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Recent Development on Catalytic Reductive Amination and Applications[#]

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Abstract: Reductive amination is one of the most useful and versatile methods for the preparation of' amines in biological and chemical systems. The present review focuses on the development of catalytic reductive amination from beginning to recent ones, where we attempted to thoroughly illustrate an account of utility of various reagents including organocatalyst, symmetric and asymmetric (Ru, Rh, Ir*)* complexes, boron, tin or silicon reagents etc for enantio- and/or chemoselective reactions under different reaction conditions with emphasis on the yields of the reaction products and stability of the reagents used. Emerging applications of this reaction for the development of chiral ligands, pharmacologically active molecules, combinatorial scaffold, and key step in the total synthesis of some interesting natural products is also reviewed briefly.

Keywords: Reductive amination; Homogeneous catalyst; Heterogeneous catalyst; Boron reagents; Tin and Silicon reagents; Organocatalyst.

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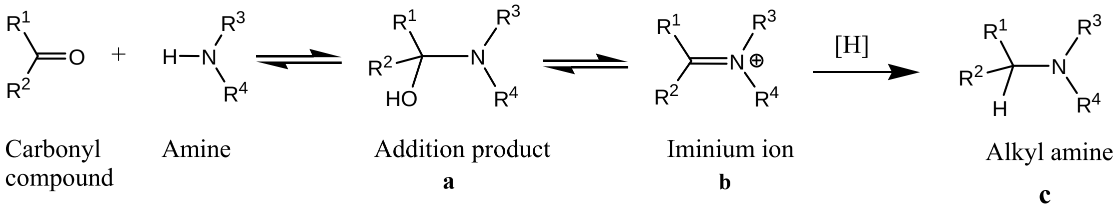
1. INTRODUCTION

Reductive amination, where a mixture of an aldehyde or ketone and an amine is treated with a reductant in one-pot fashion, is one of the most useful and versatile methods for the preparation of amines and related functional compounds in chemical and biological systems [1]. The amines, thus obtained are very useful in industry that have found wide-spread applications as intermediates for pharmaceuticals, dyes, resins, fine chemicals, solvents, textile additives, disinfectants, rubber stabilizers, corrosion inhibitors, and in the manufacture of detergents and plastics. The scientific investigations by Stanley L. Miller and Harold C. Urey in mid of the 19th century during synthesis of amino compounds led to believe that amination reaction plays an important role in origin of life. Amination, where an amine group is introduced into another molecule, can be achieved by a number of ways including reaction with ammonia or amine, reductive amination, electrophilic amination, and the Mannich reaction. Among all these methods, reductive amination is one of the oldest, but most powerful and widely used synthetic transformations to access different kinds of amines [1e-g].

The reaction of aldehydes or ketones with ammonia and amines (primary or secondary) in presence of a reducing agent to give primary, secondary or tertiary amines respectively, is known as reductive amination of the carbonyl compounds or reductive alkylation of the amines (**Scheme 1**). The reaction involves the initial formation of addition product as an aminol intermediate or carbinol amine, which under the suitable reaction conditions dehydrates to form an imine. The imine on protonation forms an iminium ion that subsequently on reduction resulted to the respective alkylated amine [2].



Scheme 1: Reductive amination

Imine bond formation proceeds with dehydration within a single molecule, or between two molecules containing amino and carbonyl groups and a C=N bond is formed either intra- or inter-molecularly. They can participate in a number of ways such as it may revert back to the original compound containing amino and carbonyl groups (known as hydrolysis), or upon introduction of a second amine, the original imine may either exchange (known as transimination) or may exchange the two R groups of two imines (known as metathesis). Many external considerations including solvent, concentration, temperature, pH, steric and electronic factors can influence the equilibrium. Imine bond formation occurs under equilibrium control, and addition of H_2O to an imine may result to hydrolysis and drive the condensation in the opposite direction, leading to the recovery of the starting material. It is common to drive the reaction towards completion by removing H_2O as it is formed, either by separating it physically or by adding a drying agent. The reductive amination is described as a direct reaction when the carbonyl compound and the amine are mixed with the proper reducing agent without prior formation of the intermediate such as imine or iminium salt. A stepwise or indirect reaction involves the preformation of the intermediate imine followed by its reduction in a separate step [3].

The amination reaction is equally important in chemistry and biology where reductive amination, an important transformation of aldehydes and ketones into amines using simple operations leads to key molecules [4]. We have recently used reductive amination for the synthesis of a variety of biologically active molecules and synthetic intermediates both in solution and solid phases [5].

2. METHODS OF REDUCTIVE AMINATION

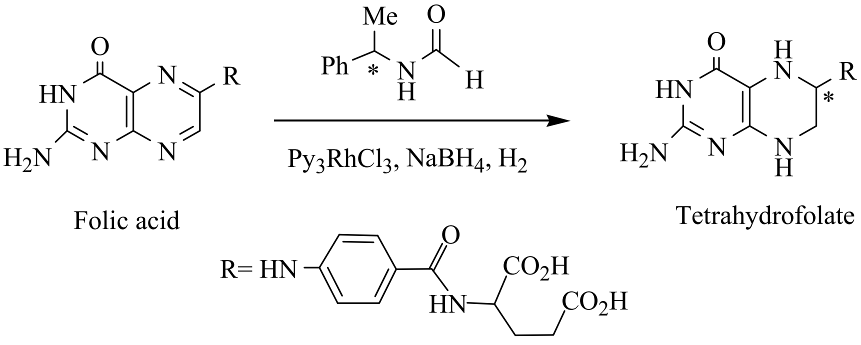
Reductive amination is categorized on the basis of reducing agents used in a particular reaction.

2.1. CATALYTIC HYDROGENATION

Catalytic hydrogenations, a group of versatile processes for the reduction of multiple bonds in organic compounds have been used successfully in reductive amination too. Depending upon the nature of catalyst used during reaction, these are classified as (i) Homogeneous catalytic reductive amination, and (ii) Heterogeneous catalytic reductive amination.

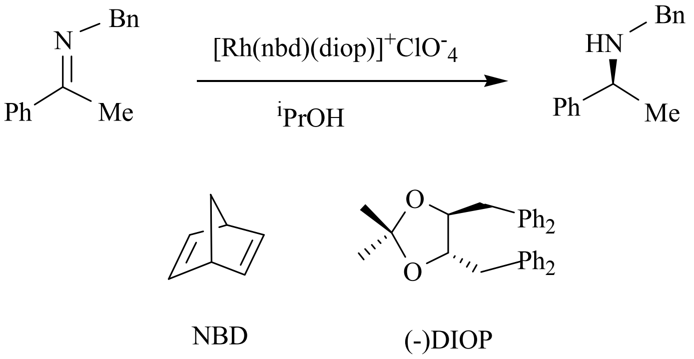
2.1.1 HOMOGENEOUS CATALYTIC REDUCTIVE AMINATION

Various metals such as Fe, Ru, Os, Rh, Ir, Ni, Pd and Pt and their complexes with inorganic ligands have been used in practice for hydrogenation of unsaturated organic compounds since very beginning [6]. With the advancement of organometallic chemistry [7], both symmetric and asymmetric complexes of Ru, Ir and Rh play a crucial role in reductive amination reaction viz. asymmetric hydrogenation [8-17]. Boyle *et al.* [9a] hydrogenated the -C=N bond in folic acid using a chiral rhodium complex to get dihydrofolic acid (**Scheme 2**). Tetrahydrofolate serve as an essential co-factor in the biosynthesis of nucleic acid.



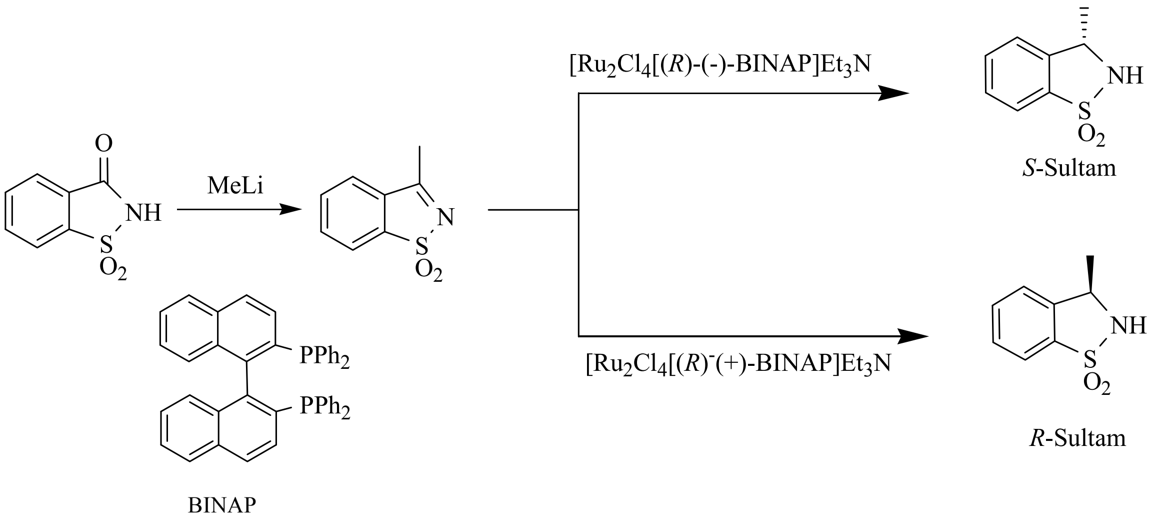
Scheme 2: Synthesis of Dihydrofolic acid

Scorrano *et al.* [10a] reported the asymmetric hydrogenation of imines using a catalytic amount of chiral $[Rh(nbd)(diop)]^{+}ClO_4^{-}$ (**Scheme 3**). Alterations in the optical property of the catalyst with the solvents used indicated the interaction of the solvent in the coordination sphere of the metal in such a manner to affect the geometry of the transition state.



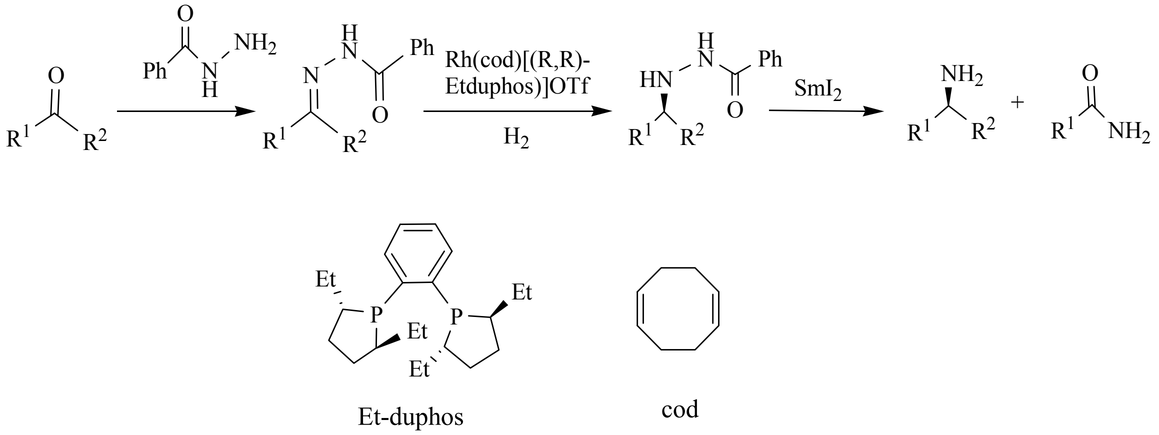
Scheme 3: Asymmetric hydrogenation of imines using a chiral Rhodium catalyst

Chiral Ruthenium complexes were used as effective chiral catalysts in asymmetric reductions of imines [11]. Oppolzer *et al.* [12] hydrogenated cyclic *N*-arylsulfonyl imines to enantiomerically pure Sultam using chiral *Ru*- BINAP complex (**Scheme 4**).



Scheme 4: Hydrogenation by a *Ru*- BINAPcomplex

Burk *et al.* [13] developed highly enantioselective hydrogenation of *N*-acylhydrazones derived from acetophenone or pyruvates and benzoylhydrazine in the presence 0.2 mol % of with a cationic Rh(I)-DuPHOS complex (**Scheme 5**).



Scheme 5: Enantioselective hydrogenation of *N*-acylhydrazone derivatives

Many other catalysts were also developed for enantioselective hydrogenation as shown below. Osborn [14] and Spindler [15] group developed independently the enantioselective hydrogenation of imines with two different chiral Ir- complexes as shown below (**Figure 1**). These catalysts exhibited reasonable catalytic activities with moderate to good enantioselectivities.

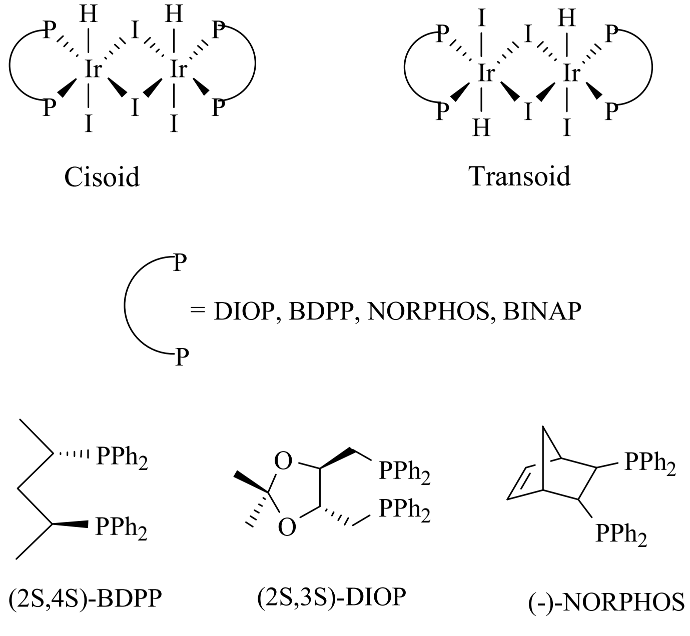


Figure 1:

Varying results of enantioselectivity were observed by changing ligands (P-P) and the imines (I, II, III) (**Figure 2**).

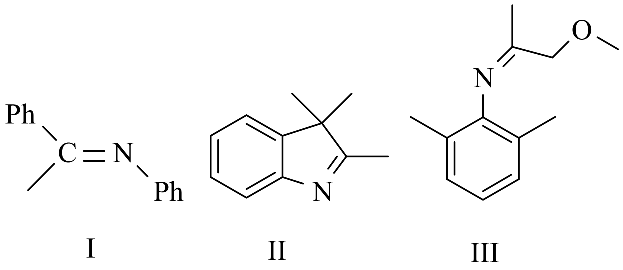


Figure 2:

Osborn *et al.* [14] synthesized a new type of C_2-symmetrical tridentate phosphine ligand for *in situ* preparation of an Ir catalyst in asymmetric hydrogenation of imines (**Figure 3**).

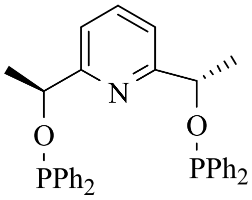
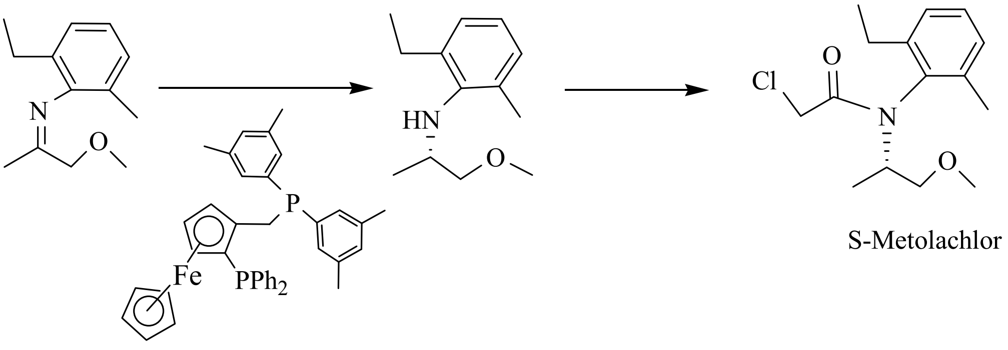


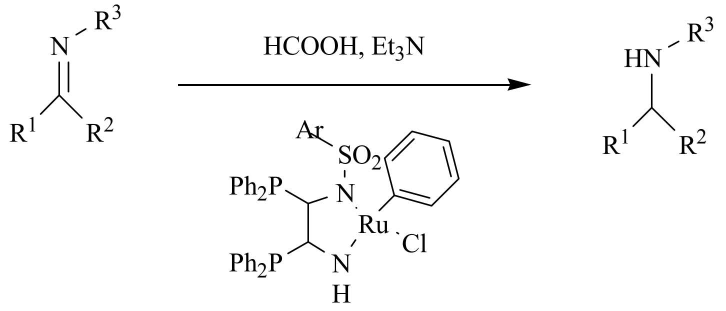
Figure 3:

Spindler *et al.* [15] has developed an industrial scale synthesis of a potent herbicide (*S*)-metolachlor using a new type of ferrocenylphosphine bound Iridium catalyst (**Scheme 6**).



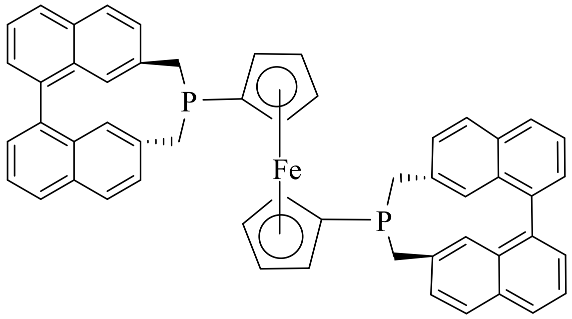
Scheme 6: Synthesise of (*S*)-metolachlor

Noyori *et al.* [16] reported an effective reductive amination protocol *via* transfer hydrogenation of imines using stable organic materials as hydride donors (**Scheme 7**). A variety of cyclic imines were reduced using formic acid- triethylamine mixture under mild conditions in the presence of 0.1-1 mol % of chiral diamine-bound Ruthenium complex.



Scheme 7: Reductive amination by chiral diamine-bounded Ruthenium complex

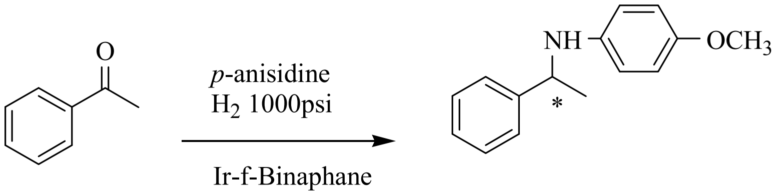
Zhu and Zhang [17a] reported an excellent reactivity and enantioselectivity using chiral ligand, *f*-Binaphane for Ir-catalyzed asymmetric hydrogenation of acyclic imines (99% ee) (**Figure 4**).



f-Binaphane 1,1'- bisphosphanoferrocene

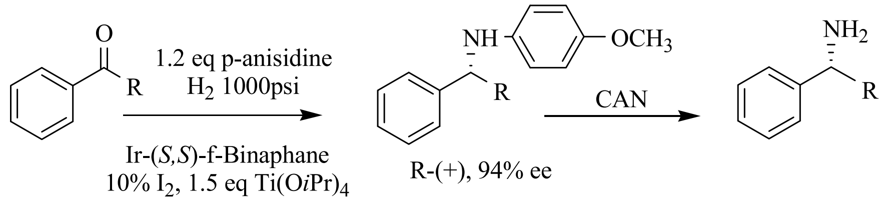
Figure 4:

The asymmetric hydrogenation of *N*-(1-phenylethylidene) aniline with *Ir- f-Binaphane* complex offered promising results with moderate to good enantioselection (84% *ee*) (**Scheme 8**). However, the ketones could not be hydrogenated by Ir complexes under the same conditions.



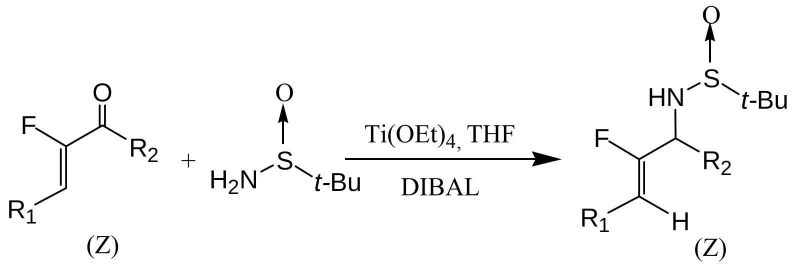
Scheme 8: Asymmetric hydrogenation of *N*-(1-phenylethylidene) aniline

The presence of Ti(O-*i*-Pr)$_4$ and I$_2$ during asymmetric reductive amination of aryl ketones with *Ir-f-Binaphane* catalyst offered high enantioselectivity with high order of catalytic acitivity. A number of chiral primary amines were synthesized from acetophenones through a two-step asymmetric reductive amination process (**Scheme 9)** [18]. Very recently Ganamgari *et al.* reported Iridium carbene complexes in direct reductive amination of aldehydes [19].



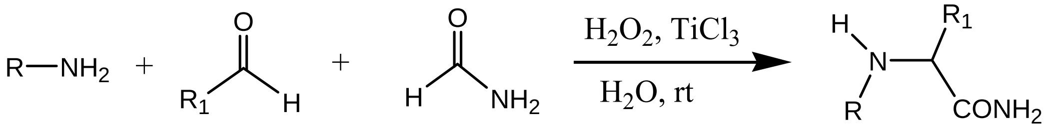
Scheme 9: Two-Step Asymmetric Reductive Amination Process

$Ti(OEt)_4$ catalyzed one-pot reductive amination of α-fluoroenones (α-fluoro-α,β-unsaturated ketones) *via* sulfinyl imine furnish *t*-butylsulfinamide in good yields and high diastereoselectivities using the common coordinating reagents including 9-BBN and DIBAL-H. X-ray analysis confirmed the S configuration for the newly created stereogenic center in *t*-butylsulfinamide, which was obtained from the corresponding Ellman (*S*)-sulfinamide using DIBAL-H as reducing agent [20].



Scheme 10: $Ti(OEt)_4$ catalyzed asymmetric reductive amination of α-Fluoroenones

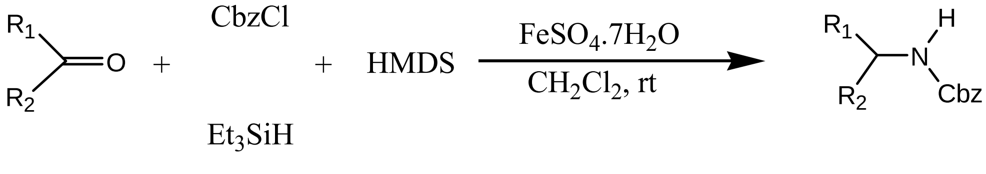
Two facile approaches leading to α-amino ester include either the addition of nucleophilic species (*e.g.,* organometallic reagents or cyanide ion) or alkyl radicals to the electrophilic glycine equivalents. Porta *et al.* [21] established a new strategy where instead of a cyanide ion, carbamoyl radical serve as a carboxylate synthon leading to α-amino acid amides. Ti(III) and Ti(IV) ions played important roles in generation of the intermediate reactive partners in a one-pot multicomponent reaction, therefore aqueous-formamide co-solvent, imines derived from aldehydes were found to undergo carbamoylation in good yields and may be visually monitored by observing the change of color (from blue to yellow) that occurs upon addition of H_2O_2 to the reaction mixture.



Scheme 11: Aqueous H_2O_2/ $TiCl_3$/$HCONH_2$ promoted synthesis of α-Aminoamides

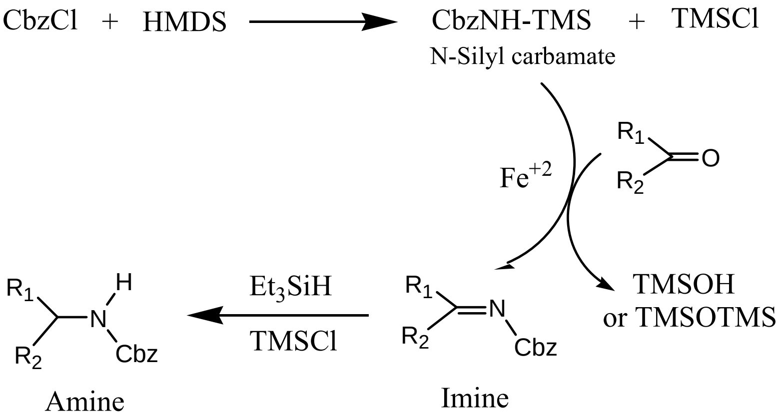
In addition of both an ultimately non-toxic TiO_2 metal residue and the reduction of waste solvents, the last step of this MCR synthesis is irreversible and that makes this methodology comparatively advantageous and more significant from an economically and ecofriendly point of view.

Yang et al. developed a catalytic four-component reaction of carbonyl compounds with HMDS, CbzCl and Et_3SiH to produce protected primary amines by a novel tandem nitrogen protection and direct reductive amination of carbonyl compounds [22]. In the presence of 5 mol % of $FeSO_4.7H_2O$, a wide variety of aldehydes and ketones were transformed into their corresponding protected primary amines in good to excellent yields using this MCR strategy (**Scheme 12**).



Scheme 12: Iron-catalyzed 4CR synthesis of protected amines through reductive amination

The mechanism of this MC amine synthesis has been presented in **Scheme 13**. The chemistry is further extended to masked carbonyl compounds including acetals, ketals, or vinyl ethers, where the CbzCl first reacts with HMDS and *in situ* generates the *N*-silylcarbamate along with chlorotrimethylsilane. $FeSO_4{\cdot}7H_2O$ itself or in combination with TMSCl catalysed the reaction of carbonyl compound with CbzNH-TMS that afforded imine, that on catalysis with together triethylsilyl hydride and TMSCl through direct reductive amination afforded the protected amines [22].



Scheme 13: Mechanism involved in MC amine synthesis

2.2 Heterogeneous Catalytic Reductive Amination

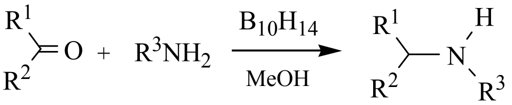
An economical and cost-effective direct reductive amination of imines with hydrogen using heterogeneous catalyst [23] such as *Pt*, *Pd*, *Ni* or *Ru* metals is in practice for a long time on an industrial scale. Recently Hosseini *et al.* developed a two-step reductive amination procedure using PtO_2 [24], for a library of pyrrolidinone-containing dipeptide analogues in high yield and diastereoselectivity too [24a]. The yield of the amines depends on the molar ratio and the structure of the substrates. However, sometimes it leads to a mixture of products resulting in low yields of the desired products [25]. The series limitations include the compounds with reducible functional groups and carbon-carbon multiple bonds [26] and sometimes the catalytic efficiency of the catalysts are compromised during reactions of compounds with divalent sulfur [27].

3. Reductive Amination with Boranes and Borohydrides

Boron compounds used in usual reductions of carbonyl compounds have also been used in the reductive amination of carbonyl compounds. Few of the representative examples are given below.

3.1 Reduction with Decaborane

Decaborane, a mild hydride reagent, has successfully been used by Yoon *et al.* [28] in reductive amination of carbonyl compounds to respective amines in good yields. It acts as dual catalyst for the two reactions *i.e.* imine formation and its subsequent reduction to the amine (**Scheme 14**).



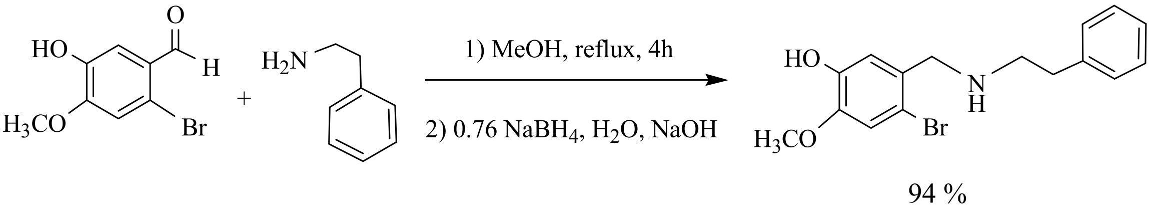
Scheme 14: Reduction by Decaborane

3.2 With Sodium Borohydride ($NaBH_4$)

$NaBH_4$ is known to reduce imines in the same manner as it reduces carbonyl group in aldehydes and ketones [17]. It has extensively been used in reductive aminations. However, its application is limited, as it reduces other reducible functionalities present in the same molecule.

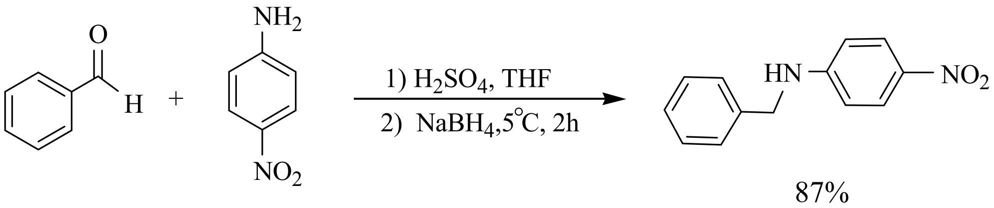
To eliminate the possibility of any other carbonyl group in being reduced in a one pot synthesis it is always essential that the carbonyl group is completely converted to imine. Therefore, it is favored for alkylation of amines favoring imine formation. Weak electrophilic carbonyl groups, poor nucleophilic amines and sterically hindered reactive centres do not favor the completion of imine formation. Therefore, with these substrates it is likely that neat $NaBH_4$ will not give good yields. The possibility of imine formation can be increased either by addition of other reagents or increase in temperature. Effect of various factors such as (a) solvent effect, (b) acidic additivies, (c) Zinc salts, (d) Titanium salts and (e) dehydrating agents during such reaction have been reported for better yields.

a. **Solvent effects:** Generally, methanol favors imine formation more than tetrahydrofuran (THF) or 1,2 dichloroethane.



Scheme 15:

b. **Acidic additivies:** The reactivity of the imines is enhanced with the addition of an acid. Reactions in acid-buffers and sulphuric acid in THF mixtures is know to give best result.



Scheme 16:

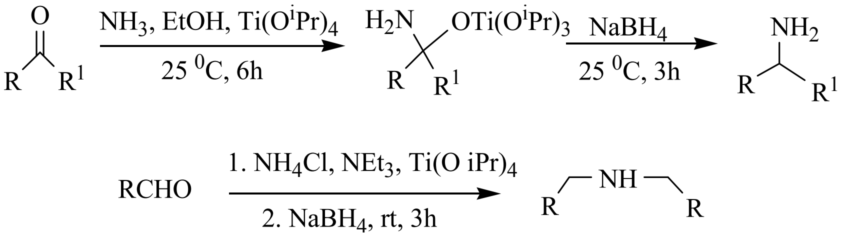
It should be noted that acid catalyzes the decomposition of $NaBH_4$ into:

$$NaBH_4 \quad + \quad 4H_2O \longrightarrow 4H_2 \quad + \quad NaB(OH)_4$$

To counter this side-reaction, Rohm and Haas have a special $NaBH_4$ product form that allows for slow release, *viz* VenPure AF caplets. [Reference]

c. **Zinc salts:** $ZnCl_2$ and $Zn(CF_3COO)_2$ in an inert solvent such as THF or isopropyl acetate yielded the amines from aldehydes in high yields *via* the *in-situ* formation of $Zn(BH_4)_2$.

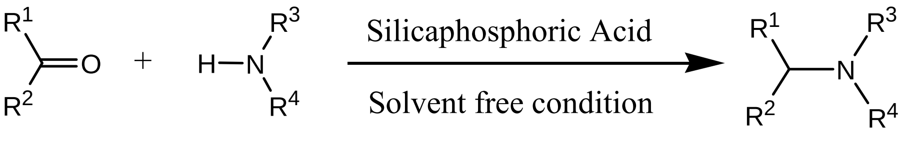
d. **Titanium salts:** $TiCl_4$ and $Ti(^iOPr)_4$ can be used to promote abstraction of H_2O during imine formation. Ti $(O^iPr)_4$–$NaBH_4$ has been used by Bhattacharya *et al.* in such reactions [29b]. Primary amines were obtained exclusively with ketones and the reaction conditions were compatible with various acid-labile groups such as N-Boc, carbamate, acetal and ketal. On the other hand, the reactions with aldehydes afforded chemoselectively the symmetrical secondary amines. This system is compatible with many functional groups such as chloro, methoxy, cyano, nitro and urethane. Syntheses of secondary amines are particularly significant in view of their usefulness as versatile pharmacophores, ligands and synthetic intermediates.



Scheme 17: Chemoselective synthesis of symmetrical secondary amines

e. **Dehydrating agents:** Several dehydrating agents such as molecular sieves and anhydrous metal sulphates encourage the imine formation. Water can also be removed azeotropically with benzene or toluene.

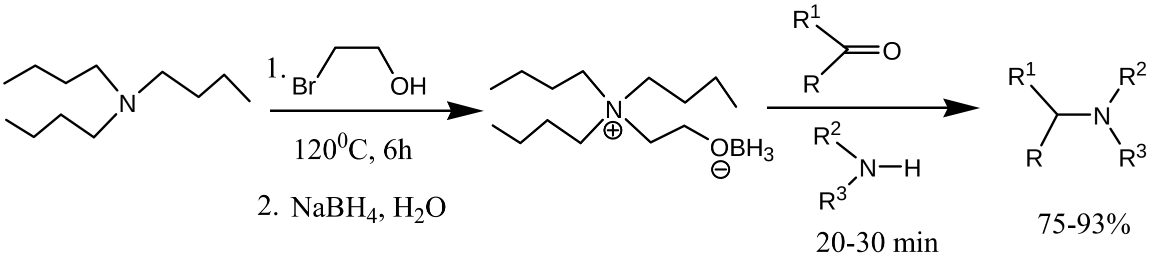
Very recently Alinezhad *et al.* described a solvent free method for the synthesis of amines by reductive amination of carbonyl compounds using $NaBH_4$ in the presence of silica phosphoric acid at room temperature. The method is versatile, chemoselective, fast, and high yielding [30].



Scheme 18: SiO_2 Phosphoric acid catalyzed reductive amination

Asymmetric reductive amination was applied for the synthesis of N-carbobenzyloxy-N1-phthaloyl-cis-1,2-cyclohexanediamine in enantiomerically pure form through *in situ* imine formation of (*R*)-phenylethylamine in the presence of $NaBH_4$–isobutyric acid followed by Curtius rearrangement [31]. $NaBH_4$ wet clay-microwave [32], $NaBH_4$ in micellar media [33], borohydride exchange resin [34], Ti(O-i-Pr)$_4$–$NaBH_4$ [35] and $NaBH_4$-$NiCl_2$ [36], $NaBH_4$/$ZnCl_2$ [37], $NaBH_4$/guanidine hydrochloride in H_2O [38] and $LiBH_4$ [39a] alone or in presence of Zn/AcOH [39b] were introduced for the efficient and selective reductive amination purpose.

Room temperature ionic liquids (IL) are known as designer solvents. Their properties including hydrophilicity, hydrophobicity, viscosity, Lewis acidity, and density may be altered by changing the cation and the counter anions and so these are recognized as green recyclable alternative reaction media for the immobilization of transition metal based catalysts, Lewis acids, and enzymes. Their high polarity and ability to solubilize both organic and inorganic compounds may result to enhance the reaction rates and also can provide higher selectivity than conventional solvents that results their green credentials towards increasing applications in organic synthesis.

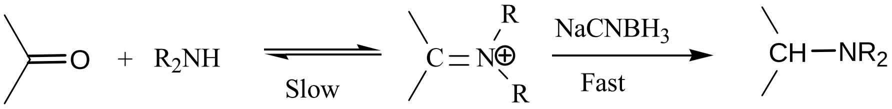


Scheme 19: Ionic liquid mediated reductive amination

Very recently, Mohanazadeh *et al.* developed 2-(tributylamino)-ethoxyborohydride as inexpensive ionic liquid for the reductive amination of amines with aldehydes or ketones and reported a procedure with marked improvements in terms of operational simplicity, increased yields, short reaction times (20-30 min), and mild and neutral conditions [40].

3.3 Sodium Cyanoborohydride ($NaBH_3CN$)

$NaBH_3CN$ has been extensively been used in reductive amination with remarkable selectivity [41]. The advantage with $NaBH_3CN$ is its stability in relatively strong acid solutions (pH = 3), its solubility in hydroxylic solvents such as alcohols, and its different selectivity at different pH values. This selectivity allows a convenient direct reductive amination procedure [42]. However, limitations associated with the method are that the reactions sometimes require up to fivefold excess of the amine, usually reactions are slow and sluggish with aromatic ketones and weakly basic amines, and often result in contamination of products with cyanide. The reagent itself is highly toxic and often results in highly toxic byproducts such as HCN and NaCN during work-up of the reaction.

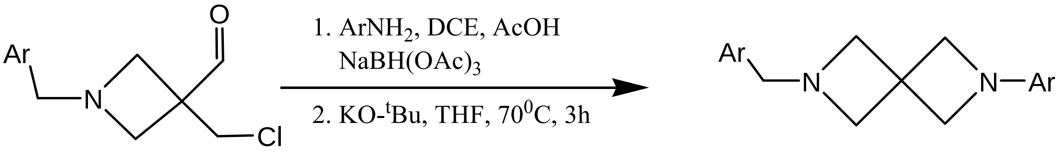


Scheme 20: Reduction by Sodium cyanoborohydride

Khan *et al.* developed 7-fluoro-3-aminosteroids series with potential antimicrobial activities by the nucleophilic fluorination of 7-β-hydroxysteroids, followed by reductive amination with spermidine in the presence of $NaBH_3CN$ [43]. The same reductive amination method has been applied by Rele *et al.* for the development of β-(1,3)-GlcA-GlcNAc dimeric and tetrameric glycoclusters through the conjugation of disaccharide groups onto a diaminodiamide aromatic scaffold aimed towards the study for carbohydrate-carbohydrate interaction [44a]. Yoon *et al.* synthesized aminoceramide mimetic for the conjugation to N-linked oligosaccharides having multivalent GlcNAc by reductive amination with aminoceramide using $NaBH_3CN$ [44b]. Tetrabutylammonium cyanoborohydride was used for the reduction of iminium salt to 8-azaestrone methyl ethers [45].

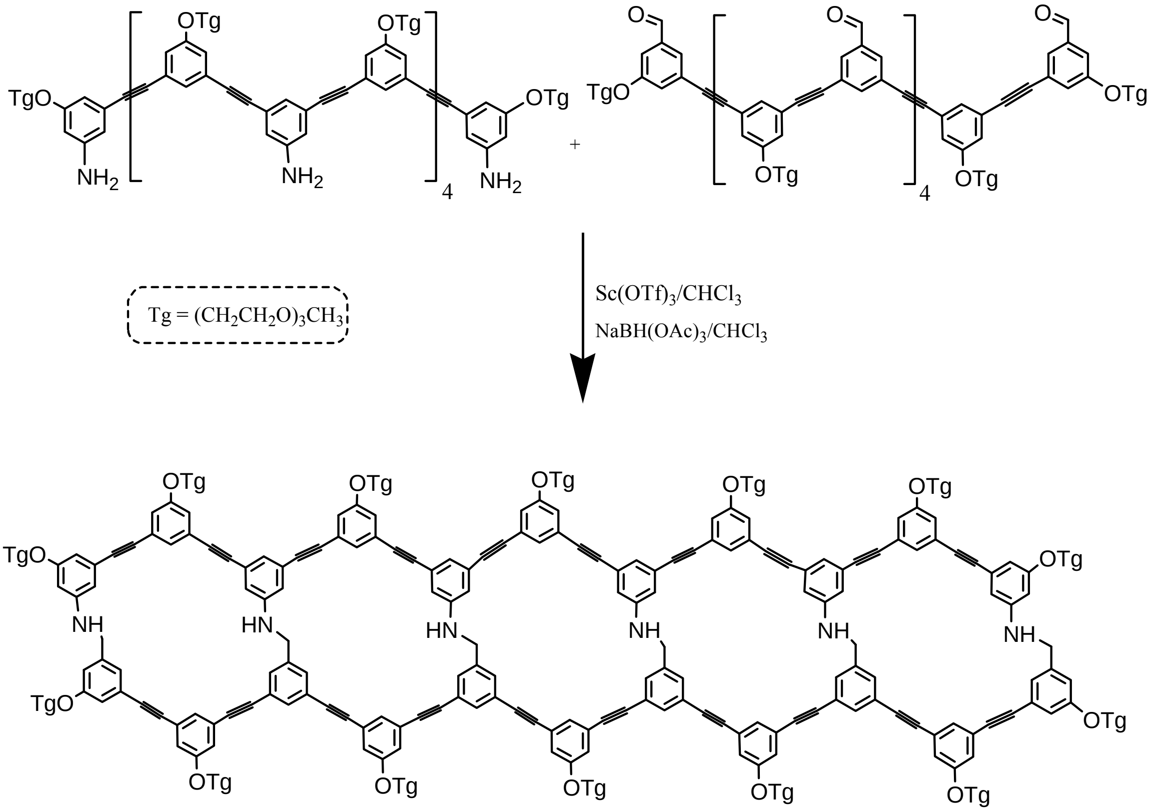
3.4 Sodium Triacetoxyborohydride

$NaBH(OAc)_3$ is a mild reducing reagent of general purpose that exhibits remarkable selectivity during reductive amination process [4,46]. Acyclic and cyclic ketones, aliphatic and aromatic aldehydes, primary and secondary amines including a variety of weakly basic and nonbasic amines are the effective substrates during reductions with $NaBH(OAc)_3$. Acetic acid has been used as co-catalyst occasionally. It can be used during reduction of compounds with acid sensitive functional group such as acetals and ketals and also in presence of other reducible functional groups such as C-C multiple bonds, cyano and nitro group. The steric and the electron withdrawing effects of the three acetoxy groups stabilize the boron-hydrogen bond. However, aromatic and unsaturated ketones and some sterically hindered ketones and amines when used as substrates do not give the desired results. Spirocyclic *bis*-azetidines, an interesting system has been synthesized by the reductive amination of chloro aldehyde with amines through first forming the iminium ion in dichloroethane in the presence of one equivalent of AcOH latter on treatment with $NaBH(OAc)_3$ followed by cyclization (**Scheme 21**) [47].



Scheme 21: Synthesis of Spirocyclic *bis*-azetidines

Moore *et al.* have synthesized the self assembly of [n]-rung molecular ladders using imine bond formation to cross-link discrete *m*-phenylene ethynylene oligomers. The rungs were constructed upon imine bond formation in $CHCl_3$ between an oligomer bearing six aldehyde group with a complementary oligomer functionalized having six amino groups and the ladders was trapped by irreversible reduction of the imine bonds with $NaBH(OAc)_3$ as shown in **Scheme 22** [48a]. Very recently the imine bond formed by the reversible condensation of an amine and an aldehyde and its applications as a dynamic covalent bond in the template-directed synthesis of molecular compounds has been nicely reviewed by Meyer *et al.* [48b].

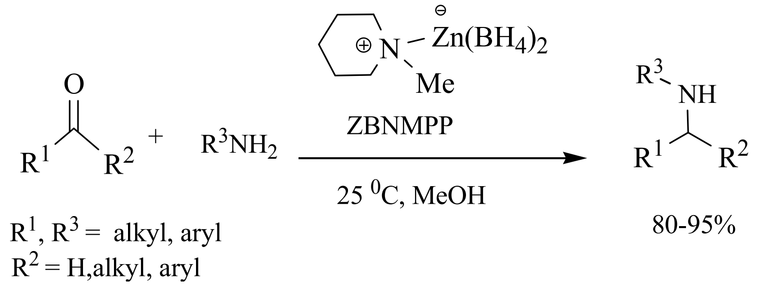


Scheme 22: Synthesis of a [6]-rung molecular ladder

Recently, Morandi *et al.* utilized $NaBH(OAc)_3$ for the selective reductive amination of carbonyl telechelic to tri- and tetrafunctionalized oligoisoprene [49].

3.5. Zinc Borohydride and its complexes as $ZnCl_2$, SiO_2 or *N*-Methyl-piperidine

$Zn(BH_4)_2$ [50], $Zn(BH_4)_2$–$ZnCl_2$ [51] and $Zn(BH_4)_2$–SiO_2 [52] were also utilized for reduction of imines or iminium intermediates during reductive amination reaction. Tajbakhsh *et al.* have very recently introduced *N*-methylpiperidine zinc borohydride (ZBNMPP) for efficient and chemoselective reductive amination of aldehydes and ketones [53].

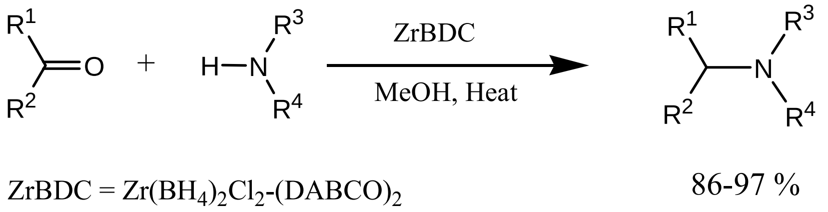


Scheme 23: Reduction by *N*-Methyl-piperidine Zinc Borohydride

It is an inexpensive as well as stable and safe-to-handle under neutral condition (pH = 7). The imine or iminium intermediates are converted easily to the corresponding amine even in presence of other functional groups and unsaturation.

3.6. Zirconium complex as catalyst for imine reduction

Firouzabadi *et al.* has used dichloro-*bis*(1,4-diazabicyclo[2.2.2] octane) tetrahydroborato zirconium (ZrBDC) for the successful reduction of imines, enamines, reductive amination of aldehydes or ketones and reductive methylation of amines. This compound is stable under mild aqueous acidic conditions (pH 4–6) and survives in H_2O for several days without losing its reducing abilities [54].



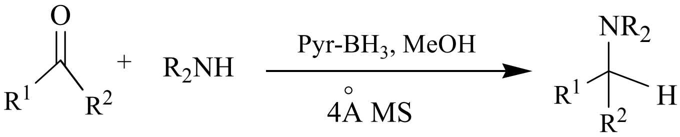
Scheme 24: $Zr(BH_4)_2Cl_2$-$(DABCO)_2$ catalyzed reductive amination

Heydari *et al.* developed a one-pot efficient reductive mono-alkylation method of amines or its functional derivatives such as hydroxyl amine or hydrazine using $LiClO_4$ (for *in situ* generation of imine, iminium ion, oxime, and hydrazone), and zirconium borohydride-piperazine complex as reducing agent [55]. The method is selective, useful for acid-sensitive moieties too and offers a wide range of synthetic utilities including the syntheses of the N-alkylated hydroxylamines or hydrazines.

3.7 REDUCTIVE AMINATION WITH AMINE-BORANE REAGENTS

3.7.1 Pyridine-Borane (Pyr-BH_3)

Di Mare *et al.* reported in situ reductive amination with different amines and carbonyl compounds using methanolic Pyr-BH_3 and 4Å molecular sieves [56].



Scheme 25: Reductive Amination Using Methanolic pyr-BH_3

Usually pyr-BH_3 of commercial origin is utilized without further purification. Due to its instability to heat and violent decompositions its industrial application is not recommended.

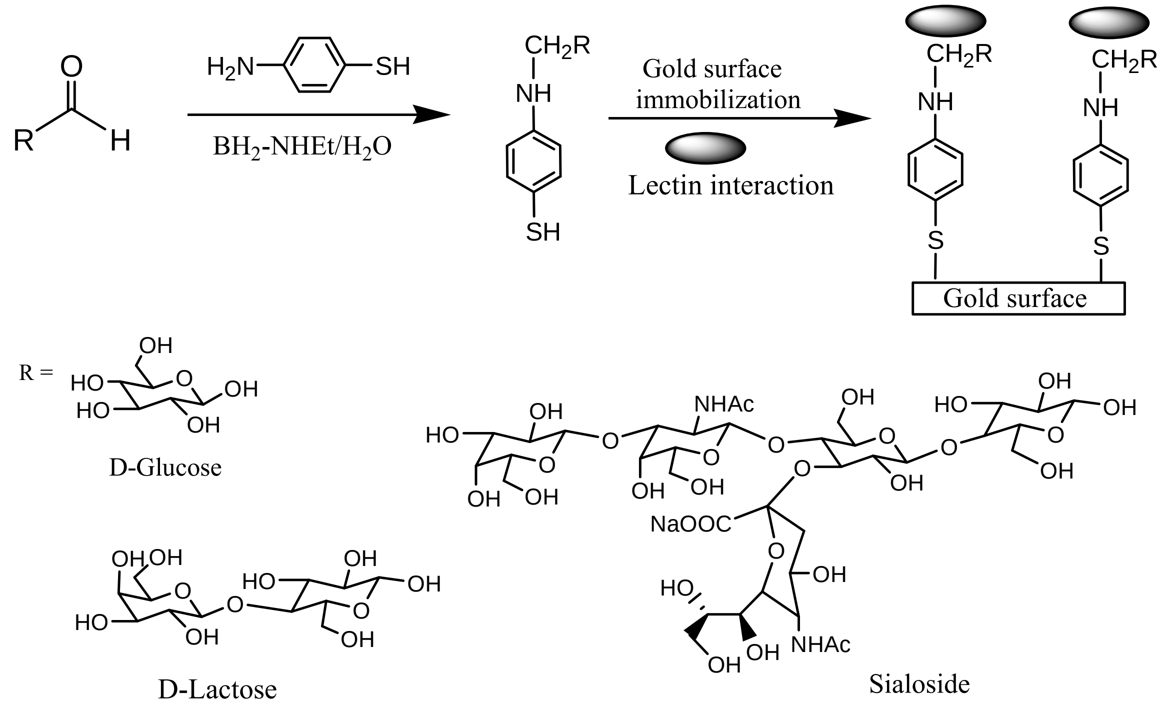
3.7.2 α-Picoline-Borane

Kikugawa *et al.* [57] reported one-pot reductive amination of aldehydes and ketones with amines using α-picoline-borane, a cheap and commercially available reducing agent an alternative to $NaBH_3CN$ and pyr-BH_3 but superior to pyr-BH_3 because of its commercially availability, crystalline nature and relatively more stability. MeOH/H_2O has been used as solvent for the reactions but neat conditions in presence of small amount of AcOH is also successful. The reaction in water as solvent offers a great opportunity for green chemistry.

3.7.3 Dimethylamine-Borane

Very recently Seo *et al.* developed a new coupling reagent with an aldehyde group of the terminal reducing sugar in the carbohydrate including D-glucose (monosaccharide), D-lactose (disaccharide), and GM1 pentasaccharide using dimethylamine borane (BH_2NHEt) for diverse carbohydrate types where direct oriented immobilization onto a gold surface is accomplished by coupling the amine group of a thiol group-bearing amino phenyl disulfide

[58]. This was successfully used for the studies of carbohydrates–biomolecule interactions and carbohydrate sensor or array development for diagnosis and screening.



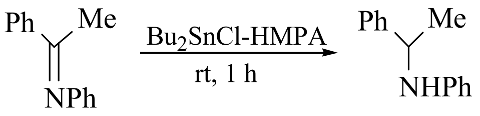
Scheme 26: Reductive amination for immobilization of Carbohydrates

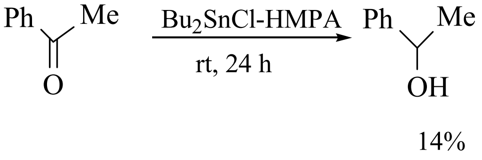
4. Tributyl Tin Hydride (Bu_3SnH) and Silicone Hydride derivatives

Bu_3SnH, *n*-Bu_2SnClH-HMPA, Et_3SiH–TFA, Ti(O-*i*-Pr)$_4$, and silicon hydrides such as polymethylhydrosiloxane and $PhSiH_3$–Bu_2SnCl_2 promote effective reduction of imines in chemo- and enantioselective manner [59, 60].

4.1 *n*-Bu_2SnClH-HMPA

Baba et al developed Bu_2SnClH-HMPA as a chemoselective reducing agent for imines. *N*-*R*-phenethylidene phenylamine was reduced to the respective secondary amine even at ambient temperature [61].



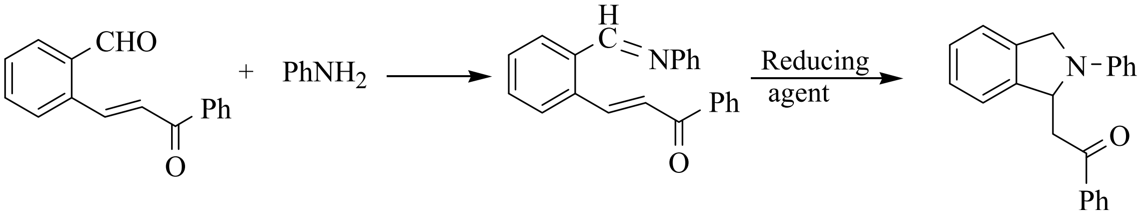


Scheme 27: Reductive amination by Bu_2SnClH_6 and a ligand HMPA

The very low reducibility of the respective carbonyl compound under same conditions emphasizes its excellent chemoselectivity during direct reductive amination.

4.2 Di-*n*-Butyliodotin Hydride (*n*-Bu_2SnIH)

It is an excellent reducing agent for the intramolecular reductive amination. Many nitrogen heterocycles were prepared *via* one-pot reductive amination of bifunctional substrates with an aldehyde and enone groups [62].



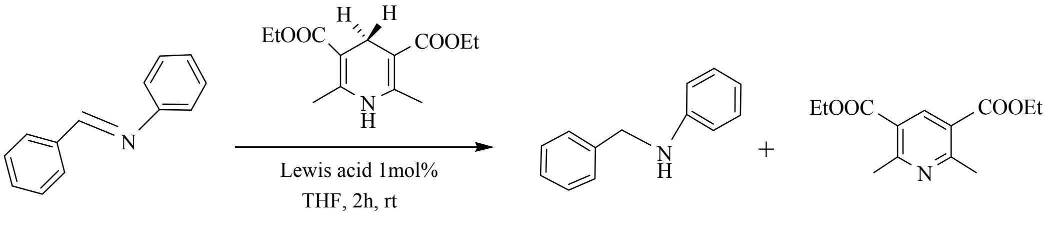
Scheme 28: One-pot reductive amination by Iodotin hydride

5. CHIRAL ORANO CATALYST IN REDUCTIVE AMINATION

Taking a clue from biochemical reactions involving NADH, a group of dihdropyridines have been used in direct reductive amination reactions.

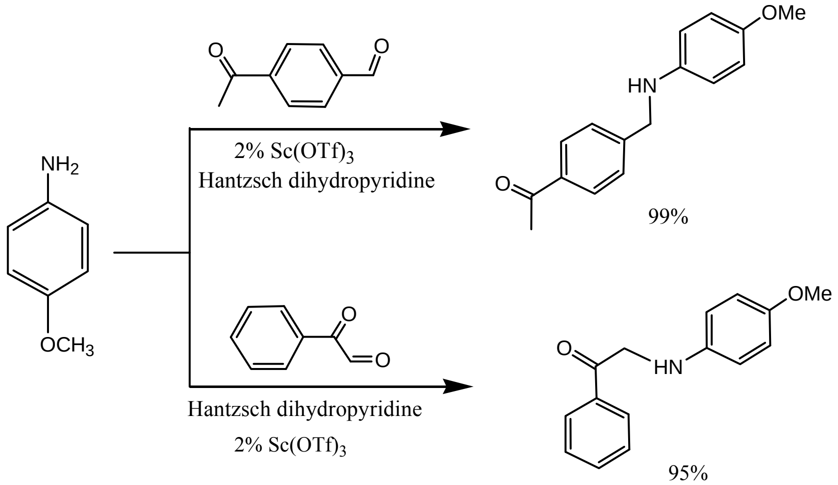
5.1 Hantzsch Dihydropyridine (HDHP) and Scandium Triflate as a Catalyst

For the direct reductive amination of aldehydes and ketones, Ohsawa *et al.* [62] used Hantzsch dihydropyridine as a reducing agent for imines in the presence of a catalytic amount of Lewis acid (1 mol% of $Sc(OTf)_3$ or $Sn(OTf)_2$) (**Scheme 29**).



Scheme 29: Reductive amination by Hantzsch dihydropyridine

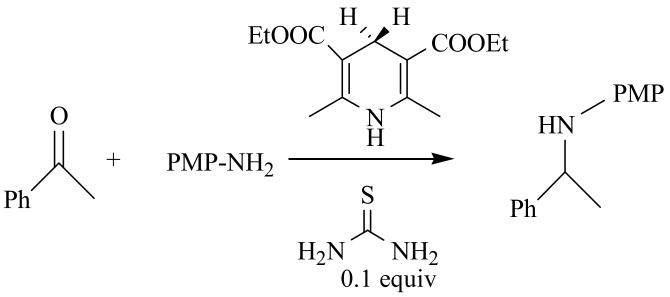
The reduction through Hantzsch dihydropyridine in $Sc(OTf)_3$ is completely chemoselective for aldehyde-derived imines over ketone-derived ones as shown in **Scheme 30** [63].



Scheme 30: Chemoselective reductive amination by Hantzsch dihydropyridine

5.2 Hantzsch Dihydropyridine and Thiourea as an Organocatalyst

Very recently Menche *et al.* reported the direct reductive amination of ketones, which exclusively relies on hydrogen bonding for imine activation. The reaction is mediated by catalytic amount of thiourea organocatalyst for hydrogenation transfer [64].



Scheme 31: Reductive amination using Hantzsch dihydropyridine

A variety of aromatic and aliphatic aldimines were reduced to give the respective amines under *N,N*-di-(3’,5’-tri-fluoromethyl) phenyl thiourea (**Fig. 5**) catalyzed through hydrogen-bonding activation with Hantzsch 1,4-dihydropyridine as the hydrogen source [65].

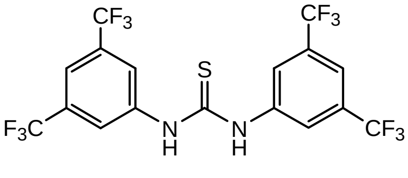
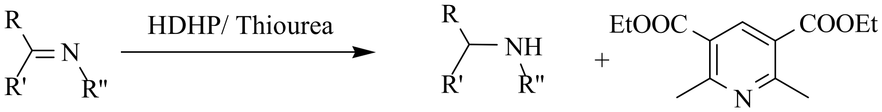


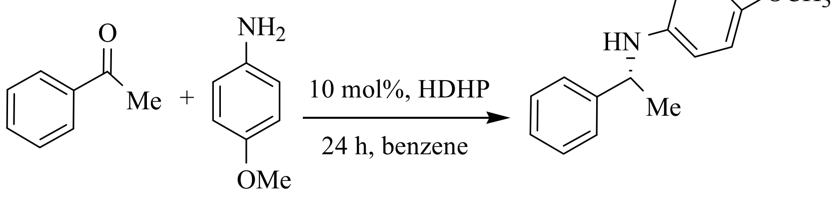
Figure 5

The first step consists in an equilibrium of ketone and amine with ketimine, which might be rate determining. Imine is un-affected without thiourea. However, reaction occurs only after hydrogen bond activation by thiourea to give intermediate C=N moiety which may be hydrogenated by the Hantzsch ester to produce amine adduct. For the catalytic cycle to proceed, a transfer of thiourea is required, to give complex with concomitant liberation of the final product *i.e.* amine.



Scheme 32: Reductive amination using Hantzsch dihydropyridine

Mac Millan *et al.* [69d] reported the first organocatalytic reductive amination, a biomimetic reaction that allows the asymmetric coupling of complex with chiral hydrogen-bonding catalysts and Hantzsch esters. They proposed that exposure of ketone and amine to a chiral hydrogen-bonding catalyst [66] results in an iminium species formation in presence of a suitable HDHP in asymmetric manner [67] (**Scheme 33).**

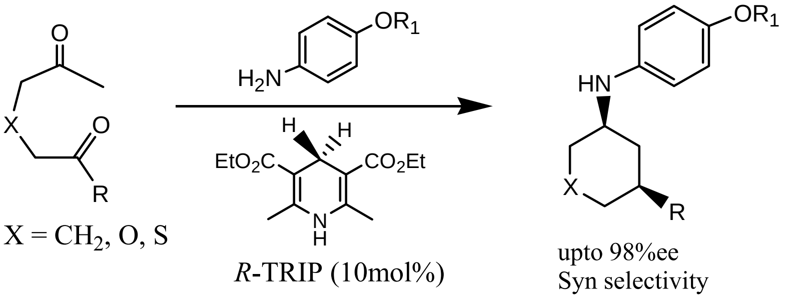


Scheme 33: Chiral hydrogen-bonding catalysts and Hantzsch esters

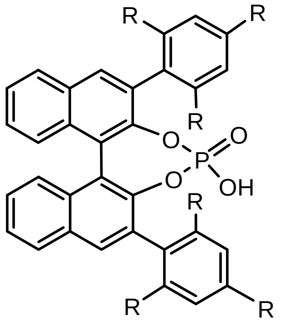
A series of biologically active sterically hindered aromatic amines were synthesized through one-pot reductive amination protocol using Hantzsch dihydropyridine organocatalyst [68].

5.3 Hantzsch Dihydropyridine and TRIP as an Organocatalyst

On the basis of the observations about the strong catalytic activity of salts consisting of chiral phosphate anion and chiral or achiral ammonium cation towards transfer hydrogenations of unsaturated aldehydes and ketones with Hantzsch esters [69], Hoffmann *et al.* recently reported the Bronsted acid catalyzed asymmetric imine reductions and reductive aminations [70].



Scheme 34: TRIP catalyzed reductive amination



R= i-Pr, (*R*)-TRIP

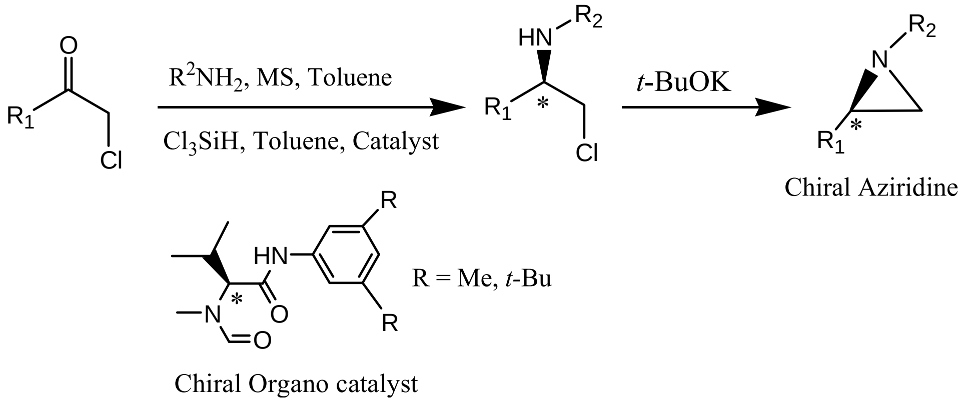
Figure 6

Hantzsch ester and *p*-TsOH catalyzed reductive amination of 2,6-heptandione with *p*-anisidine in toluene at 35 °C afforded methylcyclohexylamine derivative in racemic mixture. Very recently List *et al.* found a very high diastereo and excellent enantioselectivities in the product, if the substituted 2,6-diketones was treated with 1.5

equiv of *p*-alkoxyanilines in the presence of 2.2 equiv of Hantzsch ester and (*R*)-3,3'-*bis*(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate [(*R*)-TRIP, **Figure 6**] at 50 °C in cyclohexane and molecular sieves. Using this strategy the heterocyclic products were also found in high enantioselectivity. List *et al.* proved that in the final reductive amination step, the catalyst (*R*)-TRIP plays a crucial role for the observed *cis*-selectivity, however phosphoric acids catalyzed reaction alternatively to give the corresponding *trans*-isomer [71].

5.4 Valine derived amides as organocatalyst for chiral aziridines synthesis

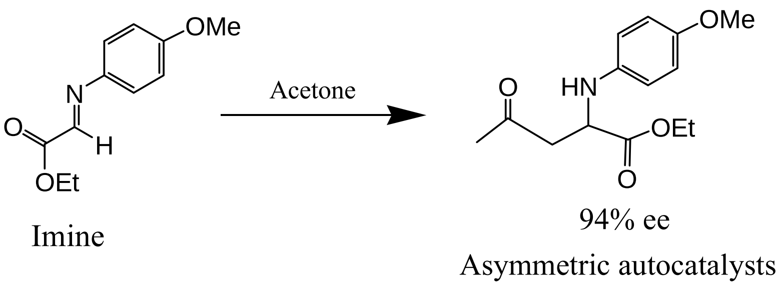
Aziridine ring not only constitutes the key structural feature in many of natural products, but also has served as important intermediates, chiral building blocks, auxiliaries, and ligands. Very recently, Malkow *et al.* developed an efficient synthesis of 1,2-diaryl aziridines by the enantioselective reductive amination of α-chloroketones using valine derived amides as chiral organocatalyst in a high enantiomeric excess [72].



Scheme 35: Enantioselective synthesis of aziridines

5.5 Functionalized amino acids as auto organocatalyst

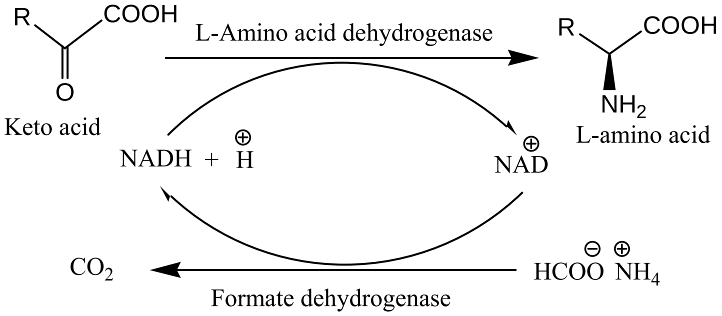
Asymmetric autocatalysis is the process of automultiplication of a chiral compound in which the chiral product acts as a chiral catalyst for its own formation [73]. Addition of acetone to imine *e.g.* N-protected amino ethylglyoxylate afforded functionalized amino acids. When 0.3 equivalents of reaction product at 99% ee were added to a mixture of acetone and the prochiral substrate, newly formed product could be isolated with 94% ee. Computational studies revealed that it acts as efficient chiral catalyst for its own formation [74].



Scheme 36: Functionalized amino acids as auto organocatalyst

6. FDH-cofactor based reductive amination of keto acid

Amino acid dehydrogenases (AADHs) catalyzed the reductive amination of R-keto acids to R-amino acids, with the concomitant oxidation of the cofactor NAD(P)H. Out of large number of identified AADHs, only few ones are industrially useful for the synthesis of enantiomerically pure R-amino acids such as alanine dehydrogenases (AlaDH), glutamate dehydrogenases (GluDH), phenylalanine dehydrogenases (PheDH) and even more leucine dehydrogenases (LeuDH). All of these dehydrogenases catalyze the reductive conversion of R-keto acids selectively to the L-amino acids having *S*-configuration [75].



Scheme 37: FDH-based enzymatic reductive amination to enantiomeric L-amino acid

Most of the synthetic work with LeuDHs has been performed with the enzymes from several *Bacillus* species and from *Thermoactinomyces intermedius*, which appeared to be

NADH-dependent. A number of different process concepts have been explored to efficiently operate the reductive amination process as depicted in **Scheme 37**. Lutz *et al.* [76a] developed processes with enzymes in EMR, and few groups are engaged in the development of whole cell processes [76b].

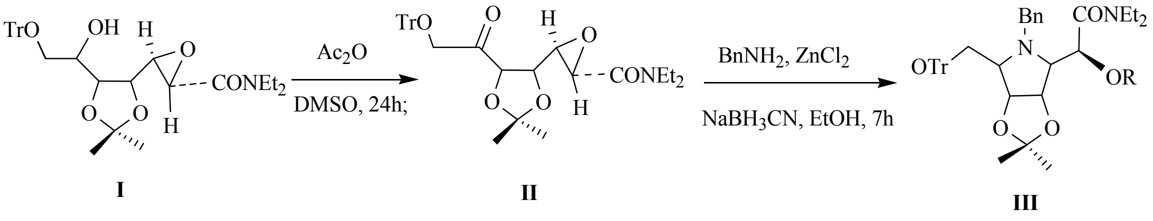
7. SOME MORE REPRESENTATIVE SYNTHETIC APPLICATIONS

Reductive amination is an important synthetic tool in organic synthesis, with enormous application in modern organic chemistry for the synthesis of chiral ligands and biologically important molecules.

7.1 Iminosugars *via* Reductive Amination of Epoxyamide

Iminosugars as glycosidase inhibitors for development of new drugs in several infectious, parasitic and metabolic diseases have been synthesized using reductive amination protocols [77].

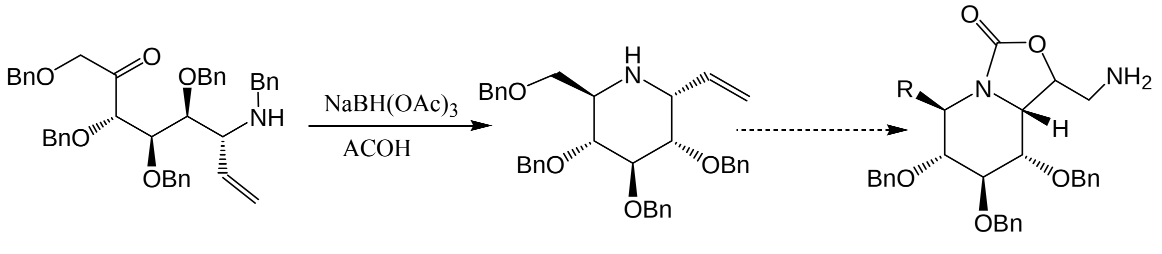
One pot reductive amination led to the formation of biologically significant pyrrolidines as shown below. The ketone (II) is obtained by oxidation of alcohol (I), which latter on treatment with ethanolic solution of benzylamine and zinc chloride in the presence of sodium cyanoborohydride afforded compound III (**Scheme 38**). The reduction of the imine and subsequent regioselective epoxide ring opening (SN^2) results to pyrrolidines *via* 5-exo intramolecular manner with (*S*)-configuration as the only isolable product.



Scheme 38: Stereoselective synthesis of pyrrolidine iminosugar

Intramolecular reductive amination of (2R,3R,4R,5S,6R)-N-Benzyl-3,4,5-tris(benzyloxy)-

2-benzyloxymethyl-6-(eth-2-enyl)piperidine afforded the C-vinyl nojirimycin derivative that on subsequent series of reaction afforded a library of nojirimycin based bicyclic iminosugars [78].


R = CH_2OH, COOH

Scheme 39: Intermolecular reductive amination for nojirimycin based bicyclic iminosugar

7.2 Double Reductive Amination

Polyhydroxylated pyrrolidines and piperidines were obtained via double reductive amination of the dicarbonyl sugars with primary amines using $NaCNBH_3$ as reducing agent [21b]. It is a direct and relatively short synthesis of 1-deoxynozirimycin, 1-deoxymannojirimycin and many other pyrrolidine azasugars as Glycosidase inhibitors. The latter has a great therapeutic value for the treatment of viral infections, cancer, diabetes and obesity [79].

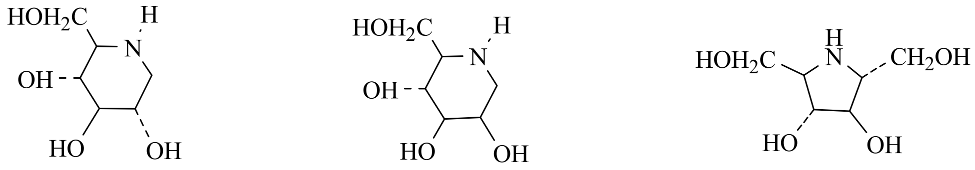
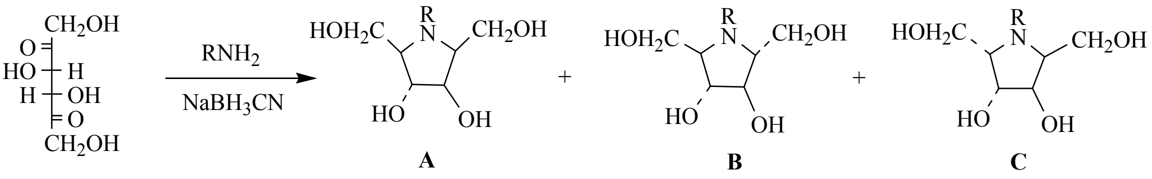

1-Deoxynozirimycin 1-Deoxymannojirimycin Pyrrolidine azasugars

Figure 7

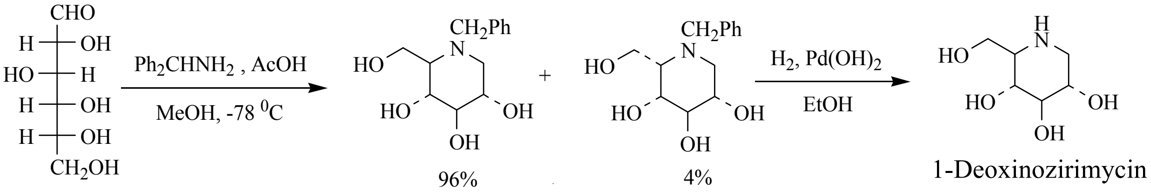
Several pyrrolidine derivatives were also prepared by reaction of D-fructose and primary amines using $NaCNBH_3$ as reducing agent.


5-Keto-D-fructose

When R = Ph_2CHNH_2, A:B:C = 86:8:6

Scheme 40: Synthesis of pyrrolidine ring by double reductive amination

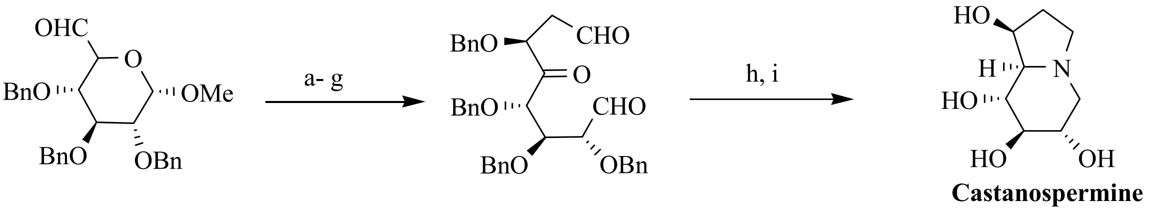
Double reductive amination of D-glucose with benzhydryl amine afforded a 96:4 mixture of D-glucitol: L-iditol in 70% yield. Removal of the benzyl group afforded 1-deoxynozirimycin**.** Where as D-xylo-hexos-5-ulose on double reductive amination with α-N-Boc-lysine methyl ester gave a 4:1-mixture of (10R)-N-methoxycarbonyl-(1-N-Boc-amino) pentyl-1-deoxynojirimycin [80].



Scheme 41: Synthesis of 1-deoxynozirimycin

7.3 Triple Reductive amination

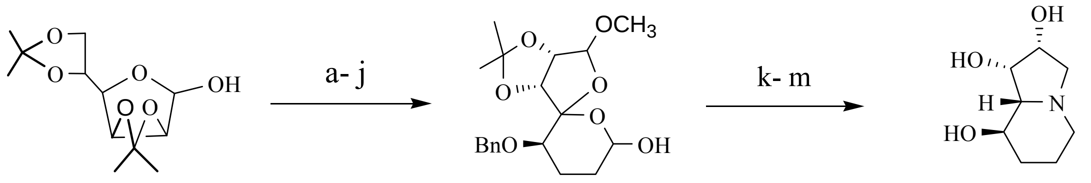
The polyhydroxindolizidine alkaloids such as castanospermine [81] and swainsonine [82] exhibiting potent glycosidase inhibitory activity have been obtained via triple reductive amination. Mootoo *et al.* [81a] described the synthesis of castanospermine via novel triple-reductive amination strategy on a carbohydrate-derived tricarbonyl precursor as shown in **Scheme 42**.



Reagents and conditions:(a) allyl bromide, Sn, CH_3CN-H_2O (10:1), ultrasound; (b) BnBr, NaH, n-Bu_4NI, DMF; (c) IDCP, CH_2Cl_2-MeOH; (d) Zn, 95% EtOH, (e) Swern oxidation; (f) O_3, CH_2Cl_2, -78 °C then Ph_3P; (g) THF-9 M HCl; (h) 1.3 equiv of NH_4HCO_2, 30 equiv of $NaCNBH_3$, MeOH; (i) 10% Pd/C, MeOH-HCOOH

Scheme 42: Synthesis of Castanospermine

The synthesis of Swainsonine has also been reported by Mootoo *et al.* [82] in very good yield by using reductive amination (**Scheme 43)**.



Swainosonine

Reagents and conditions: (a) PMBCl, NaH, n-Bu_4NI, DMF; (b) HOAc; (c) $NaIO_4$; (d) ATMS, BF_3OEt_2; (e) BnBr, NaH, n-Bu_4NI, DMF; (f) IDCP, CH_2Cl_2-MeOH; (g) Zn, 95% EtOH, (h) BH_3, THF, Na_2O_2; (i) Swern oxidation; (j) DDQ, Et_3N, CH_2Cl_2-H_2O; (k) NH_4HCO_2, $NaCNBH_3$, MeOH; (l) 10% Pd-C, MeOH-HCOOH; (m) HCl, THF-H_2O.

Scheme 43: Synthesis of Swainsonine

7.4 Synthesis of Pyrrolizidinone Amino Acid

Pyrrolizidinone amino acids (**Figure 8**) are rigid dipeptide surrogates in which the peptide backbone is constrained within a fused 5, 5-bicyclic structure [83].

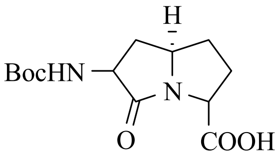
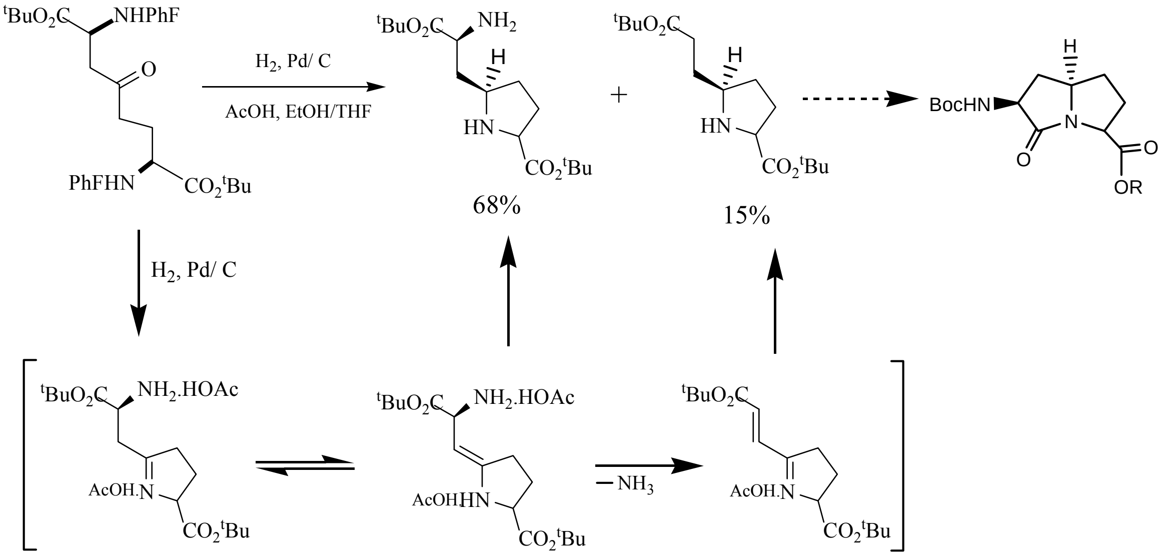


Figure 8

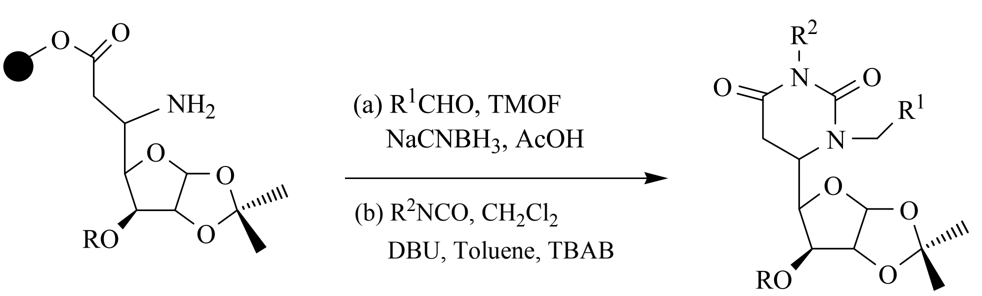
Enantiopure (3*S*, 5*R*, 8*S*)-3-[*N*-(Boc) amino]-1-azabicyclo [3.3.0] octan-2-one 8-carboxylic acid (**Scheme 44**) was synthesized via multi-step process involving reductive amination as a key step in the synthesis [83c]. In the reductive amination, hydrogenation of diamino substrate with Pd-C as catalyst in 9:1 EtOH/AcOH proceeded by cleavage of the phenylfluorenyl groups, intramolecular imine formation, protonation, and hydrogen addition to the iminium ion intermediate.



Scheme 44: Synthesis of Pyrrolizidinone Amino Acid

7.5 Synthesis of C-Nucleoside Analogs

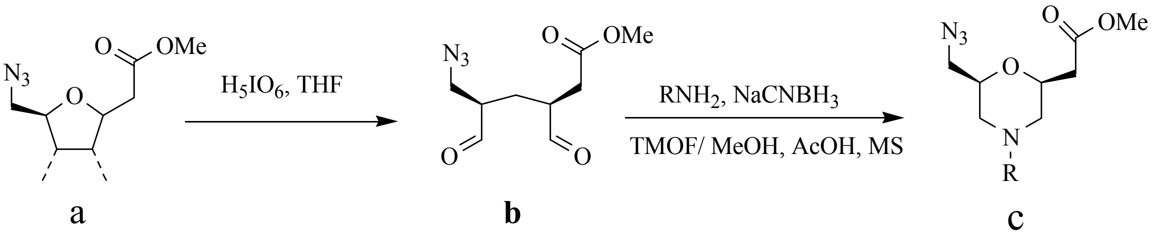
We have recently utilized this strategy for the development of a combinatorial library of C-nucleoside analogs on solid support (Wang resin). Thus aldehydes were reacted with resin bound amino glycosylated amine in presence of sodium cyanoborohydride/ trimethyl orthoformate to give the resin bound intermediate which undergoes cyclorelease amidation reaction on heating with DBU, afforded the desired C-nucleoside analogs with enzyme inhibitory activity (**Scheme 45**) [5a]. Few series of C-nucleosides with sugar both in pyranose and furanose form have also been developed by conventional method.



Scheme 45: Synthesis of C-Nucleoside Analogs

7.6 Morpholine based Amino Acids

Overhand *et al.* synthesized several morpholine based amino acid using double reductive amination as an important step [84]. The desired amino acids (c) were obtained after slow addition of an appropriate amine in MeOH, acidified with AcOH (pH= 5) in advance, to a mixture of (b) and $NaCNBH_3$.



Scheme 46: Synthesis of morpholine amino acid

7.7 Total Syntheses of (-)-Papuamine (I) and (-)-Haliclonadiamine (II)

Pentacyclic alkaloid Papuamine (I) and Haliclonadiamine (II), isolated from *Haliclona* a thin red sponge that overgrows and kills coral reef have been synthesized using this reaction [85].

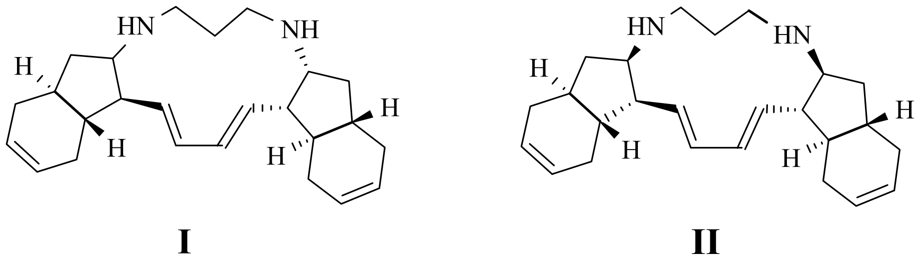
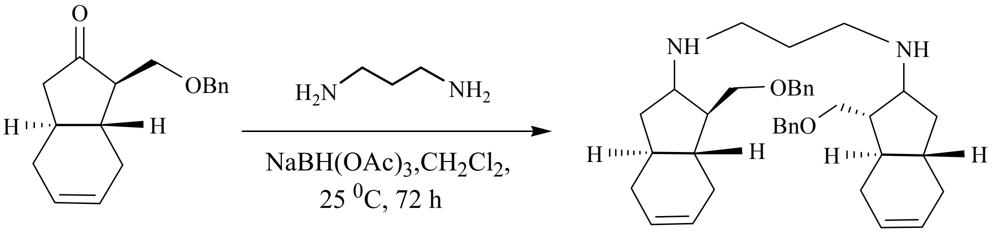


Figure 9:

The reaction consists in reductive amination with 1, 3-diaminopropane using sodium triacetoxyborohydride as a mixture of diastereomers (3.4:1) favoring the symmetrical diamine (**Scheme 47**).



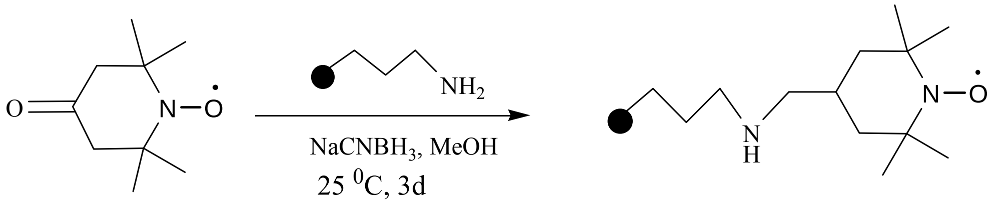
Scheme 47: Reductive amination for the synthesis of Papuamine

7.8 Synthesis of *N*-Chitosan useful for fiber development

Very recently the synthesis of PEG-N-chitosan was developed *via* reductive amination. Jian *et al.* showed the extents of PEGylation increased with reducing chain lengths of either chitosan or polyethylene glycol and electrospinning of PEG550-N,O-chitosan145 (at 25% in DMF) produced fibrous structure intermixed with beads. The efficiency of fiber formation and the uniformity of fibers were improved by increasing the solution [86].

7.9 Synthesis of TEMPO

Silica supported TEMPO (2, 2, 6, 6- tetramethylpiperidine-1-oxyl) catalyst useful in organic synthesis has been prepared by reductive amination [87] as shown below.

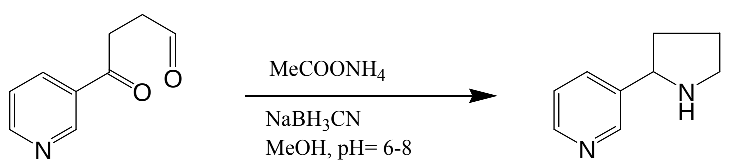


Scheme 48: Synthesis of silica supported TEMPO

7.10 Synthesis of Azaheterocycles

The pyrrolidine and piperidine heterocycles are the structural foundation of natural alkaloids and synthetic biologically active substances with a broad spectrum of pharmacological activities. These are applicable for the manufacture of herbicides, light-resistant polymers, plasticizers, accelerators of the vulcanization of rubber, special solvents, and catalysts of condensation reactions.

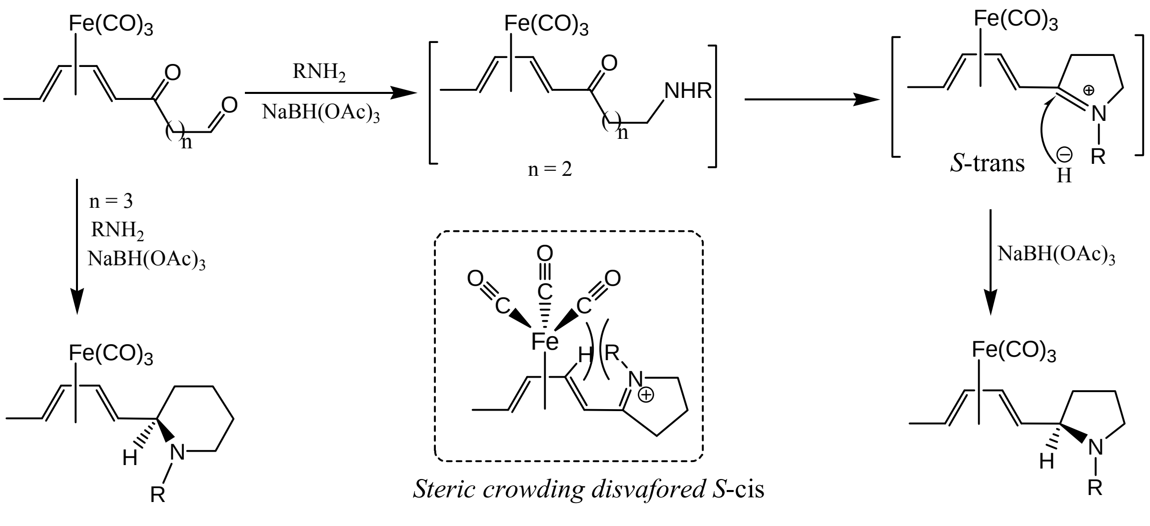
The synthesis of saturated five and six-membered azaheterocycles was developed by the use of hydride amination of aldehydes and ketones or catalytic intra- and intermolecular hydroamination of dicarbonyl compounds or ketones and amines of the furan series [88]. Catalytic hydroamination in liquid and vapor phases (catalytically activated hydrogen), formic acid and its derivatives (the Leuckart reaction), and complex metal hydrides (hydride amination) as the reducing agents were used for this purpose.



Scheme 49: Synthesis of Nornicotine

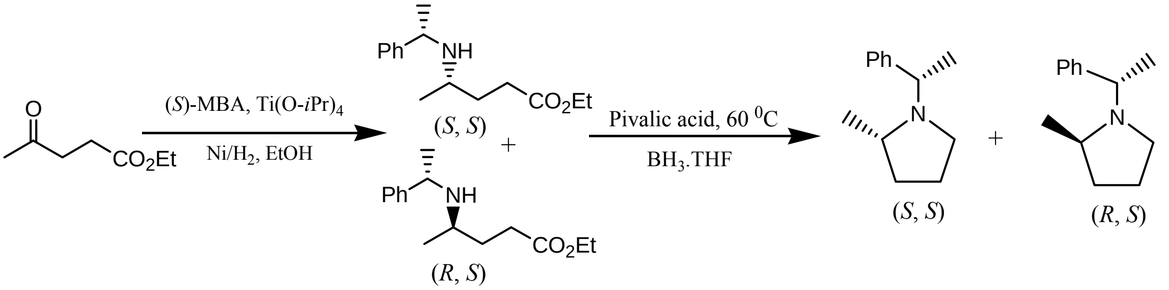
NaCNBH$_3$, a milder reducing agent than KBH$_4$, induces the reductive amination of polyoxo compounds, sometimes even with retention of the oxo functions. Considering the solubility and stability of the reducing agent, the reaction was carried out in methanol, water, and acetonitrile at pH 6-8, since at such pH values the imino group is reduced much more rapidly than the carbonyl group. Borch *et al.* have demonstrated the applicability of this reaction to the synthesis of nornicotine [89].

1,5-Keto-aldehyde having a side-chain of an η^4-dienetricarbonyliron complex in the presence of NaBH(OAc)$_3$ undergoes a double reductive amination sequence with primary amines and provide the corresponding piperidine products in good to excellent yield (**Scheme 50**). The dienetricarbonyliron complex plays an important role as powerful chiral auxiliary in this cascade process that exerting complete control over the stereoselectivity of the reaction, with the formation of a single diastereoisomeric product. After double reductive amination reaction, the tricarbonyliron moiety was removed using CuCl$_2$ and to afford the corresponding 2-dienyl-substituted piperidine [90].



Scheme 50: Stereoselective double reductive amination route to pyrrolidines and piperidines

Reductive amination of *t*-butyl acetylacetonate with α-methylbenzylamine (α-MBA) in the presence of H_2/Raney-Ni and Ti(O*i*Pr)$_4$, would allow a direct access to amino esters in good to high distereo selectivities. Using this protocol, the reductive amination product of ethyl 2-oxo-4-phenylbutanoate gave an advanced homophenylalanine building block for ACE inhibitor drugs and of ethyl levulinate followed by treating with pivalic acid and then BH_3-THF to give the protected chiral 2-methylpyrrolidine as an advanced amine intermediate for pharmaceutical drugs e.g. ABT-239 [91].

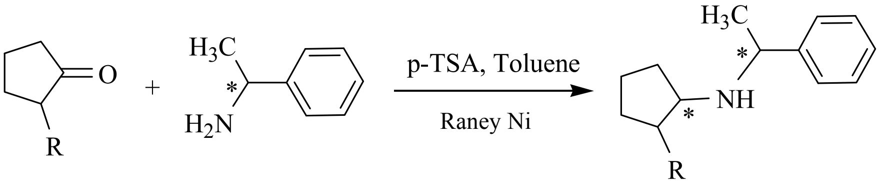


Scheme 51: Selective synthesis of unnatural amino asters

Besides these, several biologically actives heterocycles including 1,3,5-trisubstituted 1,4-diazepin-2-ones [92], 1-substituted benzimidazoles [93], Buflavine analogues [94], 4-functionalized Quinolines [95], Diazabicyclo [4.3.0]nonene based peptidomimetics [96], 5-epihyacinthacine A5 and ent-5-epihyacinthacine A4 [97] were synthesized by reductive amination. Recently (5R,2'S,5'S,6'S)-ribosyl-diazepanone, a core ribosyl seven-membered heterocycle of liposidomycins (a nucleoside antibiotic) was synthesized by reductive amination of an ribosylamino ester and an amino aldehyde followed by a peptidic coupling [98]. 3,4-Disubstitued piperidine derivatives were prepared without hydroxyl group protection of D-Ribose *via* a simple reductive amination reaction using 5% Pd [99]. Wong *et al.* developed a diastereoselective Pd-mediated reductive amination chemistry in connection with the chemoenzymatic synthesis of azido ketoses or aldoses prepared from aldolase reactions to five- or six-membered deoxy aza sugars [100]. The method received extensive importance as both enzymatic reactions and reductive aminations were conducted in aqueous solution without protection of the functional groups.

6.12 Synthesis of amidines

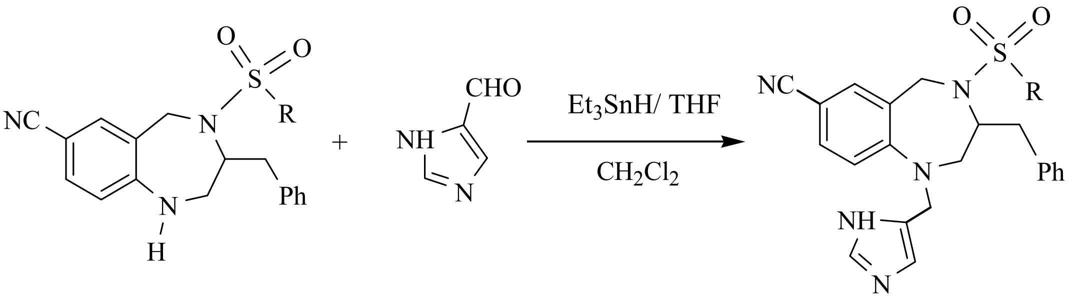
Mono and bicyclic amidines were prepared by asymmetric reductive amination and followed by subsequent lethargic reaction as presented in **Scheme 52** [101].



Scheme 52: Synthesis of amidines by asymmetric reductive amination

Condensation of the racemic 2-substituted cyclopentanones with optically active (*R*)-(+)- and (*S*)-(–)- 1-phenylethylamine respectively, led to the formation of imines which were hydrogenated in situ with Raney nickel at room temperature in a Parr shaker for a period of 5-11 days affording diastereomerically pure secondary *cis*-2-substituted N-(1-phenylethyl)- cyclopentamines in good yield.

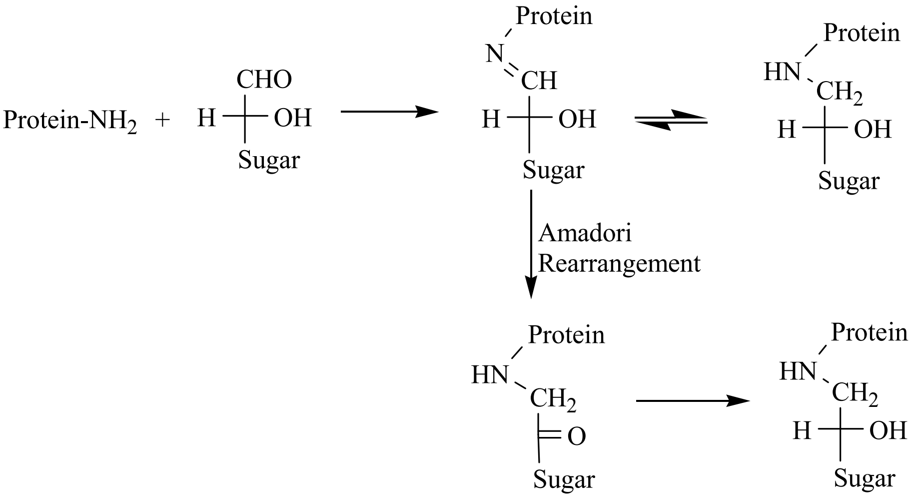
Chen *et al.* [102] reported an improved synthesis of 1-(4-imidazolyl)-methyl-4-sulfonyl-benzodiazepine as farnesyltransferase inhibitors, involving a novel reductive N-alkylation method (**Scheme 53**).



Scheme 53: Synthesis of 1-(4-imidazolyl)-methyl-4-sulfonylbenzodiazepine

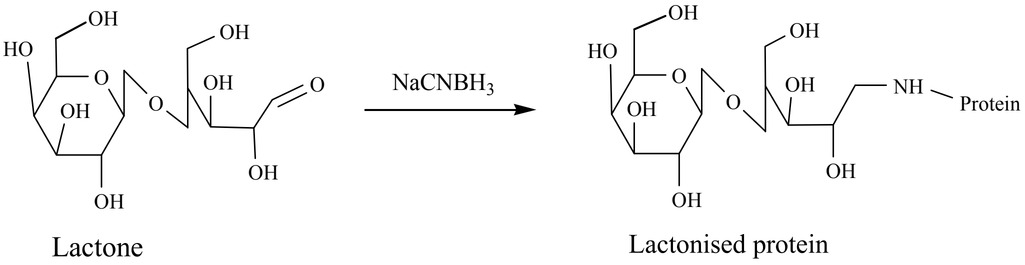
7. BIOLOGICAL APPLICATIONS

Large alkyl substituents in proteins are introduced by reductive alkylation method for enhancing the hydrophobicity and decreasing the solubility of many the proteins. The free aldehyde from of reducing sugar has been coupled to protein by reductive amination [103-106]. The reactions of hemoglobin with glucose and glyceraldehydes have also been studied in detail in order to understand its nonenzymatic glycosylation. Reactivity in the presence of reducing agents appears to reflect rates of aldimine formation, whereas those in its absence appear to reflect the slower rearrangement to a ketoamine (**Scheme 54**).



Scheme 54: Reductive amination of reducing sugar with proteins

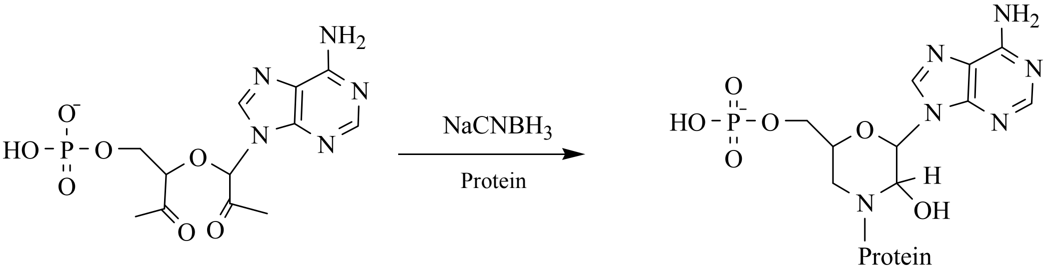
Like other modification of its amino termini, the reaction of hemoglobins with glyceraldehydes and glycol aldehydes inhibit its polymerization [107]. Di-, tri- and higher oligosaccharides can be used to prepare a wide variety of more complex amino-1-deoxyglycitol derivatives as shown in **Scheme 55**.



Scheme 55: Synthesis of amino-1-deoxyglycitol derivatives

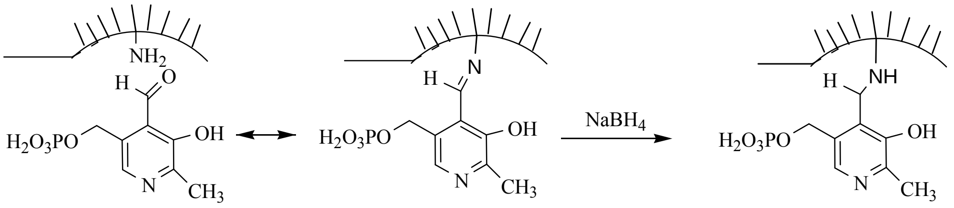
Several sugar derivatives with isolated aldehydic group of sugars have also been coupled to proteins by reductive alkylation. This reaction has also been used to introduce amino groups into the terminal galactose moiety of glycopeptides and glycoproteins, converting them into 6-amino-6-deoxygalactose [108] and various N-substituted 6-amino-6-deoxy-galactose derivatives [109, 110]. The reductive amination reaction has also been used to incorporate proteins into aminoglucose derivatives of polyacrylamide [111] and to prepare reagents which can be used to incorporate the oligosaccharides into proteins [112, 113].

Dialdehyde derivatives of nucleosides, nucleoside 5'-mono, di-, triphosphate, NAD, other dinucleotides, t-RNA and other polynucleotides with a pair of vicinal hydroxyl groups has been prepared in a single step from the parent compound and coupled to lysine residues in the nucleotide binding sites of proteins by reductive alkylation [114-117].



Scheme 56: Reductive alkylation in proteins

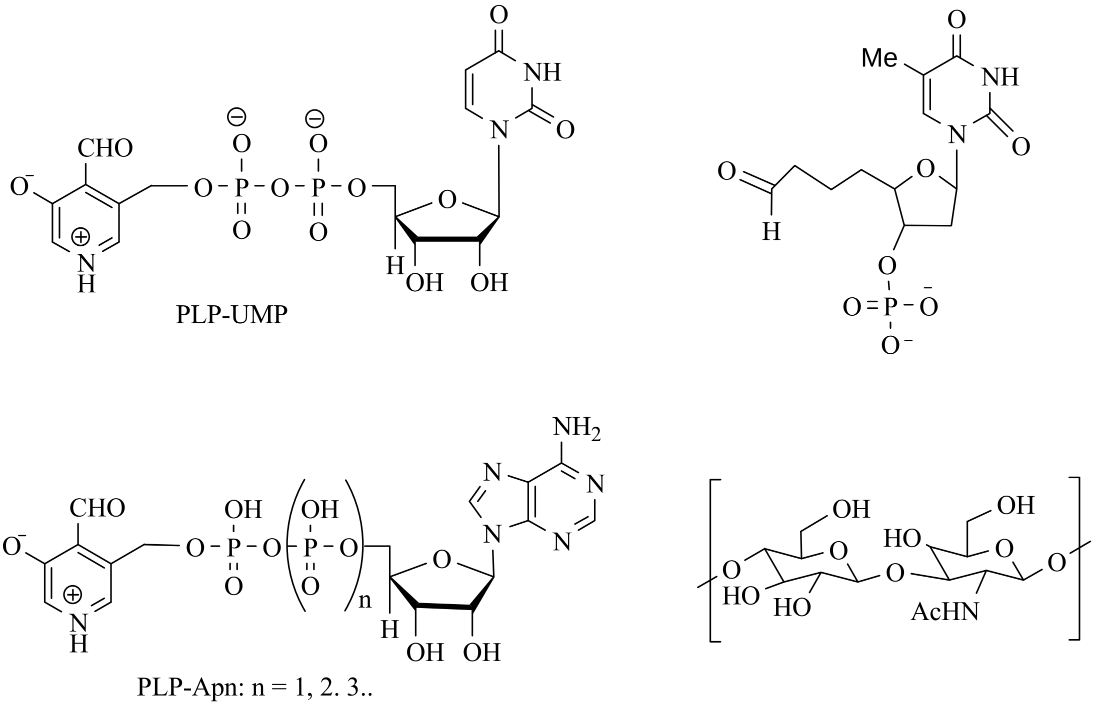
The higher reactivity of pyridoxal phosphate with amino groups and its ability to interact with phosphate binding sites of proteins enabled its use as an affinity label for phosphate, phosphate ester, and other anion binding sites [118].



Scheme 57: Pyridoxal phosphate binding sites with proteins

A conjugate of pyridoxal phosphate and uridine 5′-phosphate, pyridoxal diphosphouridine has been used as an affinity level for the UDPG binding sites of glycogen synthase [119]. Reduction with sodium borohydride, however, rendered its reversiblity and led to the isolation of a fluorescent peptide presumably from the UDPG binding site.

Similar conjugates of pyridoxal phosphate with adenosine 5′-mono, di-, and triphosphates and guanosine 5′-monophosphate have been used to label nucleotide binding sites in a number of enzymes [120]. Many other carbonyl compounds have been used for the reductive alkylation of proteins (**Figure 10**) [121-128].


PLP-UMP

PLP-Apn: n = 1, 2. 3..

Figure 10

Szoka *et al.* [128] synthesized HA-lipid conjugates of defined length by generation of a free aldehyde group at the nonreducing end of hyaluronic acid, ozonolysis followed by subsequent reduction of the generated ozonide. The resulting aldehyde functionalized HA is then coupled to dipalmitoyl phosphatidylethanolamine (DPPE) using reductive amination chemistry. Silverman *et al.* recently reported the use of covalently attached

DNA as a structural constraint for rational control of macromolecular conformation; reductive amination was employed to attach each strand of the duplex DNA constraint to RNA constraint, utilizing an aldehyde as the 5′-terminus of the DNA and 2′-amino-2′-deoxy-RNA [129].

CONCLUSION

The present review illustrates various reagents used for reductive amination reactions. The chemical and biological significance of reductive aminations is also reviewed systematically aiming to be more informative, interesting and useful for readers. Wherever possible, methods of preparation of complex reducing agents and limitations of reducing agents are also described. Emerging applications of this reaction for the development of chiral ligands, pharmacologically active molecules, combinatorial scaffold, and key step in the total synthesis of some interesting natural products as well as their role in a number of important biological processes is presented. Reductive amination, a simple and versatile reaction, undoubtedly will be applied even more widely in the future both in synthetic and biological system.

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ABBREVIATIONS

AADHs	Amino acid dehydrogenases
ACE	Angiotensin converting enzyme
BINAP	S(-)-2,2'-Bis(diphenylphosphino)-1'1-binaphthyl
BDPP	(2S, 4S)-Bis-(diphenylphosphino) pentane
Et-DUPHOS	1, 2-Bis (ethyl-phosphino) benzene
(*R*)-TRIP	(*R*)-3,3’-*bis*(2,4,6-triisopropylphenyl)-1,1’-binaphthyl-2,2’-diyl hydrogen phosphate
9-BBN	9-Borabicyclo[3.3.1]nonane
COD	Cyclo-octa-1,5-diene
DABCO	1,4-Diazabicyclo[2.2.2]octane
n-Bu_2SnIH	Di-*n*-Butyliodotin Hydride
DIBAL-H	Diisobutylaluminum hydride
ZrBDC	Dichloro-bis(1,4-diazabicyclo[2.2.2]octane)tetrahydroborato zirconium
DIOP	[2,2-Dimethyl-1,3-dioxolane-4,5-di-yl-*bis*-(methylene)]-*bis*-diphenylphosphine
DPPE	Dipalmitoyl phosphatidylethanolamine

ee	Enantiomeric excess
EMR	Enzyme-membrane reactor
HDHP	Hantzsch dihydropyridine
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HA	Hyaluronic acid
IL	Ionic liquid
$LiClO_4$	Lithium perchlorate
(S)-MBA	α-Methylbenzylamine
ZBNMP	*N*-Methylpiperidine zinc borohydride
MCR	Multi component reaction
NAD	Nicotinamide adenine dinucleotide
NBD	Norboran-2,5-diene
NORPHOS	Norboranphospholane
KBH_4	Potassium borohydride
$Sc(OTf)_3$	Scandium triflate
$NaBH_4$	Sodium borohydride
$NaBH_3CN$	Sodium cyanoborohydride
$NaBH(OAc)_3$	Sodium triacetoxyborohydride
TEMPO	2, 2, 6, 6- tetramethylpiperidine-1-oxyl
PTSA	*p*-Tolyl sulphonic acid
Bu_3SnH	Tri butyl tin hydride
TMS	Tri methyl silyl
$Ti(O\text{-}i\text{Pr})_4$	Titanium tetra isopropoxide