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Reductive cross-coupling reactions (RCCR) between C=N and C=O for β-amino alcohol synthesis

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Dedicated to Professor Alain Krief, on the occasion of his retirement

Contents

1. Introduction

Vicinal amino alcohols (β-amino alcohols or 1,2-amino alcohols) are among the most important tools that chemists have used to tune the stereoselectivity of asymmetric reactions. They have been

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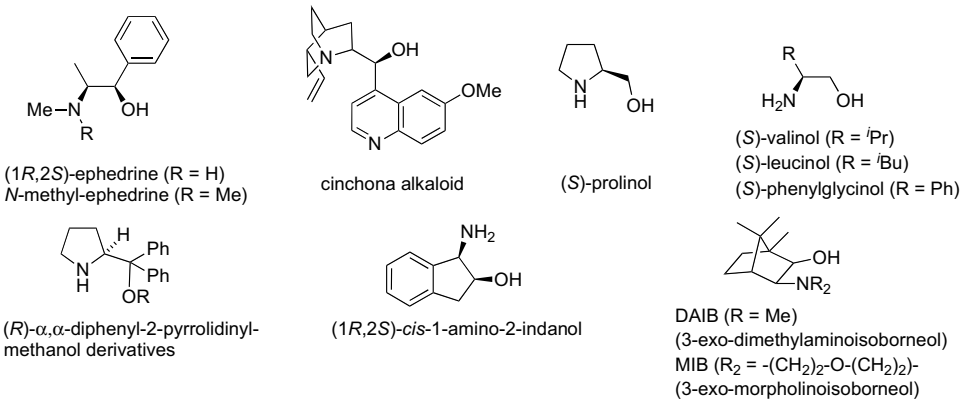


Figure 1. β-Amino alcohol catalysts or ligands from the chiral pool.

used extensively in asymmetric synthesis as chiral auxiliaries and catalysts,[1] and as precursors of chiral oxazaborolidines[2] and oxazolines.[3]

1.1. General background

Since the first developments of asymmetric synthesis, chiral β-amino alcohols have emerged as privileged motifs for chirality transfer. At the dawn of the asymmetric synthesis era, naturally occurring β-amino alcohols (such as ephedrine, *N*-methyl-ephedrine, cinchona alkaloids, …) or amino acid derivatives (prolinol, valinol, phenyglycinol) were used almost exclusively (Fig. 1).[4] Depending on the desired applications, one or both heteroatoms can bind to a Lewis acid, transition metal or achiral starting material. Initially used as accelerating ligands in reactions involving organometallic reagents,[5] chiral β-amino alcohols have also found numerous applications in organocatalysis.[6,7] In particular, α,α-disubstituted 2-pyrrolidinyl-methanol derivatives have shown a great number of applications as catalysts for different asymmetric transformations.[8] They have been successfully used in Corey–Bakshi–Shibata (CBS)[9] reduction of ketones,[10] α-arylation of aldehydes,[11] Michael addition of aldehydes to nitroalkenes,[12] Friedel–Crafts alkylation of pyrroles,[13] crossed-aldol reactions of acetaldehyde,[14] nucleophilic addition of oxazolones to α,β-unsaturated aldehydes,[15] both intermolecular[16] and transannular[17] Diels–Alder reactions, as well as domino[18] or cascade[19] transformations.

In addition, a number of natural products containing a vicinal amino alcohol moiety have demonstrated distinctive biological activities (Fig. 2). For example, the dipeptide, bestatin, containing a *syn* α-hydroxy-β-amino acid, possesses immunomodulatory activity and is clinically used as an adjuvant in cancer chemotherapy.[20] The dihydroisocoumarin AI-77-B is a unique gastroprotective agent,[21] and PM-94128 is an antitumor agent.[22] A number of biomolecules contain a β-amino alcohol moiety including the serine and threonine amino acids, as well as sphingosine, a structural component of membranes that was recently found to be involved in cell signalling.[23] Sulfobacin B, a sphingosine analogue, was demonstrated to exhibit anti-thrombotic activity.[24] Myriocin, a structurally similar lipid, has potent immunoregulatory activity.[25] Cyclic structures containing a vicinal amino alcohol moiety have also found important applications as bioactive molecules. In particular, iminosugars are a class of glyco-processing enzyme inhibitors that have found applications in anticancer, antiviral, diabetes and metabolic disease therapies.[26] Among them, anisomycin[27] and swainsonine[28] have been studied as anticancer agents, and castanospermine[29] has been a lead model for the development of the clinically used antiviral, celgosivir.[30]

The importance of vicinal amino alcohols as tools for synthetic chemists, as challenging natural targets, and as models for drug

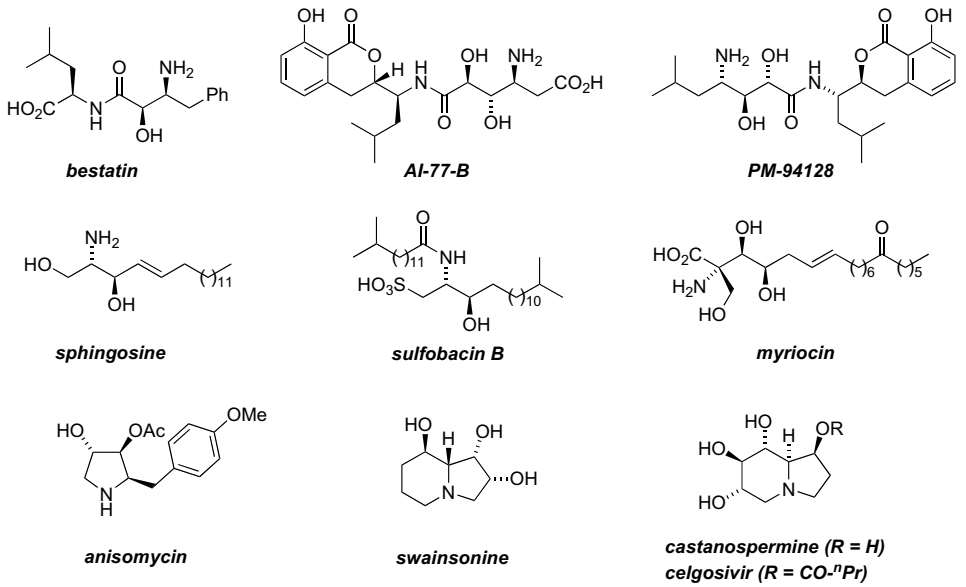
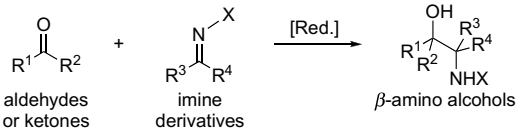


Figure 2. Examples of biologically active β-amino alcohols.

design have stimulated extensive efforts directed towards their synthesis.[1d,31] Methods have been proposed for the synthesis of their cyclic,[32] β-fluoroalkyl,[33] and long-chain[34] derivatives. The most frequent approaches have relied on the asymmetric hydrogenation of prochiral amino ketones[35] or nucleophilic additions onto α-amino carbonyl compounds.[36] Intramolecular amination of allylic alcohols using the trichloroacetimidate technology has also proved useful in many cases.[37] Finally, the discovery of Sharpless aminohydroxylation of alkenes represents an important breakthrough in the stereoselective synthesis of β-amino alcohols.[38] Herein, we wish to survey the approaches that gave access to amino alcohols by reductive cross-coupling reactions of imine derivatives with carbonyl compounds.

1.2. Scope

In the search for novel amino alcohol structures of large diversity and increased complexity, methods involving the creation of a C–C bond between the amine and alcohol functionalities are particularly attractive. These imply the reaction of imino compounds with carbonyl compounds (Scheme 1), and require activation of at least one of the partners, in order to reverse its original electrophilicity at the α-carbon atom into nucleophilicity (*umpolung*). Alternatively, both partners can be activated by single-electron transfer to produce open-shell species that can combine to produce, after protonation, β-amino alcohols.



Scheme 1. Reductive cross-coupling reactions for β-amino alcohol synthesis.

The reductive cross-coupling reaction of imine derivatives and carbonyl compounds appears to be particularly adequate for the generation of a large variety of vicinal amino alcohols. However, this reaction has been much less developed than the homocoupling of imines[39] (producing vicinal diamines[40]) or that of carbonyl compounds (pinacol coupling),[41] due to selectivity issues and to the possible occurrence of competing homocoupling side reactions. In this report, we wish to present the different approaches that have been reported to induce selective cross-coupling reactions of imines, iminium salts, oximes hydrazones, and nitrones with aldehydes or ketones (Scheme 2).

1.3. Mechanistic issues

Depending on the substrates and the reaction conditions, different mechanisms have been proposed for these reductive coupling reactions. Some processes have been considered as radical processes (Scheme 3, Eqs. 1 and 3), while others have been suggested to involve more or less ionic 'organometallic' intermediates (Scheme 3, Eqs. 2 and 4), depending on the conditions used to promote electron transfer.

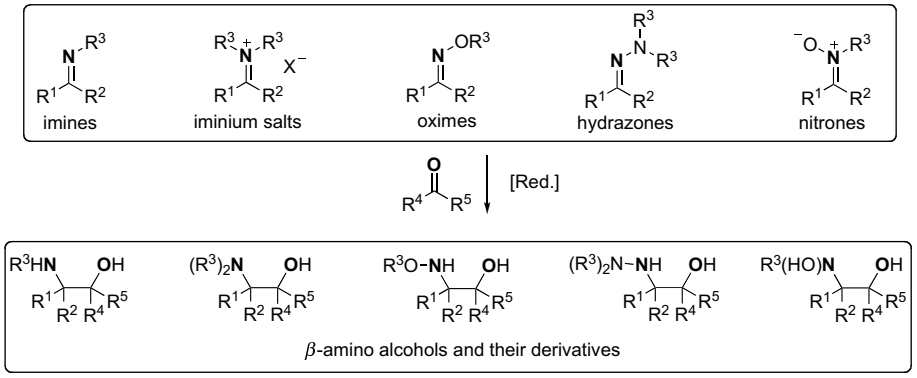
In some cases, initial reduction of a carbonyl partner followed by addition of the resulting intermediate (ketyl radical or dianion) onto a C=N group was assumed (Scheme 3, pathway a). In others, initial reduction of a C=N group and addition of the resulting intermediate onto a C=O group was postulated (Scheme 3, pathway b). Furthermore, it is not always clear if the bond-forming process involves the coupling of two radicals, the addition of a radical on a C=X π-bond, or the addition of an ionic 'organometallic-type nucleophile' to a C=X π-bond.

If intermediate ketyl radical anions are involved, the C=N groups can thus be considered as radical acceptors and, for this reason, some examples of reductive coupling reactions involving such partners have already been surveyed in previous *Tetrahedron Reports* by Fallis[42] and Friestad,[43] that covered the addition of carbon-centered radicals to imines and related compounds.

As mentioned previously, the reductive cross-coupling reactions described herein always imply activation of at least one of the substrates by electron transfer. In the following sections, the methods described for β-amino alcohol syntheses will be presented according to the conditions used to induce the initial electron transfer, i.e., cathodic electroreduction, use of metals, use of tributyltin hydride and, finally, use of samarium diiodide as reducing agents.

2. Electroreductive cross-coupling reactions (CCR)

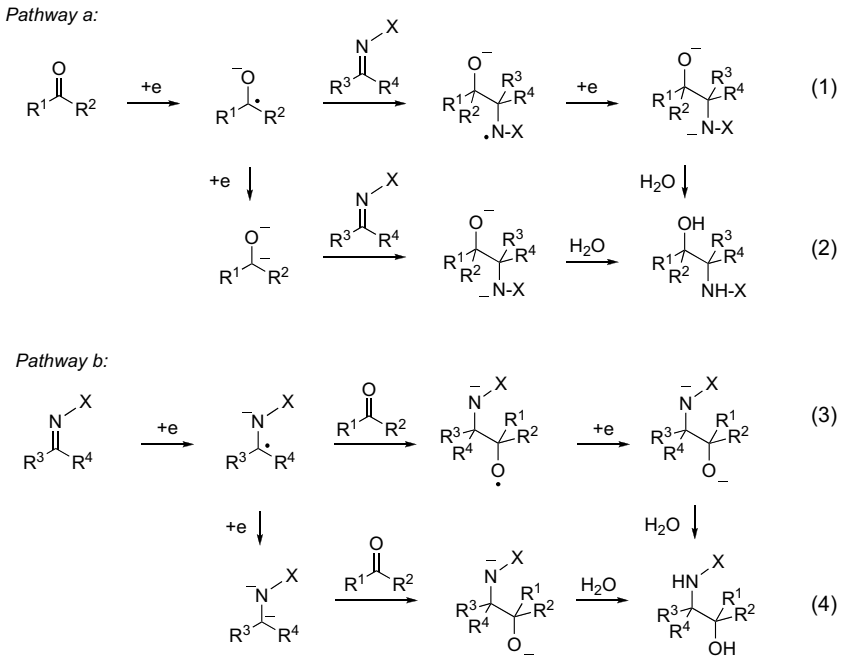
Since the pioneering work of Kolbe,[44] organic electrochemistry has emerged as a powerful tool, both for functional group interconversions and for C–C bond-forming reactions.[45] A renewed interest has recently arisen, as electrosynthesis is being recognized as an effective, non-residue-producing method to induce chemical



Scheme 2. Reductive coupling reactions covered in this review.

Examples illustrated in the schemes have been selected in a manner that we considered to be the most representative of the generality of the discussed process. The number of examples described in the primary literature is given, as well as the range of yields and indications of the stereoselectivity, to facilitate comparisons and synthetic planning. Whenever possible, mechanistic issues are discussed.

reactions by electron transfer.[46] In electroreductive reactions, electrons generated at a cathode are trapped by organic substrates in solution, that further evolve towards the products either by C–C

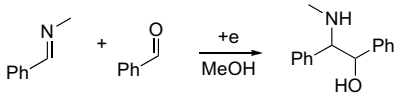


Scheme 3. Mechanistic proposals for imino-pinacol cross-coupling reactions.

bond formation or by protonation. Herein, the electroreductive cross-coupling reactions of carbonyl compounds with 'acyclic' imines, in non-acidic media, will be presented separately from those involving pyridinium salts as the C=N partner.

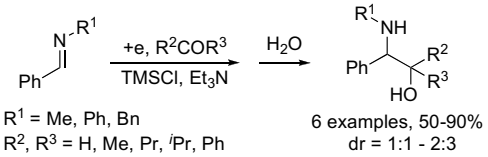
2.1. Electroreductive CCR of carbonyl compounds and acyclic imine derivatives

Although the cathodic behaviour of imine derivatives has been well studied,[47] examples of electroreductive cross-coupling reactions involving both C=N and C=O functionalities are not numerous. The cross-coupling reaction between *N*-methyl benzylidene amine (**1**) and benzaldehyde (**2**) has been first reported in 1975, to produce *N*-methyl-1,2-diphenyl-2-amino-ethanol (**3**) (Scheme 4).[48]



Scheme 4.

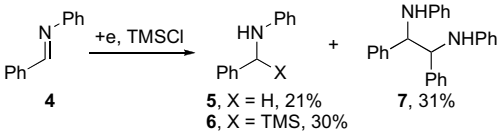
Next, the electroreductive cross coupling of imine derivatives with carbonyl compounds was mostly explored by Shono's group, who exemplified the coupling reaction of *C*-aromatic imines with aldehydes or ketones, to afford 2-amino alcohols in moderate-to-good yields (Scheme 5).[49] However, *C*-aliphatic imines are not appropriate substrates in this transformation, thus limiting its generality. The reaction procedure involved the application of a constant current of 0.2 A until consumption of the starting imines



Scheme 5.

had been achieved (4–5 F/mol), and required a 3-fold excess of chlorotrimethylsilane (TMSCl) and triethylamine.

If TMSCl was omitted from the reaction mixture, only the reduced amine **5** (X=H, see Scheme 6) was obtained in more than 90% yield after electroreduction of a mixture of *N*-phenyl benzylidene imine (**4**) and a carbonyl compound.



Scheme 6.

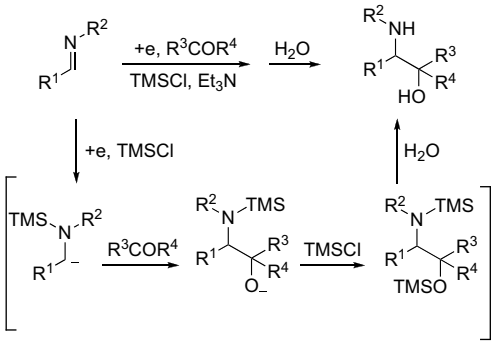
When electroreduction of *N*-phenyl benzylidene imine (**4**) was carried out in the absence of an electrophile, the α-trimethylsilyl amine **6** (X=TMS) was obtained, together with the reduced amine **5** (X=H) and the homo-coupling product **7** (Scheme 6).

These results led to the assumption that *C*-aromatic imines are electrochemically reducible under the reaction conditions, but not *C*-aliphatic imines. The authors thus postulated that such electroreductive cross-coupling reactions were initiated by electron transfer(s) to the imine derivatives and *N*-silylation; subsequent reaction of the resulting anion with the carbonyl partners would lead to the products, after protonation and hydrolysis of the silyl groups (Scheme 7).[49]

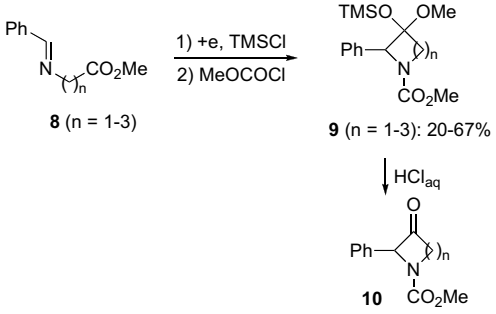
Under similar reaction conditions, imino esters **8** afforded cyclized products **9**, which were easily hydrolyzed to the corresponding ketones **10** (Scheme 8).[49]

Interestingly, the *C*-aromatic chiral imino ester **11**, prepared from L-valine methyl ester, was also electrocyclized to the azetidine **12**, stereoselectively.[49] The enantiomeric excess of **12** was determined to be 85%. The relative configurations in **12** were assigned from NOE enhancement. The high stereoselectivity was explained by the fact that both the phenyl and isopropyl groups are equatorial in the most stable intermediate **A** (Scheme 9).

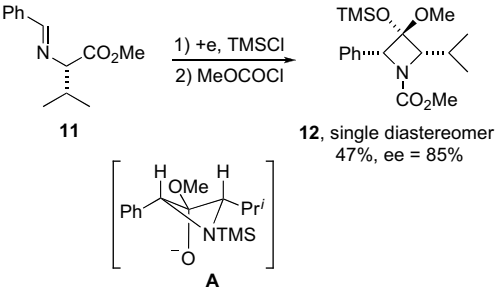
Later, Shono's group extended this synthetic approach and demonstrated highly efficient reductive cross-coupling of ketones



Scheme 7.

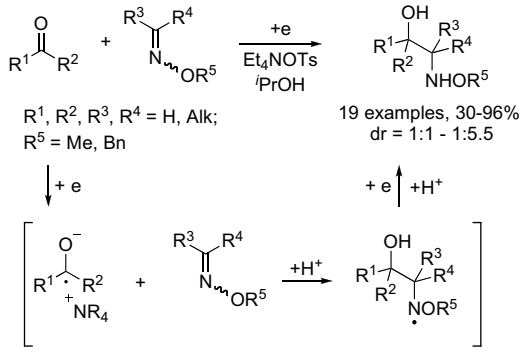


Scheme 8.



Scheme 9.

with several types of *C*-aliphatic imine derivatives, such as oxime ethers, *N*,*N*-dimethylhydrazones, and nitrones.[50] For example, aldoxime and ketoxime methyl or benzyl ethers have been reacted with a variety of aliphatic ketones under electroreductive conditions, to afford the corresponding β-alkoxyamino alcohols (Scheme 10). The electroreduction was carried out with an Sn cathode in a catholyte of ^{i}PrOH containing Et_4NOTs under a constant current of



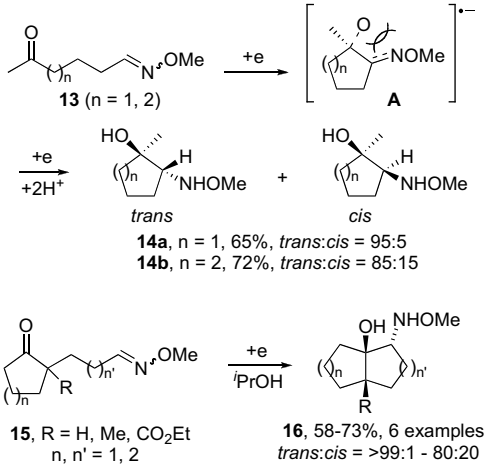
Scheme 10.

0.2 A. Electroreduction with a Pb or Cd cathode gave similar results as with an Sn cathode, whereas a cathode made of Ag, Cu, Zn, or C-fiber gave a somewhat lower conversion, and no reduction occurred with a Pt cathode. The yields decreased when the coupling was performed in EtOH, ^{t}BuOH, or DMF. The effect of the cationic part of the supporting electrolyte is interesting: tetraalkylammonium salts such as Et_4NOTs and Et_4NClO_4 have been shown to be essential for the electroreductive coupling, whereas only reduction of the ketone partners to alcohols took place when $LiClO_4$ was used as the electrolyte.

The reductive coupling reactions of *O*-methyl and *O*-benzyl aldoximes (Scheme 10; R^3=H, R^4=Alk, R^5=Me or Bn) with ketones afforded the coupling products in very high yields, whereas those involving *O*-methyl ketoximes (R^3, R^4=Alk, R^5=Me) gave comparatively low yields of the desired products.

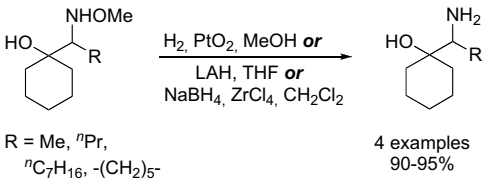
With regard to a possible reaction mechanism, the authors proposed in this case the initial formation of anion radicals from aliphatic ketones that would add to oximes (Scheme 10). A second one-electron transfer and protonation would subsequently yield β-alkoxyamino alcohols. The initial reduction of the carbonyl partners was supported by the fact that *O*-methyl oximes were not electrochemically reducible under the same reaction conditions (Sn cathode in ^{i}PrOH containing Et_4NOTs). This coupling reaction was effective in protic solvents such as ^{i}PrOH and was not hampered by the addition of 1 equiv of water in the reaction mixture. The authors were thus to propose radical rather than anionic species to be the key active intermediates in this RCCR.[51]

In a similar manner to that of *C*-aromatic imino esters, the intramolecular version of the electroreductive coupling between aliphatic ketones and *O*-methyl oximes provided cyclic β-methoxyamino alcohols in good yields and excellent diastereoselectivity.[50] Thus, the electroreduction of linear δ- or ε-keto *O*-methyl oximes **13**, carried out under the same conditions as for the intermolecular coupling reactions, gave the corresponding five- and six-membered cyclic products **14a**,**b** as mixtures of diastereomers (Scheme 11). The trans-selectivity was explained by the electronic repulsion between negative charges on the oxygen and nitrogen atoms in the intermediate **A**. Starting from the cyclic keto-oximes **15**, intramolecular coupling provided bicyclic hydroxyl-methoxyamines **16** in preparative yields. In all cases, the configuration of the major isomers was determined to be trans (Scheme 11).



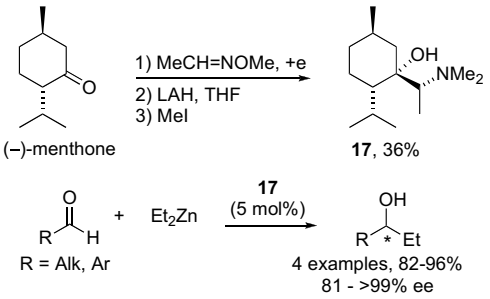
Scheme 11.

Shono et al. also showed that the coupling products can be easily converted into the corresponding β-amino alcohols by reduction, and that three different methods are efficient for cleavage of the *N*-methoxy group (Scheme 12).



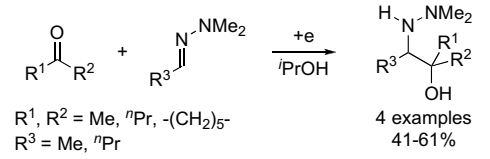
Scheme 12.

This methodology was applied to the intermolecular cross coupling of (−)-menthone and *O*-methylacetaldoxime, followed by reduction, to obtain the chiral ligand **17**, useful for the enantioselective addition of diethylzinc to aldehydes (Scheme 13).[50] Interestingly, although four diastereoisomers might have been formed in this heterocoupling reaction, only two were actually obtained. The major isomer (85:15) was transformed into β-*N*,*N*-dimethylamino alcohol **17** by reduction with LAH and methylation. Several chiral secondary alcohols could be obtained in excellent yields and high enantioselectivity when the addition of diethylzinc to aldehydes was carried out in the presence of a catalytic amount of **17**.



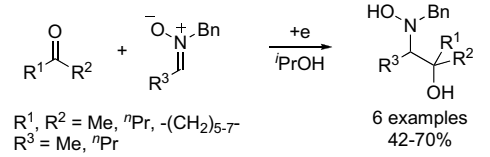
Scheme 13.

Hydrazones and nitrones have also been involved in electroreductive coupling reactions with ketones, but in these cases the number of examples is fewer when compared to oximes.[50] Electroreduction of a mixture of ketones and *N*,*N*-dimethylhydrazones carried out with an Sn cathode in ^{i}PrOH afforded β-hydrazino alcohols in moderate yields (Scheme 14).



Scheme 14.

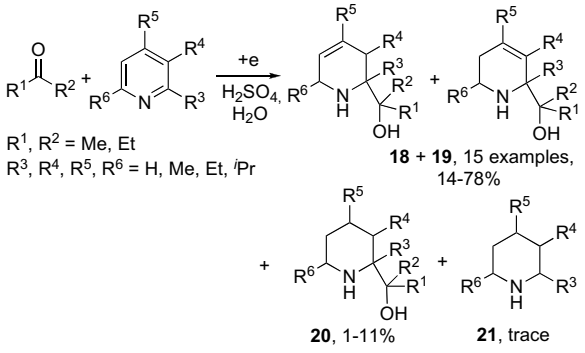
Similar electroreductive cross coupling of symmetrical aliphatic ketones with aldonitrones resulted in the formation of β-*N*-hydroxyamino alcohols (Scheme 15). By analogy with the electroreductive cross coupling of ketones with oxime ethers, the mechanism of these reactions was proposed to proceed via the addition of ketyl anion radicals, arising from aliphatic ketones, to hydrazones or nitrones.



Scheme 15.

2.2. Electroreductive CCR of carbonyl compounds and pyridinium salts

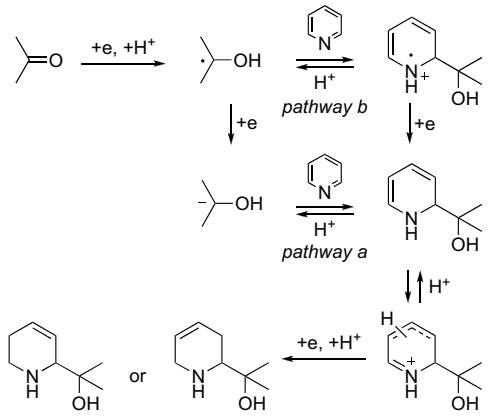
Electroreductive cross-coupling reactions of aliphatic ketones with protonated pyridines were first described by Nonaka's group.[52] Efficient hetero-coupling generally occurred when using substrate couples so that, in a defined set of electrolytic conditions, one is reduced to form an active intermediate, while the other is not reducible and acts as an electrophilic acceptor of the intermediate. The supporting electrolyte was shown to play a crucial role in this process. Using aqueous sulfuric acid as the electrolyte, a mercury cathode and a platinum disc anode and applying a controlled cathode potential of −1.30 V, an efficient cross coupling of ketones and pyridine derivatives was demonstrated (Scheme 16).[53] The products were mixtures of two isomers (**18** and **19**) and a small amount of 2-piperidinyldialkylcarbinol **20**. Isomers **18** and **19** could not be separated either by gas chromatography or by fractional distillation. Traces of piperidine **21** were by-produced only at a considerably negative potential (around −1.40 V), as the reduction potential of pyridine (−1.35 V vs SCE) is more negative than that of acetone in aqueous sulfuric acid. In the case of non-substituted pyridine and mono-substituted derivatives, the efficiency of the reductive cross coupling leading to **18** and **19** was good, but it markedly decreased for polysubstituted alkylpyridines, while a considerable amount of alcohol (R^1R^2CHOH) was formed. This was explained by the effect of steric hindrance. No cross-coupling product was isolated when amino-pyridines (R^3 or R^4 or R^5=NH_2) were used as substrates. The reaction of pyridine derivatives with aldehydes was shown to be less efficient than with ketones, the cross-coupling products consisting of a number of hydropyridine derivatives bearing one, two, or three alkyl and/or α-hydroxyalkyl substituents on the pyridine ring.



Scheme 16.

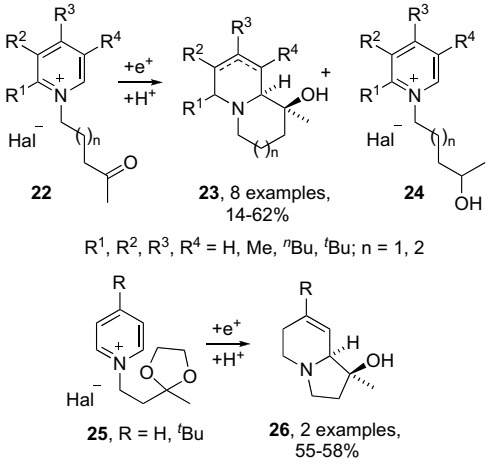
The mechanism of these reactions was at first proposed to involve the formation of anionic species derived from the carbonyl compounds, that would undergo nucleophilic addition to activated pyridine derivatives (Scheme 17, pathway a).[53] However, because these cross-coupling reactions proceeded favourably only in a strongly acidic medium, a radical mechanism for this process (Scheme 17, pathway b) was subsequently put forward.[54] The formation of an anionic intermediate derived from acetone was also excluded, since no occurrence of the coupling of acetone with a polar acetylenic triple bond compound adsorbed on the cathode was observed.

An intramolecular version of the cathodic cross coupling between a ketone and a pyridinium salt, en route to heterobicyclic systems, was presented by Schäfer et al.[55] In this work, oxoalkylpyridinium halides **22** (readily available by nucleophilic substitution of halogenated ketones with pyridines) could be cyclized under mild electroreductive conditions, as the arene is activated for the reduction by quaternization of its nitrogen atom (Scheme 18).



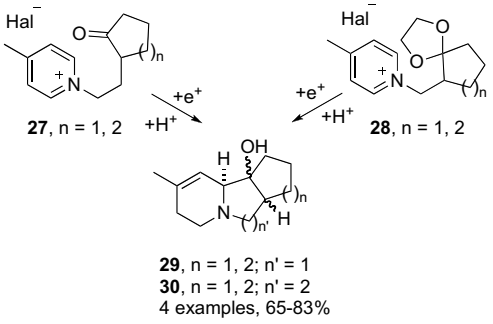
Scheme 17.

The potential-controlled electrolysis of **22** at −1.37 V (relative to SCE) in 10% aqueous sulfuric acid resulted in the formation of **23** (quinolizines for n=1 and octahydropyrido[1,2-*a*]azepines for n=2), and small amounts of the corresponding alcohols **24**. In all cases, two isomers (differing by the position of their double bond) of **23** were obtained and these could not always be separated by liquid chromatography. Of related interest is the reductive cyclization of **25**, which led to the indolizine **26** as a single diastereomer (Scheme 18).



Scheme 18.

Further expanding the scope of this reaction, the cathodic cyclization of *N*-(oxoalkyl)pyridinium salts **27** and **28**, derived from 4-methylpyridine and cyclic ketones, afforded functionalized indolizidines **29** (n'=1) and quinolizidines **30** (n'=2) in high yields (Scheme 19).[56] By a variation of the ring size and the



Scheme 19.

length of the chain linking the coupling partners, a series of tricyclic products was obtained as mixtures of separable diastereomers. This work is significant in that the pyridinium salts are easily available, they do not need to be purified, and they were fully converted into cyclised products. Another advantage of the method lies in the use of aqueous sulfuric acid as the solvent, so that no supplementary supporting electrolyte is needed, thus facilitating the workup procedures. The proposed mechanism for this transformation involves the reversible addition of a hydroxyalkyl radical intermediate to the pyridinium ring (Scheme 17, pathway b).

Electrochemical methods have thus allowed the successful intermolecular and intramolecular cross coupling of carbonyl compounds with imines and pyridine derivatives, to yield β-amino alcohols. Electro-induced intramolecular RCCR generally produced cyclic products in good yields and with good stereoselectivities in favour of the *trans* β-amino alcohols. However, maybe because organic chemists have a tendency to overestimate the difficulties in setting up electrochemical experiments, these methods have not been widely used in synthetic organic chemistry. This is unfortunate, especially since the required equipment is neither rare nor extremely expensive.

3. Metal-mediated reductive cross-coupling reactions

Besides electrochemical reductions, a large range of reductive reactions in organic chemistry have been mediated by the use of metals as electron donors. The metals that have been mostly used in such applications are those that are easily oxidized. Two types of metals fall into this class:

- the alkali and alkaline earth metals (in particular Li, Na, K, Mg) which have been widely used as reducing agents, as well as Zn, a late transition metal: these metals share in common a high propensity to donate one or two electrons in order to accommodate a complete valence shell;
- the low-valent transition metals (columns IV and V of the periodic table) like Ti, Zr, V, Nb or Ta.

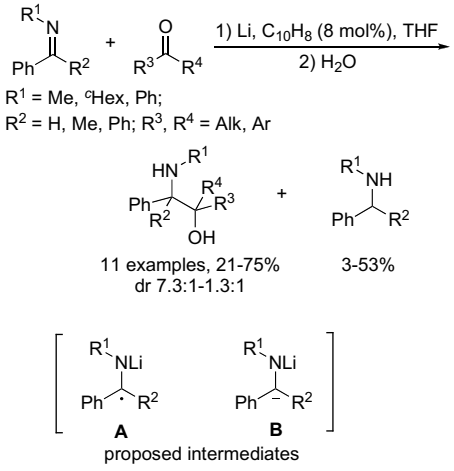
In the following sections, the methods involving metal-induced reductive cross coupling of imine derivatives and carbonyl compounds to access β-amino alcohols will be surveyed.

3.1. RCCR mediated by Li, Mg, and Zn

The preparation of vicinal diamines by homo-coupling of imines in the presence of lithium, sodium or magnesium as reducing agents has been known for a long time.[57] In contrast, hetero-coupling of imines with carbonyl compounds using these metals has not been extensively developed. Alkali and rare earth alkali metals often exhibit strong reducing power ($E^{\circ}_{(Li+/Li0)}$=−3.05 V; $E^{\circ}_{(Mg++/Mg0)}$=−2.67 V)[58] that may impede chemoselectivity and lead to a mixture of products.

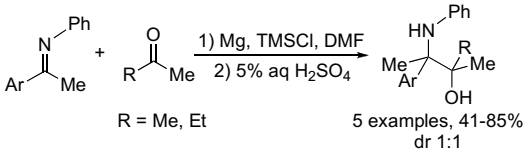
The reductive cross coupling of *C*-aromatic imines with aldehydes and ketones was effected upon treatment of mixtures of these substrates with an excess of lithium powder, in the presence of catalytic amounts of naphthalene (Scheme 20).[59] The in situ reaction of lithiated imines with carbonyl compounds in a Barbier-type process provided β-amino alcohols in moderate yields. Variable amounts of amines resulting from the reduction and protonation of the starting imines were always formed, together with the desired products. The proposed mechanism involves an electron transfer from lithium naphthalenide to the imine, giving successively the intermediate species **A** and **B**. Intermediate **B** would either react with the carbonyl compounds or trap a proton from the reaction medium (probably from the α-position of the

carbonyl group). However, the unavoidable side formation of amines and other by-products arising from homo-coupling of the starting imines may lessen the interest of this method for practical synthetic use.



Scheme 20.

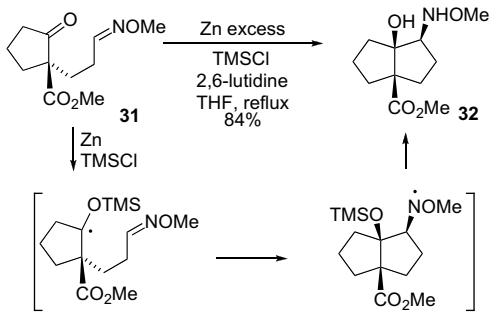
Magnesium, originally used for pinacol coupling of carbonyl compounds, is also effective in inducing the cross coupling of *C*-aromatic (or *C*-hetero-aromatic) imines and aliphatic carbonyl compounds, albeit with no diastereoselectivity (Scheme 21).[60] It was suggested that the reaction might be initiated by electron transfer from Mg metal to the imino group of acetophenone imines, as their reduction potentials (E_p=−2.04 to −2.24 V vs Ag/AgCl) are less negative in comparison with those of aliphatic carbonyl compounds and TMSCl (E_p=more negative than −3.00 V). Addition of TMSCl was essential for the reactions to proceed smoothly, possibly through continuous activation of the Mg surface.



Scheme 21.

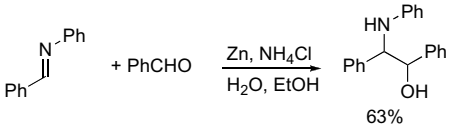
Among the zero-valent metals that have been used as reductants in organic synthesis, zinc is probably the cheapest and the most user friendly. Recognized a long time ago as a versatile reductant by Clemmensen,[61] zinc ($E^{\circ}_{(Zn++/Zn0)}$=−1.22 V)[58] was used over the years in many reductive processes, including reductive homo- and hetero-coupling reactions. The first example of metal-induced RCCR involving C=N and C=O groups was reported by Corey and Pyne in 1983.[62] In their pioneering work on intramolecular 'aza-pinacolic' coupling, δ-oxo oximes were shown to undergo reductive cyclization upon treatment with zinc powder, in the presence of trimethylsilyl chloride. The authors suggested that the zinc–TMSCl system would induce electron transfer and silylation of the ketone to produce an α-trimethylsilyloxy radical, which would add to the δ,ε-C=N group, thus forming a 5-membered ring cyclic species (Scheme 22). The radical resulting from cyclization would then be trapped by H-atom abstraction from the solvent and the TMS ether would hydrolyse in the work-up process. For example, through this Zn-induced intramolecular coupling, the chiral oxime **31** was transformed into the bicyclic product **32** in good yield.

More recently, an intermolecular reductive cross coupling of *N*-benzylidene aniline and benzaldehyde was achieved in an aqueous



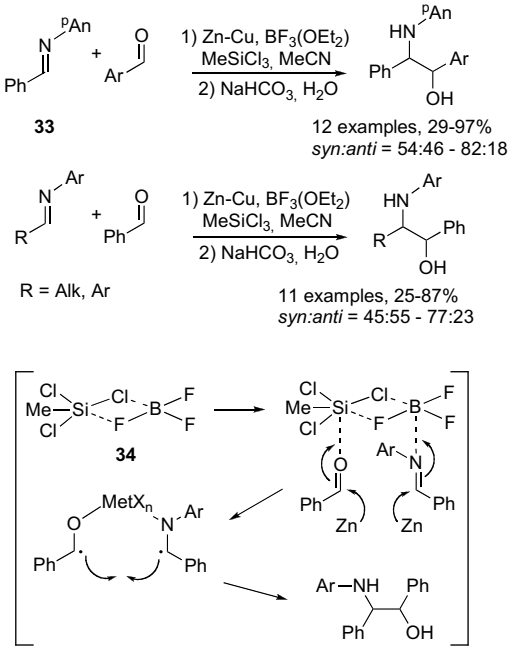
Scheme 22.

medium, by using zinc powder and NH_4Cl as an additive (Scheme 23).[63] The authors underlined the advantages of this non-moisture-sensitive method in terms of cost, safety, ease of handling and environmental concerns. However, their study focussed on the homo-coupling of imines, and the general character (and the eventual stereoselectivity) of the cross-coupling reaction of imines and carbonyl compounds was not demonstrated, since only a single example was reported.



Scheme 23.

Shimizu and co-workers have also reported a Zn-induced cross coupling of various aldimines and aldehydes using zinc, boron trifluoride etherate, and methyltrichlorosilane.[64] A range of aromatic aldehydes was used in cross-coupling reactions with *N*-benzylidene *p*-anisidine (**33**). The reaction of benzaldehyde with various imines was also investigated (Scheme 24). The corresponding β-amino alcohols were obtained in moderate-to-excellent yields. The reaction of **33** with aliphatic aldehydes did not result in β-amino alcohols. Generally, the moderate yields of



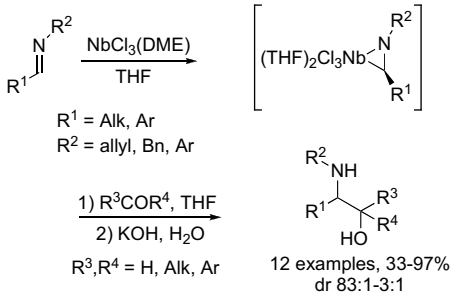
Scheme 24.

cross-coupling products (β-amino alcohols) were due to homo-coupling side reactions, as well as reduction of the starting imines. According to the authors, a possible reaction mechanism would involve the formation of a bimetallic complex **34** from boron trifluoride etherate and methyltrichlorosilane. Coordination of both the aldehyde and the imine to **34**, followed by zinc-mediated reduction of the resulting intermediate via an SET mechanism and subsequent coupling of the radical species, would afford the β-amino alcohols.

Although its diastereoselectivity was not high, this reaction offered an operationally simple and general method for the synthesis of 1,2-diaryl β-amino alcohols.

3.2. RCCR mediated by Nb, Zr, Ta, and Ti

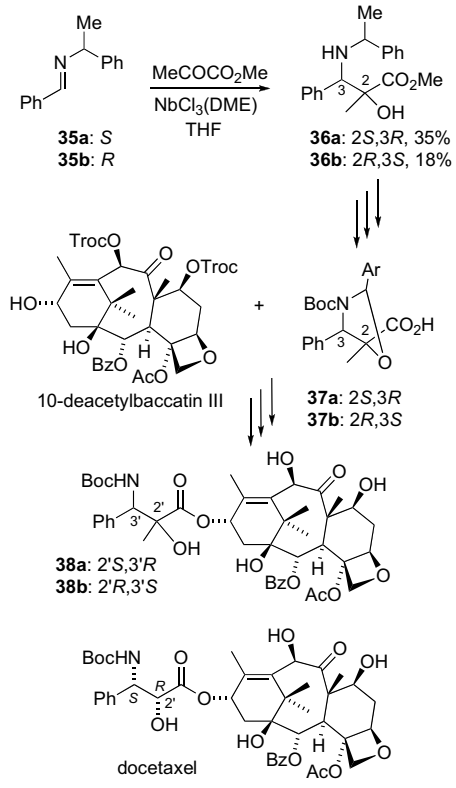
In 1987, Pedersen and Roskamp reported the first *intermolecular* coupling of *C*-aryl or *C*-alkyl imines with aldehydes or ketones, yielding β-amino alcohols from a large variety of substrates.[65] The reaction was promoted by a low-valent niobium complex, $NbCl_3(DME)$, that was obtained and used in organic synthesis for the first time. Reaction of this reagent with imines was suggested to produce metalla-aziridine intermediates, that would react with carbonyl compounds via coordination and insertion into the metal–carbon bond (Scheme 25). The resulting β-amino alcohols were obtained in moderate-to-excellent yields and with good diastereoselectivities. The reactions with aldehydes were *syn* (*threo*) selective. Lower yields were observed with enolisable imines (R^1=CH_2CH_2Ph, 33% yield). The simplicity of the $NbCl_3(DME)$ preparation and storage makes this a useful and quite general method for the rapid assembly of the β-amino alcohols from readily available starting materials.



Scheme 25.

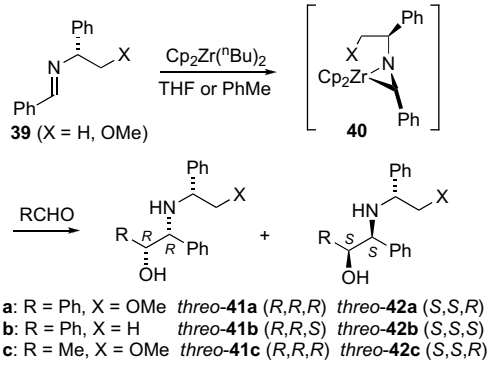
The synthetic utility of this Nb^{III}-induced RCCR was demonstrated by Greene and co-workers, who applied it as the key step for the synthesis of the side chain of docetaxel analogues possessing anticancer activity.[66] Starting from (*S*)- or (*R*)-*N*-benzylidene-1-phenyl-ethylamines (**35a**,**b**) and methyl pyruvate, they obtained chiral β-amino alcohols **36a** and **36b** in moderate yields, but in enantiopure form (Scheme 26). After several steps, both isomers were converted into the free acids **37a** and **37b**, the esterification of which with protected 10-deacetylbaccatin III provided the C-2 methylated analogues of docetaxel **38a**,**b**. (2′*R*,3′*S*)-2′-Methyl-docetaxel **38b** exhibits a significantly greater cytotoxicity (KB-VI cells) and better inhibitory activity in microtubule depolymerization assays than docetaxel (Taxotere®).

Chiral *C*-aromatic aldimines **39** were shown to undergo zirconium-induced cross-coupling reactions with aldehydes, to afford exclusively the *syn* amino alcohols **41a–c** and **42a–c** (Scheme 27).[67] This transformation was presumed to also involve a metalla-aziridine intermediate, as in the case of the niobium-mediated reaction. Zircona-aziridines **40** were supposed to be formed in situ by the reaction of imines **39** with the putative zirconocene ('Cp_2Zr'). As



Scheme 26.

in the niobium-mediated reactions, the subsequent cross-coupling reactions were *syn* (*threo*) selective. Interestingly, the authors showed a remarkable temperature effect on the sense asymmetric induction by the chiral auxiliaries: the ratio of the two possible *threo* isomers can be excellent, and the major isomer depends on the reaction temperature (Table 1).

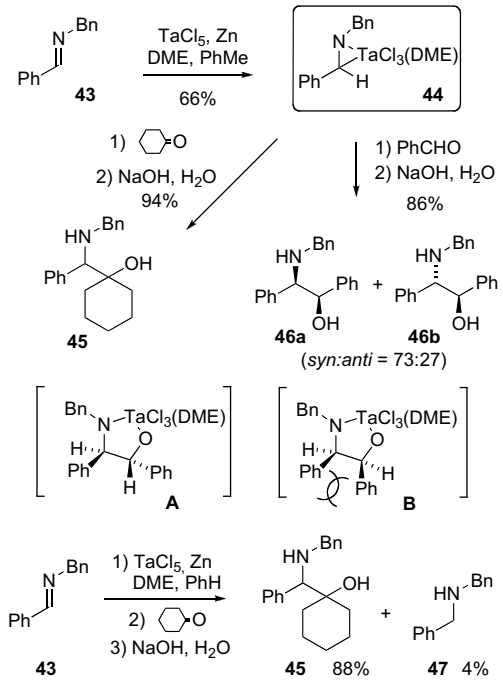


Scheme 27.

Table 1
Zirconium-induced cross coupling of *C*-aromatic aldimines **39** with aldehydes

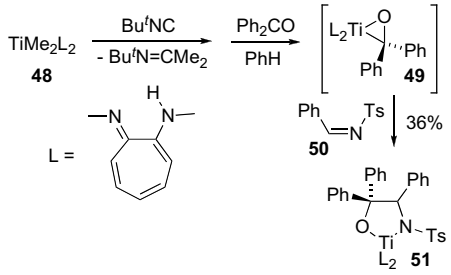
R	X	Solvent	Temperature (°C)	Yield (%)	**41**/**42**
Ph	OMe	THF	0	75	94/6
Ph	OMe	THF	66	84	5/95
Ph	OMe	Toluene	23	83	88/12
Ph	OMe	Toluene	60	80	4/96
Ph	H	THF	23	70	97/3
Ph	H	THF	66	77	64/36
Me	OMe	Toluene	23	50	87/13
Me	OMe	Toluene	60	35	5/95

The formation of metalla-aziridines was unambiguously demonstrated by the group of Takai, who succeeded in characterizing the tantala-aziridine **44**, formed upon treatment of *N*-benzyl benzylidene imine (**43**) with a low-valent tantalum species generated from the reduction of $TaCl_5$ by Zn (Scheme 28).[68] The tantalum–imine complex **44** was isolated as dark red crystals in 66% yield and was characterized by crystallography. Reaction of **44** with cyclohexanone or benzaldehyde afforded the coupling products **45** and **46a**,**b**, respectively, in excellent yields. In the case of benzaldehyde, the observed *syn* selectivity was explained by the aldehyde approaching **44** to form a tantalacycle **A** that is less hindered than **B**. The coupling of *N*-benzyl benzylidene imine (**43**) with cyclohexanone could also be accomplished without isolation of the intermediate **44**, to afford β-amino alcohol **45** in 88% yield, along with 4% dibenzylamine (**47**).



Scheme 28.

Finally, titanium reagents have been employed as reductants for the cross-coupling reaction of *N*-tosyl benzylidene imine (**50**) with benzophenone (Scheme 29).[69] At first, treatment of $TiMe_2L_2$ **48** (L=*N*,*N*′-dimethylamino troponiminate) with *tert*-butyl isocyanide led to the elimination of *N*-*tert*-butyl acetonimine and formation of a low-valent titanium species, which is trapped by benzophenone. Insertion of imine **50** into the η^2-carbonyl complex **49** would then result in the formation of a titanium amido-alkoxide **51**. This complex **51** was isolated and its structure



Scheme 29.

established by crystallographic analysis. It should be emphasized that the insertion of an imine into η^2-carbonyl complexes is not common. This mechanism contrasts with the other related metal-mediated processes, that were supposed to rather involve insertion of carbonyl compounds into (niobium[65] or zirconium[67]) η^2-imine complexes.

Porta and co-workers proposed another low-valent titanium-mediated RCCR which was applied to the synthesis of β-amino-α-hydroxyesters.[70] Treatment of a solution containing equimolar amounts of methyl phenylglyoxylate (**52**), an aromatic aldehyde and aniline with $TiCl_3$ resulted in the formation of *syn* β-amino-α-hydroxyesters **53** in good yields (Scheme 30). The only by-products were dimethyl diphenyltartrate (**54**) and methyl mandelate (**55**). Mechanistically, the first step of the reaction was suggested to be the formation of radical **A** followed by dimerization to a Ti^{IV}-chelated diol **B**, via a single-electron process. A sequential Ti^{IV}-catalyzed intramolecular heterolytic cleavage of **B** then regenerates **52**, which is reduced back to **B** by the excess of Ti^{III}, and forms the stabilized Ti^{IV}-ene diolate **C**. The latter is assumed to be the reactive intermediate in the formation of **53**. The Ti^{IV}-enolate **C**, once formed, can be oxidized via a metal-to-ligand electron transfer to the stabilized capto-dative radical **A**.

Suprisingly, when this reaction was carried out with preformed arylimines, lower yields than in the tricomponent condensation were observed. The larger proportions of dimer **54** (17–34%) obtained in this two-step variant of the reaction seem to indicate that the imine, when present at higher concentration than that generated under equilibrium conditions (Scheme 31), may irreversibly form a complex with Ti^{IV}, thereby hampering formation of the chelate complex **B**, a prerequisite for the heterolytic cleavage to occur. Ti^{III} is a highly specific catalyst for these tricomponent reactions as it can perform, almost uniquely, three functions: (a) as a reducing agent it promotes the one-electron dimerization of **52**, (b) in its higher oxidation state Ti^{IV} catalyzes the heterolytic cleavage of **B**, and (c) by coordinating the aldehydic oxygen atom, it would activate the carbonyl group towards attack by an amine.

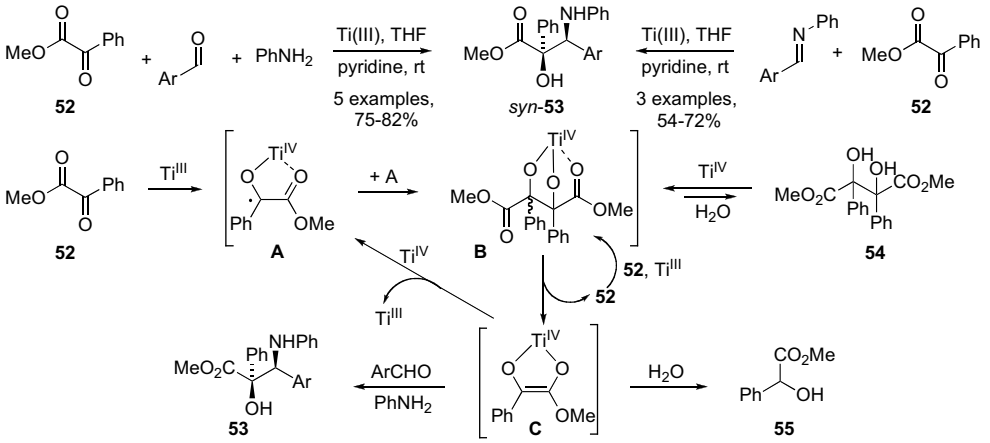
As can be deduced from the above examples, even though metal-induced RCCR have provided a variety of β-amino alcohols, only the method proposed by Roskamp and Pedersen[65] has been applied to a large variety of *C*-aliphatic and *C*-aromatic partners, thus offering better synthetic potential. Two distinct types of mechanisms have been proposed: formation of radical intermediates by single-electron transfer (to the carbonyl or to the imine partner, depending on the conditions and/or authors' hypotheses), and formation of metalla-aziridine complexes. While the stereoselectivity of the alkali and alkaline earth metal-induced reactions is generally poor, low-valent niobium-, zirconium-, tantalum- and titanium-induced RCCR afford selectively *syn* β-amino alcohols.

4. Bu_3SnH-mediated reductive cross-coupling reactions

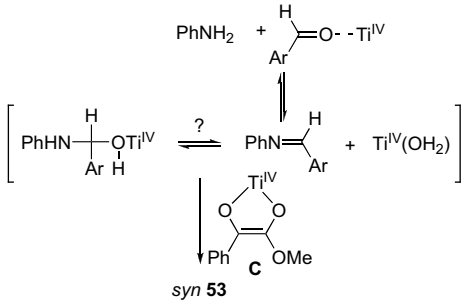
Among the organometallic hydrides that have been used as reducing agents, tributyltin hydride has been the most employed. This reagent promoted intramolecular radical C–C bond formation towards cyclic vicinal amino alcohols.

4.1. Oxime ethers

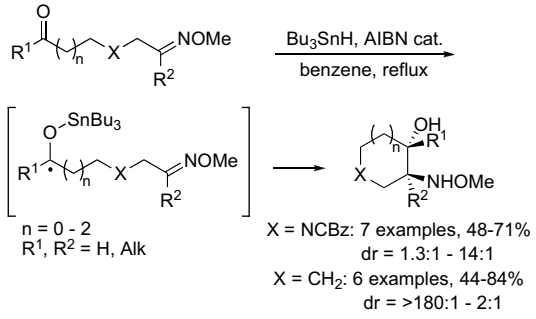
In the presence of catalytic amounts of AIBN (azo-bis-isobutyronitrile), tributyltin hydride generates a tributyltin radical, that reacts with carbonyl compounds to produce stannylated ketyl radicals. The stannyl radical addition-cyclization of oxime ethers tethered with a carbonyl group provides an entry to five- to seven-membered heterocyclic amino alcohols, as shown by the group of Naito (Scheme 32, X=NCBz).[71] Among two stereoisomers, *trans*



Scheme 30.



Scheme 31.



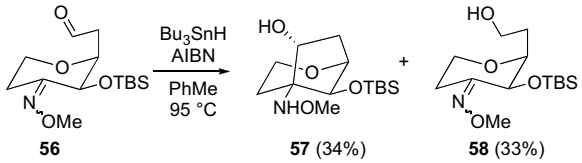
Scheme 32.

amino alcohols are generally obtained as major products which would be formed via transition states exhibiting less electron repulsion between the stannyloxy ketyl group and the nitrogen and/or oxygen atom of the oxime ether.

The group of Fu described similar results in the preparation of five- and six-membered aminocyclitols from carbonyl-oxime ethers (Scheme 32, X=CH_2) and, in this case, high trans diastereoselectivities were observed.[72] However, the formation of these aminocyclitols proved inefficient when two contiguous quaternary centers had to be produced.

When the process was applied to carbohydrate-derived substrates various degrees of diastereoselectivities were observed, the trans products always being major.[73]

The transannular cyclization of oxime ether **56** allowed a diastereoselective access to **57**, an intermediate for nucleoside analogue synthesis (Scheme 33).[74] However, the reduction of the aldehyde function into a primary alcohol was an important side reaction, producing **58**.



Scheme 33.

4.2. Hydrazones

Kim and Kee demonstrated the feasability of the Bu_3SnH-mediated cyclization of carbonyl-tethered hydrazones.[75] In their study, particular hydrazones were used, namely 2-phenyl-*N*-aziridinyl imines. Upon addition of a stannylated ketyl radical on such a hydrazone, an intermediate iminyl radical is produced, that undergoes aziridinyl ring opening and elimination of styrene and nitrogen. Consequently, although this type of cyclization is similar to the one described above for carbonyl-tethered oximes, it does not yield β-amino alcohols.

5. SmI_2-mediated reductive cross-coupling reactions

Since its introduction by Kagan,[76] samarium diiodide (SmI_2) has become one of the most popular and versatile single-electron-transfer reductants in organic synthesis, especially in reactions involving carbonyl compounds.[77] Its mild reducing power ($E^{\circ}_{(Sm^{++}/Sm^{+++})}=-1.33$ V vs $Ag/AgNO_3$)[78] allows excellent chemoselectivities and can be tuned by the addition of water, alcohols or coordinating agents such as hexamethylphosphoramide (HMPA) or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU).[79] Thus, it should be of no surprise to the reader that numerous cross-coupling reactions between carbonyl compounds and imine derivatives (oximes, imines, iminium salts, hydrazones, and nitrones) have been achieved by using samarium diiodide as a reducing agent. This reagent has been used to mediate both intra- and intermolecular variants of RCCR and has proved to be particularly useful in the development of asymmetric RCCR, due to the possibiliy to perform the reactions at low temperatures.

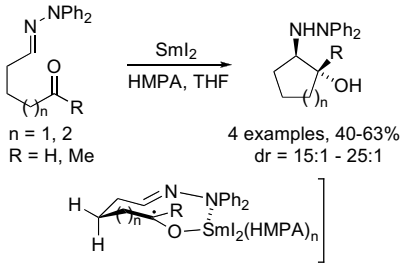
5.1. Intramolecular RCCR

Intramolecular reductive cross-coupling reactions give access to cyclic β-amino alcohols. Although less often used than linear amino alcohols, cyclic β-amino alcohols have also proved to be useful ligands or auxiliaries for asymmetric synthesis.[1a,80] Furthermore, the development of synthetic methods towards cyclic β-amino alcohols

has been stimulated by the occurrence of these moieties in a number of natural products and in relevant leads in medicinal chemistry.[32] In particular, aminocyclitols are a class of sugar mimetics containing a cyclic β-amino alcohol core, and exhibiting potent glycosidase inhibition.[81] Since the mid-1990s, the SmI_2-mediated reductive cyclization of carbohydrate-derived oxime ethers or hydrazones containing δ- and ε-carbonyl groups has been extensively studied, and the investigations in this field published before 2001 have already been included in a review on radical additions to C=N bonds.[43]

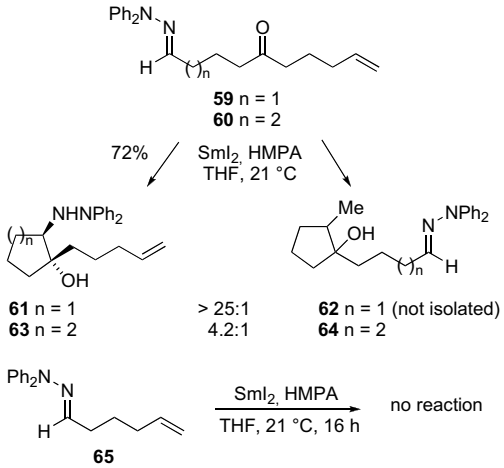
5.1.1. Hydrazones

Sturino and Fallis established that *N*,*N*-diphenylhydrazones are good acceptors for SmI_2-generated ketyl radicals, and applied the cyclization of carbonyl-tethered hydrazones to the synthesis of nitrogen-functionalized cyclopentanes and cyclohexanes.[82] In the presence of HMPA as an additive (1.5 ml/mmol of substrate), the SmI_2-promoted intramolecular reductive coupling of δ- and ε-aldo- and keto-hydrazones afforded α-hydrazino alcohols in modest yields, but excellent diastereoselectivities (Scheme 34). The trans-selectivity of the cyclization was explained by a nine-membered-ring radical template with the large *N*,*N*-diphenyl substituent adopting a pseudo equatorial orientation and the axial oxygen helping to minimize *gauche* interactions. The synthetic utility of these reactions was further enhanced by conversion of the cyclic hydrazines into amines, by using excess SmI_2 on acyl derivatives or by hydrogenolysis.



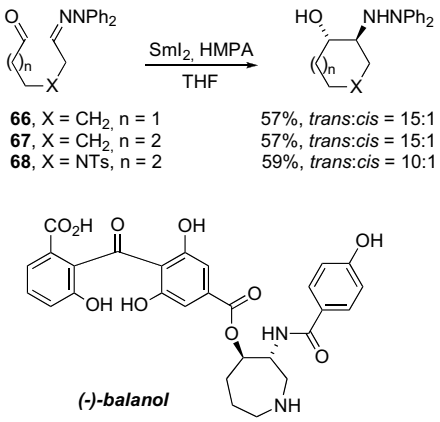
Scheme 34.

The same authors investigated the reactivity profile of the samarium ketyl radical towards the C=N bond of a hydrazone and the C=C bond of an alkene (Scheme 35).[83] It was demonstrated that, at room temperature, with SmI_2/HMPA, ketone **59** (n=1) cyclized exclusively to the β-hydrazino alcohol **61** as a single trans diastereomer in 72% isolated yield, with no trace of **62** being produced. Under the same conditions, ketone **60** (n=2) generated both possible cyclic alcohols **63** and **64** from 6-*exo* hydrazone and 5-*exo* alkene cyclization, respectively (4.2:1). This competitive 'radical clock'-type cyclization of hydrazones and alkenes established that 5- and 6-*exo* hydrazone radical cyclizations are faster than the corresponding 5-*exo* alkene ring closure. The possibility of electron transfer to the imine double bond was ruled out in these cyclizations, as the unsaturated hydrazone **65** is inert in the same conditions.



Scheme 35.

This SmI_2-promoted intramolecular carbonyl-hydrazone reductive coupling was used by Skrydstrup et al. for the synthesis of the fully functionalized hexahydroazepine ring of balanol, in racemic form (Scheme 36).[84] The cyclization of homologous carbonyl-hydrazones **66** (X=CH_2, n=1) and **67** (X=CH_2, n=2) resulted in the corresponding β-hydrazino alcohols in the same yield (57%), with high trans-selectivity (trans/cis >15:1), providing an efficient entry not only to six-, but also to seven-membered carbocycles. In the case of the ε-oxo-hydrazone **68** (X=NTs, n=2), the formation of the hexahydroazepine ring occurred with a slightly reduced stereoselectivity (trans/cis ratio of 10:1). Again, the use of the electron-donating ligand HMPA was essential for the cyclizations to occur. This additive appeared to modulate the rate constants for the ring formation and the competing intermolecular pinacol homocoupling, a side reaction that predominated in the absence of HMPA. Replacement of the SmI_2/HMPA system by $SmBr_2$ or $SmCl_2$ as the reducing agents did not yield the expected cyclization products, but instead promoted the reduction of the aldehyde functions to the corresponding primary alcohols.



Scheme 36.

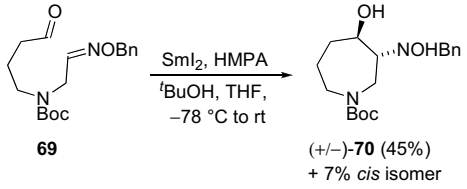
Later, Chiara and Garcia have also used the SmI_2-induced ketone-hydrazone cross-coupling methodology to overcome stereoselectivity issues in efforts to access trehazolamine (see Scheme 45).[85] In the 5-*exo*-*trig* cyclization of an intramolecularly tethered hydrazone, again, the *trans* amino alcohol was formed preferentially, en route to the desired cis–trans configuration in natural trehazolamine.

5.1.2. Oxime ethers

The general reactivity of oxime ethers under reductive conditions is close to that of *N*,*N*-dialkylhydrazones, as already discussed.[50] As with hydrazones, oxime ethers have also been considered as radical acceptors in the cyclization of carbonyl-tethered oxime ethers. The β-*N*-alkoxyamino alcohols resulting from reductive cyclization can be efficiently converted in situ into the corresponding aminocyclitols by N–O reductive cleavage using excess samarium diiodide and water.

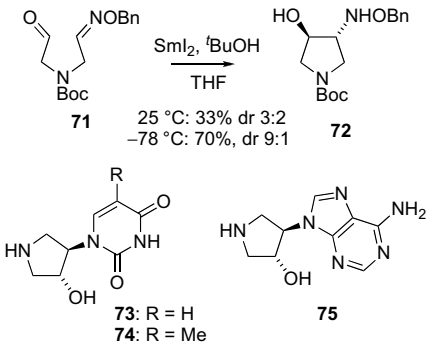
The group of Naito, independently from that of Skrydstrup,[84] investigated the total synthesis of (−)-balanol using the SmI_2-

promoted radical cyclization of oxime ether **69** as a key step (Scheme 37).[86] The trans/cis ratio (6.6:1) that was observed, even though lower than that from the cyclization of the related keto-hydrazone **68** (Scheme 36), compares favourably with that from the Bu_3SnH-induced cyclization of **69** (2.6:1).[86b] The resulting racemic hexahydroazepine **70** was then optically resolved by using an immobilized lipase from *Pseudomonas* sp.



Scheme 37.

The corresponding 5-*exo*-*trig* cyclization of δ-oxo oxime ether **71** was found to be feasible in the absence of HMPA, the latter being advantageously replaced by *tert*-butanol. The stereoselectivity and chemical yield of **72** were shown to be dependent on the reaction temperature (Scheme 38).[87] The method was used successfully to prepare biologically relevant targets such as nucleoside analogues **73**, **74** and **75**.

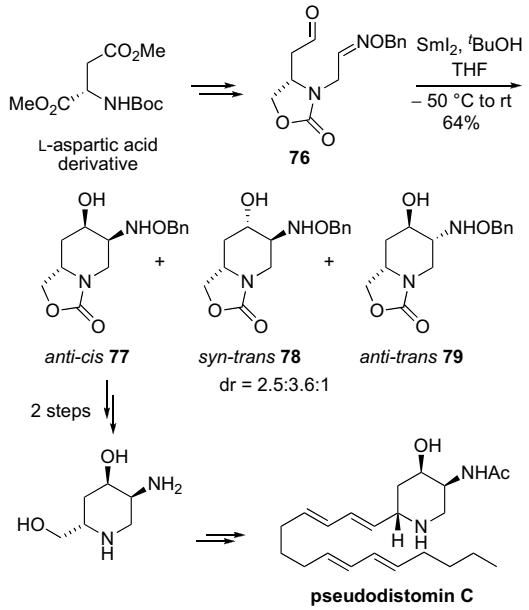


Scheme 38.

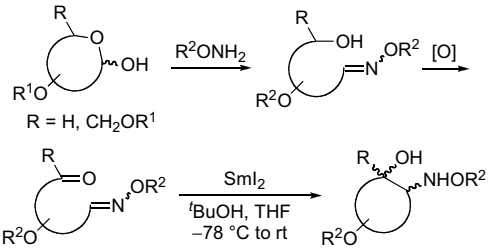
The same group constructed enantiopure substituted piperidines applying a similar strategy to the chiral L-aspartic-derived ε-oxo oxime ether **76** (Scheme 39).[88] The SmI_2-induced 6-*exo*-*trig* cyclization of **76** afforded the three diastereomers **77**, **78** and **79**, the major product **78** exhibiting a trans configuration. The *anti*-*cis* isomer **77** was converted into (2*S*,4*R*,5*S*)-2-hydroxymethyl-5-amino-4-piperidinol, which is regarded as a synthetic precursor of pseudodistomins.

The groups of Chiara and Marco-Contelles have developed the synthesis of highly functionalized aminocyclitols from carbohydrates, using keto-oxime ether reductive cyclization as the key step (Scheme 40). Highly functionalized keto-oximes were prepared in only two steps from the readily available *O*-protected sugar hemiacetals, i.e., by condensation with *O*-benzyl hydroxylamine and subsequent oxidation of the released hydroxyl group. The SmI_2-induced reductive coupling reaction can be performed in a one-pot sequence if a Swern oxidation is used, allowing the direct transformation of hydroxyl-tethered oxime ethers into the corresponding aminocyclitols. These authors observed that the stereochemistry of these cyclizations is independent of the geometry of the starting oxime ethers.

For example, upon treatment with SmI_2 in the presence of *tert*-butanol, δ-oxo-oxime ether **80**, of D-*arabino* configuration, smoothly cyclized to the *N*-benzyloxy aminocyclitol derivative **81**, exhibiting trans,trans relative configuration across the amino

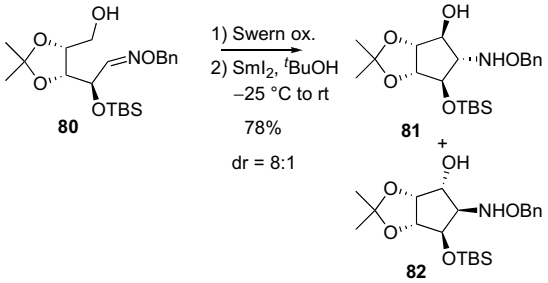


Scheme 39.



Scheme 40.

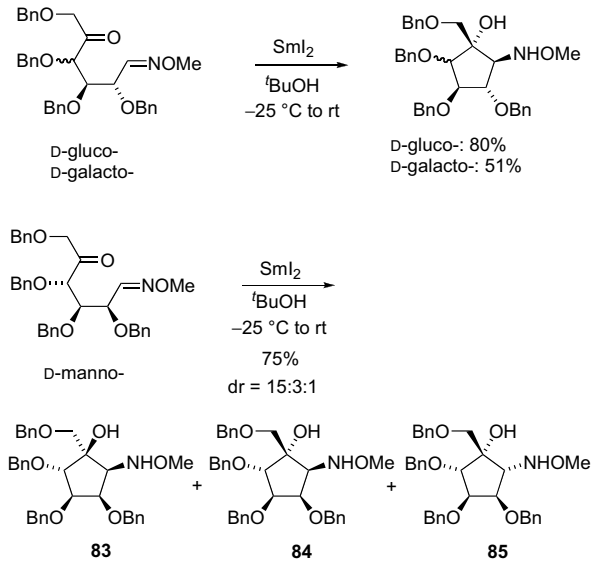
functonality, as the major product (Scheme 41).[89] Only two diastereoisomers were obtained (**81** and **82**), when four could have been expected.



Scheme 41.

Similarly, the 5-*exo*-*trig* cyclizations of δ-oxo-oxime ethers in the D-*gluco*, D-galacto and D-*manno* series were diastereoselective in favour of the trans products (Scheme 42). Interestingly, a single diastereomer was obtained in the case of tetra-*O*-benzyl derivatives of D-glucose and D-galactose.[90] However, the keto-oxime derived from D-mannose yielded three diastereomers (**83**/**84**/**85**=15:3:1). Comparatively, the 6-*exo*-*trig* cyclizations of sugar-derived ε-oxo-oxime ethers proved less stereoselective and yielded mixtures of diastereomers.[90]

Chiara[91] and Giese[92] independently reported the use of this approach to prepare trehazolamine and its epimers, from D-glucose and D-mannose. Trehazolamine is the aglycone of trehazolin,



Scheme 42.

a natural product with promising agrochemical applications, since it is the best known inhibitor (active at nanomolar concentrations) of trehalase, an enzyme that is essential for the survival of insects, fungi and nematodes (Fig. 3).[93]

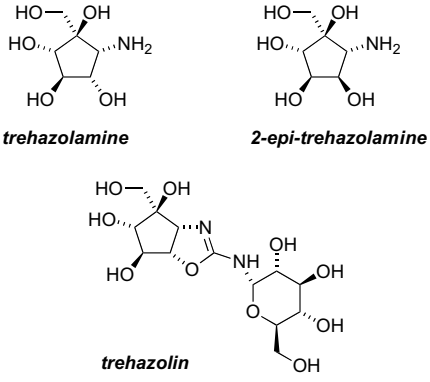
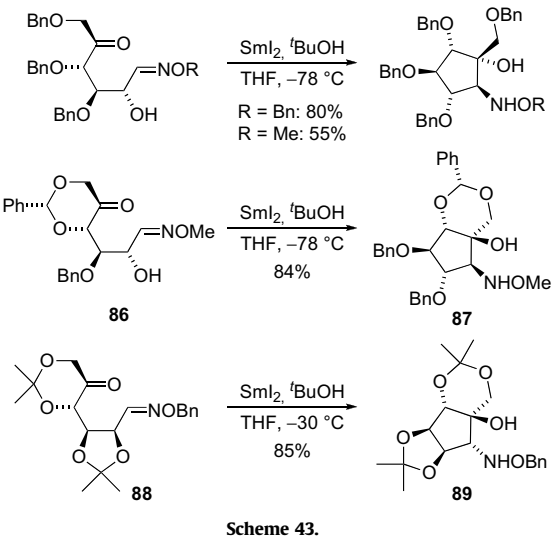


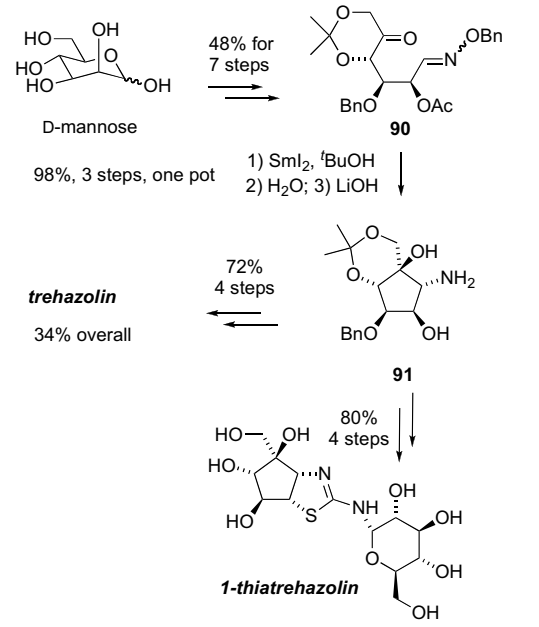
Figure 3. Trehazolin, an antifungal agent, and related compounds.

Interestingly, the stereochemical outcome of the cyclizations could be tuned by the nature of the protecting groups in carbohydrate-derived keto-oximes. In particular, using a cyclic ketal to connect the oxygen atoms at the C-4 and C-6 positions in **86**, the stereoselectivity of the SmI_2-induced cyclisation could be inverted to afford the *cis* amino alcohol **87** with the desired configuration at the quaternary center (Scheme 43).[92] Conversely, when two isopropylidene ketals were used as protecting groups in the D-mannose derivative **88**, again a *trans* β-amino alcohol (**89**) was obtained, as a single diastereomer.[94]

These observations led Chiara et al. to design compound **90** as a key carbocyclization precursor to achieve a highly efficient route to trehazolin from D-mannose in 34% overall yield, and 14 steps (Scheme 44).[95] The hydroxyl group vicinal to the oxime ether was conveniently differentiated to allow further manipulations in the resulting cyclitol. A trehazolin analogue, 1-thiatrehazolin, was also synthesized from **90** by treatment with excess SmI_2, in a very high-yielding tandem process. Fully stereoselective coupling, followed by in situ N–O reductive cleavage and addition of LiOH (for in situ hydrolysis of the ester group), afforded aminocyclopentitol **91**, which was converted into 1-thiatrehazolin in good overall yield.[96]

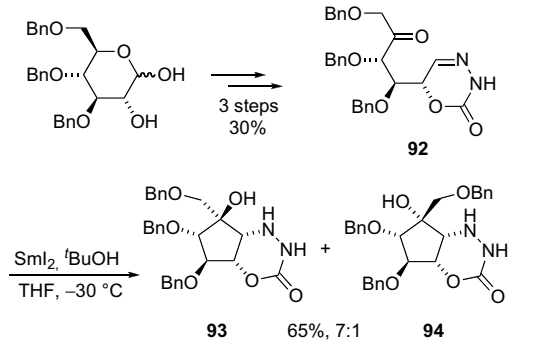


Scheme 43.



Scheme 44.

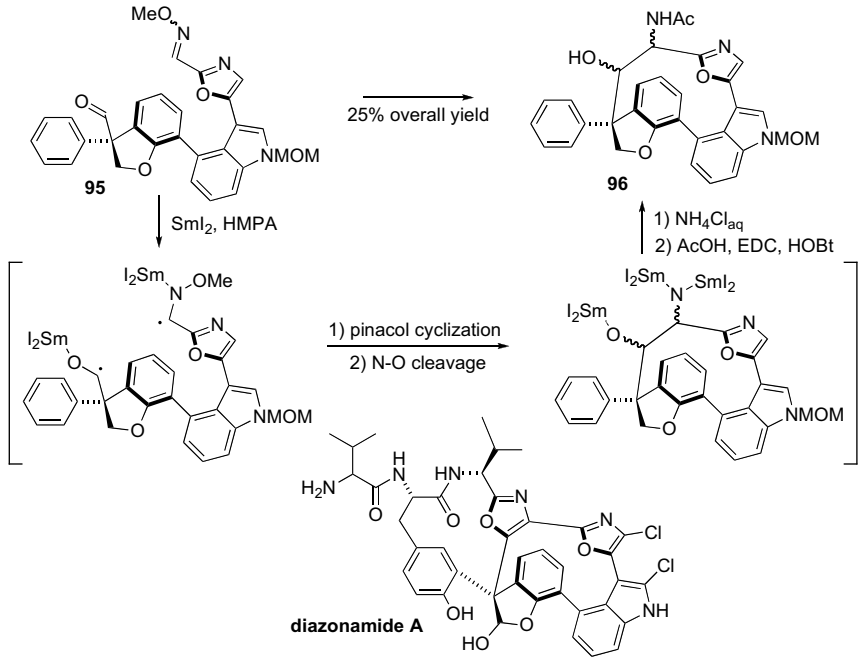
As mentioned previously, Chiara et al. have also prepared cyclic amino alcohols from an intramolecularly tethered hydrazone **92** with control of the stereochemistry at the new aminated centre (Scheme 45).[85] This approach complements the existing reductive



Scheme 45.

coupling methodologies in that it allows the preparation of diastereomeric cyclic amino alcohols that are not accessible via reductive cyclization of substrates containing acyclic imino groups. The fully functionalized trehazolin cyclitol was synthesized as a mixture of isomers **93** and **94**.

An interesting application of the ketyl-oxime intramolecular coupling for the synthesis of diazonamide A was proposed by Nicolaou and co-workers (Scheme 46).[97] SmI_2-induced heteropinacol-based macro-cyclization of aldehyde-oxime **95** allowed the construction of the 12-membered-ring aromatic core of the target molecule **96**, in 25% yield, and as a mixture of stereoisomers.



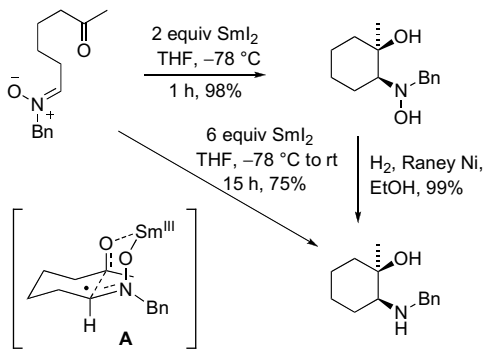
Scheme 46.

intermediate **A**. As this stereochemical outcome differs from that of the reductive keto-hydrazone or keto-oxime ether cyclizations, a different mechanism was thought to operate in this case.

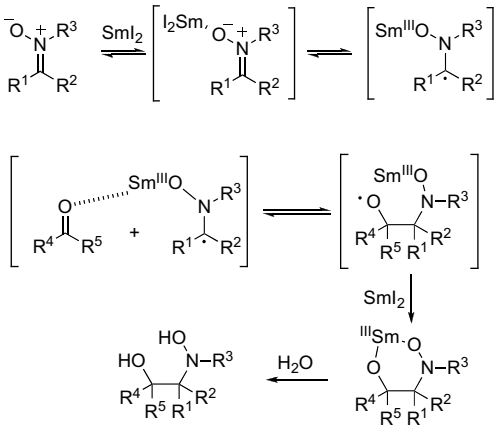
The mechanism of the SmI_2-mediated ketone-nitrone cyclizations was proposed to involve an initial electron transfer to the nitrone functionality, and a subsequent attack of the resulting α-azanucleophilic intermediate species on the carbonyl group (Scheme 48). The preferred reduction of the nitrone functionality, rather than that of the carbonyle, can be rationalized by a favoured inner-sphere electron transfer from Sm^{II} to the nitrone carbon atom following coordination of the samarium diiodide to the nitrone oxygen atom (Lewis base).

5.1.3. Nitrones

The intramolecular reductive coupling of keto-nitrones has been disclosed a few years ago.[98] It was found that, upon treatment with SmI_2 at −78 °C, ε-keto nitrones cyclize smoothly to yield the corresponding β-*N*-hydroxyamino alcohols in high yields and in short reaction times (Scheme 47). The use of additives such as HMPA or proton sources that had previously proved to be necessary to ensure good yields was unnecessary when the C=N partner was a nitrone. Furthermore, direct access to β-amino alcohols was made effective by using excess samarium diiodide and allowing the reaction mixture to reach room temperature. Remarkably, excellent diastereoselectivities were observed in these couplings, in favour of the cis products, that could be explained by the occurrence of a chelated

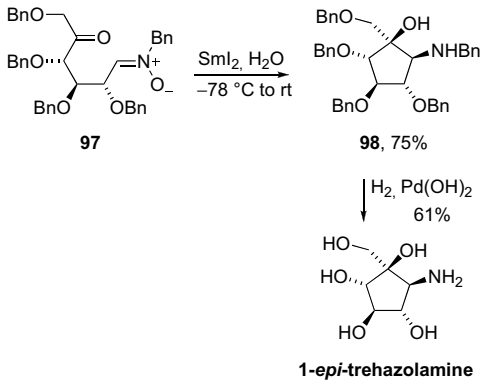


Scheme 47.



Scheme 48.

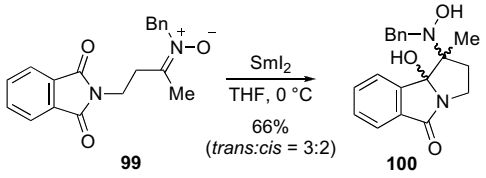
This SmI_2-promoted ketone-nitrone coupling allowed the preparation of an original aminocyclitol **98**, from the glucose-derived keto-nitrone **97**, thus demonstrating the utility of such C–C bond formation in target-oriented synthesis and the compatibility of the method with functionalized substrates (Scheme 49).[99] Aminocyclitol **98** was directly obtained as the pure cis diastereoisomer, by a one-step cyclization/N–O bond cleavage using excess SmI_2 in the presence of water. The C-1 epimer of



Scheme 49.

trehazolamine was then readily produced after hydrogenolysis of the benzyl groups.

The group of Chiara has shown recently that not only ketones, but also phthalimides, react intramolecularly with nitrones in the presence of SmI_2.[100] For example, SmI_2-induced cyclization of the phthalimido-nitrone **99**, at 0 °C, afforded diastereomeric five-membered-ring α-hydroxy lactams **100** in 66% yield (Scheme 50). In this case, the stereoselectivity was weak and the trans isomer was obtained as the major product (trans/cis=3:2). The authors proposed that this reaction was initiated by the chemoselective single-electron-transfer reduction of the phthalimido group by SmI_2 to generate a ketyl radical anion intermediate, the nitrone then behaving as a radicophile. This proposition was based on the relative redox potentials for organic molecules containing imide and oxime[101] or nitrone[102] groups in solution, and on DFT calculations of the relative electron affinities.

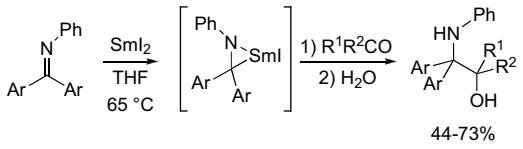


Scheme 50.

As can be seen from this section, the intramolecular cross coupling of C=O and C=N groups to produce cyclic β-amino alcohols has been largely explored in the last decade. Whilst most of the imine derivatives yield *trans* β-amino acohols as the major products, the cyclization of keto-nitrones affords *cis* β-amino alcohols. The complementarity of the reactions described above allow access to a large variety of cyclic β-amino alcohols.

5.2. Intermolecular RCCR

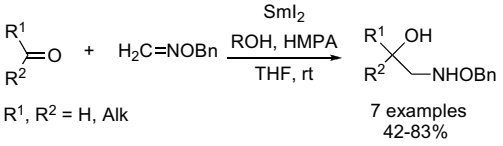
The pioneering work of Imamoto and Nishimura on the SmI_2-mediated homocoupling of imines also revealed the first examples of cross coupling of imines with carbonyl compounds, induced by this reagent.[103] Benzophenone or fluorenone anils, after treatment with SmI_2 in refluxing tetrahydrofuran, reacted with aliphatic ketones to afford the corresponding β-amino alcohols in acceptable yields (Scheme 51). This procedure, however, was applicable neither to *C*-aromatic aldimines that are prone to reductive dimerization nor to *C*-aliphatic imines that did not undergo reduction under these conditions; it is thus limited to the cross coupling of *C*-aromatic ketimines with ketones. The authors suggested that the reaction sequence involved an organosamarium species as



Scheme 51.

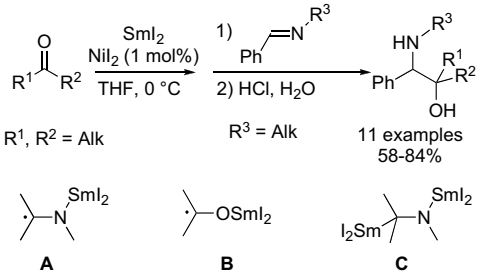
a reactive intermediate, and indicated that treatment with D_2O in place of the carbonyl compound provided the corresponding *C*-deuterated amine in quantitative yield.

A year later, Hanamoto and Inanaga reported on the SmI_2-mediated intermolecular coupling of aliphatic carbonyl compounds with *O*-benzyl formaldoxime, and invoked ketyl radical addition to the formaldoxime.[104] This transformation allowed effective aminomethylation of aliphatic aldehydes and ketones in the presence of HMPA and an alcohol as a proton source (Scheme 52). The addition of HMPA was essential in this reaction as, in its absence, decomposition of the oxime ether and reduction of the carbonyl compounds took place and no coupling products were obtained. Aliphatic aldehydes and ketones could be used as substrates, but this approach was restricted only to aminomethylation; the reaction of 4-phenyl-2-butanone with *O*-benzyl oximes prepared from benzaldehyde, crotonaldehyde, 2-phenylpropionaldehyde, and 4-*tert*-butylcyclohexanone in place of formaldehyde did not afford the coupling products. The *N*-benzyloxy group of the coupling products could be easily eliminated to generate the corresponding free aminomethyl alcohols by PtO_2-catalyzed hydrogenolysis.



Scheme 52.

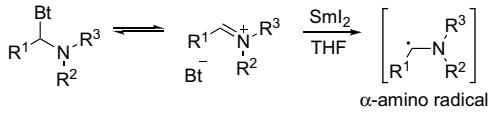
In a study on the samarium diiodide-mediated reductive dimerization of *C*-aromatic imines into vicinal diamines, Machrouhi and Namy have found that catalytic amounts of NiI_2 strongly accelerated these reactions, as well as the heterocoupling of such imines with aliphatic ketones (Scheme 53).[105] A similar catalytic effect of nickel diiodide was not observed for the pinacolization of non-aromatic ketones, thus favouring the selectivity of their cross-coupling reaction with imines. The nickel diiodide catalyst was suggested to facilitate single-electron transfer from samarium diiodide to the imine species. To ensure the success of the heterocoupling, the reaction procedure involved slow imine addition to a mixture of SmI_2, NiI_2 (1 mol %) and an excess of aliphatic ketone. Although the formation of small amounts (5–10%) of vicinal diamine was always observed, this methodology allowed a variety of β-amino alcohols to be obtained in good isolated yields. Aromatic



Scheme 53.

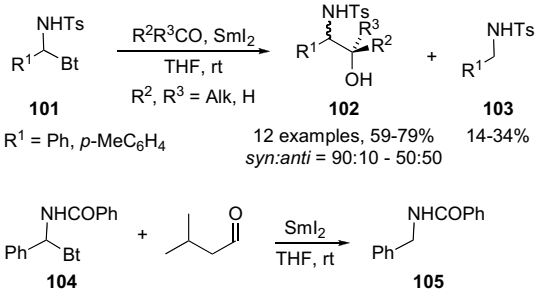
ketones were not good substrates in these cross-coupling reactions, as their homo-coupling reaction competed. A possible reaction pathway was proposed via a single-electron transfer to give a radical anion intermediate **A** (Scheme 53). As pinacol coupling products of aliphatic ketones were not obtained, it was assumed that ketyl radicals **B** were not formed in substantial amounts, which led the authors to rule out the formation of β-amino alcohols through coupling of radicals **A** and **B**. The possible addition of dianions **C** onto ketones was also discarded as, in the presence of EtOD in a large excess, the homo-coupling of the imine still readily occurred without reduction to the monoamine and any incorporation of deuterium. Consequently, the most plausible mechanism for the discussed hetero-coupling reactions would imply the formation of a radical anion intermediate **A**, that would add to carbonyl compounds.

As already mentioned for electroreductive cross-coupling reactions (Section 2.2), the relatively poor electron-accepting ability of the imine functional group can be overcome by the use of the more reactive iminium cations as the C=N partner in RCCR. This strategy has been adopted in some SmI_2-mediated reactions, using *N*-(*N*′,*N*′-dialkylaminoalkyl)benzotriazole adducts as iminium precursors.[106] The latter dissociate in solution by smooth elimination of a benzotriazolyl anion. In the presence of samarium diiodide, a single-electron transfer to the resulting iminium cation would produce an α-amino radical, as postulated by the group of Aurrecoechea (Scheme 54).[107]



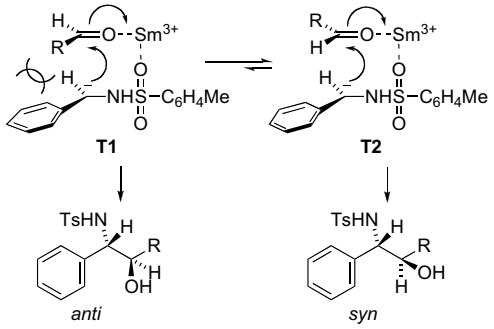
Scheme 54.

Along these lines, Zhang and co-workers have studied the SmI_2-induced elimination of benzotriazolyl groups from *N*-(α-benzotriazol-1-ylalkyl)sulfonamides and *N*-(α-benzotriazol-1-ylalkyl)amides and the subsequent hetero-coupling with carbonyl compounds (Scheme 55).[108] In the presence of excess aliphatic aldehydes or ketones (2 equiv), *C*-aryl iminiums from sulfonamides **101** were converted into the cross-coupling products **102** in fair-to-good yields, although tosylamines **103** were always formed as by-products. On other hand, under the same conditions, a mixture of *N*-((1*H*-benzotriazol-1-yl)phenyl-methyl)benzamide (**104**) and *iso*-valeraldehyde afforded solely the reduction product **105**. *C*-Alkyl iminiums from aliphatic benzotriazolylsulfonamides (**101**, R^1=alkyl) also led to reduction products exclusively.



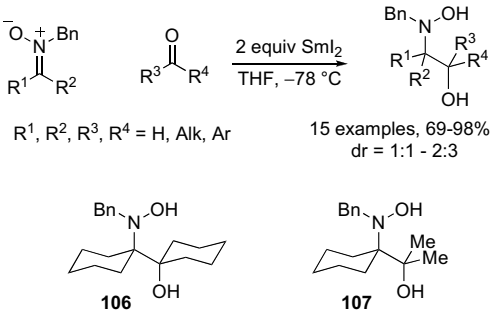
Scheme 55.

A tentative explanation for the preferential formation of the *syn* over the *anti* products was given by the authors. Considering a probable involvement of α-sulfonamido carbanions in these cross-coupling reactions and the strong oxophilicity of lanthanides, transition states **T1** and **T2** have been proposed (Scheme 56). The less sterically hindered **T2** would be more propitious, especially in the case of aldehydes (R^2 or R^3=H, Scheme 55), which afforded *syn*/*anti* ratios of products superior to 80:20; for the ketones, when R^2 and R^3 are comparable in size (Scheme 55), the selectivity vanished (*syn*/*anti*≈50:50).



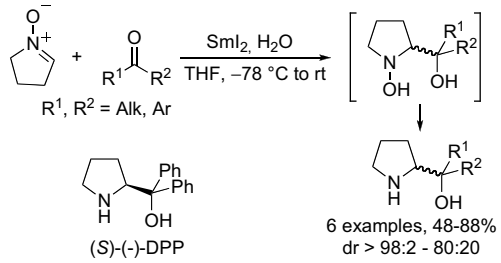
Scheme 56.

Nitrones, which can also be considered as iminium *N*-oxides, are also 'activated imines' for reductive cross-coupling reactions.[109] Like sulfonamide iminiums (see above), nitrones exhibit a Lewis-basic center at their oxygen atom that favours coordination of oxophilic samarium diiodide, and electron transfer is thus facilitated. Highly efficient intra- (see Section 5.1.3) and inter-molecular RCCR could be performed between nitrones and aldehydes or ketones, in the presence of samarium diiodide (Scheme 57).[98] The cross coupling of nitrones with aldehydes and ketones occurred with excellent chemoselectivities, to form β-hydroxyamino alcohol derivatives in high yields, without the need for additives like the toxic HMPA. Side reactions, such as homo-coupling or reduction of starting materials, were not observed, except when aromatic aldehydes were used as the substrates, in which case their pinacol coupling was the prevailing transformation. Using this method, new C–C bonds could be formed between two fully substituted centers. As examples, the bis-quaternary amino alcohols **106** and **107** have been prepared in high yields (respectively, 77 and 98%). Disappointingly, however, when diastereomers were to be produced, diastereomeric mixtures were obtained with very poor selectivity.



Scheme 57.

This method allows efficient access to both β-amino alcohols and their *N*-hydroxyamino analogues, a class of compounds that had not been well documented previously.[110] Recently, the cross-coupling reaction of nitrones with carbonyl compounds was applied to the preparation of a series of α,α-disubstituted 2-pyrrolidinyl-methanols, an important class of catalysts (Scheme 58).[111] SmI_2-mediated coupling of 1-pyrroline-*N*-oxide with a variety of aliphatic and aromatic ketones provided symmetrically (R^1=R^2) and unsymmetrically (R^1≠R^2) substituted α,α-disubstituted



Scheme 58.

2-pyrrolidinyl-methanols, in racemic form. The latter compounds are not easily accessible by other routes, and the method opens access to novel classes of prolinol derivatives, that may find interesting applications in organocatalysis or as metal ligands.[8] The obtained racemic products, which are analogues of DPP,[9] could be resolved through an original esterification of the intermediate *N*-hydroxy prolinols.

5.3. Asymmetric versions of RCCR

In the previous sections, methods to induce RCCR were shown to be diastereoselective to various extents. However, the enantioselective versions of these transformations have remained challenging. Although, in principle, chiral complexes of Sm(II) could be designed for promoting enantioselective reactions, there is relatively little published work on chiral modifications of Sm(II) reagents.[112] The addition of the chiral phosphine oxide (*R*)-BINAPO to SmI_2 allowed the enantioselective synthesis of γ-butyrolactones (yields 16–71%; ees 26–89%) by SmI_2-mediated reductive addition of aromatic ketones to acrylic and methacrylic esters.[112a] The group of Inanaga reported the diastereo- and enantioselective hydrodimerization of β-monosubstituted acrylic acid amides induced by a combination of SmI_2, (*R*)-BINOL (2 equiv per Sm), and TMEDA (yields 20–70%; ees 44–85%).[112b] Skrydstrup et al. have investigated the addition of chiral electron-donating ligands **108**–**111** (Fig. 4) in an attempt to induce enantioselectivities in the reductive cyclization of carbonyl-hydrazone **66**, during their synthetic studies towards the hexahydroazepine fragment of (−)-balanol (see Scheme 36).[84] However, only **111** showed visible signs of complexation to the divalent lanthanide ion with a change in the solution color from blue to purple. This was also manifested in the subsequent cyclization studies, where the ligand **111** helped in promoting the ring formation in **66** (Scheme 36) in good yield, whilst the reaction was not effective with **108**–**110** as additives. Nevertheless, this reaction was characterized as having a poor diasteroselectivity and essentially no asymmetric induction (ee=5%).

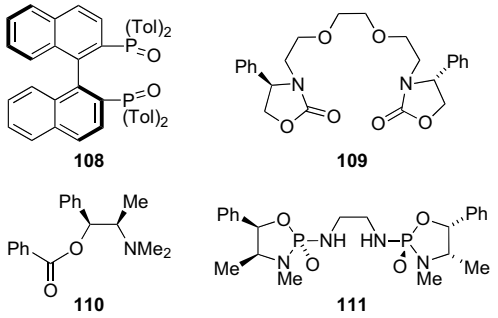
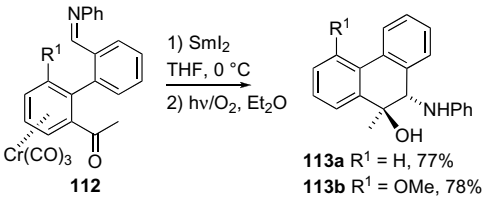


Figure 4. Chiral ligands evaluated for enantioselective SmI_2-mediated cyclization of carbonyl-hydrazones.

The difficulty in developing enantioselective reactions promoted by samarium diiodide was explained by the fact that the coordination sphere in lanthanide complexes is not well defined and notoriously labile, with high coordination numbers (6–9 for Sm(II)) and a multitude of potential coordination structures.[113] Consequently, most of the approaches that have been developed towards asymmetric versions of SmI_2-induced reactions have been based on the use of chiral auxiliaries in the substrates.

5.3.1. Planar chiral induction

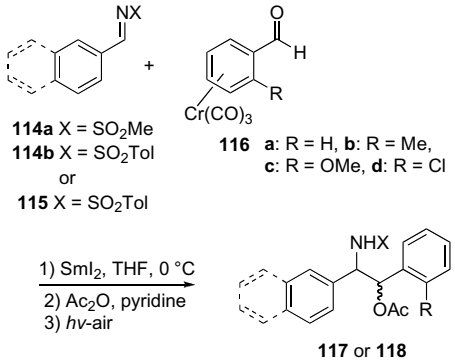
The stereoselective synthesis of optically active β-amino alcohols was first proposed by the group of Uemura, who used the planar chirality of arenechromium or ferrocenyl complexes to develop asymmetric versions of RCCR. For example, cyclic *trans* β-amino alcohols **113a**,**b** were prepared in enantiomerically pure form by SmI_2-mediated intramolecular pinacol coupling of the chiral mono-$Cr(CO)_3$ complexes of biphenyl derivatives **112**, and oxidative decomplexation of the chromium tricarbonyl auxiliary (Scheme 59).[114]



Scheme 59.

The stereochemical outcome of the cyclization was demonstrated by an X-ray analysis of **113b**, and was explained by an approach of samarium diiodide from the *exo*-side of the $Cr(CO)_3$ moiety, generating a ketyl radical intermediate. This intermediate would adopt preferentially a chelated conformation in which the two arene rings are not coplanar, thus avoiding steric hindrance between the substituents at the 6- and 6′-positions, and subsequent cyclization would yield *trans* β-amino alcohols.

The intermolecular RCCR of *N*-sulfonyl arylidene amines **114a**,**b** or **115** with tricarbonylchromium-complexed arylaldehydes **116a**–**d** produced β-amino alcohol derivatives **117** or **118** in good yields, with no formation of homo-coupling products, (Scheme 60, Table 2).[115]



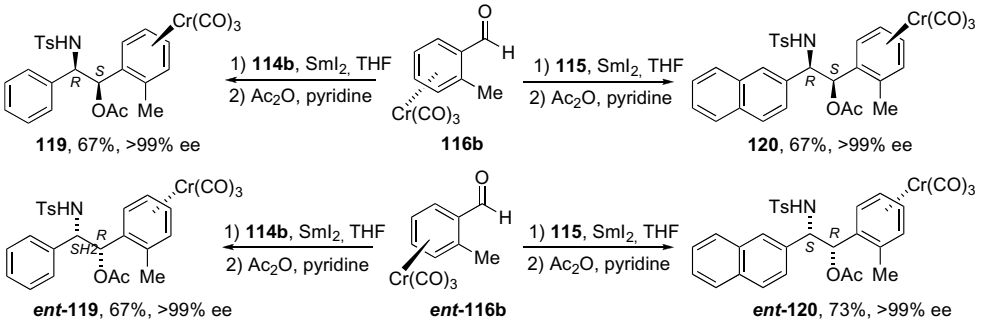
Scheme 60.

Table 2
SmI_2-mediated intermolecular RCC of *N*-sulfonyl arylidene amines with chromium-complexed arylaldehydes

Imine	Aldehydes	Yields (%)	*syn*/*anti*
114a	**116a–c**	63–89	60/40 to 67/33
114b	**116a–d**	33–73	95/5 to 97/3
115	**116a–c**	67–89	78/22 to 94/6

However, the *syn*/*anti* selectivity was significantly dependent on the nature of the substrates. *N*-Tosyl imines were better substrates than *N*-mesyl imines, and their RCCR with $Cr(CO)_3$-complexed arylaldehydes having electron-withdrawing substituents were found to be the best, both in terms of yields and diastereoselectivities. *syn* β-Amino alcohols were always formed as the major products.

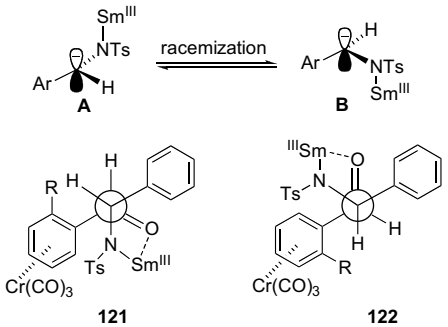
As an illustration, the optically pure aldehyde **116b** and its enantiomer ***ent*-116b** were independently reacted with *N*-tosyl imines **114b** or **115** to give the chromium-complexed β-amino alcohols **119** or **120**, in good yields and excellent enantiomeric excesses (Scheme 61). Accordingly, both enantiomers of the α,β-diaryl *syn* β-amino alcohols were stereoselectively prepared by SmI_2-mediated intermolecular RCCR of *N*-tosyl arylidene amines with *ortho*-substituted planar chiral benzaldehyde-chromium complexes.



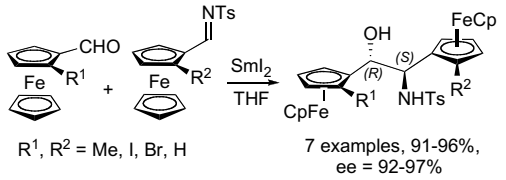
Scheme 61.

The same research group appreciably extended their synthetic approach in demonstrating that application of the ferrocenyl chiral auxiliary resulted in the complementary formation of *anti* β-amino alcohols.[117] In this case, planar chiral ferrocenyl aldehydes and *N*-tosyl imines were treated with samarium diiodide to afford exclusively enantiomerically pure *anti* β-amino alcohols in excellent yields (Scheme 63). In general, the absolute stereochemistry of the β-amino alcohols was governed by the planar chirality of the ferrocenylidene amines, regardless of the presence or absence of a substituent on the ferrocene carboxaldehyde ring. In an alternative combination, the cross coupling of a non-chiral *N*-tosyl ferrocenylidene amine (R^2=H) with chiral 2-substituted ferrocene carboxaldehydes was found to be controlled by the planar chirality of the ferrocene carboxaldehydes (Scheme 63).

The observed *syn* stereoselectivity was rationalized by considering the configurationally equilibrated reactive species **A** and **B**, generated by SmI_2 reduction of imines **114b** and **115**, that would undergo a dynamic kinetic resolution in their cross coupling with chiral benzaldehyde-chromium complexes (Scheme 62).[115] It was thus proposed that **A** and **B** would rapidly equilibrate at their newly created stereogenic center, and that each enantiomer of the planar chiral *ortho*-substituted benzaldehyde-chromium complexes could exclusively intercept one of the configurational species, depending on their absolute configuration. As it is known that the carbonyl oxygen of *ortho*-substituted benzaldehyde-chromium complexes exists preferentially in an *anti*-conformation with the *ortho*-substituent,[116] the transition states **121** and **122** were considered, accommodating coordination of the samarium with both the imine nitrogen and carbonyl oxygen atoms. The (+)-planar chiral benzaldehyde-chromium complex **116** would react preferentially through the transition state **121**, with minimal steric hindrance, to give the *syn* β-amino alcohol **119**. The corresponding antipode (−)-*ent*-**116** would react preferentially with **B**, giving the antipode amino alcohol derivative via the transition state **122**.

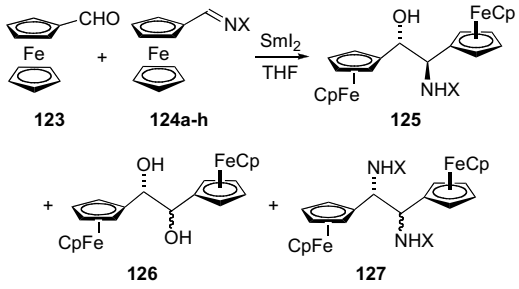


Scheme 62.



Scheme 63.

The effect of the substituent on the nitrogen atom of the ferrocenylidene amine derivatives **124a–h** on the efficiency of their RCCR with ferrocene carboxaldehyde **123** to produce the vicinal amino alcohols **125** was also evaluated by Uemura's group (Scheme 64, Table 3). Only the *N*-sulfonyl imines were good substrates for these RCCR, with the *N*-alkyl and *N*-aryl imines, hydrazones and *N*-sulfonyl hydrazones yielding only homo-coupling products **126** (and **127** when X=Ph).



Scheme 64.

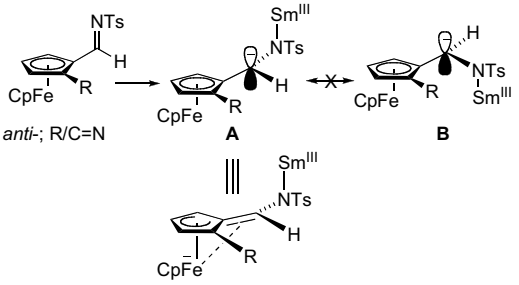
Regarding the reaction mechanism of the ferrocene carboxaldehyde and *N*-tosyl ferrocenylidene amine RCCR, the authors proposed an initial reduction of the imine partner by SmI_2, based

Table 3
SmI_2-mediated RCC of ferrocenylidene amine derivatives with ferrocene carboxaldehyde **123**

Imine **124**	X	**125** (%)	**126** (%)	**127** (%)
124a	Me	0	95	0
124b	Bn	0	96	0
124c	Ph	0	96	95
124d	NMe_2	0	98	0
124e	$NHSO_2Ph$	0	92	0
124f	SO_2Ph	92	Trace	0
124g	Ts	88	Trace	0
124h	Ms	94	Trace	0

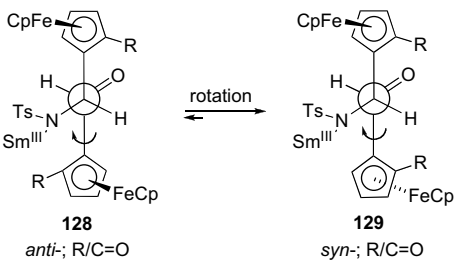
on the relationship between the efficiency of these cross-coupling reactions and the reduction potentials of the substrates (−2.3 V for **123**; −2.4 V for **124a**; −2.0 V for **124c**; −1.8 V for **124g**; −1.7 V for **124h**). Moreover, reduction of *N*-tosyl imine **124g** with SmI_2 in the presence of MeOD in THF gave the corresponding deuterated amine in good yield. The reactive intermediates were thus proposed to be ionic, rather than radical, species.

The stereoselectivity of the cross-coupling reactions involving planar chiral *N*-tosyl *ortho*-substituted ferrocenylidene amines was interpreted as follows. Again, the approach of SmI_2 would occur on the *exo*-side of the ferrocenylidene imines, in a conformation accommodating the C=N double bond oriented *anti* relative to the *ortho*-substituent, to generate the dianion intermediate **A** (Scheme 65). The configurational stability of **A** (that does not epimerise to **B**) was attributed to an interaction of the *p*-orbital of the α-carbon with the d-orbital of the iron, in which originates an *exo*-cyclic double-bond character.



Scheme 65.

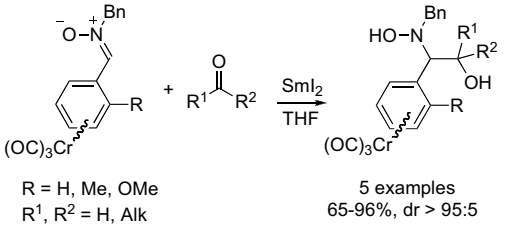
Addition of the intermediate **A** to *ortho*-substituted ferrocenyl carboxaldehydes would thus occur through the transition states **128** or **129** (Scheme 66). It can be considered that, initially, the *N*-tosyl group would be oriented *anti* to the carbonyl oxygen of the arylaldehydes, due to dipole–dipole repulsion. As the carbonyl oxygen of planar chiral ferrocene carboxaldehydes also exists preferentially in the *anti* conformation relative to the *ortho*-substituent, when planar chiral arylaldehydes would react with a dianion intermediate **A**, a severe steric interaction between the FeCp rings of both substrates would appear in the transition state **128**. Therefore, the *anti*-oriented transition state **128** was proposed to isomerize to the alternative *syn*-oriented transition state **129**, to afford *anti* β-amino alcohols.



128 *anti-*; R/C=O **129** *syn-*; R/C=O

Scheme 66.

Finally, the planar chirality of arene-metal complexes has also been used by Chavarot et al. to induce excellent stereoselectivities in the intermolecular cross coupling of enantiopure $Cr(CO)_3$-complexed *ortho*-substituted nitrones with carbonyl compounds (Scheme 67).[118] Interestingly, the use of excess SmI_2 (6 equiv) could directly produce β-amino alcohol complexes in good yields, in a one-pot sequence, by reduction of the in situ-generated hydroxylamine. Demetalation was effected by refluxing the arenechromiumcarbonyl products in pyridine.



Scheme 67.

5.3.2. Centered chiral induction

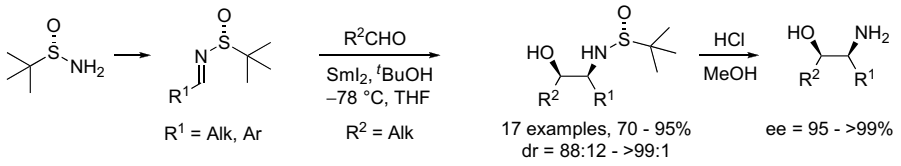
Quite recently, the SmI_2-mediated intermolecular cross coupling of chiral *tert*-butanesulfinyl aldimines with aliphatic aldehydes has been independently disclosed by the groups of Lin[119] and Bentley[120] for the asymmetric synthesis of β-amino alcohols (Scheme 68). The chiral *tert*-butanesulfinyl aldimines (Ellman's imines), prepared from the enantiopure *tert*-butanesulfinamides, exhibit sulfur-centered stereogenicity with powerful chiral-directing properties.[121] Excellent diastereomeric and enantiomeric excesses were obtained in these reactions. The use of a small excess of the aldehyde substrate and *tert*-butyl alcohol was found to be essential for the achievement of high yields.

Both *C*-aromatic and *C*-aliphatic aldimines were suitable partners, indicating the compatibility of the method with a great variety of substrates and its large scope. However, the method could not be applied to aromatic aldehydes, their pinacol homo-coupling being an important side reaction. Cleavage of the sulfinyl group under acidic conditions was subsequently accomplished to afford the unprotected β-amino alcohols with excellent enantiomeric excesses.

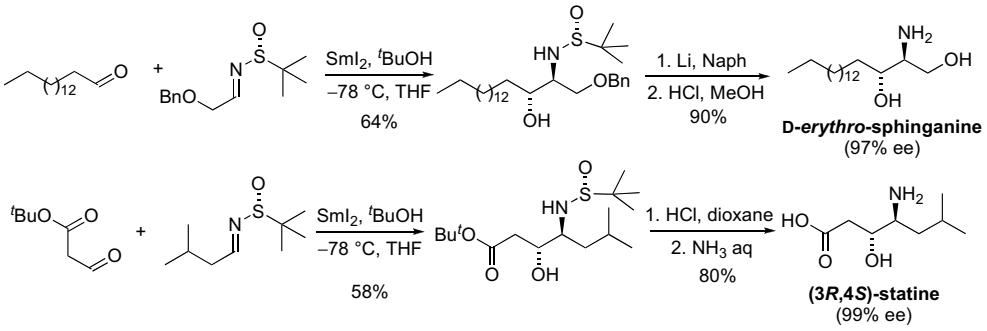
To further demonstrate the synthetic value of this method, Xu, Lin and co-workers applied it to the rapid preparation of two biologically active compounds, D-*erythro*-sphinganine and (3*R*,4*S*)-statine (Scheme 69).[119] The product yields and enantiomeric excesses make this approach one of the most convenient and direct for the synthesis of these biologically active natural products.

The groups of Wang, Xu and Lin have also used the SmI_2-mediated reductive cross coupling of (*R*)-*N*-*tert*-butanesulfinyl imine **131** with 4-pivaloxybutanal (**130**) as a key step for the asymmetric synthesis of the human NK-1 substance P receptor antagonists, (+)-CP-99,994 and (+)-L-733,060 (Scheme 70).[122] In the coupling step, the *anti* β-amino alcohol **132** (dr 90:10) was obtained in 78% yield, with excellent enantiomeric excess (>99%). Inversion of configuration at the carbon atom bearing the hydroxyl group and ring closure on the intermediate **132** gave the targeted disubstituted piperidines in satisfactory yields. Conceptually, this approach provides facile access to important 2,3-disubstituted piperidine derivatives of all possible configurations.

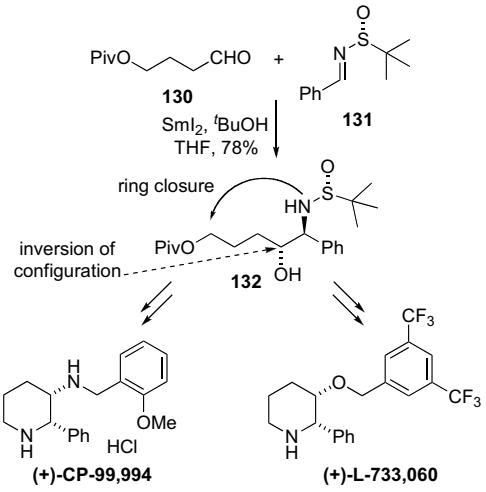
As mentioned above, Bentley's group independently found that the cross coupling of *N*-*tert*-butanesulfinyl imines with aliphatic aldehydes provides efficient asymmetric synthesis of β-amino



Scheme 68.

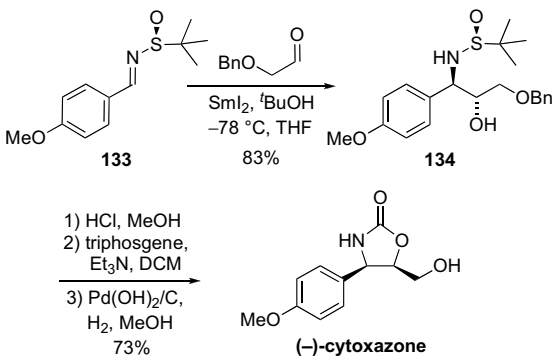


Scheme 69.



Scheme 70.

alcohols.[120] It was used as a key step for the synthesis of a naturally occurring cytokine modulator, (−)-cytoxazone, which has been shown to inhibit the Th2 cell signaling pathway (Scheme 71). SmI_2-mediated reductive coupling of (*S*)-imine **133** with benzyloxyacetaldehyde resulted in the formation of the *anti* β-amino alcohol **134** which, after transformations, gave a high overall yield of cytoxazone.



Scheme 71.

6. Conclusions

The first examples of reductive cross coupling of carbonyl compounds with imine derivatives have been reported 40 years ago. However, some of the methods described for these transformations have been mostly useful for intramolecular reactions (cyclizations) and for the exclusive formation of cyclic vicinal amino alcohols (aminocyclitols). On the other hand, the intermolecular cross-coupling reactions of carbonyl compounds and imine derivatives were often complicated by side reactions such as homocoupling or reduction of the substrates. Probably for this reason, only a few acyclic β-amino alcohols have been synthesized by way of an RCCR.

Intermolecular RCCRs were successful, however, when the C═O– and C═N-containing substrates exhibited sufficiently different redox properties. The use of nitrones, and sulfonyl and sulfinyl imines, all exhibiting an oxygen atom with strong coordinating properties in the vicinity of the reducible C═N bond, has proved beneficial for efficient SmI_2-mediated cross coupling of a large variety of substrates. It is likely that coordination of the reducing agent to this oxygen atom facilitates an electron transfer to the imine partner and the subsequent RCCR. Both intra- and intermolecular SmI_2-mediated RCCRs using these substrates (nitrones, and sulfonyl and sulfinyl imines) have given access to highly substituted and functionalized β-amino alcohols in excellent yields. Furthermore, asymmetric versions have been designed, that have been applied successfully to diastereo- and enantioselective syntheses of β-amino alcohols.

New synthetic strategies for the preparation of enantiopure β-amino alcohols are in high demand. The use of RCCRs, involving formation of the C–C bond between their amine and alcohol functionalities, appears to be a versatile route for accessing a large variety of substituted amino alcohols from readily available substrates (carbonyl compounds and imine derivatives). The current asymmetric versions of RCCRs all rely on the introduction of chiral auxiliaries in the substrates. The development of enantioselective

methods using chiral ligands or additives not covalently bound to one of the substrates would undoubtedly further expand the scope of these reactions. It can be expected that this area of research will continue to stimulate efforts from chemists in the future.

Acknowledgements

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