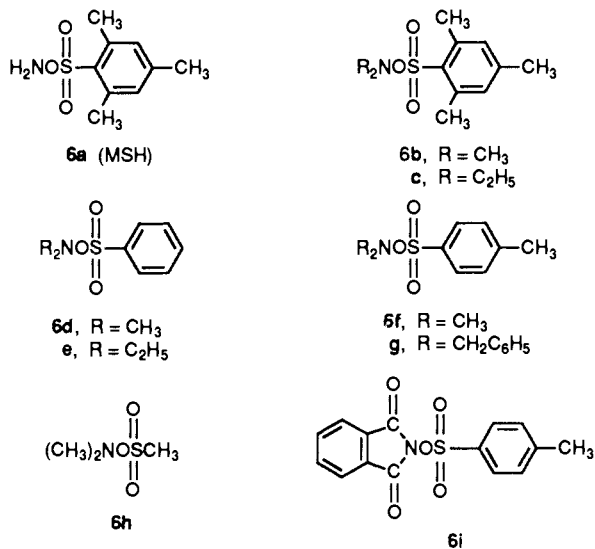
hydroxylamine	RM	scheme	ref
6a	CHNa(CN) ₂	eq 21	80, 83
6b	R(Ar)Li	25	81
6c	R(Ar)Li	25, eq 22	81, 82
6d,e	R(Ar)Li	25	81
6f	C ₆ H ₅ MgBr		84
6h	RLi, (RC≡C) ₂ LiCu	eq 23, 26	85, 86

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.

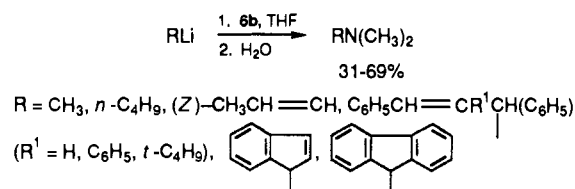
E. With *O*-Sulfonylhydroxylamines

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*-(tosyl-oxy)phthalimide (**6i**) have been tried (Table 4).



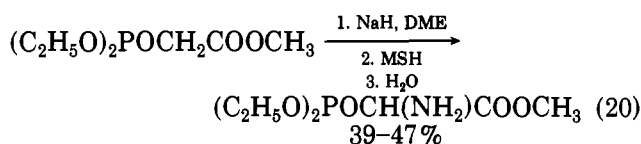
Methods for the syntheses of various *O*-sulfonylhydroxylamines have been published.^{72,74,75} Tamura and co-workers have summarized the synthesis and properties of MSH and other *O*-sulfonylhydroxylamines and discussed their synthetic applications in reactions with various types of nucleophiles and 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 decompose⁸² on standing at room temperature; however, when kept in a freezer, a sample in a

SCHEME 25

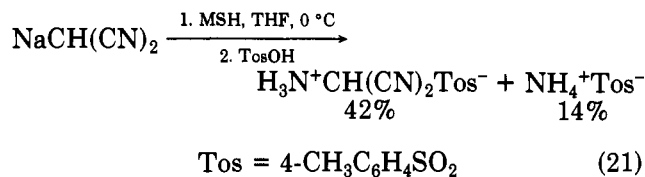


plastic bag containing Drierite showed no change in its decomposition point after 6 weeks.

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).



Aminomalonitrile tosylate, a key starting material in the synthesis of a number of heterocyclic compounds, has been synthesized from malonodinitrile by using MSH⁸⁰ (eq 21) under mild conditions with a simple

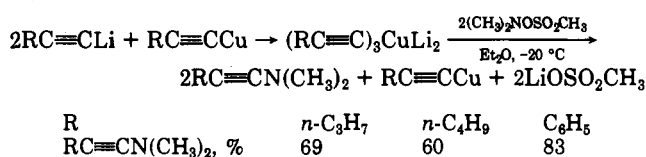


workup procedure. Amination followed by addition of *p*-toluenesulfonic acid led directly to a mixture of aminomalononitrile tosylate and ammonium tosylate. The latter was formed from the decomposition of MSH, presumably in the same manner as suggested for DPH (**4b**). The use of DPH did not result in expected amination.

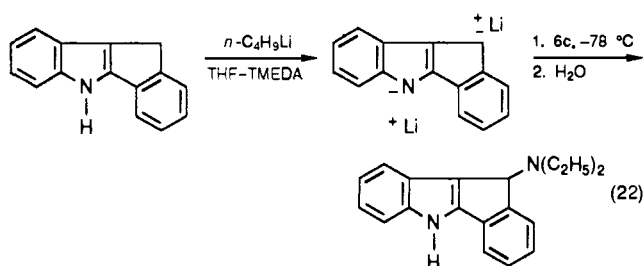
Boche and co-workers converted alkyl-, alkenyl-, and aryllithium compounds into tertiary amines in good yields by using the *N,N*-dialkyl-*O*-(arylsulfonyl)hydroxylamines **6b–e**, and the scope of the amination with *N,N*-dimethyl-*O*-(mesitylsulfonyl)hydroxylamine (**6b**) was investigated systematically (Scheme 25).⁸¹ α -Naphthyllithium and α -naphthylmagnesium bromide were aminated with **6b** or **6d** in 9% and 69% yields, respectively. Amination 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. Amination 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

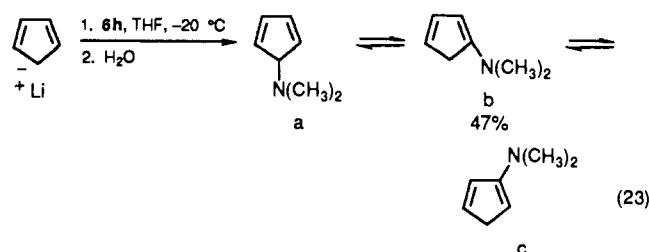
SCHEME 26



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

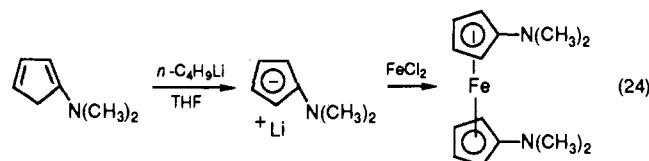


Boche and co-workers used **6h** for the electrophilic amination of cyclopentadienyllithium (eq 23).⁸⁵ The



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).

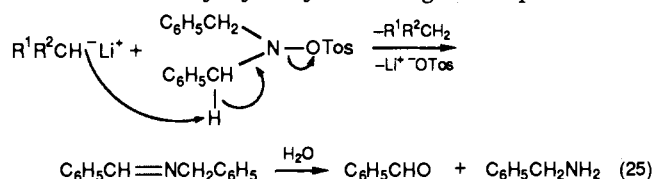


1-Alkynylcuprates, prepared from 1-alkynyllithiums, could be electrophilically aminated with **6h** in good yields (Scheme 26).⁸⁶ When 1-alkynyllithium reagents and 1-alkynylmagnesium bromides were allowed to react with **6h**, they gave no aminated products or only traces thereof, respectively. For 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.

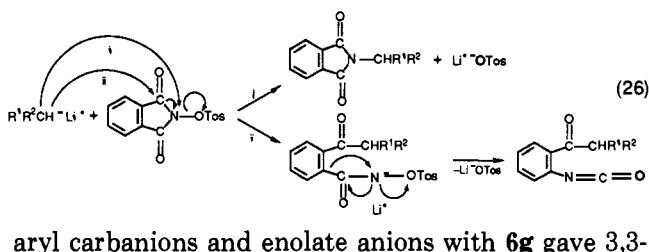
Finally, dialkylation of alkyl- and alkenyllithium derivatives can be carried out effectively by using **6b** as the aminating reagent, and 1-alkynyllithiums can also be dialkylated by using **6h** via organocopper intermediates.

Dibenzylaminations of a series of carbanions with *N,N*-dibenzyl(*p*-tolylsulfonyl)hydroxylamine (**6g**) were

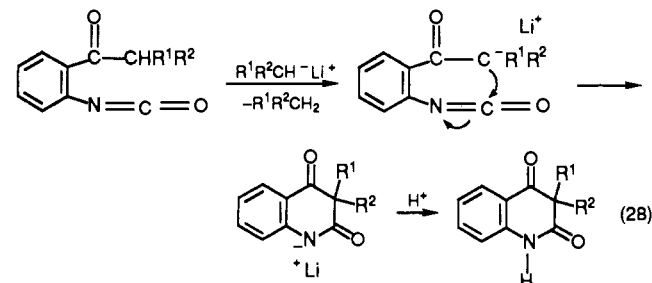
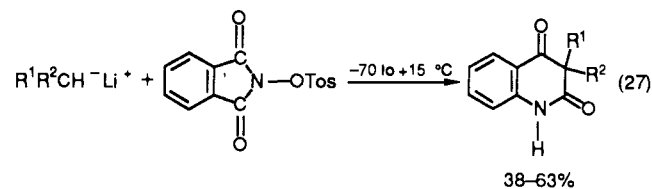
recently attempted by Sheradsky.⁸⁷ It was found that, unlike the reactions of the corresponding dimethyl and diethyl derivatives of *O*-(mesitylsulfonyl)hydroxylamine (**6b,c**), which result in dialkylation,⁸¹ the reaction of **6g** with a series of carbanions led always to the Schiff base via elimination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



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).



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**

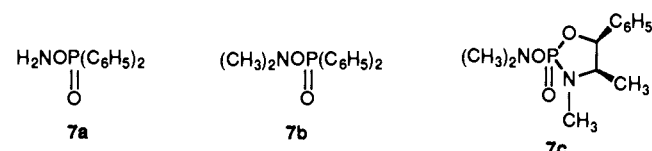
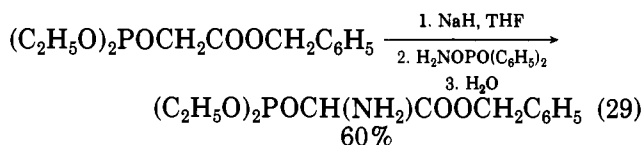


TABLE 5. Amination of Carbanions with *O*-Phosphinyldiarylamines (7a-c)

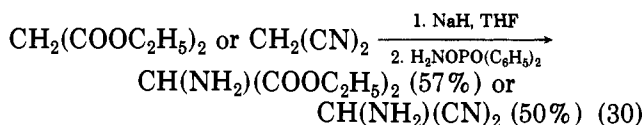
hydroxyl-amine	RM	scheme	ref
7a	R(Ar)MgBr, R(Ar)Li RCNa(COOR) ₂	eq 31, 27 eq 30	85, 90, 91 90
7b	R(Ar)MgBr, R(Ar)Li (RC≡C) ₂ LiCu RC(CN)Li(OSi(CH ₃) ₃)	27 28 29	91 86 92
7c	RMgX, RLi RCHLiCOOR	eq 32 30	93 93

have been discussed in detail⁸⁸ 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.

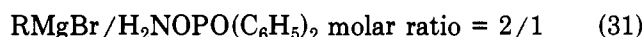
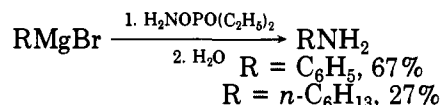
The preparation of primary amines from carbanions by using **7a** has been described by two groups. Colvin and co-workers⁹⁰ found that **7a** acts as a good aminating reagent toward some stabilized carbanions and Grignard reagents. Reaction of the sodium salt of benzyl diethylphosphonoacetate (1 equiv) 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-



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

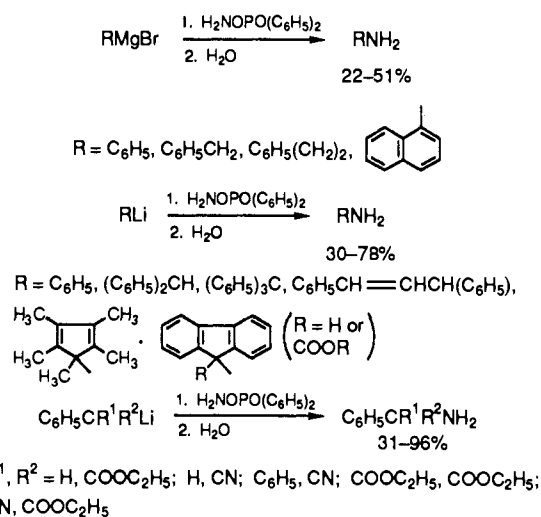


nations using the corresponding lithium salts were considerably less effective. For the amination of Grignard reagents, phenyl- and hexylmagnesium bromides were allowed to react with **7a** in THF at -78 °C. The use of phenyllithium produced only traces of aniline (eq 31).

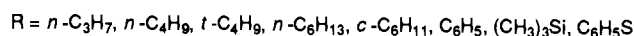
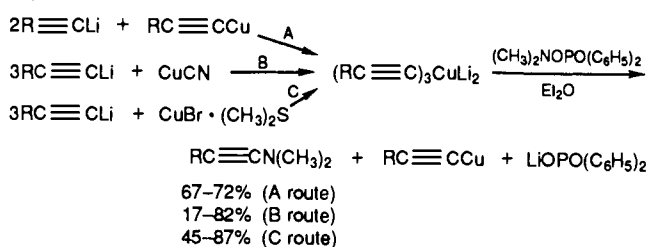


Boche and co-workers used⁹¹ **7a** and **7b** for the amination of a series of Grignard reagents, organolithium derivatives, and lithium enolates (Scheme 27). With alkyl and aryl Grignard and organolithium reagents, moderate yields of the corresponding amines were obtained. The amination yield was found 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.

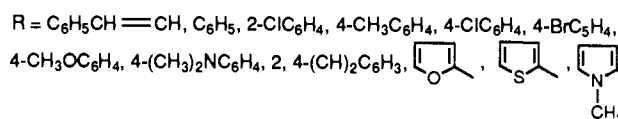
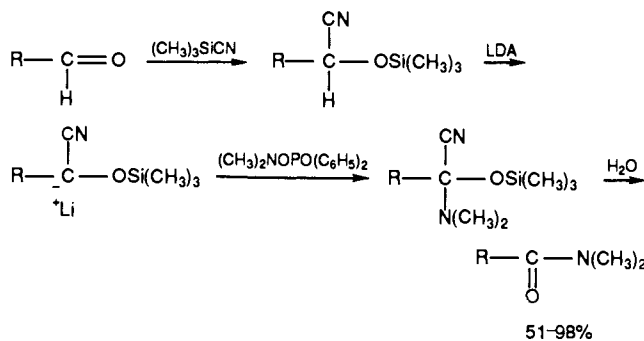
SCHEME 27



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**.

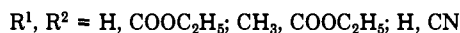
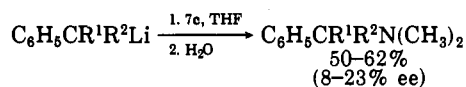
It was reported⁸⁶ that **7b** instead of **6h** could also be successfully used in the amination of cyclopentadienyllithium;⁸⁵ **7b** was also used to convert 1-alkynyllithium cuprates derived from 1-alkynyllithiums into 1-alkynylamines, and these reactions were reported to give yields comparable to 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)

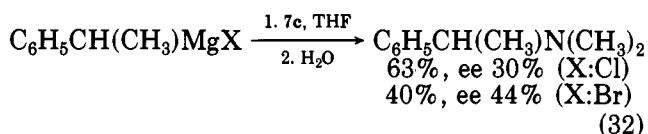
azide	RM	scheme	ref
8a	ArMgBr	31	103
	ArLi	32-34, eq 36, eq 37	104, 106, 108, 109
	C ₆ H ₅ CH ₂ CH ₂ MgBr		103
8b	C ₆ H ₅ MgBr	eq 38	110
8c	R(Ar)MgBr	36, 37, eq 39	101, 111, 112
8d-h	C ₆ H ₅ MgBr,	36, 37	111
	C ₆ H ₅ CH ₂ CH ₂ MgBr		
8i	ArMgBr, ArLi	38, eq 40	113, 114
8j	ArLi	40, 41	115, 116
8k	ArMgBr, ArLi	42	117

SCHEME 30



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.

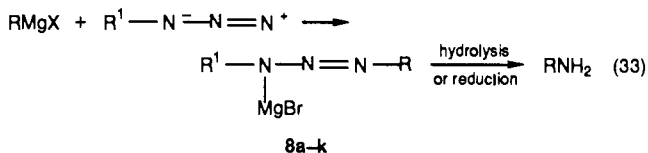
The chiral amination reagent (2*R*,4*S*,5*R*)-2-[*O*-(*N,N*-dimethylhydroxylamino)]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (7c) was prepared and reacted with a number of lithium enolates and Grignard reagents in THF at -15 °C to yield chiral tertiary amines (Scheme 30 and eq 32, respectively).⁹³



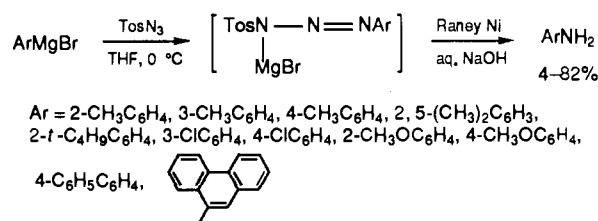
As outlined, the introduction of amino and dimethylamino groups via 7a and 7b, respectively, provides an easy synthetic method for the amination of a variety of Grignard reagents, organolithium reagents, and lithium enolates. Even in those cases where only moderate to fair yields are obtained, the reaction 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.



SCHEME 31



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

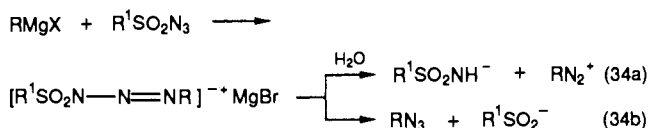
RN₃

- | | |
|---|--|
| 8a, R = 4-CH ₃ C ₆ H ₄ SO ₂ (Tos) | f, R = CH ₃ SCH ₂ |
| b, R = (C ₆ H ₅) ₂ Si | g, R = CH ₃ OCH ₂ |
| c, R = C ₆ H ₅ SCH ₂ | h, R = (CH ₃) ₃ SiOC(<i>i</i> -C ₃ H ₇) |
| d, R = 4-CH ₃ OC ₆ H ₄ SCH ₂ | i, R = (CH ₃) ₃ SiCH ₂ (TMSMA) |
| e, R = C ₆ H ₅ OCH ₂ | j, R = R ¹ CH=CR ² |
| | k, R = (C ₂ H ₅ O) ₂ PO (DPPA) |

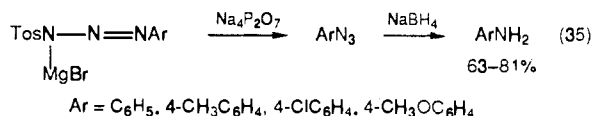
toluenesulfonyl azide (8a), (phenylthio)methyl azide (8c), (trimethylsilyl)methyl azide (TMSMA; 8i), and diphenyl phosphorazidate (DPPA, 8k) have been extensively investigated. The azide 8a is a shock-sensitive reagent,¹⁰⁰ 8c was reported to be stable and could not be detonated by shock.¹⁰¹ However, 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 reported⁹⁷ 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).

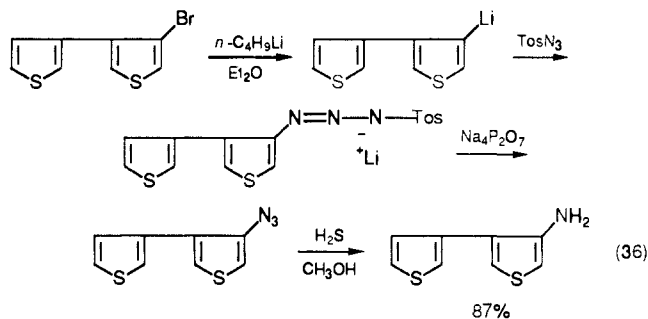


p-Toluenesulfonyl azide (8a) was found¹⁰² to give only *p*-toluenesulfonamide and a diazo compound on reaction with carbanions. However, the reaction of 8a with aryl Grignard reagents followed by reductive workup led to the isolation of arylamines in good yields in a one-pot procedure (Scheme 31).¹⁰³ 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



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



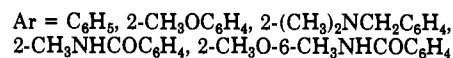
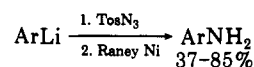
isomeric ortho-substituted bromothienyls with *n*-butyllithium in diethyl ether at -70°C , and a diethyl ether solution of 1 equiv of **8a** was added at the same temperature. The mixture was stirred for 5 h at -70°C . When the temperature had reached -10°C , the resulting triazene salt was filtered, 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.

The utility of **8a** for introducing amino groups into ortho-lithiated aromatic compounds¹⁰⁵ 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

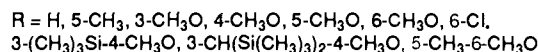
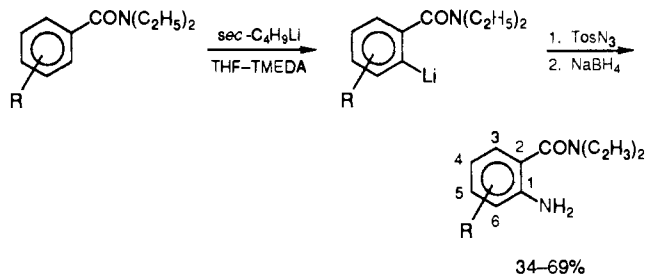
Ortho-amination of lithiated tertiary benzamides¹⁰⁷ with **8a** provided a short route for the synthesis of diversely substituted anthranilamides in modest to good yields (Scheme 33).¹⁰⁸ Substituted *N,N*-diethylbenzamides (1 equiv) were lithiated with *sec*-butyllithium in THF-TMEDA at -78°C for 1 h 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 $\text{MgBr}_2 \cdot 2\text{Et}_2\text{O}$ leads to insignificant improvement in the yield of the anthranilamide.

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

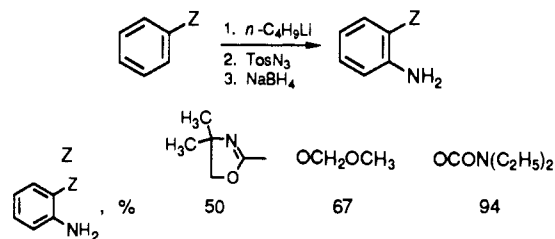
SCHEME 32



SCHEME 33

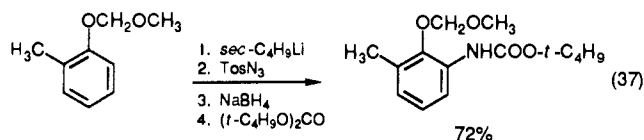


SCHEME 34



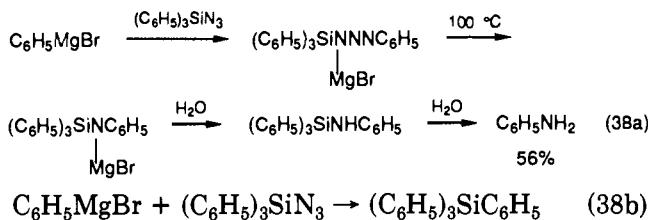
The procedure followed was identical with that used for diethylbenzamides, whereas the methoxymethoxy case required metalation with *tert*-butyllithium at 0°C in diethyl ether.

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



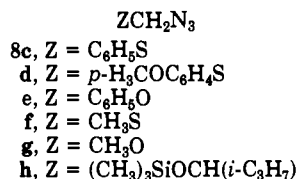
The oxidative coupling reaction of methoxy-substituted, ortho-lithiated benzamides with anilidochloro- or anilidocyanocuprates was reported to yield *N*-aryl-anthranilamides in moderate yields. This class of compounds was further converted into acridones. This work represents the second example⁶⁷ of 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 reported¹¹⁰ to aminate Grignard reagents. The triazene salt formed from the reaction of phenylmagnesium bromide with **8b** decomposed at $100\text{--}120^\circ\text{C}$ 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).



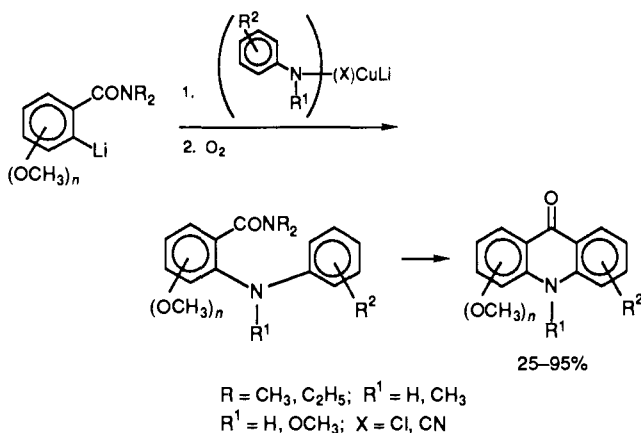
(Phenylthio)methyl azide (**8c**)^{101,111} was used successfully for the amination of aryl- and alkylmagnesium bromides by Trost and Pearson. Direct utilization of organolithium compounds failed because of the lower acidity of the lithium salts. Addition of 1 equiv of MgBr_2 in THF to 1 equiv of aryllithium 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 comparison¹¹¹ of various heteroatom-substituted methyl azides, ZCH_2N_3 (**8c–h**). The experiments established the order $\text{c} \sim \text{d} > \text{f} > \text{g} \gg \text{e} \sim \text{h}$, 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.

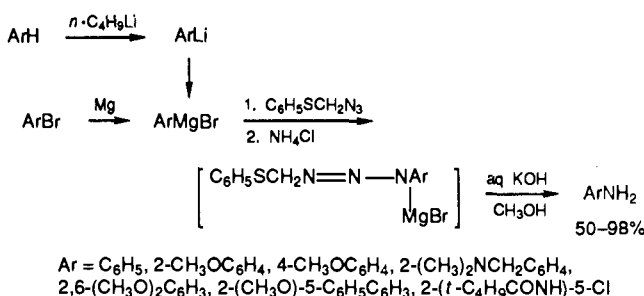


The structure of the initial addition product, **27a** or **27b**, was investigated¹¹¹ by quenching it with acetic anhydride to produce the acylated triazenes, **28a** or **28b** (Scheme 38). The adduct(s) formed in the reaction of phenethylmagnesium bromide with **8c** were quenched and a single product 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

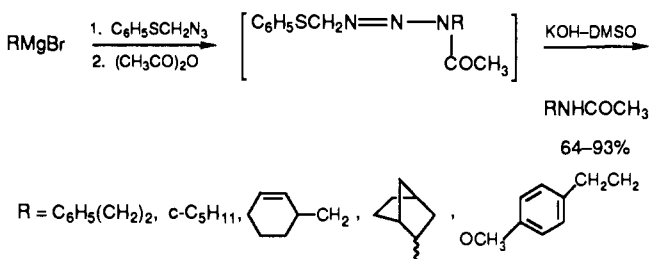
SCHEME 35



SCHEME 36

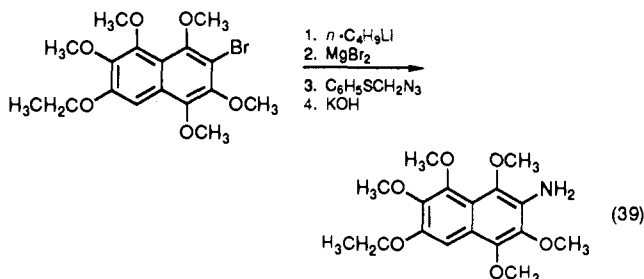


SCHEME 37

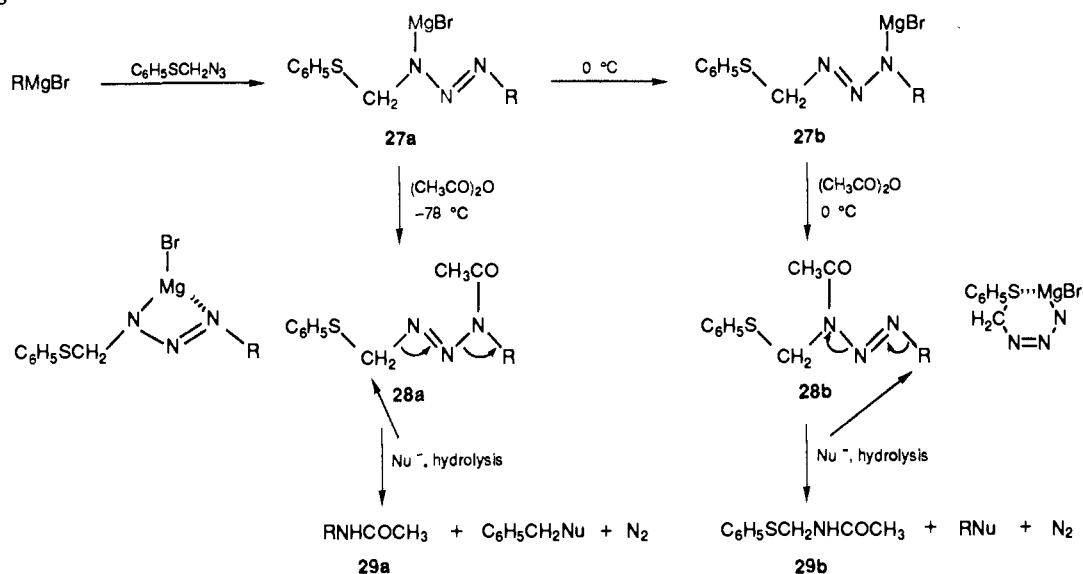


to four- and six-membered-ring chelates, respectively. An explanation depending upon the mechanism of attack of carbon onto an azide function was given for the exclusive kinetic formation of the thermodynamically less stable magnesium salt. Thus, treating phenethylmagnesium bromide with **8c**, quenching 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 $\text{S}_{\text{N}}2$ transition state. This study revealed that the addition of a Grignard reagent to azides proceeds by a stereochemically controlled pathway.

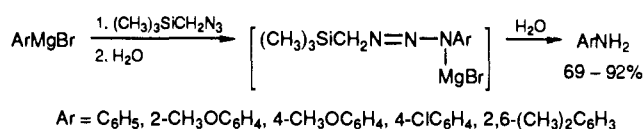
In a five-step synthesis of the naphthalene nucleus of Streptovaricin D in 33% overall yield, **8c** was used for introduction of the amino group (eq 39).¹¹²



SCHEME 38

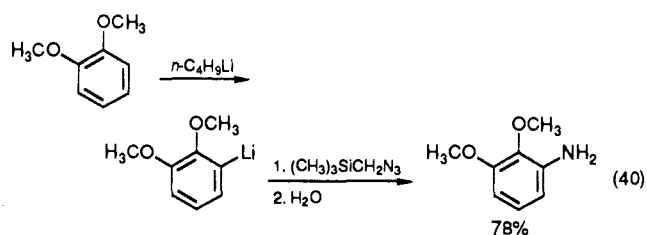


SCHEME 39



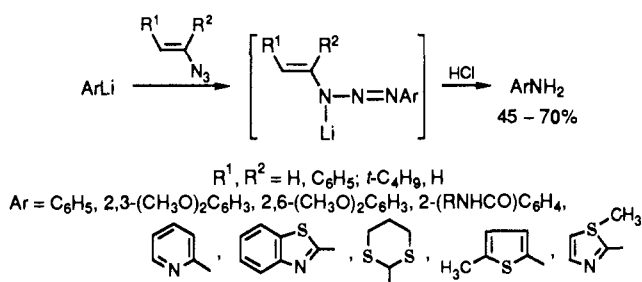
Another heteroatom-substituted methyl azide, (trimethylsilyl)methyl azide (TMSMA; **8i**), was used by Nishiyama and Tanaka for the amination of aryl Grignard and aryllithium compounds (Scheme 39).¹¹³ This process required merely a neutral hydrolysis to decompose the intermediate triazenes. In a typical 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



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 ary-

SCHEME 40

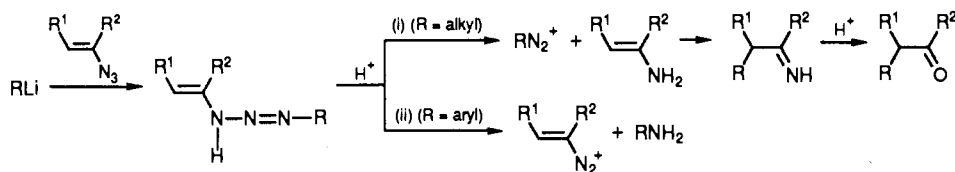


lamines in good yields (Scheme 40). In a typical procedure, **8j** (1 equiv) is added to an organolithium reagent (1 equiv) in THF at -78°C . The mixture is allowed to warm to room temperature and is worked up with aqueous acid or base to recover the amines. Unlike (phenylthio)methyl azide (**8c**), 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**.

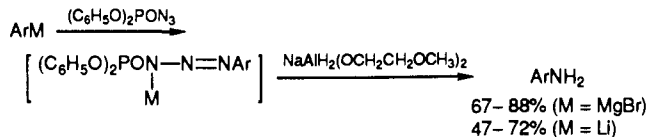
The attack of organolithium reagents on vinyl azides (**8j**) was reported^{115,116} to proceed via formation of triazene intermediates, which were isolated. In the case of the hydrolysis of triazenes obtained from alkyllithium reagents, alkyl group transfer to carbon takes place via a diazonium compound 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 found¹¹⁷ 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:

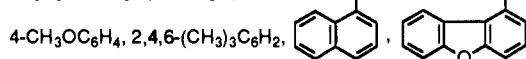
SCHEME 41

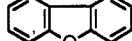


SCHEME 42

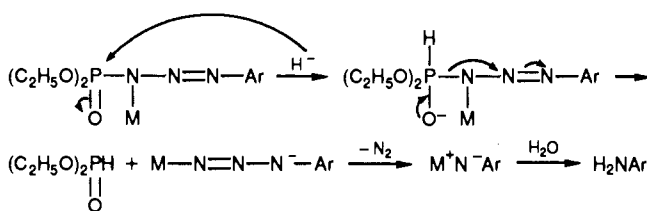


Ar in ArMgBr : C_6H_5 , 4- ClC_6H_4 , 4- $\text{CH}_3\text{C}_6\text{H}_4$,



Ar in ArLi : 2,6- $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3$, 2,5- $(\text{CH}_3\text{OCH}_2\text{O})_2\text{C}_6\text{H}_3$, 

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.

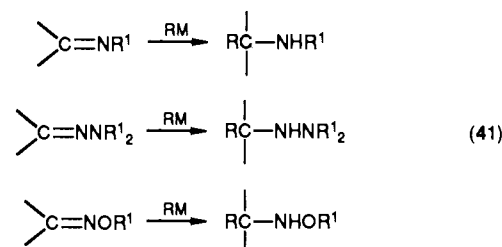
A plausible mechanism for the reductive decomposition of phosphorotriazenes with hydrides is given in Scheme 43.

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

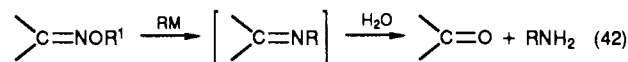
of azides—except in a few cases with **8a**¹⁰³ and **8c**¹¹¹—in useful yields. Since aromatic and heteroaromatic lithium compounds are readily accessible by direct lithiation or lithium-halogen exchange, the use of azides represents a useful method for the synthesis of aromatic and heteroaromatic amines 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



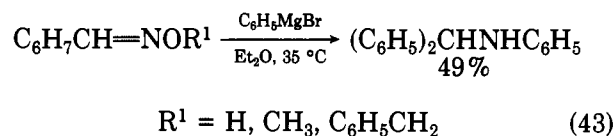
It was found that ketoximes can also serve as electrophilic aminating reagents for Grignard reagents and organolithium reagents (eq 42).



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.

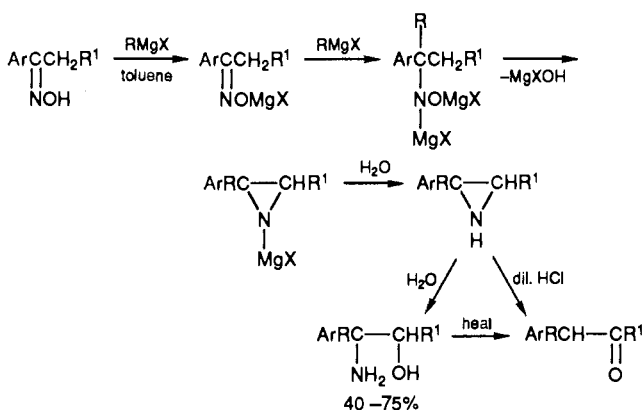
The addition of organometallic reagents to oximes¹¹⁸ has found limited applicability since oximes are often less electrophilic and less easily activated than the corresponding imines. In addition, the synthesis of the addition products requires the use of a considerable excess of organolithium reagents. α -Deprotonation of oximes and their *O*-alkyl derivatives with aryllithium compounds is a facile reaction resulting in the formation of dianions, which can alkylated^{119–122} or acylated¹²³ with high regioselectivity.

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



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

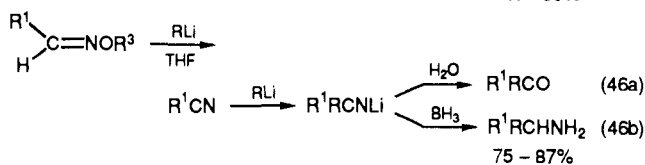
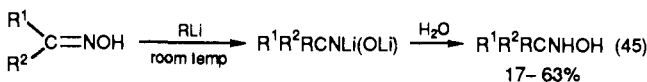
SCHEME 44



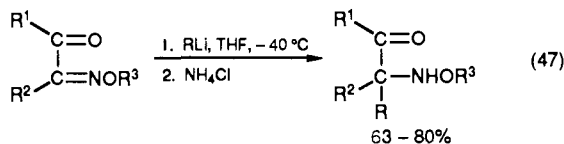
timines as side products (eq 44),¹²⁵ and *N*-arylformamide and aryl cyanide were isolated as intermediates.



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).



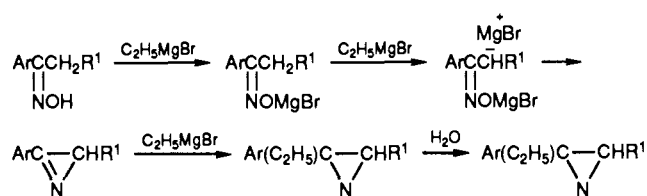
Organolithium reagents have been recently reported¹²⁸ to react with glyoxylate- and pyruvate-derived oximes to provide an efficient and direct route for the synthesis of unusual α -*N*-hydroxyamino acids (eq 47).



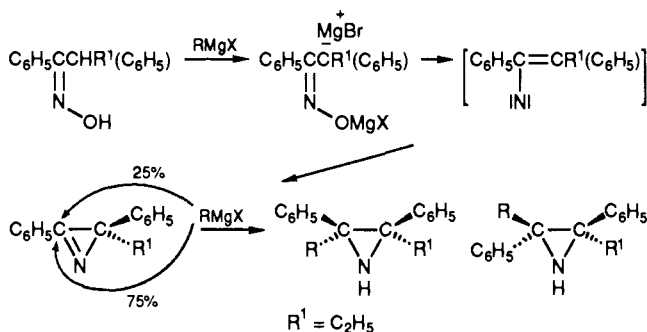
The formation of ethylenimines (aziridines) from alkyl or aryl ketoximes and Grignard reagents was first reported by Hoch and co-workers.^{129–131} Subsequently, Campbell and co-workers showed that aryl Grignard reagents react with alkylaryl or dialkyl ketoximes to yield either ethylenimines or β -amino 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



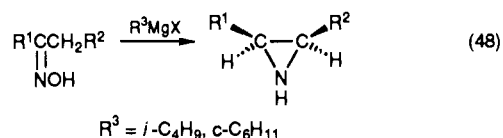
SCHEME 46



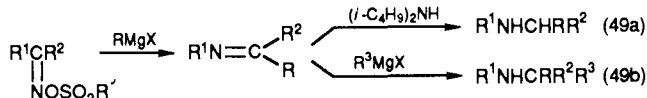
The reactions of cyclooctanone oxime tosylates with organolithium reagents were also investigated.¹⁴² Reactions of oximes with Grignard reagents leading to aziridines were briefly reviewed.¹⁴³

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 regioselective 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



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

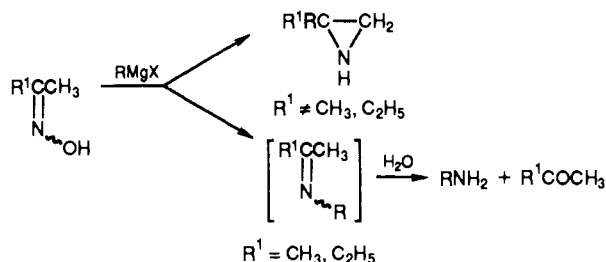


So far, oximes **9a–e** and *O*-substituted derivatives **9f–k** have been used for preparation of primary amines (Table 7).

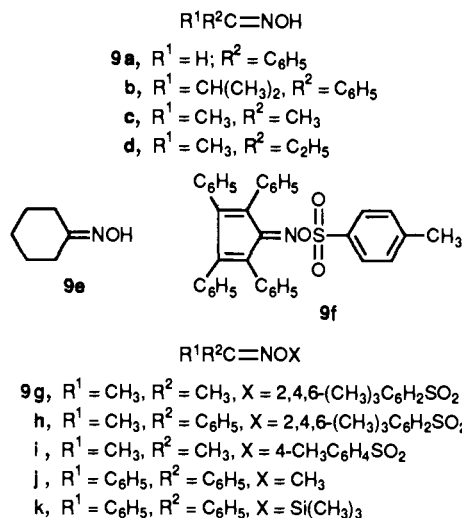
TABLE 7. Amination of Carbanions with Oximes (9a-k)

oxime	RM	scheme	ref
9a	$\alpha\text{-C}_{10}\text{H}_7\text{MgBr}$	eq 50	154
9b	$\text{C}_6\text{H}_5\text{MgBr}$	eq 51	136
9c	$\text{R}(\text{Ar})\text{MgX}, \text{C}_6\text{H}_5\text{Li}$	47, 48	154, 158
9d	$\text{C}_6\text{H}_5\text{Li}$	49	154
9e	$\text{C}_6\text{H}_5\text{MgBr}$	50	147
9f	$\text{ArMgBr}, \text{ArLi}$	51	159
9g-k	ArMgBr	eq 53	160

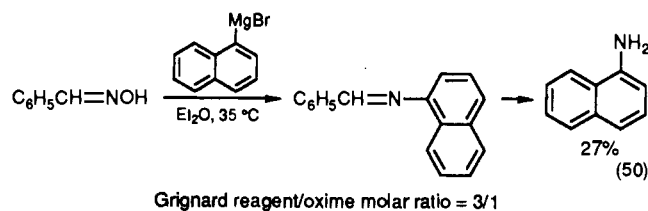
SCHEME 47



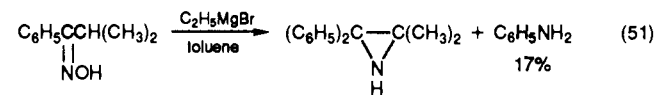
The first example of the use of oximes for the amination of a Grignard reagent was the reaction of benzaldoxime (9a) with α -naphthylmagnesium bromide,



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

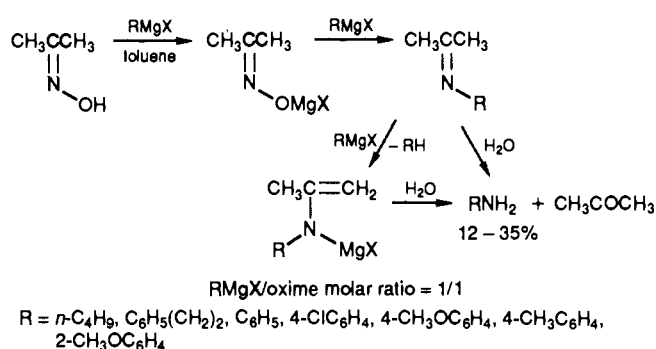


Isobutyrophenone oxime (9b) produced aniline as well as the Hoch-Campbell product in its reaction with phenylmagnesium bromide (eq 51).¹³⁶

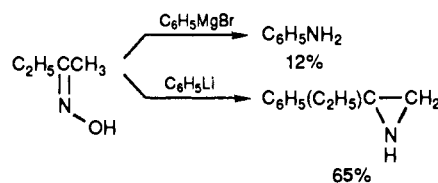


Alverne, Laurent, and co-workers have reported that the reactions of acetone and butanone oximes with Grignard reagents do not yield aziridines, but primary amines, and that the ketone can be isolated (Scheme 47).^{154,158} The reaction of acetone oxime (9c) with aryl

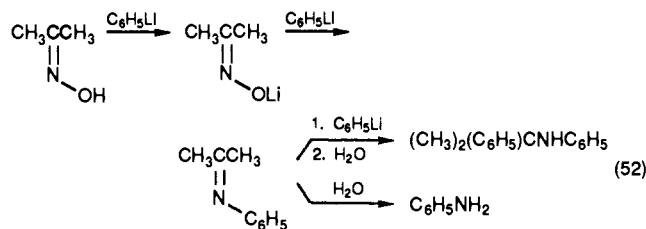
SCHEME 48



SCHEME 49



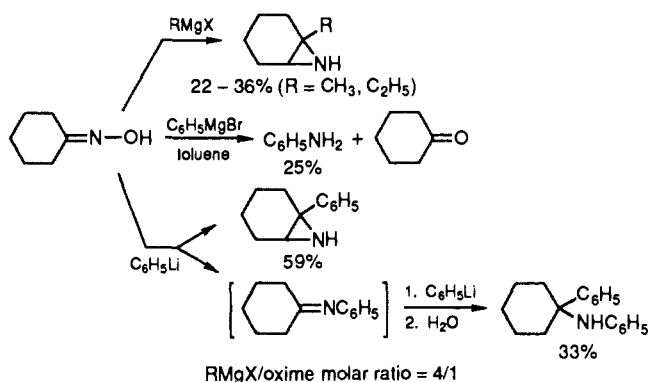
and alkyl Grignard reagents gave primary amines in good yields;¹⁵⁸ however, 2 or 3 equiv of the Grignard reagent appears to be required for amination, since by increasing the ratio of RMgX:oxime from 1:1 to 2:1, the yield of amines almost doubled. Using a ratio of 3:1 was reported not to change the yield 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,



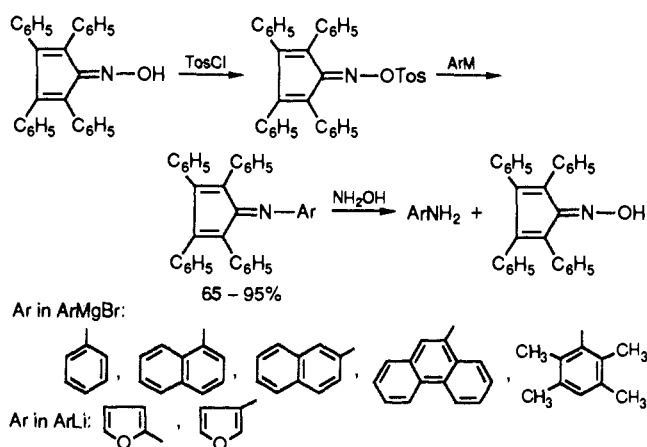
the reaction of butanone oxime (9d) with phenyllithium was reported to result in the isolation of an aziridine (Scheme 49).¹⁵⁴ Cyclohexanone oxime (9e) reacted with alkyl Grignard reagents and phenylmagnesium bromide to produce aziridines and aniline, respectively; however, the reaction with phenyllithium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

Murdoch and co-workers reported¹⁵⁹ 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).

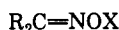
SCHEME 50



SCHEME 51

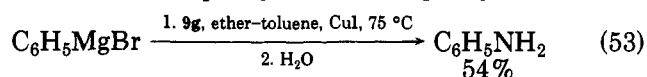


We have used a number of O-substituted ketoximes, R₂C=NOX, for the amination of phenylmagnesium bromide and found acetoxime *O*-mesitylenesulfonate (**9g**) to be a good amino-transfer reagent.¹⁶⁰ The amination yield decreases in the order **9g** > **9h** > **9i** >> **9j** > **9k**. The conditions for the amination of aryl Grig-



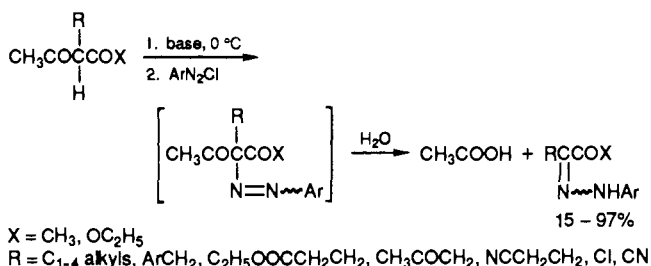
- 9g**, R = CH₃; X = 2,4,6-(CH₃)₃C₆H₂SO₂
9h, R = C₆H₅; X = 2,4,6-(CH₃)₃C₆H₂SO₂
9i, R = CH₃; X = 4-CH₃C₆H₄SO₂
9j, R = C₆H₅; X = CH₃
9k, R = C₆H₅; X = Si(CH₃)₃

nard 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

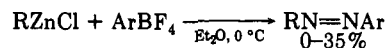


resulted in a lower yield. Use of diphenylcopper(I) magnesium bromide at -20 °C gave aniline in 25% yield. Further work to reduce the reaction time still more and to improve the amination yield is in progress.

SCHEME 52



SCHEME 53



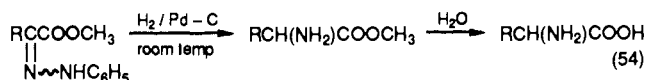
- R = *t*-C₄H₉, C₆H₅CH₂, C₆H₅, 4-ClC₆H₄,
4-CH₃CC₆H₄, 2,4,6-(CH₃)₃C₆H₂
Ar = C₆H₅, 4-ClC₆H₄, 4-CH₃OC₆H₄, 2,4,6-(CH₃)₃C₆H₂

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.

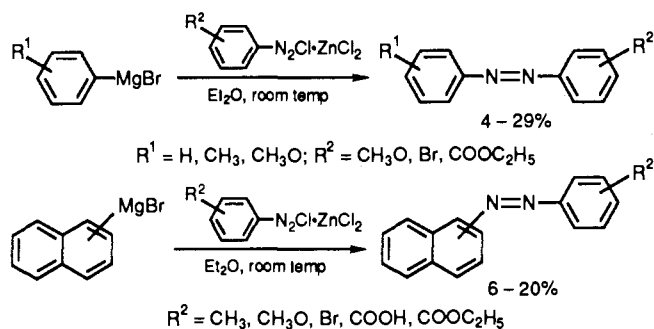
The α -hydrazono or α -azo esters formed are easily reduced to α -amino acid esters in nearly quantitative yields when treated with hydrogen in the presence of palladium on carbon¹⁶² and can then be hydrolyzed to the α -amino acids (eq 54).



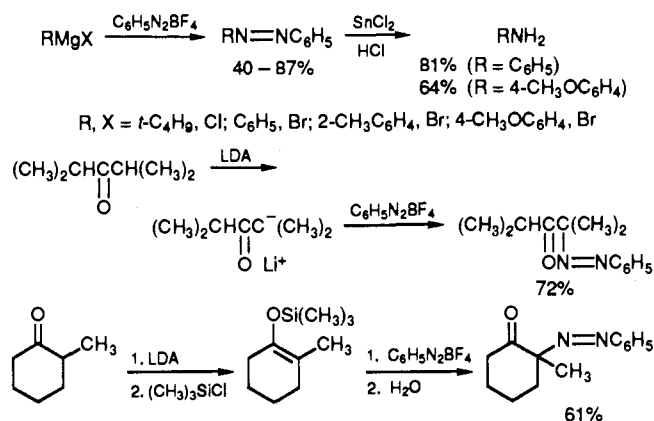
Simple esters do not work in the Japp-Klingemann reaction; in addition the reaction is not applicable to α -disubstituted acetoacetates, which are possible starting materials for α -disubstituted amino acids, since the success of the reaction requires the presence of an acidic hydrogen.

Organomagnesium, -lithium, -zinc, -cadmium, and -mercury compounds were subjected to the Japp-Klingemann reaction.¹⁶³⁻¹⁶⁵ It was found¹⁶³ 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



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

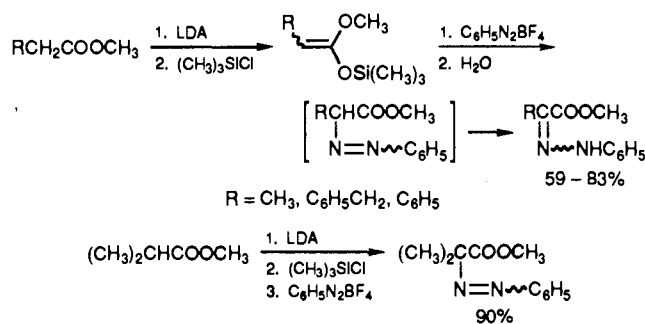
Arylmagnesium bromides were reacted with substituted benzenediazonium chloride-zinc chloride double salts¹⁶⁴ in diethyl ether at 0 °C or at room temperature to yield azo compounds in low yields (Scheme 54).

Later, it was reported that¹⁶⁵ 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 tetrafluoroborate¹⁶⁶ 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.

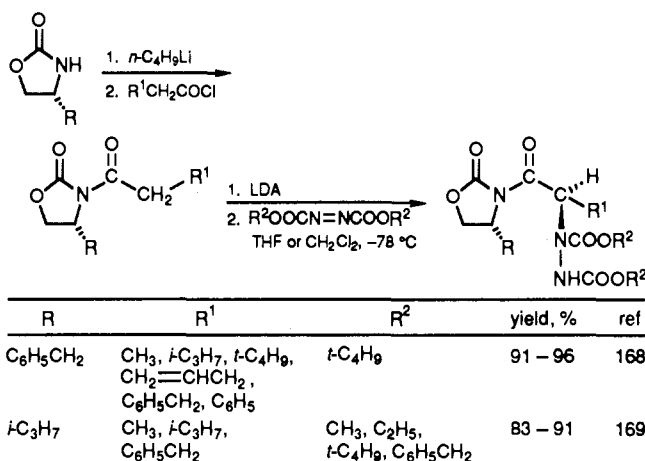
Recently, it was observed¹⁶⁷ that the silicon enolates of esters (i.e., silyl ketene acetals) also react with benzenediazonium tetrafluoroborate (10b) to give α -azo or α -hydrazono esters, which are converted to α -amino esters upon hydrogenolysis (Scheme 56). Disubstituted silyl ketene acetals afforded 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

SCHEME 56



SCHEME 57



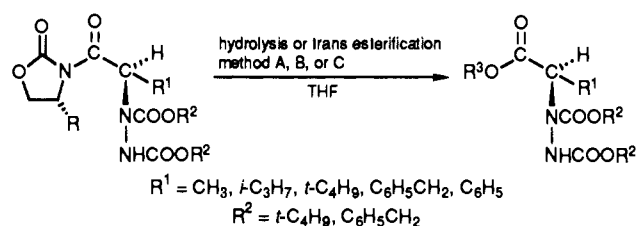
for introducing an amino group onto the α -carbon atom of simple esters.

J. With Dialkyl Azodicarboxylates

It has been recently reported¹⁶⁸⁻¹⁷⁰ 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.

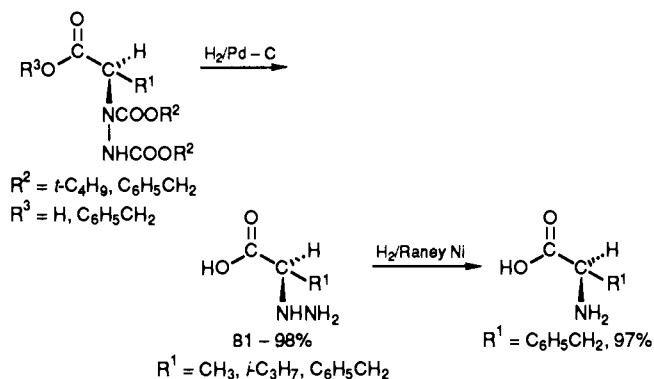
Dialkyl azodicarboxylates (DAAD) react with the lithium enolates derived from the *N*-acyloxazolidinones^{168,169} to provide the hydrazide adducts in excellent yields (Scheme 57). In a typical experimental procedure, *N*-acyloxazolidinones, obtained by *N*-acylation of oxazolidinones, were converted to their lithium enolates¹⁷⁰⁻¹⁷³ (1.1 equiv of LDA, THF, -78 °C), and a solution of the DAAD (1.2 equiv, CH₂Cl₂, -78 °C¹⁶⁸ or 1.1 equiv, THF, -78 °C¹⁶⁹) was added. The reactions were then immediately quenched with glacial acetic acid¹⁶⁸ or ammonium chloride solution.¹⁶⁹ A conventional isolation procedure afforded the diastereomerically pure hydrazides¹⁶⁸ 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 R² group on the aminating reagent increases, the ratio improves (CH₃ < C₂H₅ < CH₂C₆H₅ < *t*-C₄H₉). Similarly, a greater bulk of the acyl side chain also increases the stereoselectivity (CH₃ < CH₂C₆H₅ < *i*-C₃H₇). 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



method (reagent and conditions)	R ³	yield, %	ref
A (LiOH, 2:1 THF - H ₂ O, 3 h, 0 °C)	H	82 - 85	168, 169
B (CH ₃ OMgBr, CH ₃ OH, 30 min, 0 °C)	CH ₃	71 - 89	168
C (C ₆ H ₅ CH ₂ OLi, THF, 2 h, -50 °C)	C ₆ H ₅ CH ₂	51 - 96	168, 169

SCHEME 59



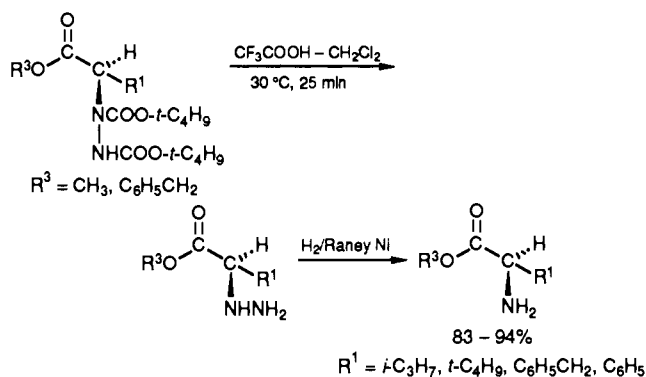
synthetically advantageous.¹⁶⁹ Dialkyl azodicarboxylates (DAAD) are commercially available reagents. Procedures have been published for preparation of DBAD.^{174,175}

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 found¹⁶⁹ to be the reagent of choice for carrying out the desired transesterification without concomitant racemization.

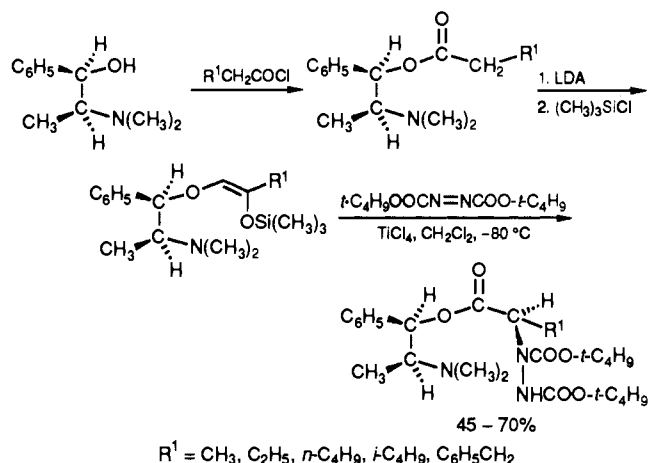
α -Hydrazides were hydrogenolyzed on palladium-carbon to the free α -hydrazino acids, and Raney nickel was used¹⁶⁹ to hydrogenolyze α -hydrazino acids^{176,177} to the parent α -amino acids without detectable racemization (Scheme 59). In an alternative method for the conversion of α -hydrazido derivatives 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-TiCl₄ complex with silicon enolates derived from *O*-acyl-*N*-methylephedrine has been shown to be a practical method¹⁷⁰ (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)-TiCl₄ complex (1 equiv, CH₂Cl₂, -80 °C) gave the hydrazides in good yield and with high stereoselectivity.

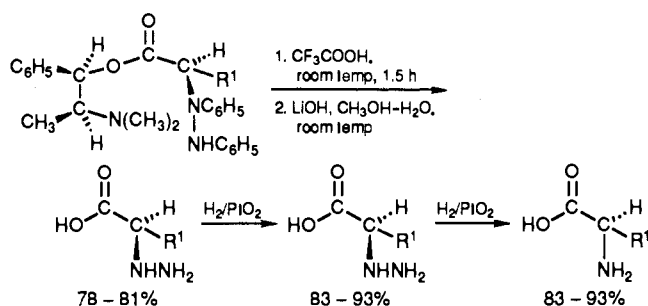
SCHEME 60



SCHEME 61



SCHEME 62



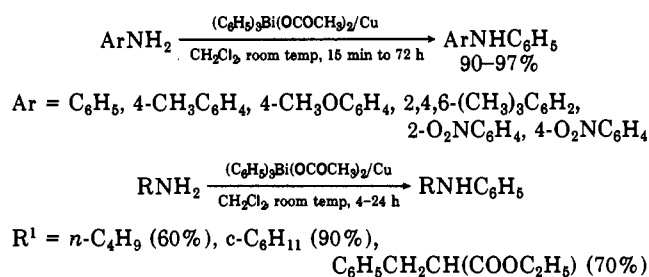
For removal of the *N*-methylephedrine moiety, the hydrazide adducts were converted to α -hydrazino esters, which were hydrolyzed to give α -hydrazino acids. Reduction with hydrogen over platinum oxide gave the corresponding α -amino acids in high yields and optical purity (Scheme 62).

K. With Amines

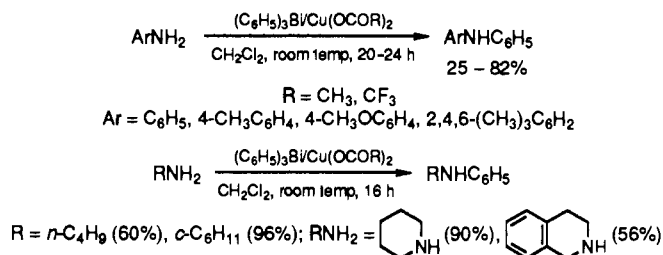
In a new development, Barton and co-workers have found that pentavalent and trivalent phenylbismuth compounds^{178,179} and tetravalent phenyllead compounds¹⁸⁰ are able to *N*-arylate amines in the presence of catalytic amounts of copper or stoichiometric amounts of copper(II) diacylates.

Aliphatic and aromatic primary and secondary amines are mono- or di-*N*-phenylated by triphenylbismuth diacylates [(C₆H₅)₃Bi(OCOR)₂] under copper catalysis^{178,181} or by triphenylbismuth [(C₆H₅)₃Bi] in the presence of copper(II) diacylate¹⁷⁹ in mild, selective, and high-yielding reactions.

SCHEME 63



SCHEME 64



Reactions of substituted anilines and aliphatic amines with (C₆H₅)₃Bi(OCOCH₃)₂ (1.1 equiv) in dichloromethane in the presence of copper (0.1 equiv) at room temperature afforded¹⁷⁸ 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, (C₆H₅)₃Bi(OCOCF₃)₂, was found to be the most efficient since its use decreased the reaction time remarkably.

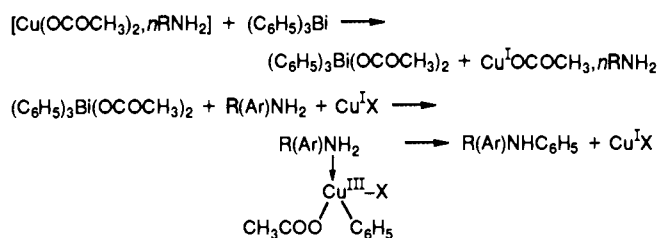
The N-phenylation of amines by triphenylbismuth diacetate catalyzed by copper diacetate was reported,¹⁸¹ however, the reaction required a large excess of the amine.

Amines react with (C₆H₅)₃Bi in the presence of copper diacylate (0.5 equiv) to give good yields of the mono-phenylated derivatives¹⁷⁹ (Scheme 64). Stoichiometric use of the copper(II) salt gave the best yields, in contrast to the catalytic amount required in the (C₆H₅)₃Bi(OCOR)₂ + Cu species system. Whereas in the (C₆H₅)₃Bi(OCOR)₂ + Cu or Cu(II) systems the yields are mostly related to the steric hindrance of the amine, the (C₆H₅)₃Bi + Cu(OCOR)₂ system shows also a dependence on the basicity of the amine.

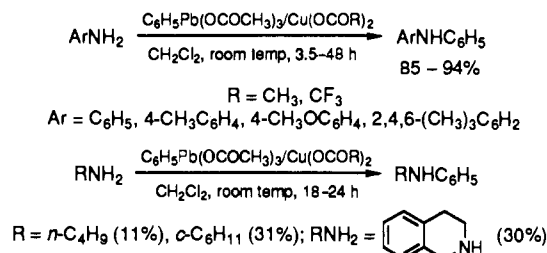
The proposed mechanism¹⁷⁹ for the phenylation with phenylbismuth reagents involves an in situ oxidation of (C₆H₅)₃Bi by the Cu(OCOCH₃)₂-amine complex to give (C₆H₅)₃Bi(OCOCH₃)₂, which subsequently reacts with a copper(I) species to give a phenylcopper(III) species which, in turn, phenylates the amine (Scheme 65). The reaction of amines with lithium dialkyl- or diarylcuprates was already stated to yield N-alkylated or N-arylated amines⁶⁷ (Scheme 22).

Lastly, the copper-catalyzed phenylation of aromatic and aliphatic amines using (C₆H₅)_xPb(OCOCH₃)_{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 C₆H₅Pb(OCOCH₃)₃

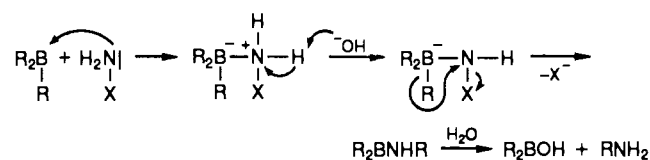
SCHEME 65



SCHEME 66



SCHEME 67

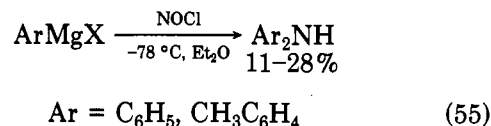


with aliphatic or alicyclic amines gave the corresponding N-phenyl derivatives in poor to modest yields. Thus, the (C₆H₅)₃Bi(OCOR)₂ + Cu system is much superior. At present, one limitation of the procedure is when an expensive aryl halide has to be used to prepare the bismuth derivative, since at least 2 equiv of C₆H₅ is lost from (C₆H₅)₃Bi(OCOR)₂, with only one being used in the reaction.

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

L. Miscellaneous Reactions

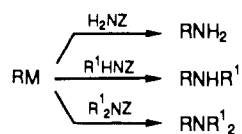
The reaction between phenylmagnesium bromide and nitrosyl chloride was investigated^{183–185} and the product was found to be diphenylamine and not nitrosobenzene as reported in the earlier literature.¹⁸⁶ Nitrosobenzene and diphenylnitric oxide were, however, detected as reaction intermediates.¹⁸⁷ Symmetrical 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



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



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 ₃ MgBr	1a-1	26	20	1
2	CH ₃ Li	1a-2	7	30	7
3	CH ₃ Li	2a-CH ₃ Li	80	43	16
4	CH ₃ Li	6b	45	81	25
5	CH ₃ Li	6e	39	81	25
6	C ₂ H ₅ MgCl	1a-1	57	20	1
7	C ₂ H ₅ MgCl	1d-1	29	26	4
8	C ₂ H ₅ MgBr	1a-1	28	20	1
9	C ₂ H ₅ MgBr	2a-1	67	44a	10
10	C ₂ H ₅ MgBr	2a-2	81	45	11
11	C ₂ H ₅ MgBr	2b-1	46	44b	10
12	C ₂ H ₅ Li	2a-CH ₃ Li	78	43	16
13	(C ₂ H ₅) ₂ Zn	1a-3	46	30	9
14	(C ₂ H ₅) ₂ Zn	1a-2	17	30	9
15	(C ₂ H ₅) ₂ Zn	1f ^d	70	36	9
16	(C ₂ H ₅) ₂ Zn	1g	78	36	9
17	(C ₂ H ₅) ₂ Zn	1g	71	36	9
18	C ₆ H ₅ (CH ₂) ₂ MgCl	1a-1	74	20	1
19	C ₆ H ₅ (CH ₂) ₂ MgCl	1b	34	24	2
20	C ₆ H ₅ (CH ₂) ₂ MgCl	1c	18	25	3
21	C ₆ H ₅ (CH ₂) ₂ MgCl	1d-1	30	26	4
22	C ₆ H ₅ (CH ₂) ₂ MgCl	2a-2	68	45	11
23	C ₆ H ₅ (CH ₂) ₂ MgBr	8a-1	25	103	31
24	C ₆ H ₅ (CH ₂) ₂ MgBr	8c	80	111	37
25	C ₆ H ₅ (CH ₂) ₂ MgBr	9c-2	48	158	48
26	4-CH ₃ OC ₆ H ₄ (CH ₂) ₂ MgBr	8c	75	111	37
27	<i>n</i> -C ₃ H ₇ MgCl	1a-1	58	20	1
28	<i>n</i> -C ₃ H ₇ MgCl	1g	52	27	5
29	<i>n</i> -C ₃ H ₇ MgBr	1a-1	27	20	1
30	<i>n</i> -C ₃ H ₇ MgBr	2a-2	85	45	11
31	(<i>n</i> -C ₃ H ₇) ₂ Zn	1d-2	17	30	9
32	<i>i</i> -C ₃ H ₇ MgCl	1a-1	65	21	1
33	<i>i</i> -C ₃ H ₇ MgCl	1d-1	23	26	4
34	<i>i</i> -C ₃ H ₇ MgBr	1a-1	37	21	1
35	<i>n</i> -C ₄ H ₉ MgCl	1a-1	59	20	1
36	<i>n</i> -C ₄ H ₉ MgCl	1b	29	24	2
37	<i>n</i> -C ₄ H ₉ MgCl	1c	15	25	3
38	<i>n</i> -C ₄ H ₉ MgCl	1d-1	59	26	4
39	<i>n</i> -C ₄ H ₉ MgCl	1e	72	27	5
40	<i>n</i> -C ₄ H ₉ MgCl	1f ^e	85	27	5
41	<i>n</i> -C ₄ H ₉ MgCl	1g	36	27	5
42	<i>n</i> -C ₄ H ₉ MgCl	1g	43	27	5
43	<i>n</i> -C ₄ H ₉ MgCl	2a-2	58	45	11
44	<i>n</i> -C ₄ H ₉ MgBr	1a-1	27	20	1
45	<i>n</i> -C ₄ H ₉ MgBr	2a-2	63	45	11
46	<i>n</i> -C ₄ H ₉ MgBr	2a-CH ₃ Li	16	43	16
47	<i>n</i> -C ₄ H ₉ MgBr	9c-1	15	158	48
48	(<i>n</i> -C ₄ H ₉) ₂ Mg	1a-4	97	23	—
49	<i>n</i> -C ₄ H ₉ Li	1d-3	39	30	7
50	<i>n</i> -C ₄ H ₉ Li	2a-CH ₃ Li	77	43	16
51	<i>n</i> -C ₄ H ₉ Li	2g-CH ₃ Li	63	61	17
52	<i>n</i> -C ₄ H ₉ Li	2h-CH ₃ Li	68	61	18
53	<i>n</i> -C ₄ H ₉ Li	6b, 6d	47	81	25
54	<i>sec</i> -C ₄ H ₉ MgCl	1a-1	70	21	1
55	<i>sec</i> -C ₄ H ₉ MgCl	1b	46	24	2
56	<i>sec</i> -C ₄ H ₉ MgCl	1c	21	25	3
57	<i>sec</i> -C ₄ H ₉ MgCl	1d-2	23	26	4
58	<i>sec</i> -C ₄ H ₉ MgCl	2a-1	73	44a	10
59	<i>sec</i> -C ₄ H ₉ MgCl	2a-CH ₃ Li	67	43	16
60	<i>sec</i> -C ₄ H ₉ MgCl	2g-CH ₃ Li	62	61	17
61	<i>i</i> -C ₄ H ₉ MgBr	2a-2	90	45	11
62	<i>t</i> -C ₄ H ₉ MgCl	1a-1	60	20	1
63	<i>t</i> -C ₄ H ₉ MgCl	1b	45	24	2
64	<i>t</i> -C ₄ H ₉ MgCl	1c	24	25	3
65	<i>t</i> -C ₄ H ₉ MgCl	1d-1	30	26	4
66	<i>t</i> -C ₄ H ₉ MgCl	2a-1	74	44a	10

TABLE VIII (Continued)


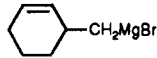
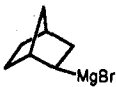

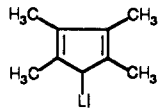
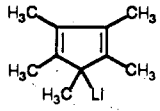
entry	RM	aminating reagent	yield, ^c %	ref	scheme
67	<i>t</i> -C ₄ H ₉ MgCl	2a-2	70	45	11
68	<i>t</i> -C ₄ H ₉ MgCl	10a	40 ^d	165	55
69	<i>t</i> -C ₄ H ₉ MgBr	1a-1	20	21	1
70	<i>t</i> -C ₄ H ₉ Li	2a-CH ₃ Li	80	43	16
71	<i>t</i> -C ₄ H ₉ Li	2g-CH ₃ Li	30	61	17
72	<i>n</i> -C ₅ H ₁₁ MgCl	1d-1	21	26	4
73	<i>n</i> -C ₅ H ₁₁ MgCl	1g	34	27	5
74	<i>n</i> -C ₅ H ₁₁ MgCl	2a-2	46	45	11
75	<i>n</i> -C ₅ H ₁₁ MgBr	2a-2	65	45	11
76	<i>sec</i> -C ₅ H ₁₁ MgCl	1a-1	72	21	1
77	<i>sec</i> -C ₅ H ₁₁ MgBr	1a-1	32	21	1
78	<i>i</i> -C ₅ H ₁₁ MgCl	1a-1	55	20	1
79	<i>i</i> -C ₅ H ₁₁ MgCl	2a-1	80	44a	10
80	<i>i</i> -C ₅ H ₁₁ MgCl	2a-2	60	45	11
81	<i>i</i> -C ₅ H ₁₁ MgBr	1a	27	20	1
82	<i>i</i> -C ₅ H ₁₁ MgCl	2a-1	71	44a	10
83	<i>i</i> -C ₅ H ₁₁ MgBr	2a-2	65	45	11
84	<i>i</i> -C ₅ H ₁₁ MgBr	1b-1	62	44b	10
85	<i>t</i> -C ₅ H ₁₁ MgCl	1a-1	66	21	1
86	<i>t</i> -C ₅ H ₁₁ MgCl	2a-2	49	45	11
87	<i>n</i> -C ₆ H ₁₃ MgBr	7a-1	27	90	eq 31
88	BrMg(CH ₂) ₅ MgBr	2a-2	63	45	11
89	BrMg(CH ₂) ₆ MgBr	2a-2	51	45	11
90	BrMg(CH ₂) ₁₉ MgBr	2a-2	53	45	11
91		6b	47	81	25
92	<i>c</i> -C ₆ H ₁₁ MgBr	2b-1	62	44b	10
93	<i>c</i> -C ₆ H ₁₁ MgBr	6f	14	84	—
94	<i>c</i> -C ₆ H ₁₁ MgBr	8c	93	111	37
95		8c	64	111	37
96		8c	70	111	37
R = Allylic, Benzylic					
97	CH ₂ =CHCH ₂ MgBr	2a-2	40	45	11
98	C ₆ H ₅ CH=CHCH(C ₆ H ₅)Li	6b	37	81	25
99	C ₆ H ₅ CH=C(<i>t</i> -C ₄ H ₉)CH(C ₆ H ₅)Li	6b	31	81	25
100	C ₆ H ₅ CH=C(C ₆ H ₅)CH(C ₆ H ₅)Li	6b	38	81	25
101	C ₆ H ₅ CH=C(C ₆ H ₅)CH(C ₆ H ₅)Li	6c	39	81	25
102	C ₆ H ₅ CH=CHCH ₂ MgCl	1a-1	14	22	—
103	C ₆ H ₅ CH=CHCH ₂ MgCl	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 ₆ H ₅ CH ₂ MgCl	1a-1	85	20	1
108	C ₆ H ₅ CH ₂ MgCl	1b	63	24	2
109	C ₆ H ₅ CH ₂ MgCl	1c	34	25	3
110	C ₆ H ₅ CH ₂ MgCl	1d-1	32	26	4
111	C ₆ H ₅ CH ₂ MgCl	1e	75	27	5
112	C ₆ H ₅ CH ₂ MgCl	1e	70	27	5
113	C ₆ H ₅ CH ₂ MgCl	1f ^e	95	27	5
114	C ₆ H ₅ CH ₂ MgCl	1f ^a	90	27	5
115	C ₆ H ₅ CH ₂ MgCl	1f ^b	78	27	5
116	C ₆ H ₅ CH ₂ MgCl	1g	28	27	5
117	C ₆ H ₅ CH ₂ MgCl	1g	43	27	5
118	C ₆ H ₅ CH ₂ MgCl	2a-2	57	45	11
119	C ₆ H ₅ CH ₂ MgCl	2b-1	79	44b	10
120	C ₆ H ₅ CH ₂ MgCl	7a-2	70	91	27

TABLE VIII (Continued)

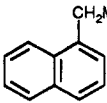
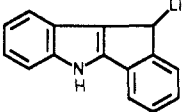
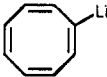
entry	RM	aminating reagent	yield, ^c %	ref	scheme
121	C ₆ H ₅ CH ₂ MgBr	7a-2	51	91	27
122	C ₆ H ₅ CH ₂ Li	2a-CH ₃ Li	97	43	16
123	C ₆ H ₅ CH ₂ Li	7a-2	30	91	27
124	C ₆ H ₅ CH ₂ Li	8j	60	115	40
125	C ₆ H ₅ CH(CH ₃)MgCl	7c	63	93	eq 32
126	C ₆ H ₅ CH(CH ₃)MgBr	7c	40	93	eq 32
127		1a-1	47	22	—
128		6c	43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

TABLE VIII (Continued)

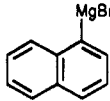
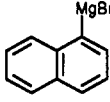
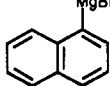
entry	RM	aminating reagent	yield, ^c %	ref	scheme
182	2-CH ₃ OC ₆ H ₄ MgBr	8a-1	63	103	31
183	2-CH ₃ OC ₆ H ₄ MgBr	8c	98	101	36
184	2-CH ₃ OC ₆ H ₄ MgBr	8i	73	113	39
185	2-CH ₃ O ₆ H ₄ MgBr	9c-1	18	158	48
186	2-(CH ₃) ₂ NCH ₂ C ₆ H ₄ Li	8a-1	52	106	32
187	2-(CH ₃) ₂ NCH ₂ C ₆ H ₄ Li	8i	41	113	39
188	2- <i>t</i> -C ₄ H ₉ C ₆ H ₅ MgBr	8a-1	19	103	31
189	2-CH ₃ OC ₆ H ₄ Li	2a-CH ₃ Li	96	43	16
190	2-CH ₃ OC ₆ H ₄ Li	8a-1	75	106	32
191	2-CH ₃ OC ₆ H ₄ Li	8i	35	113	39
192	2-C ₆ H ₅ CH ₂ C ₆ H ₄ MgBr	8a-1	71	103	31
193	2-CH ₃ OCH ₂ OC ₆ H ₄ Li	8a-4	67	108	34
194	2-(C ₂ H ₅) ₂ NCOOC ₆ H ₄ Li	8a-4	94	108	34
195	2-CH ₃ NHCOOC ₆ H ₄ Li	8a-1	37	106	32
196	2-(C ₂ H ₅) ₂ NCOOC ₆ H ₄ Li	8a-4	40	108	33
197	2-(C ₂ H ₅) ₂ NCOOC ₆ H ₄ Li	8j	52	115	40
198	3-CH ₃ C ₆ H ₄ MgBr	8a-1	79	103	31
199	3-ClC ₆ H ₄ MgBr	8a-1	41	103	31
200	4-CH ₃ C ₆ H ₄ MgBr	8a-1	66	103	31
201	4-CH ₃ C ₆ H ₄ MgBr	8a-2	67	103	eq 35
202	4-CH ₃ C ₆ H ₄ MgBr	8k	88	117	42
203	4-CH ₃ C ₆ H ₄ MgBr	9c-2	70	158	48
204	4-CH ₃ C ₆ H ₄ Li	1a-2	16	30	7
205	4-C ₆ H ₅ C ₆ H ₄ MgBr	8a-1	62	103	31
206	4-CH ₃ OC ₆ H ₄ MgBr	8a-1	51	103	31
207	4-CH ₃ OC ₆ H ₄ MgBr	8a-2	77	103	eq 35
208	4-CH ₃ OC ₆ H ₄ MgBr	8c	72	101	36
209	4-CH ₃ OC ₆ H ₄ MgBr	8i	69	113	39
210	4-CH ₃ OC ₆ H ₄ MgBr	8k	84	117	42
211	4-CH ₃ OC ₆ H ₄ MgBr	9c-1	12	158	48
212	4-CH ₃ OC ₆ H ₄ MgBr	10a	64	165	55
213	4-ClC ₆ H ₄ MgBr	8a-1	49	103	31
214	4-ClC ₆ H ₄ MgBr	8a-2	63	103	eq 35
215	4-ClC ₆ H ₄ MgBr	8i	92	113	39
216	4-ClC ₆ H ₄ MgBr	8k	79	116	42
217	4-ClC ₆ H ₄ MgBr	9c-1	20	158	48
218	4-BrC ₆ H ₄ MgBr	2b-1	58	44b	10
219	2,5-(CH ₃) ₂ C ₆ H ₃ MgBr	8a-1	76	103	31
220	2,6-(CH ₃) ₂ C ₆ H ₃ MgBr	8i	79	113	39
221	2-((C ₂ H ₅) ₂ NCO)-5-CH ₃ C ₆ H ₃ Li	8a-4	82	108	33
222	2-(CH ₃ OCH ₂ O)-3-CH ₃ C ₆ H ₃ Li	8a-4	72	109	eq 37
223	2-CH ₂ O-5-C ₆ H ₃ C ₆ H ₃ MgBr	8c	91	101	36
224	2,3-(CH ₃ O) ₂ C ₆ H ₃ Li	8i	78	114	eq 40
225	2,6-(CH ₃ O) ₂ C ₆ H ₃ Li	8c	50	101	36
226	2,6-(CH ₃ O) ₂ C ₆ H ₃ Li	8j	70	115	40
227	2,6-(CH ₃ O) ₂ C ₆ H ₃ Li	8k	72	117	42
228	2,5-(CH ₃ OCH ₂ O) ₂ C ₆ H ₃ Li	8k	47	117	42
229	2-CH ₂ NHCO-6-CH ₃ OC ₆ H ₃ Li	8a-1	34	106	32
230	2-(C ₂ H ₅) ₂ NCO-3-CH ₃ OC ₆ H ₃ MgBr	8a-4	71	108	33
231	2-(C ₂ H ₅) ₂ NCO-3-CH ₃ OC ₆ H ₃ Li	8a-4	66	108	33
232	2-(C ₂ H ₅) ₂ NCO-5-CH ₃ OC ₆ H ₃ Li	8a-4	34	108	33
233	2-(C ₂ H ₅) ₂ NCO-6-CH ₃ OC ₆ H ₃ Li	8a-4	55	108	33
234	2- <i>t</i> -C ₄ H ₉ CONH-5-ClC ₆ H ₃ MgBr	8c	88	101	36
235	2-(C ₂ H ₅) ₂ NCO-6-ClC ₆ H ₃ MgBr	8a-1	36	108	33
236	2,4,6-(CH ₃) ₃ C ₆ H ₂ MgBr	2b-1	25	44b	10
237	2,4,6-(CH ₃) ₃ C ₆ H ₂ MgBr	8b	26	110	eq 38
238	2,4,6-(CH ₃) ₃ C ₆ H ₂ MgBr	8k	67	117	42
239	2-(C ₂ H ₅) ₂ NCO-5-CH ₃ -6-CH ₃ OC ₆ H ₂ Li	8a-4	69	108	33
240	2-(C ₂ H ₅) ₂ NCO-3-(CH ₃) ₃ Si-4-CH ₃ OC ₆ H ₂ Li	8a-4	69	108	33
241	4-(C ₂ H ₅) ₂ NCO-3-CH(Si(CH ₃) ₃) ₂ -4-CH ₃ OC ₆ H ₂ Li	8a-4	47	108	33
242	2,3,5,6-(CH ₃) ₄ C ₆ H ₂ MgBr	9f ^h	65	159	51
243		2a-2	38	45	11
244		6b, 6d	69	81	25
245		7a-2	31	91	27

TABLE VIII (Continued)

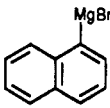
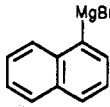
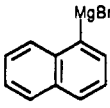
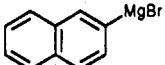
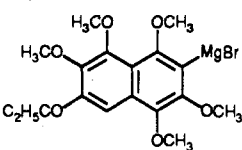
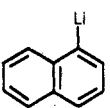
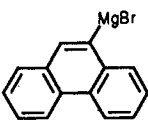
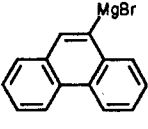
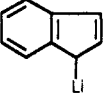
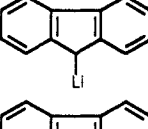
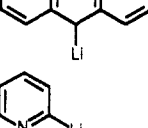
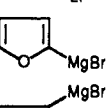
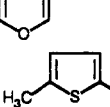
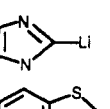
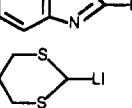


entry	RM	aminating reagent	yield, ^c %	ref	scheme
246		8k	89	116	42
247		9a	27	124	eq 50
248		9f^k	83	159	51
249		9f^k	70	159	51
250		8c	71	112	eq 39
251		6b, 6d	9	81	25
252		8a-1	54	103	31
253		9f^k	83	159	51
254		6b	57	81	25
255		6b	61	81	25
256		7a-2	30	91	27
257		8j	45	115	40
258		9f^k	78	159	51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

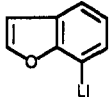
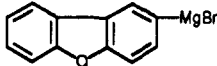
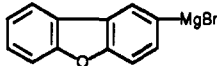
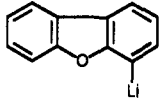
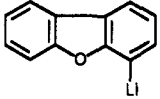
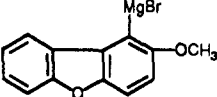
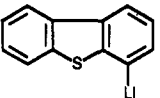
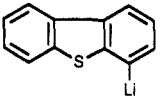
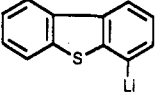
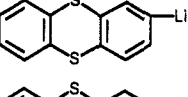
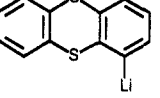
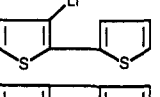
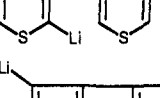
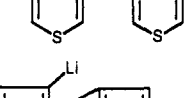
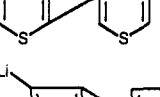
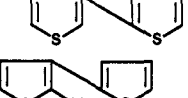
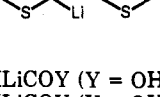
entry	RM	aminating reagent	yield, ^c %	ref	scheme
264		2a	78	51	—
265		2a	33	51	—
266		8k	71	117	42
267		2a-1	53	47	—
268		8k	58	117	42
269		2a-4	68	46a	—
270		2a-4	64	46b	—
271		2a-CH ₃ Li	55	43	16
272		8k	62	117	42
273		2a-4	63	48	—
274		2a-5	75	49, 50	—
275		8a-3	92	104	36
276		8a-3	87	104	36
277		8a-3	91	104	36
278		8a-3	93	104	36
279		8a-3	95	104	36
280		8a-3	71	104	36
281	CH ₃ CHLiCOY (Y = OH ^{l,m})	R = Enolic 11a-TiCl ₄	92	170	61, 62
282	CH ₃ CHLiCOY (Y = OH ⁿ)	11a	83 ^o	169	57-59
283	C ₆ H ₅ CHLiCOY (Y = OH ^{l,m})	11a-TiCl ₄	93	170	61, 62
284	CH ₃ SCH ₂ CHLiCOOLi	2a-3	9	33	13
285	C ₆ H ₅ CH ₂ CHLiCOOLi	2a-3	7	33	13
286	C ₆ H ₅ CH ₂ CHLiCOY (Y = OH ^{l,m})	11a-TiCl ₄	89	170	61, 62

TABLE VIII (Continued)

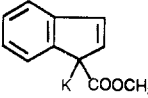
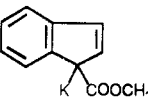
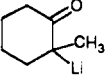
entry	RM	aminating reagent	yield, ^c %	ref	scheme
287	C ₆ H ₅ CH ₂ CHLiCOY (Y = OH ⁿ)	11b	97	169	57-59
288	<i>i</i> -C ₃ H ₇ CHLiCOOLi	1a-1	8	33	12
289	<i>i</i> -C ₃ H ₇ CHLiCOOLi	2a-3	33	33	12
290	<i>i</i> -C ₃ H ₇ CHLiCOOLi	2b-2	5	33	12
291	<i>i</i> -C ₃ H ₇ CHLiCOOLi	2c	22	33	12
292	<i>i</i> -C ₃ H ₇ CHLiCOOLi	2d	25	33	12
293	<i>i</i> -C ₃ H ₇ CHLiCOOLi	2e	18	33	12
294	<i>i</i> -C ₃ H ₇ CHLiCOOLi	3	5	33	12
295	<i>i</i> -C ₃ H ₇ CHLiCOOLi	5a	4	33	12
296	<i>i</i> -C ₃ H ₇ CHLiCOOLi	5b	5	33	12
297	<i>i</i> -C ₃ H ₇ CHLiCOY (Y = OH ⁿ)	11b	98 ^o	169	57-59
298	<i>n</i> -C ₄ H ₉ CHLiCOY (Y = OH ^{l,m})	11a-TiCl ₄	90	170	61, 62
299	<i>i</i> -C ₄ H ₉ CHLiCOOLi	2a-3	11	33	13
300	<i>i</i> -C ₄ H ₉ CHLiCOY (Y = OH ^{l,m})	11a-TiCl ₄	91	170	61, 62
301	C ₆ H ₅ CHLiCOOLi	2a-3	56	33	13
302	C ₆ H ₅ CHLiCOOLi	2f	46	33	eq 10
303	(C ₂ H ₅) ₂ POCHNaCOOCH ₃	6a-2	47	83	20
304	(C ₂ H ₅) ₂ POCHNaCOOCH ₃	7a-1	60	90	29
305	CH ₃ CHLiCOOCH ₃ ^l	10a	59 ^f	167	56
306	C ₆ H ₅ CHLiCOY (Y = OCH ₂ C ₆ H ₅ ^p)	11a	83-94 ^q	168	57, 58, 60
307	C ₆ H ₅ CH ₂ CHLiCOOCH ₃ ^l	10a	76 ^f	167	56
308	C ₆ H ₅ CH ₂ CHLiCOY (Y = OCH ₂ C ₆ H ₅ ^p)	11a	83-94 ^q	168	57, 58, 60
309	<i>i</i> -C ₄ H ₉ CHLiCOY (Y = OCH ₂ C ₆ H ₅ ^p)	11a	83-94 ^q	168	57, 58, 60
310	<i>t</i> -C ₄ H ₉ CHLiCOY (Y = OCH ₂ C ₆ H ₅ ^p)	11a	83-94 ^q	168	57, 58, 60
311	C ₆ H ₅ CHLiCOOCH ₃ ^l	10a	83 ^f	167	56
312	C ₆ H ₅ CHLiCOOC ₂ H ₅	7a-2	45	91	27
313	C ₆ H ₅ CHLiCOOC ₂ H ₅	7c	50	93	30
314	C ₆ H ₅ CHNaCOOC ₂ H ₅	4b-3	12	78	24
315	(CH ₃) ₂ CLiCOOCH ₃ ^l	10a	90 ^f	167	56
316	C ₆ H ₅ C(CH ₃)LiCOOC ₂ H ₅	4b-3	35	78	24
317	C ₆ H ₅ C(CH ₃)LiCOOC ₂ H ₅	7c	56	93	30
318	CH ₃ COCHKCOOCH ₃	3	34	68	eq 16
319	CH ₃ COCHKCOOC ₂ H ₅	3	30	68	eq 16
320	CH ₃ COCHKCOOC ₂ H ₅	4b-1	2	17	eq 16
321	CH ₃ COCHKCOOC ₂ H ₅	6a	2	17	eq 16
322		4b-1	50	69, 77	eq 17
323		7a	47	91	27
324	CH ₃ COCHKCOCH ₃	3a	28	68	eq 16
325	CH ₃ COCHKCOCH ₃	4b-1	2	17	eq 16
326	(CH ₃) ₂ CHCOCLi(CH ₃) ₂	10a	72 ^f	165	55
327		10a	61 ^f	165	55
328	C ₆ H ₅ CHLiCON(<i>n</i> -C ₄ H ₉)Li	2a-3	30	56	eq 11
329	C ₆ H ₅ CHLiCON(C ₂ H ₅) ₂	2a-3	15	56	eq 16
330	C ₆ H ₅ CHLiCN	7a-2	37	91	27
331	C ₆ H ₅ CHLiCN	7c	62	93	30
332	(C ₆ H ₅) ₂ CLiCN	7a-2	67	91	27
333	CHNa(COOC ₂ H ₅) ₂	1a-5	92	35	8
334	CHNa(COOC ₂ H ₅) ₂	4b-3	55	78	24
335	CHNa(COOC ₂ H ₅) ₂	7a	57	90	eq 30
336	CH ₃ CNa(COOC ₂ H ₅) ₂	1a-5	85	35	8
337	CH ₃ CNa(COOC ₂ H ₅) ₂	4b-3	84	78	23
338	C ₂ H ₅ CNa(COOC ₂ H ₅) ₂	1a-5	89	35	8
339	C ₂ H ₅ CNa(COOC ₂ H ₅) ₂	4b-3	74	78	23
340	<i>i</i> -C ₃ H ₇ CNa(COOC ₂ H ₅) ₂	1a-5	71	35	8
341	<i>n</i> -C ₄ H ₉ CNa(COOC ₂ H ₅) ₂	4b-3	73	78	23
342	<i>sec</i> -C ₄ H ₉ CNa(COOC ₂ H ₅) ₂	1a-5	83	35	8
343	C ₆ H ₅ CH ₂ CNa(COOC ₂ H ₅) ₂	1a-5	72	35	8
344	C ₆ H ₅ CH ₂ CNa(COOC ₂ H ₅) ₂	4b-3	73	78	23
345	C ₆ H ₅ CLi(COOC ₂ H ₅) ₂	7a	31	91	27
346	C ₆ H ₅ CNa(COOC ₂ H ₅) ₂	1a-5	70	35	8
347	C ₆ H ₅ CNa(COOC ₂ H ₅)	4b-2	53	69, 77	eq 18
348	C ₆ H ₅ CNa(COOC ₂ H ₅)	4b-3	65	78	24
349	(CH ₂ COOC ₂ H ₅) ₂ CNa(COOC ₂ H ₅) ₂	4b-3	61	78	23
350	CN(C ₆ H ₅)CLiCOOC ₂ H ₅	6b	95	81	25
351	CN(C ₆ H ₅)CLiCOOC ₂ H ₅	7a-2	96	91	27

TABLE VIII (Continued)

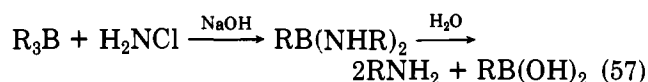
entry	RM	aminating reagent	yield, ^c %	ref	scheme
352	CN(C ₆ H ₅)CNaCOOC ₂ H ₅	4b-3	54	78	24
353	CHNa(CN) ₂	4b	—	80	eq 21
354	CHNa(CN) ₂	6a-2	42	80	eq 21
355	CHNa(CN) ₂	7a	50	90	eq 30

^a Reagents: H₂NZ, 1a-g, 2a-e, 3, 4a,b, 5a,b, 6a, 7a, 8a-c, 8i-k, 9a-f, 10a, 11a,b; R¹HNZ, 2g,h; R²NZ, 6b-f,h, 7b,c.

H ₂ NCl	RHNCl	H ₂ NOCOAr	H ₂ NOPO(C ₆ H ₅) ₂	R ¹ R ² C=NOH
1a	1e		7a	9a, R ¹ = H, R ² = C ₆ H ₅
H ₂ NBr	R ₂ NCl	5a, Ar =	(CH ₃) ₂ NOPO(C ₆ H ₅) ₂	b, R ¹ = CH(CH ₃) ₂ , R ² = C ₆ H ₅
1b	1f		7b	c, R ¹ = CH ₃ , R ² = CH ₃
HNBBr ₂	RNCl ₂	5b, Ar =		d, R ¹ = CH ₃ , R ² = C ₂ H ₅
1c	1g		7c	
NCl ₃			RN ₃	9e
1d			8a, R =	
H ₂ NOR			b, R = (C ₆ H ₅) ₃ Si	
2a, R = CH ₃			c, R = C ₆ H ₅ SCH ₂	9f
b, R = CH ₂ C ₆ H ₅			l, R = (CH ₃) ₃ SiCH ₂ (TMSMA)	C ₆ H ₅ N ₂ BF ₄
c, R = C ₂ H ₅			j, R = R ¹ CH=CR ²	10a
d, R = CH(CH ₃) ₂			(R ¹ , R ² = H, C ₆ H ₅ , t-C ₄ H ₉ , H)	ROOCN=NCOOR (DAAD)
e, R = C(CH ₃) ₃			k, R = ((C ₂ H ₅ O) ₂ PO (DPPA))	11a, R = C(CH ₃) ₃ (DBAD)
RNH ₂ CH ₃				b, R = CH ₂ C ₆ H ₅
2g, R = CH ₃				
h, R = CH(C ₆ H ₅)CH ₃				
H ₂ NOSO ₂ OH		6b, R = CH ₃		
3 (HOSA)		c, R = C ₂ H ₅		
		R ₂ NOSO ₂ C ₆ H ₅		
H ₂ NOAr		6d, R = CH ₃		
4a, Ar =		e, R = C ₂ H ₅		
4b, Ar =		6f		
(DPH)		(CH ₃) ₂ NOSO ₂ CH ₃		
		6h		

^b Key: Experimental conditions for the aminating reagents (solvent, RM/reagent molar ratio, reaction temperature, reaction time): 1a-1: Et₂O, excess, 0 °C; 1a-2: Et₂O, 3/1, -5 °C, overnight; 1a-3: petroleum ether, excess, -30 °C, overnight; 1a-4: Et₂O/dioxane, 3/1, -60 °C, 1 h; 1a-5: Et₂O, 1/2, room temperature, overnight; 1b, 1c: Et₂O, excess, -5 °C; 1d-1: Et₂O, 4/1, 0 °C; 1d-2: same as 1a-3; 1d-3: Et₂O, 3/1, -5 °C, overnight; 1e, 1f, 1g: Et₂O, excess, 0-5 °C; 2a-1: Et₂O, 2/1, -15 °C; 2a-2: Et₂O, 2/1, -15 °C, 0.5 h, reflux, 2 h; 2a-3: THF, 1/3, -15 °C, 2 h, room temperature, overnight; 2a-4: Et₂O, 3/1, -15 °C; 2a-5: Et₂O, 1/1, -15 °C; 2b-1: same as 2a-1; 2b-2, 2c, 2d, 2e: same as 2a-3; 2a-CH₃Li: Et₂O, 1/2, -15 °C, 2 h; 2g-CH₃Li: Et₂O, 1/1, -15 °C, 2 h; 2h-CH₃Li: Et₂O, 1/1, 40 °C; 3: H₂O, 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: Et₂O, 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: Et₂O, 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: Et₂O, 1/1, -70 °C, 5 h, reduction of triazene salt; 8a-4: THF, 1/1, -78 °C, 1 h, reduction of triazene salt; 8b: Et₂O, 1/1, 100 °C, decomposition of triazene salt; 8c: THF, 1/1.2, -78 to 0 °C, hydration of triazene salt; 8i: Et₂O, 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: Et₂O, 1/1, -72 °C, 2 h, -20 °C, reduction of triazene salt; 9a: Et₂O, 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, hydrolysis of α-hydrazono compound; 11a,b: THF or CH₂Cl₂, 1/1.1 or 1/1.2, -78 °C, removal of Y (oxazolidinone or N-methylephedrine moiety) by hydrolysis or esterification, hydrolysis of α-hydrazono 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-CH₃Li, 2g-CH₃Li, and 2h-CH₃Li; and N-acetyl derivatives with 8a-2 and 8c. ^d Product amine, (C₆H₅)₂NH. ^e Product amine, (n-C₄H₉)₂NH. ^f Yield of α-hydrazono or α-azo compound. ^g Product amine, (C₆H₅CH₂)NHCH₃. ^h Product amine, (C₆H₅CH₂)NHC₂H₅. ⁱ Product amine, (C₆H₅CH₂)NH(i-C₃H₇). ^j Product amine, C₆H₅C≡N(C₂H₅)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, R₃B, with monochloroamine (1a) were developed by Brown and co-workers (eq 57).¹⁹¹⁻¹⁹³

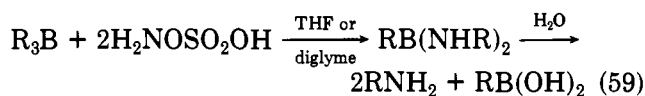


However, only two of the three alkyl groups in R₃B could be utilized since, following hydrolysis, one of the reaction products is the monoalkylboronic acid, RB(OH)₂, which reacts with 1a very slowly and thus the maximum possible yield of the amine is limited to 67%. Kabalka and co-workers aminated trialkylboranes in

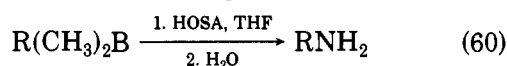
good yields with **1a** generated in situ^{194,195} and used monochloroalkylamines, **1e**, to achieve the synthesis of secondary amines (eq 58).¹⁹⁶ The reaction of tri-



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



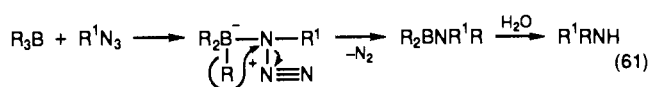
oped^{191,198-200} and well summarized by Brown and co-workers.¹⁹³ They overcame the limitation to quantitative utilization of the alkyl groups by preparing a mixed organoborane, RR_2B , in which R shows a significantly greater migratory aptitude than R^1 . For this purpose, organodimethylboranes, prepared by hydroboration of alkenes with dimethylborane, were reacted¹⁹³ with HOSA to afford the corresponding primary amines in almost quantitative yields (eq 60).



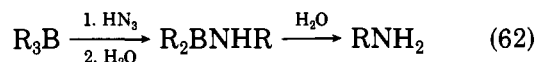
Triphenylborane, prepared from phenylmagnesium bromide and boron trifluoride, was found to react with HOSA to give aniline in 35% yield.²⁰¹ The use of MSH (**6a**),²⁰² *N*-chloro(2,4-dinitrophenyl)hydroxylamine,²⁰³ and chloramine-T²⁰⁴ in the amination of organoboranes was reported.

The suggested mechanism for the amination of organoboranes¹⁹³ 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).

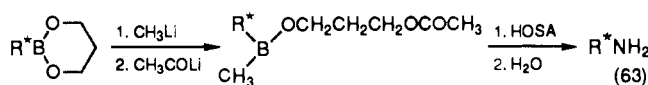
Brown and co-workers have reported²⁰⁵ that the reaction of trialkylboranes with azides followed by hydrolysis gives rise to good yields of secondary amines (eq 61). Dialkylchloroboranes ($RBCl_2$) and alkyl-



chloroboranes ($RBCl_2$) provide even better yields. Kabalka and co-workers²⁰⁶ have used hydrazoic acid generated in situ to prepare amines in good yields (eq 62).



Primary amines of very high optical purity can be obtained²⁰⁷ from the chiral boronic esters through the intermediate formation of alkylmethylborinic esters (eq 63). The preparation and use of chiral organo-



boranes²⁰⁸ and boronic esters²⁰⁹ in asymmetric synthesis have been recently reviewed.

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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