

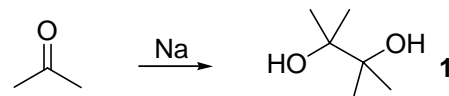
Reductive Coupling Reactions of Nitrones and Imines, Modern Versions of the Pinacol Reaction: Expanded Substrate Scope and Asymmetric Induction

Reported by Christopher G. Mayne

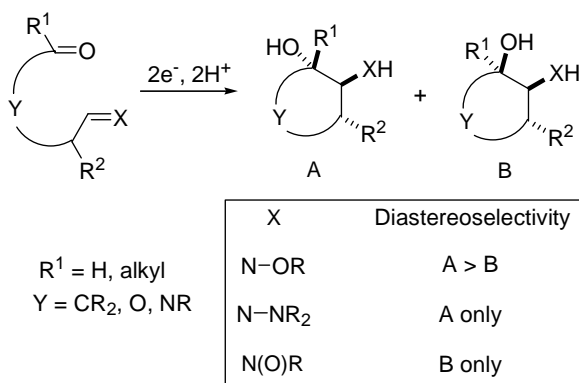
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INTRODUCTION

Pinacol coupling was first described by Fittig in 1859, when he reported the formation of 2,3-dimethyl-2,3-butanediol (**1**) from acetone and sodium metal.¹ Since then, this ketyl radical anion coupling process has undergone significant advancement, including the development of asymmetric variants.^{2, 3} Alternatives to use of strong reducing metals are low valent transition metals and lanthanides.⁴ A recent development in these reductive couplings has been the extension to carbon-nitrogen double bonds (C=N), long known to be radical acceptors,^{5, 6} particularly in radical-mediated cyclizations with alkyl halides. Much progress has also been made on intramolecular versions of these processes, due to their highly organized and stable cyclic transition states and low rates of competing homocoupling reactions (Scheme 1).



Scheme 1. Intramolecular Reductive Coupling



Intermolecular reductive coupling of C=N substrates represents an atom-efficient construction of an inherently functionalized C-C bond for the synthesis of vicinal diamines, 1,2-amino alcohols, and γ -amino esters from relatively simple starting materials. This review will cover general substrate considerations, limitations, and asymmetric variants of intermolecular reductive 1,2- and 1,4- coupling reactions involving nitron and imine components.

SUBSTRATE SCOPE

Mechanism and Reducing Agents

Reductive coupling is generally thought to proceed by a single-electron transfer (SET) from a reducing reagent to either the carbonyl compound or the C=N component, forming a radical anion. This relatively stable species then undergoes addition to the coupling partner followed by a second SET and protonation to yield a 1,2-amino alcohol. An alternative mechanism involving a second SET to the first component to generate a dianionic intermediate, however, has not been disproved.⁷ This mechanism hinges on the SET from a reducing agent to the substrate, and while it is beyond the scope of this review to cover all of the reducing reagents applied to this reaction, select examples highlight some of the important aspects.

Since the first report of imine-carbonyl cross coupling in moderate to high yields using NbCl₃ by Pederson in 1987,⁸ many other metal reductants have been employed, with varying degrees of success. Electrochemical reduction is the only method reported that allows intermolecular cross coupling of aldehydes with oxime ethers, hydrazones, and sterically hindered imines.⁹⁻¹¹ Samarium diiodide¹² (SmI₂) is the most widely used reducing agent, because its reduction potential is tunable. Although it is generally used stoichiometrically (2-3 mol equiv), SmI₂ is sometimes used in catalytic quantities (0.2 mol equiv) with Mg (8 mol equiv) as the bulk reductant, but yields are generally lower.¹³

The selective SET to nitrones occurs using SmI₂ at -78 °C without any additives. Coupling reactions of imines and carbonyl compounds, however, require elevated temperatures and hexamethylphosphoramide (HMPA), an additive capable of increasing the reduction potential of SmI₂ over a considerable range.¹⁴ Increased yields and diastereoselectivity were achieved at ambient temperatures using Lewis acids such as Yb(OTf)₃.¹³ Addition of catalytic amounts of NiI₂ accelerated the rate of SET to imines at ambient temperatures without affecting carbonyl coupling rates and allowed access to cross coupling products.¹⁵ Coupling rates have also been drastically increased using microwave irradiation at 180 °C (wattage not reported).¹⁶ Modified Sm(II) reagents such as Sm{[Si(CH₃)₃]₂}₂ showed increased diastereoselectivity for aldimines, while a SmI₂/Et₃N/H₂O mixture effected ketimine homocoupling in 80% yield¹⁷.

Imines

Cross coupling reactions involving imines suffer from competing homocoupling processes because the reduction potentials of imines and carbonyl compounds are similar,¹⁸ consequently mixtures of 1,2-amino alcohols and the symmetric 1,2-diols and 1,2-diamines are often produced. As a result, the substrate scope is significantly limited to methods which allow for a chemoselective SET to one component. The first report of cross coupling of imines in moderate to high yields employed stoichiometric NbCl₃.⁸ This reagent effectively coupled aromatic aldimines with a variety of ketones

and aldehydes, including the sterically hindered pivalaldehyde in 79% yield (dr 83:1) (Table 1, entry 1). Attempts at reductive coupling of aliphatic aldimines having α-hydrogens gave reduced yields, presumably due to isomerization of the imine to the enamine (Table 1,

Table 1. Cross Coupling of Imines.^{8,15}

Entry	Imine	Carbonyl	Reaction Conditions	Amino Alcohol	Yield (dr)
1			NbCl ₃ , THF		79% (83:1)
2			NbCl ₃ , THF		34%
3			SmI ₂ , NiCl ₂ , THF		80%

entry 2). However, in the presence of catalytic NiCl₂ coupling of *N*-benzylisobutyraldimine with acetone occurred in 80% yield (Table 1, entry 3).¹⁵ Attempts to couple activated substrates, such as benzaldehyde or aromatic imines, resulted in the formation of homocoupling products. These two examples suggest the necessity for balancing the activation of the substrates and the strength of the reductant for efficient cross coupling.

The steric bulk of the α -substituents on the imine also plays a role in substrate reactivity. Cross coupling of *N*-benzylideneaniline with diethyl ketone using lithium powder and a naphthalene catalyst yielded the corresponding amino alcohol in 75% yield. The analogous ketimine bearing an α -methyl substituent formed the cross coupling and 1,2-reduction products in 31% and 46% yield, respectively (Table 2).¹⁹ The use of electrochemical reduction significantly broadened the substrate scope of imines, allowing for the coupling of aromatic aldimines with both aliphatic and aromatic carbonyl compounds to yield amino alcohols, acyl imidazoles to yield amino ketones, and methyl acrylate to yield a γ -amino esters via 1,4-addition, all in moderate to good yields.¹¹

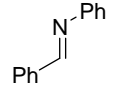
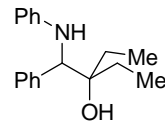
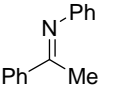
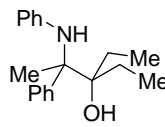
Although many 1,2-amino alcohols are accessible by imine cross coupling, it has been difficult to establish general reaction conditions that balance electronic and steric considerations appropriately. Furthermore, rate, yield, and diastereomeric selectivity vary greatly with substrate chirality,²⁰ reaction temperature,²¹ and additive.^{13, 15, 22} Homocoupling of imines and cross coupling to carbonyl compounds are both reasonably

limited to sterically unhindered aromatic aldimines and carbonyl compounds, although a few examples of low-yield coupling of aliphatic imines, ketimines, and sterically hindered substrates have been reported. Competing processes include homocoupling and imine reduction to the amine. These limitations, which prevent access to 1,2-amino alcohols and unsymmetrical 1,2-diamines, have recently been addressed by several innovative asymmetric methods.

Hydrazones and Oxime Ethers

No examples of intermolecular cross couplings of hydrazones using conventional chemical reducing reagents have been reported.¹⁰ The only cross coupling of oxime ethers reported are thus far limited to aminomethylation of aliphatic ketones with *O*-benzylformaldoxime.²³

Table 2. Imine-Ketone Cross Coupling Using Li Powder.¹⁹

2 a,b	+	Me-CH ₂ -C(=O)-CH ₂ -Me	$\xrightarrow[\text{THF}]{\text{Li powder, naphthalene (8 mol\%)}}$	3 a,b	Yield ^a
Imine				Amino Alcohol	
					75% (3%)
					31% (46%)

a. Yield of 1,2-reduction amine product in parenthesis.

Nitrones

Recently, Masson and Vallée reported that nitrones serve as versatile substrates in reductive cross coupling with ketones and aldehydes in high yield with varying degrees of diastereoselectivity using SmI₂ in THF at -78°C.²⁴ In contrast to the steric and electronic factors that limit the scope of other C=N substrates, cross coupling of nitrones is quite general, allowing for the use of aliphatic, aromatic, and sterically hindered nitrones with ketones, aldehydes, and α,β -unsaturated esters (table 3). The most impressive example of such substrate generality is the formation of a “bis-quaternary” amino alcohol (Table 3, entry 3) by the coupling of benzylcyclohexylidene amine *N*-oxide and cyclohexanone.²⁵

The cross coupling of nitrones with 1,6-ketoaldehydes compounds is chemoselective for aldehydes (Table 3, entry 2). Homocoupling and 1,2-reduction processes were not significantly competitive with cross coupling. The authors propose that the reduction proceeds through a chemoselective SET to the nitron. This mechanism is supported by several observations: in the absence of

Table 3. Samarium diiodide mediated cross coupling of nitrones.^{24,26}

Entry	Nitron	Carbonyl	Product	Yield ^a
1				93% (1:1)
2				77% (1:1)
3				80%
4				74 (>95:5) ^b
5				71%

a. Diastereomeric ratio in parenthesis. *Syn* isomer favored; b. H₂O used as an additive.

a carbonyl component, the homocoupling product was observed, cross coupling with a 1,6-dicarbonyl compounds did not yield any cyclic pinacol product, and cross coupling to ketones bearing α -cyclopropyl group yielded no ring-opened products.

In 2003, Skrydstrup and Vallée independently showed that nitrones could be reductively coupled to α,β -unsaturated esters via 1,4-addition to form substituted γ -amino acids (Table 3, entry 4),^{26,27} to α,β -unsaturated amides to form mixed α,γ -peptides,²⁶ and to propiolates to form γ -*N*-hydroxyamino- α,β -ethylenic esters (Table 3, entry 5).²⁷ In many cases, the reaction rates and yields were significantly increased with the addition of a protic additive (H₂O or *t*-BuOH). These additives, however, had no effect on couplings of α,β -unsaturated amides, presumably due to the acidic amide proton. α,β -Unsaturated esters with α -substituents, such as methacrylates, resulted in diastereomeric ratios

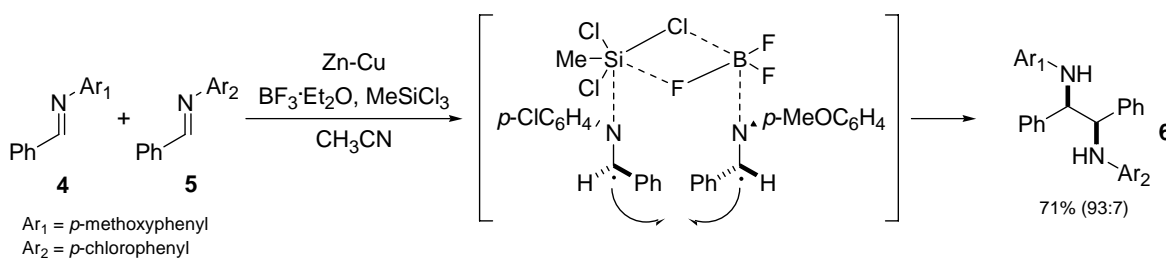
ranging from 10:1 to a single diastereomer, depending on the substitution of the nitron. Slightly lower ratios were observed for α -substituted methacrylamides (dr 7:1).

ASYMMETRIC REDUCTIVE COUPLINGS

Electronic Discrimination

Lewis acids have been applied to homocoupling reactions of imines to activate the imine and to define facial selectivity by coordination to each nitrogen, fixing the orientation of substituent bulk.^{13, 28} Shimizu and Makino developed a mixed Lewis acid system comprised of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and CH_3SiCl_3 in acetonitrile with a Zn-Cu reductant capable of differentiating between imines and aldehydes. Under these reaction conditions, *N*-benzylideneaniline was coupled to benzaldehyde to yield the *syn*-1,2-amino alcohol in 97% yield with moderate diastereoselectivity (67:35).²⁹ These conditions have also been applied to chemoselective cross coupling of imines with electron-rich (**4**) and electron-poor (**5**) aryl substituents, allowing access to synthetically important unsymmetrical *syn*-1,2-diamines³⁰ with high diastereoselectivity (Scheme 2).³¹

Scheme 2. Asymmetric Coupling of Imines.³⁰

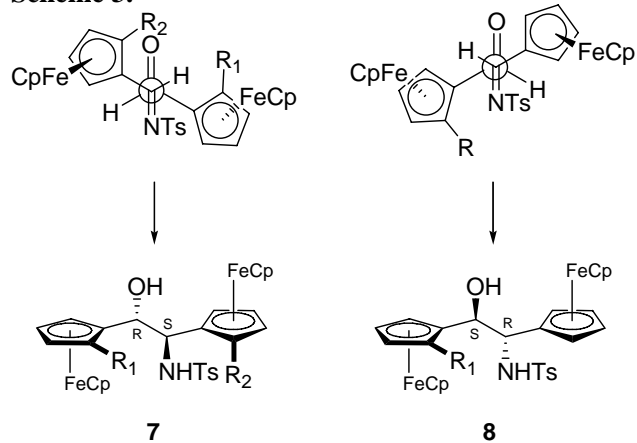


By probing the reduction potential of a series of ferrocenecarboxaldimines, Uemura found that the reduction potential could be altered by careful N-substitution.⁷ The reduction potential of ferrocenecarboxaldehyde was measured to be -2.3V, while that of the *N*-tosyl imine was decreased to -1.8V. The 0.5V difference in reduction potential allowed for chemoselective reduction of the imine over the aldehyde and the cross coupling with SmI_2/THF at 0 °C; only a trace of the pinacol product was observed ($E_{\text{Sm}^{2+}}^0 = -1.55\text{V}$).³²

Planar Chirality

In addition to chemoselectivity, Uemura also used ferrocenecarboxaldimines to engender high diastereoselectivity by exploiting planar chirality. The cross coupling of (+)-(*R*)-2-methylferrocenecarboxaldehyde and (*R*)-*N*-tosyl 2-methylferrocenyldieneamine yielded the

Scheme 3.

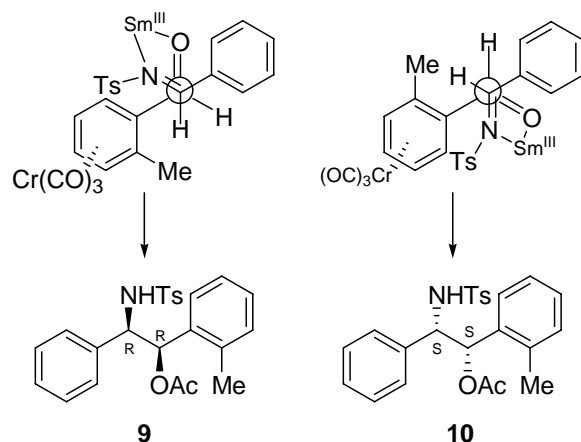


corresponding ($R_{\alpha}, S_{\alpha'}$) 1,2-amino alcohol **7** in 92% yield with 97.5:2.5 er. The stereochemistry was explained by the preferred orientation shown in Scheme 3.⁷ The ortho substituent introduces chirality into the ferrocene, which adopts the thermodynamically more stable anti conformation of the C=N bond. This conformational stability inhibits bond rotation about the ferrocene-C=N bond, providing the basis for facial selectivity imposed by the steric bulk of the ferrocene ring systems. The imine dianion and the carbonyl group align to minimize dipole-dipole repulsion, resulting in the observed anti diastereoselectivity. This transition state model was also used to explain the stereochemical outcome of cross coupling reactions of the non-planar chiral imine, which lacks an ortho substituent. The facial selectivity then becomes defined by the carboxaldehyde component, and the now achiral imine dianion effects facial discrimination to yield **8** as a single diastereomer.

A complementary approach utilizing the planar chirality of $\text{Cr}(\text{CO})_3\text{Ar}$ complexes has also been described by Uemura.^{33, 34} Cross coupling of *N*-tosyl benzaldimine and (+)-(*1S*)-*o*-methylbenzaldehyde chromium complex afforded the corresponding (*R,R*) 1,2-amino alcohol **10** in 60% yield with >99.5:0.5 er after decomplexation. In a transition state related to the previous ferrocene example, the approach of

the imine is governed by the facial selectivity of the chromium complex; however, the syn selectivity was explained by coordination of nitrogen and oxygen atoms by Sm(III), as shown in Scheme 4. Py has recently applied this approach to asymmetric cross coupling of nitrones bearing $\text{Cr}(\text{CO})_3$ complexes with acetone, cyclohexanone, pivalaldehyde and propionaldehyde, achieving high diastereoselectivities and >90% yields.³⁵

Scheme 4.



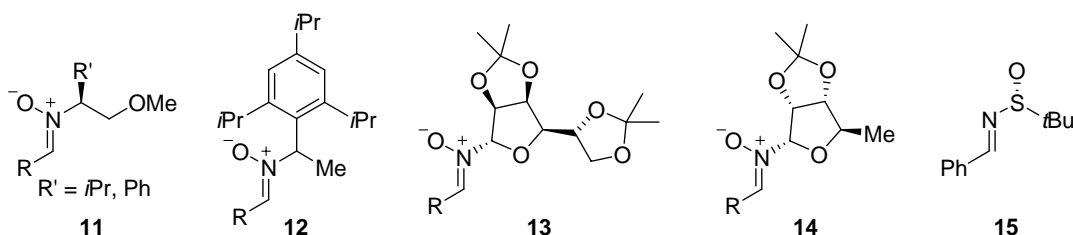
Auxiliaries

Several strategies for stereochemical control using chiral auxiliaries have been developed for conjugate coupling reactions of nitrones with acrylate/acrylamides lacking an α -substituent. Skrydstrup utilized auxiliaries attached to the acrylate or acrylamide substrates via ester and amide linkages, respectively, and was able to obtain a dr of 9:1 using (*R,S*)-*N*-methylephedrine in 70% yield.²⁶ Stereoselective couplings were achieved with nitrones bearing chiral *N*-substituents. 2-Methoxyethyl auxiliary **11** gave modest diastereomeric ratios (1.5:1 – 6:1), while the 1-(triisopropylphenyl)ethyl auxiliary **12** yielded a single diastereomer in 73% yield.²⁷ Sugar-based nitrone auxiliaries have been implemented.³⁶ Nitrones **13** and **14** derived from hydroxylamino carbohydrates were coupled to *n*-butyl acrylate, yielding single diastereomers of opposite configurations when the alkyl nitrones were

substituted at the α -position. The chiral auxiliaries of **11** and **12** were cleaved using hydrogenation conditions with concomitant reduction of the N-O bond, while the sugar-based chiral auxiliaries were cleaved by hydrolysis, each allowing access to γ -amino acids in high enantiomeric excess.

N-*tert*-Butanesulfinyl groups (**15**) have also served as chiral auxiliaries in the cross coupling of nitrones and imines to generate unsymmetrical 1,2-diamines¹⁸ in moderate to good yields with excellent diastereoselectivity. Reduced yields were obtained for sterically bulky substituents, and no reaction occurred when both nitron and imine substrates were aromatic or aliphatic. More recently, Lin has demonstrated that the reduction potential of *N*-*tert*-butanesulfinyl imines is large enough to allow chemoselective reduction and gave access to cross coupling reactions that yield 1,2-amino alcohols as single diastereomers.^{37, 38} The *t*-butylsulfinyl auxiliary was readily cleaved by acidic hydrolysis to yield enantiopure products from single diastereomers.

Chart 1. N-Substituted Chiral Auxiliaries



CONCLUSIONS

Significant development has been made since Pederson's first report of intermolecular cross coupling of imines in 1987. Much of this attention has focused on addressing the limitations of substrate scope and suppressing competing reactions. As a result, the synthesis of unsymmetrical 1,2-diamines, 1,2-amino alcohols, and γ -amino acid derivatives with high diastereoselectivity, often as enantiopure products, has been realized by a variety of high yielding asymmetric methods. These approaches have already been applied to asymmetric syntheses of taxol derivatives,³⁹ pyrrolizidine alkaloids,⁴⁰ the biologically active γ -amino acid (*R,S*)-statin,³⁷ and (*S*)-vigabatrin as a therapeutic in the treatment of epilepsy.⁴¹

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