The Electrophilic Amination of Carbanions: An Unconventional New Entry to C–N Bond Formation

Pasquale Dembech,[b] Giancarlo Seconi,[b] and Alfredo Ricci*[a]

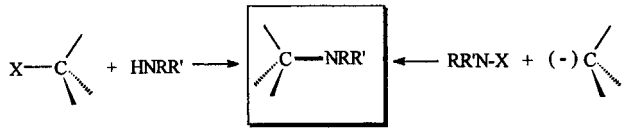
Abstract: The electrophilic amination of carbanions allows the preparation of a wide range of amines through an unconventional C–N bond-forming reaction. The concepts behind the varied synthetic approaches, classified by the nature of the aminating agent and of the organometallic species, are discussed. The mild operational conditions, the high selectivity, and the availability of the starting materials are good assets of these processes which nicely complement each other. New appealing and flexible routes can be devised, leading in several cases to the synthesis of otherwise not easily accessible N-containing compounds.

Keywords: aminations · azides · carbanions · diazo compounds · organometallic compounds · oxidations

Introduction

Over the last few years the resources devoted to research into the development of new methods for the synthesis of amines, which are fundamental building blocks in organic chemistry and important industrial targets, have been substantial and the field remains one of the most active in modern organic synthesis.[1]

Carbon–nitrogen bonds are usually formed by attack of a nucleophilic nitrogen atom at an electrophilic carbon bearing a leaving group by a SN_2-type reaction. However the majority of classical processes is hampered by difficult access to the electrophilic precursors, particularly when multifunctional derivatives are taken into consideration, and by the frequently recurring difficult reaction conditions. Moreover the direct amination of aromatic compounds remains a challenging problem of practical importance in organic synthesis. Among the various modern synthetic strategies[2] the 'electrophilic amination' of carbon nucleophiles appears as an important and unconventional C–N connective process in organic synthesis (Scheme 1).



Scheme 1. Methods of amination. Left: The attack of a nucleophilic N atom at an electrophilic C atom bearing a leaving group by a SN_2-type reaction. Right: The replacement of a C nucleophile of a good leaving group bound to an 'electrophilic N atom'.

The chemists demand for practical electrophilic [NH_2^+] equivalents, amenable to C–N bond formation falls well short of the supply of suitable reagents in a process in which a carbon nucleophile replaces a leaving group on an electrophilic nitrogen. The following account discusses recent advances in the area of electrophilic amination of carbanions and puts into perspective some new ideas addressed to develop new concepts in this field.

Discussion

Nitrenoid-like species: One of the lines along which the electrophilic amination of carbanions developed and became a synthetically useful protocol stems from the discovery by Sheverdina and Kocheskov[3] that organolithium compounds can be aminated with methyllithium-methoxamine. For interpreting this intriguing and for a long time not well understood reaction which involves the coupling of two anionic species, an interaction which should be repulsive, Beak et al. proposed[4] the transition state reached from the dimer **1** (Scheme 2).

To investigate why nitrenoids LiRN–OR′ are more electrophilic than the corresponding non-lithiated alkoxyamines HRN–OR′, model calculations have been performed by Boche and Wagner,[5] showing that the N–O bond in **2** is bridged by Li and is longer than the related bond in **3**. This would have particular significance for the nitrenoid character

[a] Prof. A. Ricci
Dipartimento di Chimica Organica, 'A. Mangini', Facoltà di Chimica Industriale
via Risorgimento 4, 40136 Bologna (Italy)
Fax: (+39) 051-2093654
E-mail: ricci@ms.fci.unibo.it

[b] Dr. P. Dembech, Dr. G. Seconi
Istituto dei Composti del Carbonio Contenenti Eteroatomi del CNR
Area della Ricerca di Bologna, Via P. Gobetti 101
40129 Bologna (Italy)

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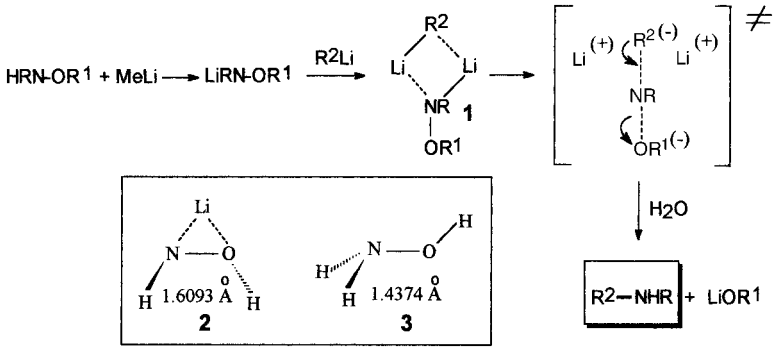
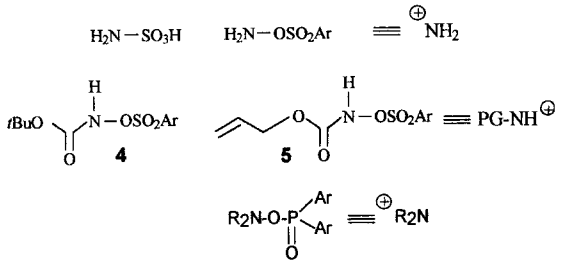


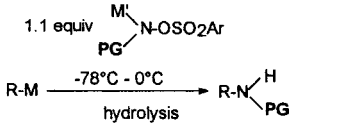
Scheme 2. Nitrenoids in electrophilic amination of organolithium compounds.

and for the facile cleavage of the N–O bond. Since in nitrenoid **2** the R′O becomes a good leaving group, these species may display amination potential similar to that of hydroxylamines possessing excellent leaving group abilities. On the other hand, the Li bonding to donor sites such as N or O might favor the essential formation of associated species in which, due to the proximity effects, the delivery of the 'electrophilic' nitrogen to the carbanion would be highly favored. The above concepts have been translated (Scheme 3) into the design and the synthesis of a number of modified hydroxylamines and of sulfonamide-type reagents for the delivery of the amino groups able to act as synthetic equivalents of the NH_2^+ (a^1-synthon).



Scheme 3. Hydroxylamine-derived aminating agents.

A variety of simple N-protected alkyl, aryl, and heteroaryl primary amines could be synthetized following this approach. The presence of easily removable protecting groups such as Boc (**4**) and Alloc (**5**) is evidently[6] of major importance in the synthesis of heteroarylamines such as 2-aminothiophene, which are otherwise not stable as free bases (Scheme 4).

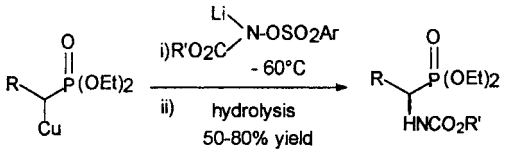


RM	M'	PG	yield%
*n*BuLi	Li	Boc	71
*s*BuLi	Li	Boc	42
*n*Bu3B	Li	Boc	81
PhCu	Li	Alloc	51
2-ThienylCu	Li	Boc	52
*s*Bu2CuLi	MgCl	Boc	57

Scheme 4. Electrophilic amination of organometallic compounds with sulfonamido-type reagents.

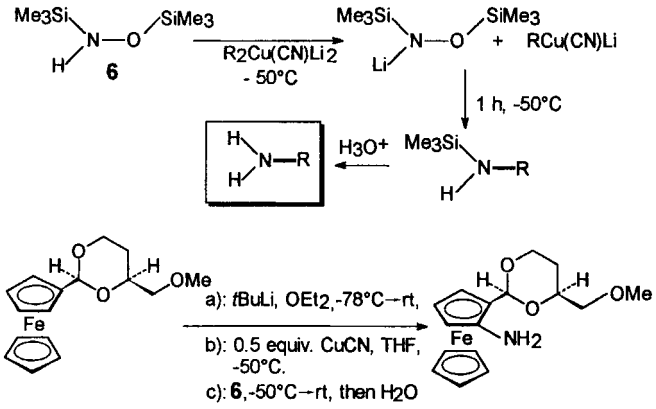
The finding that several less polar and milder reagents can suitably replace the more aggressive organolithium and Grignard reagents as the sources of C nucleophiles, has widened the scope and the applications of this methodology. Amination of organoboranes has provided a useful and mild method for introducing an amino functionality by replacement of a boron atom by a nitrogen atom: the reactions of organoboranes with N-chloramine[7] and with hydroxylamine-O-sulfonic acids[8] have been reported by Brown et al., and primary amines with high enantiomeric purity were obtained from chiral boronic esters.[9]

In several instances, for example, in the synthesis of phosphonic amino acids, α-cuprophosphonates react rapidly with lithium N-tosyloxy-*tert*-butylcarbamates, whereas the reaction with α-lithiophosphonate is unsuccessful.[10] Scheme 5 illustrates some of the chemistry associated with the use of an α-cuprophosphonate for the synthesis of phosphonic amino acids, an important class of compounds with applications as antibiotics, antiviral agents, and enzyme inhibitors.



Scheme 5. Formation of phosphonic amino acids by electrophilic amination.

The use of organocuprates emerged also as a strict requirement when using[11] silylated hydroxylamines like *N,O*-bis-trimethylsilylhydroxylamine (**6**) as the source of 'electrophilic nitrogen': in this particular case a 'higher order' (bis anionic) cuprate provides the base for the proton abstraction as well as the ligand to be transferred to the 'nitrenoid' nitrogen atom (Scheme 6).[12]



Scheme 6. Route to primary amines by electrophilic amination with *N,O*-bis-trimethylsilyl-hydroxylamine (**6**).

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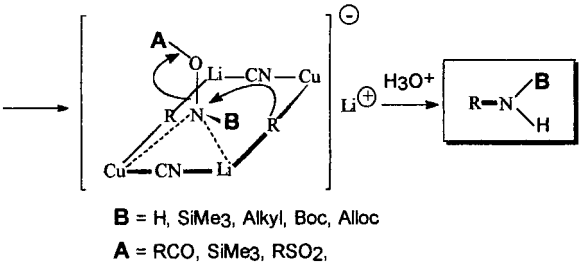
A simple, convenient and highly general method which circumvents the restricted range of applicability of most of the previously reported methodologies has beeen developed very recently[13] for synthesizing N-alkyl aromatic and alkyl heteroaromatic amines from the corresponding *N*-alkyl-*O*-trimethylsilyl hydroxylamines and aryl and heteroaryl cuprates in satisfactory to good yields.

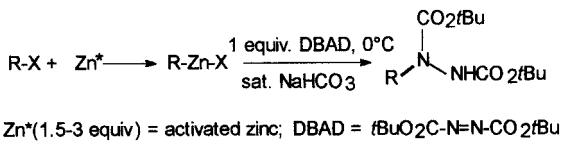
Overall the electrophilic amination involving an N-metalated sulfonamido or N-metalated hydroxylamino type system is a formal displacement of a leaving group linked to a nitrenoid species by a C nucleophile and can be mechanistically described as in Scheme 7.



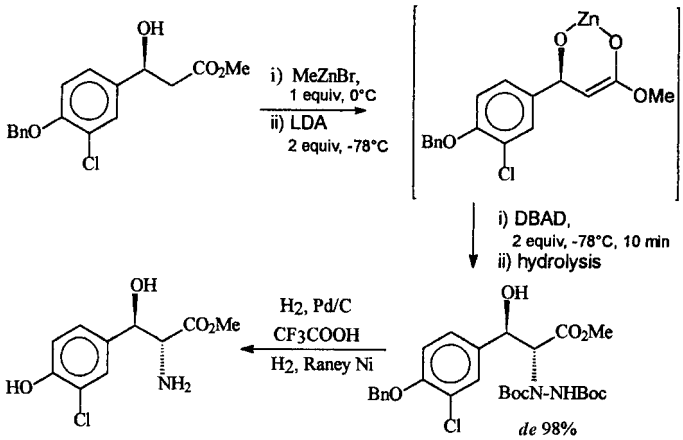
Scheme 7. Mechanistic rationale exemplified in the case of the electrophilic amination of cyanocuprates with aminating reagents bearing a good leaving group.

Nitrogenated 'neutral' reagents: the diazo, azido, and imino derivatives: A conceptually different approach toward electrophilic amination is based on the addition of carbanions to '*neutral*' aminating agents. The successful implementation of the above amination strategy was necessarily dependent on the availability of suitable nitrogen sources. Reagents in which no leaving groups are present have recently entered into common use in many applications of organic synthesis and are capable of reacting under mild reaction conditions with explicit or latent carbanions leading to a new C–N bond in a connective process. Di-*tert*-butyl-azodicarboxylate (DBAD) (**7**) which exploits the synthetic equivalence of a [Boc-N-NH-Boc]$^+$ synthon is a commercially available and highly stable compound. Its remarkable reactivity towards carbon nucleophiles has been demonstrated by recent studies in the Rieke's group.[14] They showed that main group organometallic compounds endowed with moderate electronegativity, such as functionalized organozinc reagents, and generally regarded as intermediates of low reactivity that exihibit a broad functional group tolerance[15] are able to react with DBAD under mild conditions to give the corresponding hydrazino derivatives. The latter are immediate precursors of amines by deprotection (Scheme 8).

The use of **7** is particularly valuable[7] in the *anti*-diastereoselective amination of β-hydroxyesters by the corresponding metal enolates. The Zn enolates appear particularly



Scheme 8. Electrophilic amination of organozinc halides.



Scheme 9. Asymmetric synthesis of *anti* α-amino-β-hydroxy acids.

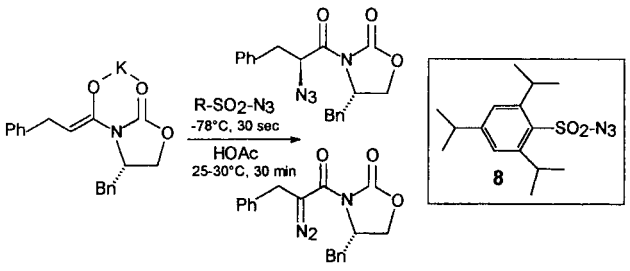
suitable for this process, providing access to α-hydrazino-β-hydroxyesters (Scheme 9).

This diastereoselective strategy has been applied to the synthesis of a number of enantiopure *anti* α-amino-β-hydroxy acid components of biologically active cyclopentanols and heterocycles. The asymmetric route to a dipeptide which constitutes the east part of vancomycin, recently reported by Genet et al.,[16] highlights the synthetic potential of this reagent. Even though DBAD has provided access to a wide range of targets, the major liability in its use is the 'packaging' of the nitrogen as delivered to the substrate. Ofsetting to some extent the benefits deriving from the use of this reagent is the need for two further steps (trifluoroacetic acid (TFA)/CH_2Cl_2 then H_2/Ra-Ni) for the N–N bond cleavage to generate the NH_2 functionality.

Notably, the imines of glyoxylates upon addition with organometallic compounds undergo alkyl transfer from the metal to the nitrogen according to an electrophilic amination pathway. This reaction discovered by Kagan and Fiaud[17] has been recently employed[18] as a synthetically useful protocol for the asymmetric synthesis of 2-azetidinones.

In connection with the use of other 'neutral' aminating agents, a seminal investigation of the features of the azido transfer in the reactions with enolates and with esters, and the partitioning of the reaction between the azide- and diazo-transfer pathways, was carried out by Evans et al.[19] These studies led to an optimization of the reaction conditions based on the use of sulfonyl azides as synthetic equivalents of $-N_3^{(+)}$ synthons. Reactions of enolates with sulfonyl azides were found to be sensitive to both the enolate counterion and sulfonyl azide structure. Several significant studies led to the use of highly electron-deficient sulfonyl azides and more recently to the use of sterically demanding sulfonyl azides of which 2,4,6-triisopropylbenzensulfonyl azide (trisyl azide) (**8**) was the most readily available example. Azidation reactions with **8** enjoy[19] considerable scope, while displaying (Scheme 10) high yields and a high level of stereoselectivity (*de* $\approx$95%). Subsequent fragmentation of triazene followed by reduction with H_2/Pd/C leads to the amino derivatives.

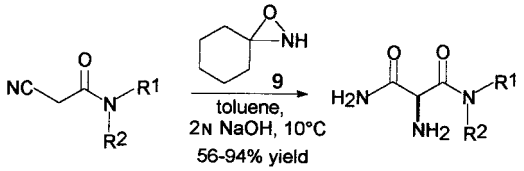
Strained heterocylic rings: The unusual reactivity, undoubtedly related to the presence of a strained three-membered



	R = *p*-NO_2-C_6H_4	*p*-CH_3-C_6H_4	2,4,6-(*i*Pr)$_3C_6H_2$
azido :	15	51	91
diazo :	70	26	-

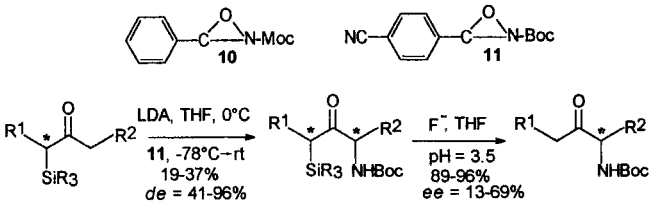
Scheme 10. Effect of sulfonyl azide structure on azide versus diazo transfer.

ring and a relatively weak N–O bond,[20] make oxaziridines highly useful as aminating agents. Ring opening of the strained three-membered rings is the key to their ability to react as both aminating and oxygenating reagents with nucleophiles. The site of nucleophilic attack at the oxaziridine ring is determined by the substitution pattern at the nitrogen. Schmitz group's careful study demonstrated[21] that N-unsubstituted oxaziridines can play an important role as electrophilic aminating reagents. They are highly reactive toward N, S, O, and C nucleophiles (*Nu*) and must be prepared and handled in inert solvents such as diethyl ether or toluene. The attack takes place at the NH group of the three-membered ring with simultaneous *Nu*–N bond formation and rupture of the N–O bond, thus making possible the synthesis of a wide range of compounds such as azines, hydrazines, diaziridines etc. The amination of C nucleophiles by spiro(cyclohexane-3′-oxaziridine) (**9**) has also been investigated for typical examples of C–H acidic compounds in which deprotonation is possible by treatment with aqueous alkali hydroxide. Surprisingly the amination was accompanied by hydration of the nitrile group in all cases (Scheme 11).



Scheme 11. Amination of C–H acidic compounds with oxaziridines.

The development of oxaziridines which would allow the direct transfer of a N-protected group to nucleophilic centers led to the synthesis of N-Moc and N-Boc oxaziridines. In contrast to the concept that oxaziridines act as aminating reagents only when the group attached to the nitrogen is small and that when it becomes larger the site of the attack is shifted from the nitrogen to the oxygen, **10** and **11** are able to transfer the N-Moc and the N-Boc fragments under mild conditions to ketone, ester, and amide lithium enolates.[22] N-Boc protected α-amino ketones of moderate enantiomeric purity were synthesized[23] by **11**-mediated electrophilic amination of an enantiopure α-silyl ketone, whereby the silyl group functions as the 'traceless' directing group (Scheme 12).



Scheme 12. Enantioselective synthesis of protected α-amino ketones by electrophilic amination with an oxaziridine.

A limitation in the use of **11** in electrophilic amination stems, however, from the substantial amount of the enolate consumed by aldol condensation with 4-cyanobenzaldehyde, reducing the yields (19–37%) of the amines.

Oxidative coupling of M-amides. The possibility of using simple and commercially available amines as the aminating agents raises the prospect of a straightforward and economic approach to C–N bond formation. For this purpose we were inspired by the well known inadvertent oxidation by dioxygen of lithiorganocuprates which leads to coupling between C ligands. This methodology appears only slightly attractive synthetically when performed on organocopper ligands R′R″CuLi with mixed ligands since only statistical ratios of the three possible products are formed. Only recently[24] have high levels of unsymmetrical ligand coupling been achieved by controlling both temperature and mode of reagents formation, thereby resulting in a novel route to the biaryl nucleus, a key unit associated with many natural products.

We found[25] that upon treatment of a bis-anionic 'higher-order' organocuprate with an equimolar amount of primary or secondary amine, a clear solution is formed which is stable for a long time. Under these operational conditions the intermediacy of dimeric amidocuprates can be inferred[26] in which the starting amine becomes a '*building block*' in the molecular architecture. Since the N atom behaves as a nontransferable cuprate ligand, it conveys fairly high stability to the cluster. Upon saturation with oxygen, the solution collapses into a heterogeneous dark mixture leading to the formation of new amino derivatives in which a new C–N bond is formed between the nitrogen of the starting amine and the anionic C ligand of the cuprate. Rationalization of the C–N bond formation in these reactions, suggested in principle the intervention, supported by EPR experiments, of long-lived free radicals (Scheme 13).

The method, which can be formally considered as related to electrophilic amination, succeeds when applied to the synthesis of a range of secondary and tertiary amines and of enamines, but fails when hydrazines were used as starting materials, since major amounts of hydrazone are formed and only trace amounts of the expected *N*-alkyl hydrazine are recovered. This drawback suggested that oxidizing power tuning as a function of the stability of the cluster intermediate and of the fragility of the substrate under oxidative conditions, may be required. As expected Cu→Zn transmetalation led, due to the covalent character of the C–Zn bond, to the more stable zinc-amidocyanocuprates. From these upon quenching with dioxygen, alkylation of hydrazines and of aliphatic

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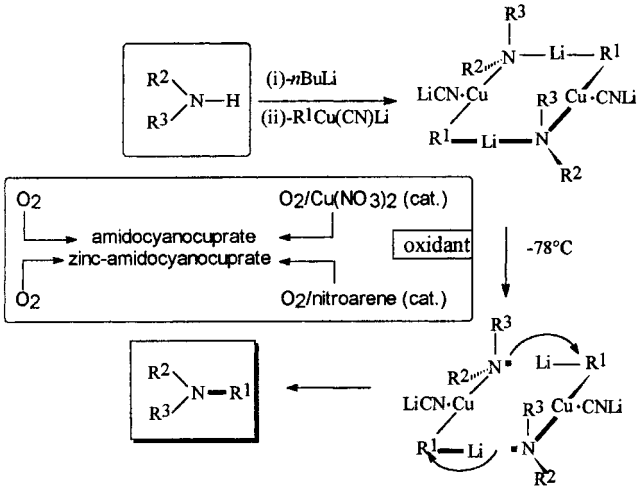

Scheme 13. Overall process for the oxidative intramolecular coupling, showing the various combinations between the organometallic clusters and the oxidizing systems.

amines took place in much higher yields but in the case of the aryl ligands the efficiency of the three-center two-electron bonds between each of the ligands and the two metals conveyed to the clusters an exceedingly high stability thus making the oxidative decompositon with dioxygen ineffective. This assumption prompted us to envision modified procedures for the oxidative decomposition of the various clusters, following the concept that an interplay of the nature of organometallic compounds and oxidants might improve the efficiency of the electrophilic amination by oxidative coupling and might convey to this procedure a general character: the unprecedented use of oxygen in the presence of substoichiometric amounts of co-oxidants such as dinitrobenze or unsupported $Cu(NO_3)_2$ proved successful.[27]

The versatility of the oxidative coupling-based electrophilic amination as a synthetic method can be seen when one casts a glance at the multitude of aliphatic, saturated and unsaturated amines, and aryl and heteroarylamines, some of which are otherwise not easily accessible, whose representative overview is shown in Figure 1.

Conclusions

The aim of this paper has been to introduce the reader several promising new concepts which have been developed quite recently, for generating new C–N bonds by 'electrophilic amination' of carbanionic species. Interest in this area has been renewed by the challenges facing preparative chemists to carry out structurally directed syntheses of amino derivatives under the mildest conditions. The applications of the reported methodologies span from very simple molecular systems to highly functionalized target compounds, and many new exciting stereoselective routes can be envisioned. Great opportunities exist for using these concepts for a wider range of reactions and substrates, also considering the generally simple operative conditions and the easy access to the starting aminating reagents.

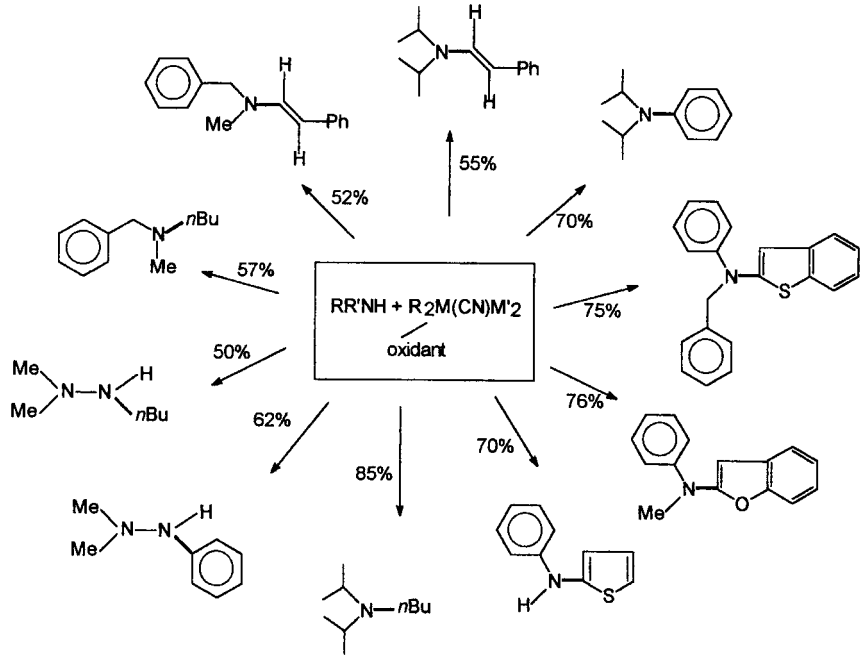

Figure 1. Examples of amines, enamines, and hydrazines obtained by oxidative intramolecular coupling.

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