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CONTENTS

CHAPTER 1

ELECTROPHILIC AMINATION OF CARBANIONS, ENOLATES, AND THEIR SURROGATES

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CONTENTS

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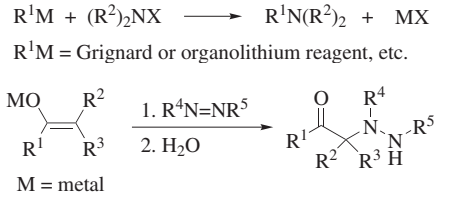
INTRODUCTION

Nitrogen-containing organic compounds are ubiquitous in nature and essential to life. They are also important intermediates and products of the chemical and pharmaceutical industries. As a consequence, chemists have developed a plethora of methods for their generation, starting with the first organic synthesis, Wöhler's preparation of urea from ammonium cyanate in 1828.[1] There are many reports of the formation of carbon-nitrogen bonds by electrophilic amination of carbanions and enolates in the early literature, but development of this method as a useful synthetic tool, especially for asymmetric synthesis, is of more recent date.

Most electrophilic aminations can be divided into two types: substitutions (e.g. Eq. 1) and additions (e.g. Eq. 2) to give products that in many cases are not amines. A detailed discussion of the conversion of these intermediates into amines is beyond the scope of this chapter, but references to relevant methods are given in the section on Experimental Conditions.



(Eq. 1)

(Eq. 2)

The initial intent to cover the subject exhaustively had to be abandoned because of the overwhelming amount of relevant literature. The following reactions are not covered but are briefly discussed, with references to reviews and seminal papers, in the section on Comparison with Other Methods: reactions of carbanions and enolates and their surrogates with nitrogen oxides, nitrite and nitrate esters, and nitroso and nitro compounds; reactions of enolates with diazonium salts, including the Japp-Klingemann reaction; the diazo transfer reaction except as it interferes with the synthesis of azides; the amination of boranes; and the Neber rearrangement.

The large number of reagents that are available for amination necessitated a deviation from the standard *Organic Reactions* format. The section on Reagents and Mechanisms includes discussion and exemplification of each reagent or reagent class as well as comments on mechanism, particularly in context of reagent-substrate combinations that can lead to more than one product. Stereochemistry is discussed in the relevant sections of Scope and Limitations.

There is only one previous comprehensive review of the electrophilic amination of carbanions;[2] shorter reviews[3–9] and reviews limited to particular reagents, substrates, or products have appeared: amination with haloamines,[10] sulfonylhydroxylamines,[11] oxaziridines,[12] oximes,[13] diazonium salts,[14,15] diazo compounds,[16] activated azo compounds,[17] azides,[18–23] and nitridomanganese(V) reagents;[24,25] amination of enolates;[26–30] and the preparation of α-amino acids by electrophilic amination.[31–34]

REAGENTS AND MECHANISMS

Preparation of Carbanions, Enolates, and Their Surrogates

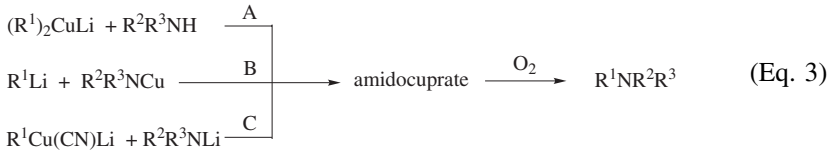
The preparation of carbanions,[35] organolithium reagents,[36,37] Grignard reagents,[38,39] and organozinc reagents[40,41] has been reviewed. For reviews on the generation of enolates see refs. 42–45. The synthesis of silyl enol ethers is reviewed in refs. 46–49, that of silyl ketene acetals in ref. 50. The term "carbanion" is used loosely without regard to aggregation or solvation.

Aminating Reagents

All aminating reagents dealt with in this chapter are listed here; references to their preparation are found in the section on Experimental Conditions. Stereochemistry is discussed in the relevant sections of Scope and Limitations. The term amination refers to the formation of a carbon-nitrogen bond, not just to the introduction of an amine group. For a quantum Monte Carlo study of electrophilic amination reagents see ref. 51.

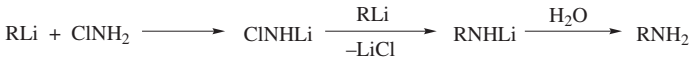
Metal Amides. Amidocuprates, when treated with molecular oxygen at low temperatures, give secondary or tertiary amines (Eq. 3). The substrates may be generated from disubstituted lithium cuprates and a primary or secondary amine (method A);[52] one equivalent of the cuprate may be used but yields are higher with three to five equivalents. Only one of the two R^1 groups enters into the product; it may be, among others, an aryl or *tert*-butyl group. Acyl and hydroxy groups in the amine are tolerated. Method B involves the reaction of an organolithium reagent with an excess of a copper amide, which in turn is generated from a lithium amide with copper(II) iodide.[52] The copper amide may be replaced by an anilido cuprate $ArN(R^3)Cu(X)Li$ where X is Cl or CN.[53] The third method (C) employs a lower-order cuprate and a lithium amide. R^1 may be alkyl, aryl, heteroaryl, or styryl. Yields in the three methods are moderate to good. Substituted hydrazines are obtained by replacing the lithium amides in method C with a lithium hydrazide, but yields are only in the 20–40% range.[54] THF is the preferred solvent in these reactions, which fail with Grignard or organolithium reagents. An eight-membered planar complex has been suggested[54] as the intermediate, which reacts with oxygen to give the product via an aminyl radical.

Yields are improved in method C when zinc cyanocuprates and co-oxidants (*o*-dinitrobenzene or copper(II) nitrate) are employed.[55]



(Eq. 3)

Haloamines. Chloramine was one of the earliest reagents investigated for the amination of Grignard reagents and organolithium compounds.[56–59] An excess of the latter is usually required because of the acidic nature of the haloamine hydrogens. Replacement of one of these by lithium to give a nitrenoid has been suggested as the first step (Eq. 4).[60] Bromamine offers no advantage over chloramine.[61] In the reactions of haloamines with Grignard reagents, yields decrease in the order of RMgCl > RMgBr > RMgI.[61] Chloramine aminates sodio malonates.[62–64] With sodium phenolates, ring-expanded products are obtained.[65] The mechanism of these reactions is unknown[62] but a nitrenoid intermediate is unlikely because of the lower basicity of the substrates. No reaction occurs between 2-lithio *N*-methylimidazole and chloramine.[66]



(Eq. 4)

Monosubstituted chloramines have not received much attention. The reaction of *N*-chloro-*tert*-butylamine with di(*tert*-butyl)magnesium gives di(*tert*-butyl) amine in 10% yield.[67] Butylmagnesium chloride and *N*-chloromethylamine produce mostly methylamine by reduction and only 14% of *N*-methylbutylamine.[68]

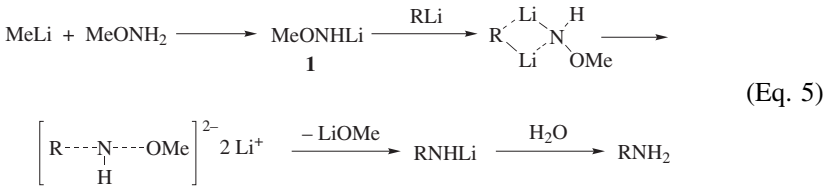
Disubstituted chloramines are claimed to not react with phenylmagnesium bromide[69] and with only very poor yields with *n*-butyl- or benzylmagnesium chloride.[68] *N*-Chlorodiisopropylamine reacts with isopropylpotassium to give triisopropylamine in 3% yield.[70] Similar low yields are obtained in the reactions of phenylethynyllithium,[71] phenylethynylmagnesium bromide,[71] or diethylzinc[72] with *N*-chlorodiethylamine. Chloramines of type ClNRCHRAr, prepared from the secondary amines with *N*-chlorosuccinimide, react with arylmagnesium chlorides to give the corresponding tertiary amines (see Eq. 62).[73] N,N-Disubstituted *N*-chloroamines react with enamines to give mixtures of α-amino aldehydes in moderate to excellent yields where the α-amino group is derived from the chloro amine in one product and from the enamine in the other (see Eq. 86). A mechanism involving aziridinium intermediates has been suggested.[74]

N,*N*-Dibromoamine,[75] *N*,*N*-dichloroalkylamines,[68,72,76] and even trichloroamine[58,77] react with Grignard or dialkylzinc reagents to give amines by reduction of the excess halogen. Yields are low and these reagents are currently of no value in synthesis.

Chloramine-T, the sodium salt of *N*-chloro-*p*-toluenesulfonamide, tosylaminates a number of in situ generated enamines of α-substituted propionaldehydes (see Eq. 78), α-substituted arylacetaldehydes, and methyl arylmethyl ketones.[78]

Hydroxylamines. A number of O-substituted hydroxylamines are electrophilic aminating reagents for introduction of unsubstituted as well as mono- and disubstituted amino groups.

N-Unsubstituted O-*Alkylhydroxylamines*. The most widely used in this category are *O*-methylhydroxylamine, and, to a lesser extent, *O*-benzylhydroxylamine. In the amination of the dianion of 3-methylbutanoic acid with $RONH_2$,[79] yields decrease in the order R = Me > Et = *i*-Pr > *t*-Bu > Bn and range from 34% for $MeONH_2$ to a trace for $BnONH_2$. However, the latter aminates organolithium and Grignard reagents (two equivalents) in fair to good yields.[80] The mechanism of the amination of organolithium reagents with *O*-alkylhydroxylamines involves the nitrenoid intermediate **1** (Eq. 5) and eventual displacement of the methoxy group by R in a counterintuitive reaction between two negatively charged species that is sterically akin to an S_N2 reaction. The mechanism is based on extensive experimental[81–85] and computational work[60,86–90] and also applies to Grignard, organozinc, and organocopper reagents.[91] However, it should be kept in mind that other mechanisms are, at least in principle, available, in view of the fact that N,N-disusbstituted *O*-alkylhydroxylamines are also aminating reagents even though a process involving a nitrenoid is impossible with these reagents. By generating the nitrenoid **1** with methyllithium only one equivalent of RLi is required. Application of this method to aminations with *O*-alkylhydroxylamines reported in the earlier literature should increase the efficiency of these reactions. An excess of the nitrenoid MeONHLi is recommended; in the reaction with *n*-butyllithium the yields of *n*-butylamine are 51% with one equivalent, 71% with two (see also Eq. 63), and 85% with four.[92]

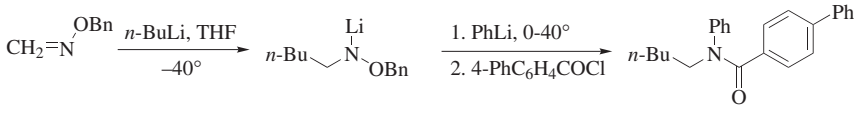


(Eq. 5)

N-Unsubstituted O-*Arylhydroxylamines*. Amination of malonic and cyanoacetic ester enolates[93] and of methyl 9-fluorenecarboxylate[94] may be carried out in fair to good yields with *O*-(2,4-dinitrophenyl)hydroxylamine. Yields are low with the more basic phenylacetic ester enolates and the anion of phenylacetonitrile, both of which partially decompose the reagent with formation of diimide.[93] This reagent provides much poorer yields than $Ph_2P(O)ONH_2$ in the amination of the anion of tetraethyl methylenebis(phosphonate).[95] The corresponding *N*-methyl derivative is unreactive in an N-amination.[94] Various analogs of the highly explosive *O*-(2,4-dinitrophenyl)hydroxylamine have been tested in N-aminations only [94,96] and *O*-(4-nitrophenyl)hydroxylamine was found to provide the highest yields and to have the highest onset temperature of explosive decomposition.[96]

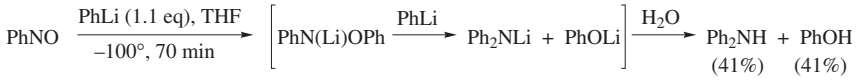
N-Monosubstituted O-*Alkylhydroxylamines*. Various *O*-methylhydroxylamine derivatives (MeONHR) aminate aliphatic and aromatic organolithium compounds: R = Me,[82,83,97] *n*-Pr and *i*-Pr,[83] benzyl,[83,85] α-methylbenzyl,[82,83,85,97]

and 2-phenylethyl.[83] The order of reactivity of BnNLiOMe toward butyllithium reagents is *n*-Bu < *s*-Bu < *t*-Bu.[85] BnNLiOMe reacts much more rapidly with these three alkyllithium reagents than its α-methyl derivative PhCHMeNLiOMe;[85] the latter is about equal in reactivity to MeNLiOMe.[97] Reagents of type $RCH_2NLiOBn$ may be prepared by addition of an organolithium reagent RLi to formaldehyde *O*-benzyl oxime (Eq. 6).[98] A nitrenoid of this class is also formed in the reaction of phenyllithium with nitrosobenzene (Eq. 7),[99] but it reacts so rapidly with unreacted phenyllithium that the possibility of trapping it with another organolithium reagent seems remote.



(47%)

(Eq. 6)

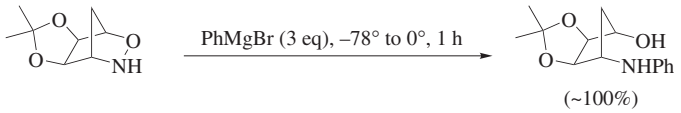


(Eq. 7)

O-Trimethylsilylhydroxylamine reagents (RNHOTMS where R is TMS or alkyl), aminate organocuprates of type $R^1_2Cu(CN)Li_2$ (see Eqs. 64 and 73), but not organolithium reagents.[100–102] Small amounts of alcohols R^1OH are formed in some reactions as a consequence of the nitrenoid **2**/oxenoid **3** equilibrium (Eq. 8), with the latter acting as a hydroxylating agent.[60,103]

2 **3** (Eq. 8)

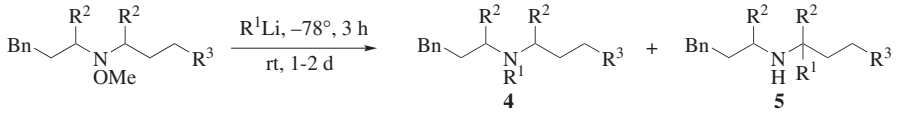
Amination with an N-monosubstituted cyclic hydroxylamine is shown in Eq. 9.[104]



(~100%) (Eq. 9)

N,N-Disubstituted O-*Alkylhydroxylamines*. In the amination with a series of N,N-disubstituted *O*-methylhydroxylamines, more bulky alkyllithium compounds react more readily (product **4**, Eq. 10).[85] The small amounts of products **5** are the result of elimination of methanol from the substrate to give the imine followed by addition of R^1Li to the latter. Reagents where R^2, R^2 is H, Me or Me, Me do not react. A single-electron-transfer process involving a nitrogen radical has

been proposed,[85] but no cyclized product is formed when R^3 is a dimethylvinyl group.



R^1	R^2	R^3	**4**	**5**
n-Bu	H	Ph	(5%)	(5%)
s-Bu	H	Ph	(47%)	(5%)
t-Bu	H	Ph	(72%)	(5%)
t-Bu	H	$CH{=}CMe_2$	(67%)	(—)

(Eq. 10)

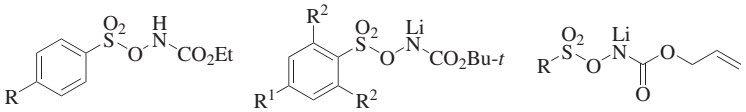
Silyl ketene acetals are aminated by the ethoxycarbonylnitrene precursor $EtO_2CN(TMS)OTMS$ to give α-ethoxycarbonylamino esters via aziridines in fair to good yields (see Eq. 124).[105]

O-*Acyl Hydroxylamines*. *O*-Acyl N-unsubstituted hydroxylamines have been used occasionally in the amination of enolates.[79,106] In the amination of the sodium salt of diethyl phenylmalonate, *O*-(4-nitrobenzoyl)hydroxylamine is somewhat more efficient than $(4\text{-}MeOC_6H_4)_2P(O)ONH_2$ (99% vs 92% yields).[106] This reagent also gives the highest yield in the N-amination of oxazolidinone anions.[107] A series of N,N-disubstituted *O*-benzoylhydroxylamines is used in the amination of alkyl- and arylzinc chlorides in the presence of a catalytic amount of $(Ph_3P)_2NiCl_2$[108] and of dialkyl-, diaryl-, and di(heteroaryl)zinc reagents in the presence of a catalytic amount of a copper(II) salt (see Eq. 36).[109–112] The disubstituted zinc reagents may be prepared in situ by reaction of Grignard reagents with a catalytic amount of zinc chloride because transmetalation is faster than the reaction of the Grignard reagent with *O*-benzoylhydroxylamine. Functional groups on the aryl ring, such as NO_2, CO_2R, and CN are tolerated and 0.6 equivalent of the disubstituted zinc reagent may be employed with a slight reduction of the yield. Arylmagnesium reagents may be aminated in this way without the intervention of the corresponding zinc reagents.[113] An S_N2 mechanism has been advanced.[113]

N-Unsubstituted O-*Sulfonylhydroxylamines*. The acidic nature of hydroxylamine *O*-sulfonic acid makes it essentially useless in electrophilic aminations of carbanions. One of the few exceptions is shown in Eq. 161. The explosive[114,115] *O*-(mesitylenesulfonyl)hydroxylamine aminates alkylzirconium complexes (see Eqs. 41 and 51),[116] acid dianions,[115] and ester enolates.[117] *O*-Arenesulfonylhydroxylamines with no ortho substituents are thermally unstable at room temperature.[11]

N-Monosubstituted O-*Sulfonylhydroxylamines*. *N*-Ethoxycarbonyl-*O*-(*p*-toluenesulfonyl)hydroxylamine (**6**) is used in the amination of enamines.[118,119] The more reactive *N*-ethoxycarbonyl-*O*-(4-nitrobenzenesulfonyl)hydroxylamine

(**7**) aminates enamines[120,121] and enol ethers[122] derived from ketones (see Eq. 96), as well as metalloimines,[123] enolates of β-dicarbonyl compounds,[124] and enamines derived from β-dicarbonyl compounds.[125] The lithium salt of *N*-(*tert*-butoxycarbonyl)-*O*-(*p*-toluenesulfonyl)hydroxylamine (**8**) aminates alkyl- and aryllithium and -copper reagents (see Eq. 69),[126–128] esters and *N*-acyloxazolidinone enolates,[126] and α-alkylphosphonamides.[129] The allyloxycarbonyl analogs **10** and **11** are similarly used.[130] The structure of the mesityl analog **9** (dimer, crystallizing with three molecules of THF) has been determined by single crystal X-ray crystallography.[131] Because this class of reagents offers a much better leaving group, the possibility exists that the nitrenoids lose the elements of $ArSO_3M$ to give nitrenes NCO_2R.[60] The involvement of these reactive intermediates has been proposed in a number of examples.



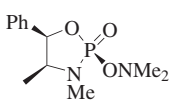
6 R = Me
7 R = O_2N

8 R^1 = Me R^2 = H
9 R^1, R^2 = Me

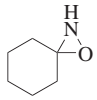
10 R = Me
11 R = 4-MeC_6H_4

N,N-Disubstituted O-*Sulfonylhydroxylamines*. Compounds of type $R^1SO_2ON(R^2)_2$ (R^1 = Me, Ph, *p*-tolyl, mesityl; R^2 = Me, Et) are versatile aminating reagents for a wide variety of substrates: aliphatic (see Eq. 35),[132,133] allylic,[133,134] olefinic (see Eq. 56),[133] acetylenic (see Eq. 60),[135] benzylic (see Eq. 53),[133,136] and aromatic[132,133] metal derivatives and enolates (see Eq. 89).[133,134] Reactions of $MeSO_2ONMe_2$ (and probably other similar reagents) with RMgI should be avoided because iodide reduces the reagent.[137] Both an electron-transfer and an S_N2-type substitution mechanism have been considered for these transformations.[136]

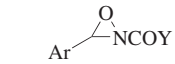
O-*Phosphinoylhydroxylamines*. The non-explosive[138] *O*-diphenylphosphinoylhydroxylamine, $Ph_2P(O)ONH_2$, aminates alkyl,[139,140] aryl,[139] ethynyl (see Eq. 60),[135] cyanomethyl, and phosphinoylmethyl (see Eq. 152)[95,141] metal derivatives and enolates of esters,[139,142] lactams (see Eq. 137),[143] α,β-unsaturated carbonyl compounds (see Eq. 153),[144] and β-dicarbonyl compounds.[139] The equally stable methoxy analog $(4\text{-}MeOC_6H_4)_2P(O)ONH_2$ has been recommended[106] as a better reagent because of its increased solubility in organic solvents at low temperatures but there is a report of a low yield and formation of a hydroxylation product in the amination of a malonic ester enolate.[145] Amination with the disubstituted analog $Ph_2P(O)ONMe_2$[146] and the chiral, non-racemic cyclic derivative **12** (see Eqs. 109 and 143)[147] has also been reported. There appear to be no mechanistic studies of these reagents but it is relevant that equimolar amounts of the substrate and the reagent or a slight excess of the latter are usually employed.



12



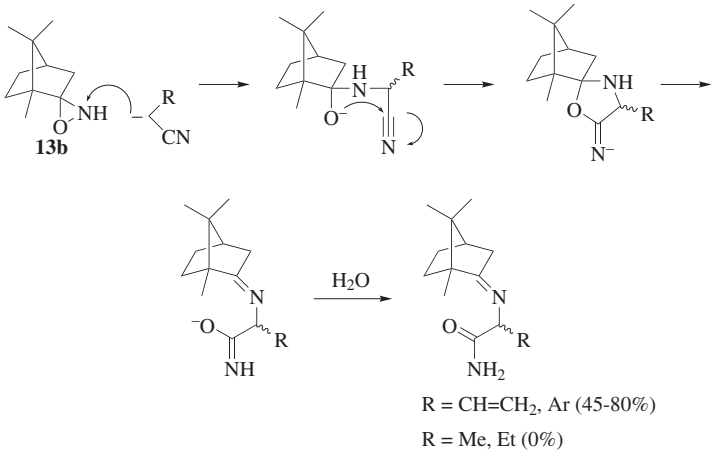
13a



Y = *t*-Bu, NEt_2, (–)-menthoxide

14

Oxaziridines. The readily synthesized 1-oxa-2-azaspiro[2,5]octane (**13a**)[148] aminates[12] enolates of β-dicarbonyl compounds,[149,150] α-cyano carbonyl compounds,[149,150] and anions derived from cyanomethyl derivatives further activated by aryl or heteroaryl groups.[150] The products are either amines, *N*-cyclohexylidene derivatives, or more complex structures (see Eq. 162). The camphor-derived oxaziridine **13b** aminates enolates of esters, β-dicarbonyl and α-cyano carbonyl compounds,[151] and anions derived from various cyanomethyl compounds.[151] Esters are aminated only if they carry an additional aryl group.[151] The products resulting from β-dicarbonyl and α-cyano carbonyl compounds are camphorimines that have lost the ester group by hydrolysis and decarboxylation. Camphorimines derived from aminations of esters retain the ester group. The cyano group in all substrates is converted into an amide group and the mechanism shown in Eq. 11 has been proposed. The first step is analogous to that of the mechanistically fairly well-established hydroxylation of enolates with *N*-sulfonyl oxaziridines[152] except that attack by the anion is on nitrogen rather than oxygen. When R is methyl or ethyl, only rearrangement products of the aminating reagent are isolated.[151]



13b

R = CH=CH_2, Ar (45-80%)

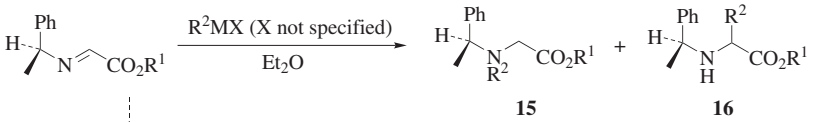
R = Me, Et (0%)

(Eq. 11)

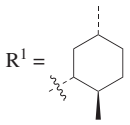
Oxaziridines **14** transfer the NCOY group to enolates of ketones (see Eq. 90),[153–156] esters (see Eq. 110),[153,155,157,158] amides,[158] *N*-acyloxazolidinones,[153,157] and β-dicarbonyl compounds,[155] anions stabilized by cyano (see Eq. 141),[155] sulfonyl (see Eq. 145),[158] and phosphinoyl[154] groups, and ketone enol ethers.[155] Yields are in the 20–60% range. The first step in these reactions is presumably attack of the enolate on nitrogen as in Eq. 11, followed by elimination of an aldehyde ArCHO and formation of the amination product. With esters,

the aldehyde may undergo an aldol reaction with the substrate enolate when LiHMDS, KHMDS, LDA, or *t*-BuLi are used as the bases to generate the enolates. This undesired side reaction is not observed with NaHMDS provided that two equivalents of the reagent are used, but yields are low.[155]

Imines. Organometallic compounds normally attack imines at the carbon atom. Predominant or exclusive attack on nitrogen may be forced by attaching one or two electron-withdrawing groups to the imine carbon atom.[159–167] In the examples of Eq. 12[161] involving a substrate with a fairly bulky group on nitrogen, the ratios of product **15** to **16** demonstrate that only the *tert*-butyl and allyl Grignard reagents attack on carbon, the former presumably for steric reasons. All cadmium reagents RCdX tested (R = Me, *n*-Pr, *i*-Pr, Bn) add normally on carbon.



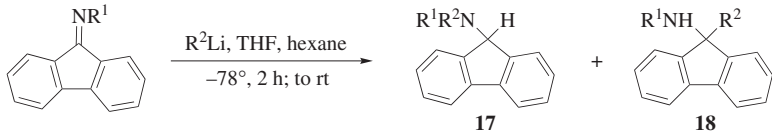
15 **16**



R^2	M	**15 + 16**	**15:16**
Et	Mg	(45-55%)	95:5
n-Pr	Mg	(44-55%)	96:4
i-Pr	Mg	(44-55%)	60:40
$CH_2CH{=}CH_2$	Mg	(45-55%)	0:100
i-Bu	Mg	(45-55%)	96:4
t-Bu	Mg	(45-55%)	0:100
Bn	Mg	(45-55%)	100:0
Bn	Cd	(55-70%)	0:100

(Eq. 12)

A second method of favoring attack on nitrogen involves systems where the imine carbon is surrounded by fairly bulky substituents and where placing a negative charge on this carbon is favored by formation of a cyclopentadienyl anion (Eq. 13).[168] A phenyl group on nitrogen reverses this trend, with product **18** now predominating over **17**.



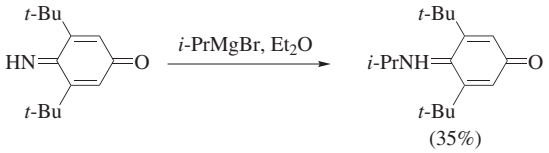
17 **18**

R^1	R^2	**17**	**18**
Me	*n*-Bu	(71%)	(0%)
n-Bu	Et	(65%)	(5%)
Ph	*n*-Bu	(15%)	(50%)

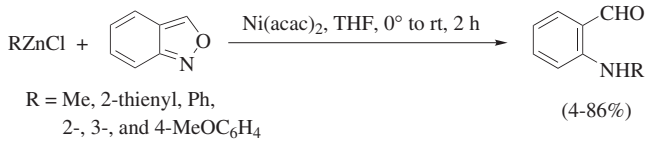
(Eq. 13)

Attack of isopropylmagnesium bromide on the hindered imine in Eq. 14 surprisingly occurs on nitrogen whereas the less bulky ethylmagnesium bromide adds to the carbonyl group.[169] Organozinc reagents react with anthranil under $Ni(acac)_2$ catalysis to give α-aminobenzaldehyde derivatives by a proposed single-electron

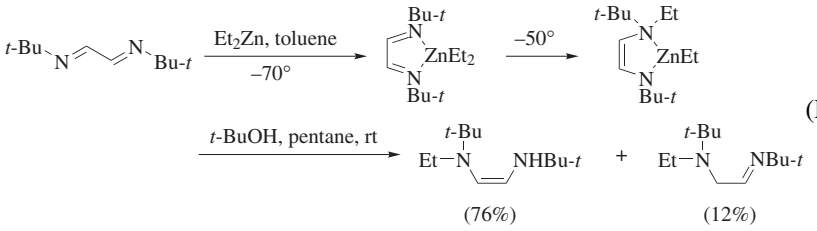
transfer mechanism (Eq. 15).[170] Diethyl zinc adds to 1,4-diaza-1,3-butadienes in a net 1,4-fashion (Eq. 16).[171]



(Eq. 14)

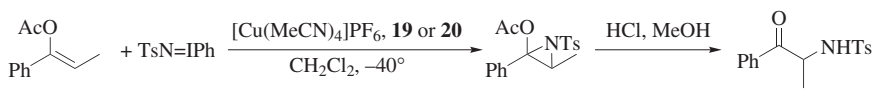


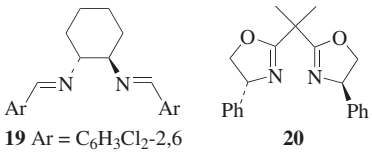
(Eq. 15)



(Eq. 16)

(*N*-Arenesulfonylimino)phenyliodinanes. [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane (TsN=IPh) and its pentafluoro analog $C_6F_5SO_2N$=IPh react readily on warming in acetonitrile with silyl enol ethers derived from acetophenones to give the α-tosylamino derivatives in high yields. The reaction is less efficient in methylene chloride, gives low yields with the trimethylsilyl ether of 3-pentanone and with 1-trimethylsilyloxybutadiene, and fails completely with 1-trimethylsilyloxycyclohexene and a ketene acetal, 1-phenoxy-1-(trimethylsilyloxy)ethylene.[172] The latter two types of substrates do react when a copper catalyst is employed, but yields do not exceed 50% (see also Eq. 92).[173] With chiral (ligand **19** or **20**) copper catalysts, modest to fair enantiomeric excesses are achieved (Eq. 17).[174] The proposed mechanism involves a slightly favored front-side attack of the enol derivative on the initially formed ligand–copper nitrene complex with formation of an aziridine, which is converted directly into the α-tosylamino product during isolation when methyl or trimethylsilyl enol ethers are used.



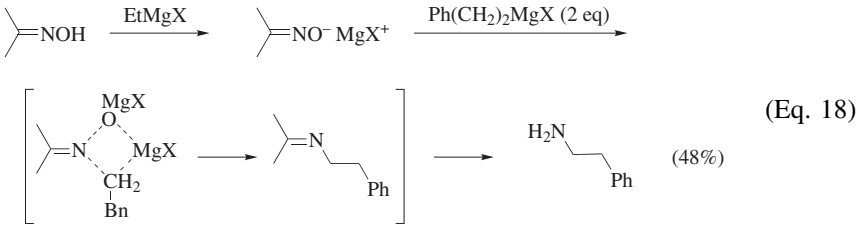


Ligand	Conversion [a]	ee
19	(>95%)	28% R
20	(61%)	52% R

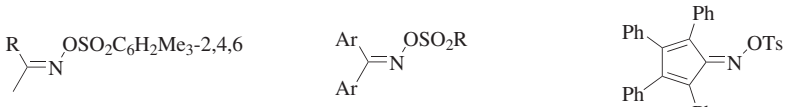
[a] based on TsN=IPh reacted

(Eq. 17)

Oximes. Reaction of alkyl- or arylmagnesium reagents with two equivalents of acetone oxime in toluene gives alkyl or arylamines, respectively, in low yields. The yields are improved by converting the oxime into the salt with ethylmagnesium halide followed by addition of the desired Grignard reagent. A mechanism involving a four-membered cyclic transition state is postulated (Eq. 18).[174a] Similar reactions with the lithium salt or methyl ether of benzaldoxime have also been reported.[175] Among the *O*-sulfonyloxime derivatives **21**[176–178] (see Eq. 61), **22**[178,179] (see Eq. 40), **23**,[180] **24**,[181] and **25**,[181,182] the dioxolane **25b** combines the advantages of high product yields in reactions with alkyl-, vinyl-, aryl-, and heteroarylmagnesium reagents with ease of hydrolysis of the initially formed imine to the amine (see Eq. 37).[182] Reactions with other types of anions do not seem to have been investigated except that phenolates (Eq. 176) and enolates of β-dicarbonyl (Eq. 175) and α-sulfonyl carbonyl compounds undergo an intramolecular version of this amination reaction. The mechanism is believed to involve direct S_N2 substitution on the sp^2 nitrogen of the oxime[13,183] rather than addition/elimination or electron transfer.



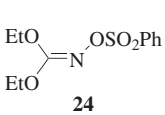
(Eq. 18)



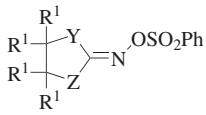
21 R = Me, Ph

22 Ar = Ph, 4-$CF_3C_6H_4$, 3,5-$(CF_3)_2C_6H_3$
R = Me, 4-MeC_6H_4

23



24

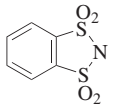


	R^1	Y	Z
25a	H	O	O
25b	Me	O	O
25c	H	NMe	O
25d	H	O	NMe
25e	H	NMe	NMe

Diazonium Salts. *Diazonium salts are potentially explosive. See the cautionary note in Experimental Conditions.* Aryldiazonium salts **26** react with alkyl- and arylmagnesium reagents,[184–191] arylzinc,[190,192,193] and aryltin reagents[194] to give azo compounds. Yields vary considerably; the best are achieved with the diazonium salt **26e**[191] (see Eq. 48). Aryldiazonium salts also react with enolates, enol derivatives, or enamines of aldehydes (see Eq. 85),[195] ketones (see Eq. 95),[185] and with silyl ketene acetals (see Eq. 121).[196,197]

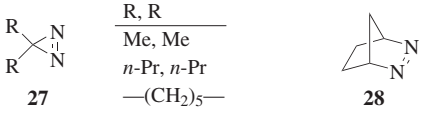
$ArN_2^+ X^-$

	X
26a	Cl
26b	$ZnCl_3$
26c	BF_4
26d	$Zn(BF_4)Cl_2$

26e X = 

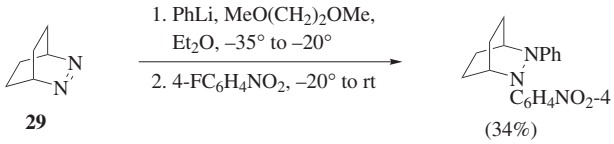
Diazo Compounds.[198] Alkyl- and arylmagnesium[199–204] and alkyllithium reagents[205] add to diazo compounds in a little-used reaction to give hydrazones. Diazo compounds add to enolates to give azines.[206] With enamines, diazo compounds give hydrazones of α-diketones.[207]

Azo Compounds. *Alkyl Azo Compounds*. The only aminations with alkyl azo compounds found in the literature involve the cyclic derivatives **27**,[208] **28**,[209] and **29**.[210] Reaction of **29** with phenyllithium followed by in situ arylation of the anion (Eq. 19)[210] is one of the few examples of tandem reactions in aminations reported thus far. Azo compounds **27** add to cyclohexyl- and phenylmagnesium reagents at −78° with fair to excellent yields,[208] and the bicyclic azo compound **28** gives an adduct with *t*-BuLi at −78° in almost quantitative yield.[209] Relief of strain no doubt is one of the driving forces for these reactions but the low temperatures involved may indicate that they could be extended to acyclic alkyl azo compounds.



R, R
Me, Me
n-Pr, *n*-Pr
—$(CH_2)_5$—

27 **28**



29

1. PhLi, $MeO(CH_2)_2OMe$, Et_2O, –35° to –20°
2. 4-$FC_6H_4NO_2$, –20° to rt

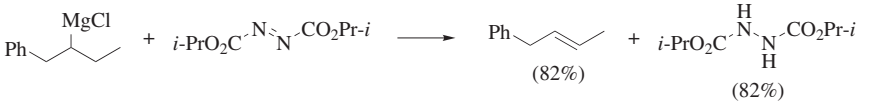
(34%) (Eq. 19)

Aryl Azo Compounds. Alkyl- (including *tert*-butyl) and aryllithium reagents add to azo benzene to give trisubstituted hydrazines in fair to excellent yields (see Eqs. 44 and 45); alkylation of the intermediate anion in situ leads to tetrasubstituted hydrazines.[211] Benzyl and heteroarylmethyl (see Eq. 54) anions and the enolate of phenylacetamide add to azo benzene in fair to excellent yields.[212] Aromatic Grignard reagents are reported to reduce azo benzene and its derivatives to the hydrazo compounds (cf. also Eq. 20).[213] The only other aryl azo compound investigated in aminations appears to be benzo[*c*]cinnoline.[214]

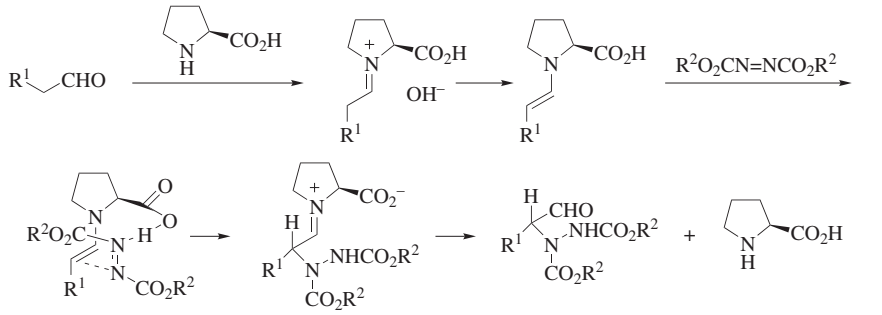
Esters of Azodicarboxylic Acid. These compounds are versatile aminating reagents for alkyl- (see Eq. 46), allenyl- (see Eq. 59), aryl- and heteroarylmetal (see Eq. 75) derivatives, and especially enolates (see Eqs. 87, 88, 115–117, and

119) and metalloimines (see Eqs. 104–106). An important new reaction involves addition of azo esters to alkenes,[215] dienes,[216] and enynes[216] in the presence of silanes catalyzed by cobalt and manganese complexes to give the more highly substituted hydrazino esters (see Eqs. 49, 52, and 55). Based on preliminary mechanistic studies of this hydrohydrazination reaction, rate-limiting addition of a metal hydride species to the double bond is followed by a fast amination step.[215]

Benzyl and *tert*-butyl esters are widely used because of their ready conversion into the hydrazines after the amination step and the presence of an aromatic chromophore in the former. Addition of the organometallic species to the ester carbonyl group does not appear to be a problem, although *tert*-butyl esters often provide higher yields. Formation of substantial amounts of an α,β-unsaturated carbonyl compound by elimination of the hydrazino ester from the desired product has been reported in the reaction of dibenzyl azodicarboxylate with the enolate of a sugar ketone.[217] Esters derived from azodicarboxylic acid and chiral alcohols have been prepared[218,219] and a chiral amide has been used in the amination of an achiral enolate (see Eq. 134).[219] The failure of a secondary Grignard reagent to add to diisopropyl azodicarboxylate is shown in Eq. 20.[220] The asymmetric amination of aldehydes (see Eqs. 76 and 77)[221–227] and ketones (see Eq. 91)[228,229] by azo esters is catalyzed by proline and its derivatives. The proposed mechanism involving a hydrogen bond from the catalyst to the N=N double bond in the transition structure is shown in Eq. 21[221] (see also ref. 224). The amination of β-keto esters by azo esters proceeds at room temperature neat or in polar solvents such as alcohols[230,231] or, as with β-aminocrotonic ester, even in petroleum ether.[230] The former reaction may be carried out enantioselectively with catalysts such as cinchona alkaloids (see Eq. 163),[231,232] chiral urea and thiourea derivatives,[233] chiral copper(bis)oxazoline complexes[234] (see Eqs. 103, 151, and 164),[235–237] and chiral palladium BINAP complexes (see Eqs. 150 and 165).[238,239]



(Eq. 20)



(Eq. 21)