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New potential of the reductive alkylation of amines

K N Gusak, Zh V Ignatovich, E V Koroleva

Institute of Chemistry of New Materials, National Academy of Sciences of Belarus
ul. F Skoriny 36, 220141 Minsk, Republic of Belarus

Available data on the reductive alkylation of amines with carbonyl compounds — a key method for the preparation of secondary and tertiary amines — are described systematically. The review provides information on the relevant reducing agents and catalysts and on the use of chiral catalysts in stereo- and enantiocontrolled reactions of amine synthesis. The effect of the reactant and catalyst structures on the reaction rates and chemo- and stereo(enantio)selectivity is considered.
The bibliography includes 156 references.

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I. Introduction

Most of the natural and synthetic biomolecules contain an amine moiety, which plays a key role in the manifestation of the therapeutic effect of amine-based drugs. This fact stimulates the search for efficient methods for synthesis of amines. The catalytic formation of the C–N bond involving an asymmetric carbon atom is of fundamental importance for organic chemistry since molecules with amine functionality are key synthons in synthesis of many important natural compounds. This is responsible for the appearance of a new area of application of the reductive alkylation reaction as a universal tool for synthesis of chiral synthons for natural and biologically active compounds containing functionalized amine moieties. In spite of its long history, this reaction remains a topical object for science and engineering.

K N Gusak Candidate of Chemical Sciences, Senior Researcher at the ICNM, NAS of Belarus.
Telephone: +37(517)237–6798, e-mail: kgusak@yahoo.com
Current research interests: the chemistry of heterocyclic compounds, multicomponent reactions in organic synthesis.
Zh V Ignatovich. Candidate of Chemical Sciences, Senior Researcher at the same Institute.
Telephone: +37(517)237–6798, e-mail: ignatovichz@inbox.ru
Current research interests: synthesis of heterocyclic compounds.
E V Koroleva Doctor of Chemical Sciences, Associate Professor, Chief Researcher at the same Institute.
Telephone: +37(517)237–6798, e-mail: evk@ichnm.basnet.by
Current research interests: the chemistry of heterocyclic compounds, synthesis of biomolecules.

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Among the approaches to the synthesis of amines, the most common methods are alkylation,[1,2] reductive alkylation,[3–9] the Mannich reaction[10] and hydrogenolysis of carboxamides.[11] The reductive alkylation of amines (or the reductive amination of aldehydes and ketones) is one of the simplest methods for synthesis of amines; currently, this method is a universal tool for the introduction of a nitrogen atom into intermediates of synthesis of natural compounds and their analogues widely demanded in chemical industry, pharmaceutics and bioengineering.

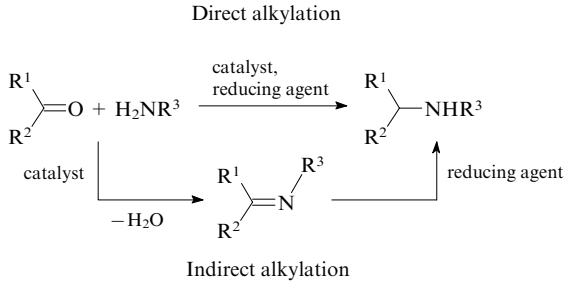
The reaction of a carbonyl compound with a primary or secondary amine in the presence of a reducing agent proceeds through an imine (iminium salt) intermediate, which is then reduced to a more substituted amine. From the standpoint of conversion of the initial amine in the reaction with a carbonyl compound, the reaction is amine alkylation, whereas from the standpoint of conversion of the carbonyl-containing substrate, the reaction is amination; therefore, it has two names.

A version of the reductive alkylation is the Leuckart–Wallach reaction in which formic acid or ammonium formate acts as a reducing agent.[12,13]

As compared to the other methods of synthesis of amines, the reductive alkylation reaction has some advantages, including the commercial availability of substrates, mild (as a rule) reaction conditions and, in most cases, high tolerance to other functional groups. As distinct from the common alkylation with alkyl halides, the reductive alkylation of amines ensures chemoselective conversion of a primary amine to a secondary amine, and a secondary amine to a tertiary amine. In recent decades, the effectiveness and attractiveness of this approach have increased significantly due to the development of the direct reductive amination (alkylation) (DRA) methodology, and the use of chiral catalysts in this reaction has enabled the stereoselective synthesis of amines.

The method of direct reductive alkylation of amines with ketones combines two reactions, the formation of imine and its reduction to amine, into a one-pot process without isolation of an intermediate compound (Scheme 1). Indirect reductive alkylation implies the isolation of an intermediate imine and its reduction with a suitable reducing agent. Reductive alkylation proceeds efficiently only in the presence of a catalyst.

Scheme 1



R^1, R^3 = Alk, Ar; R^2 = H, Alk, Ar

Available reviews[5, 6] addressing reductive alkylation with participation of hydrogen, ammonia, boron-containing reducing agents and different oxygen- and nitrogen-containing organic compounds and catalysts cover the literature only up to the beginning of 2002.

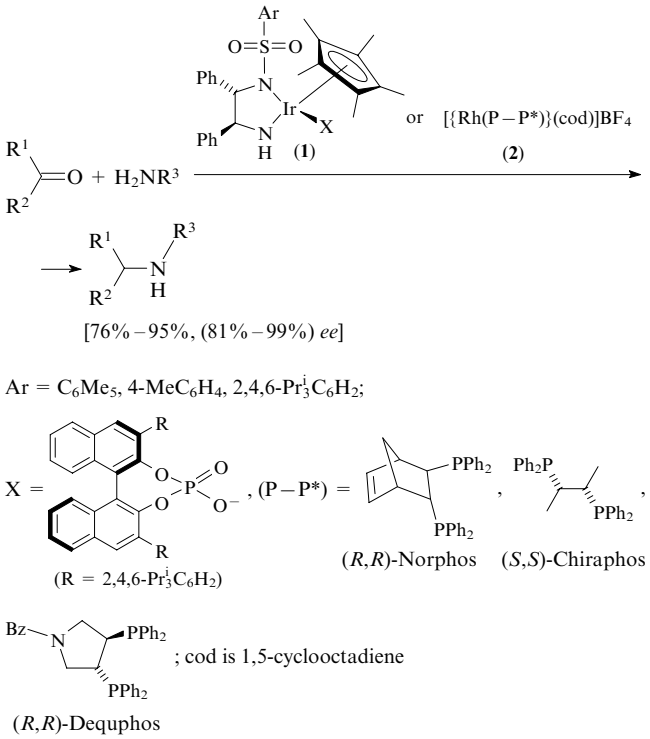
Meanwhile, a steady stream of publications about the reductive alkylation reaction and the appearance of new reagents and catalysts have prompted us to review the latest data. This review deals with methods of reductive alkylation of amines in which hydride reagents, organic compounds and complex reagents are used as the source of hydrogen and(or) the reaction catalyst. Particular attention is given to the new reaction catalysts used in stereo(enantio)selective synthesis of amines.

There are two main methods of reductive alkylation differing in the nature of the reducing agent. The first method is based on the catalytic hydrogenation of the imine formed in the reaction with hydrogen at various metal-containing catalysts (supported metals, complex metal acids, metal complexes with organic ligands). When heterogeneous Fe, Pt and Pd catalysts are used, this method is most economical for most reductive alkylation reactions used in laboratory and industry.[5, 14 – 26]

Hydrogenation with hydrogen efficiently proceeds in the presence of catalysts based on Fe^{II} (Ref. 26), Rh^{I} (Refs 16 and 17), Ru,[3] Ti (Ref. 18) and Ir (Refs 20, 21 and 27) complexes with phosphine ligands. With the use of such complex chiral catalysts of type **1** and **2**, there have been developed methods for enantioselective synthesis of amines, including the pharmaceutically important α-amino acids and key intermediates of synthesis of pharmaceutical substances containing the amine pharmacophore (Scheme 2).[17, 18, 21]

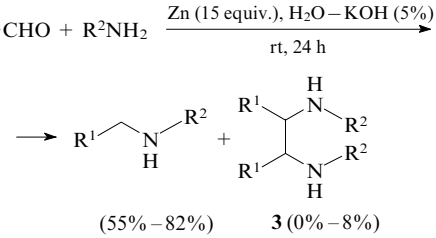
Advances in the field of catalysis for enantioselective synthesis of amines using hydrogen as a reducing agent have been addressed in recent years.[3, 14 – 16, 21, 23] However, the catalytic hydrogenation method is unsuitable for unsaturated and cyano- and nitro-containing compounds since the target amines are formed in a mixture with products of reduction of multiple bonds and functional groups.[5] Furthermore, the catalytic hydrogenation can be accompanied by the reduction of the initial carbonyl compound to give the corresponding alcohol.[5, 15, 26]

Scheme 2



In the methods of the second group, different compounds and complex systems (hydride reagents) are used as the hydrogen source. For example, the synthesis of secondary amines by reductive alkylation of primary amines with aldehydes using zinc powder in aqueous alkaline (5% KOH) media as a hydrogen source is a safe, inexpensive and facile method with minor amounts of hydrodimerization by-products **3** (⩽8%) (Scheme 3). Since the reaction is carried out in water, this protocol is important in the context of green chemistry and can be extended to a wide selection of substrates. This reaction is most efficient for aromatic aldehydes and aniline and benzylamine derivatives; the reaction of aliphatic aldehydes and amines leads to lower yields of target products.[28]

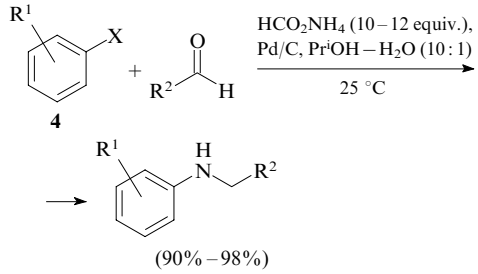
Scheme 3



R^1 = n-C_5H_{11}, Ph, 3-HOC_6H_4, 4-HOC_6H_4, 2-Fu, 1-Naph, 2-Naph;
R^2 = Bu^n, All, Bn; Fu is furyl, Naph is naphthyl

An environmentally benign reaction is the reductive alkylation of aniline derivatives (**4**, X = NH_2) and nitroarenes (**4**, X = NO_2) with aldehydes in aqueous alcohol media in the presence of ammonium formate as the hydrogen donor and a reusable Pd/C catalyst; in most cases, the protocol leads to quantitative yields of corresponding secondary amines (Scheme 4).[8]

Scheme 4



R^1 = H, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 4-F, 4-CF_3, 4-CO_2H, 4-CO_2Et, 4-OH; R^2 = H, Me, Et, Pr^n, Pr^i, Bu^t, Bu^i, n-C_5H_{11}, cyclo-C_5H_9, cyclo-C_6H_{11}, Ph, Ph$(CH_2)_2$, 4-MeC_6H_4; X = NH_2, NO_2

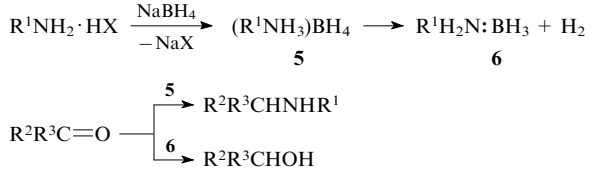
In addition to the $Zn-H_2O-HO^-$ and HCO_2NH_4–Pd/C systems, boron and silicon hydrides and some organic and organometallic compounds are among such reducing agents. All these reagents are highly chemically selective and make it possible to carry out the reductive alkylation reaction under mild conditions.[7, 29–36]

II. The use of complex boron hydrides in the reductive alkylation

Complex boron hydrides are among the reagents most widely used in various reduction reactions. A special position is held by sodium tetrahydroborate (borohydride) ($NaBH_4$) — a cheap reducing agent safe in use and storage, advantages of which were first demonstrated in the reduction of imines. Efficient methods of reductive alkylation of amines with the use of $NaBH_4$ and complex catalysts have been developed for a large number of substrates.[7, 37–43]

In the study of the reductive alkylation of amine sulfates and chlorides with the use of sodium borohydride, it has been suggested that the amine salts react with $NaBH_4$ to form ammonium borohydrides **5** and amine borane **6**. Ammonium borohydride **5** is involved in the reduction of imine, while amine borane **6** reduces the carbonyl compound to the alcohol. The yields of secondary amines in the reaction are 50%–80% in dimethylformamide and isopropyl alcohol and 10%– 30% in methanol and ethanol. In water, the alkylation does not proceed, and carbonyl compounds are reduced to alcohols (Scheme 5).[44]

Scheme 5



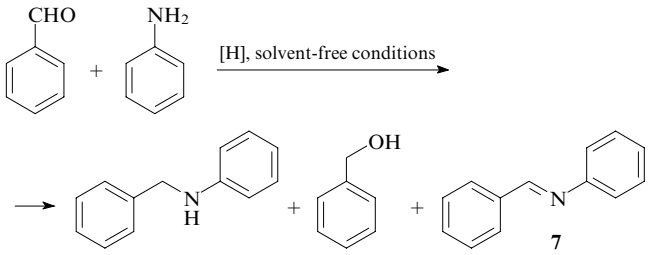
R^1 = Me, Et, Ph; R^2 = H: R^3 = Bu^n, Ph; R^2 = Me: R^3 = Me, Ph; R^2-R^3 = $(CH_2)_5$, $(CH_2)_2NMe(CH_2)_2$; X = F, Cl, I, HSO_3

Reductive alkylation of weakly basic amines leads, along with the target alkylamine, to the product of competing reduction of the aldehyde to the alcohol. The yield of the reaction products depends on the structure of both the amine and carbonyl compound: the aniline salts react with $NaBH_4$ and cyclohexanone or N-methylpiperidone to give a substituted amine in the highest yield (up to 80%); in the case of diphenylamine and diethylamine, the dominating reaction product is the alcohol (cyclohexanol).[44]

The formation of intermediate imines for their preferential (as compared to a carbonyl compound) reduction is promoted in the presence of boric, *p*-toluenesulfonic, sulfuric, benzoic and other protonic acids.[45]

It has been shown for the reaction of benzaldehyde, aniline and $NaBH_4$ in the presence of H_3BO_3 that the yield of target *N*-benzylaniline depends on the order of mixing of the reactants. The maximal yield of the product is achieved when a mixture of benzaldehyde and aniline is stirred for 10 min (which ensures the formation of imine **7**) and then a 1 : 1 mixture of $NaBH_4$ and boric acid is added. In the absence of H_3BO_3, the major reaction product is imine **7** or benzyl alcohol (Scheme 6). The nature of the acid (out of the above-listed ones) has no significant effect on the yield of the target amine, which is 85%–99%. However, this protocol is inefficient for cyclic amines; for example, the reaction of benzaldehyde with morpholine leads to the product of aldehyde reduction — benzyl alcohol.[45]

Scheme 6



The acids considerably promoting the formation of imine (H_2SO_4, *p*-$MeC_6H_4SO_3H$) are toxic and induce corrosion; therefore, there are difficulties at the stage of their removal from the reaction mixture. When the H-form of cellulose sulfate (the product of the reaction of cellulose with chlorosulfonic acid) is used as a catalyst, the reaction of benzaldehyde with morpholine and $NaBH_4$ at room temperature completes in 2 min with high yield (93%) of *N*-benzylmorpholine, while benzyl alcohol is not formed. After the end of reaction, cellulose sulfate is quantitatively filtered off and can be used again in reduction.[46]

Reductive amination at room temperature under solvent-free conditions catalyzed by carbon-based solid acid (CBSA) gives amines in 90%–96% yield.[47] Such catalysts are prepared in two stages involving sulfonation of an aromatic compound (*e.g.*, naphthalene) and incomplete carbonization of the sulfo derivative. For a wide range of amines and carbonyl compounds studied, only the reaction of cyclohexanone with morpholine gives the product in low yield (45%) because of the insufficient rate of formation of intermediate enamine and reduction of the initial ketone to cyclohexanol.

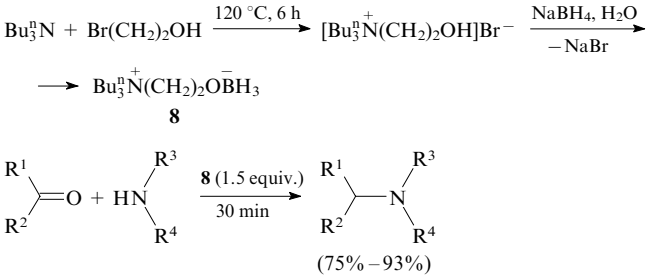
The selectivity and rate of reductive alkylation considerably increase when the reaction is carried out in ionic liquids due to their high polarity and ability to concentrate the reactants in a small volume of the reaction system.[27] Ionic liquids are green solvents; however, their production often requires large amounts of organic solvents, in particular, for purification from halogens.

The reductive amination of carbonyl compounds with sodium borohydride in an acid ionic liquid — 1-methylimidazolium tetrafluoroborate ([HMIm][BF_4]), which serves as both the solvent and catalyst, at room temperature leads to

the chemoselective transformation of aldehydes and ketones into amine in 68% – 98% yield without formation of by-products.[48]

2-(Tri-n-butylammonio)ethoxyborohydride (**8**) (ionic liquid), synthesized by the reaction of $NaBH_4$ with tri-n-butyl(2-hydroxyethyl)ammonium bromide, has been used as a reducing agent stable in storage for long periods (Scheme 7).[49]

Scheme 7



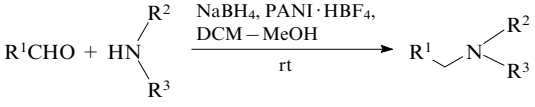
R^1 = H, Me; R^2 = Pr^n, Ph, 4-ClC_6H_4, 4-$O_2NC_6H_4$; $R^1 - R^2$ = $(CH_2)_5$;
R^3 = H: R^4 = Ph, Bn, 4-MeC_6H_4; $R^3 - R^4$ = $(CH_2)_2O(CH_2)_2$, $(CH_2)_5$

Advantages of the protocol of reductive alkylation of aromatic amines with functionalized alkyl-, aryl-, and hetarylaldehydes in water at room temperature with $NaBH_4$ and guanidinium hydrochloride as the catalyst are the lack of necessity of drying the reaction mixture components, the environmentally friendly solvent and the high yield of the target amine (81% – 98%).[50]

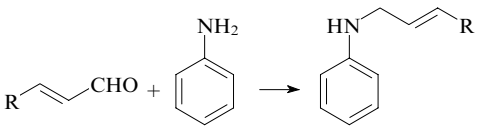
A convenient preparative procedure has been developed for the reductive alkylation with $NaBH_4$ in the presence of tungstophosphoric acid $H_3PW_{12}O_{40}$ — a strong heteropoly acid more efficient in acid catalysis than other inorganic and organic protonic acids. This acid does not induce corrosion and is readily separated from the reaction products. The use of this acid does not lead to by-products formed when mineral acids are employed; the yield of target amines is 81% – 100%.[51 – 53]

For reductive alkylation, it has been suggested to use $NaBH_4$ in combination with polyaniline (PANI) salts as acid catalysts; the salts containing mineral or solid/liquid organic protonic acid have been prepared by aqueous/emulsion polymerization. Using the $NaBH_4 - PANI \cdot HBF_4$ system in reductive amination of heterocyclic and aromatic aldehydes (including anthracene-9-carbaldehyde and its 10-methyl derivative), unsaturated aldehydes and cyclohexanone affords the target amines in high yields (85% – 96%) immediately without any side products. The $PANI \cdot HBF_4$ catalyst is recoverable and reusable without losing its potency (Scheme 8).[54]

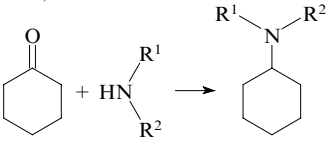
Scheme 8



R^1 = Ar, Het; R^2 = H: R^3 = Bu^n, Ph, 4-$MeOC_6H_4$,
9-ethyl-9*H*-carbazol-3-yl; $R^2 - R^3$ = $(CH_2)_5$; DCM is dichloromethane



R = Me, Ph

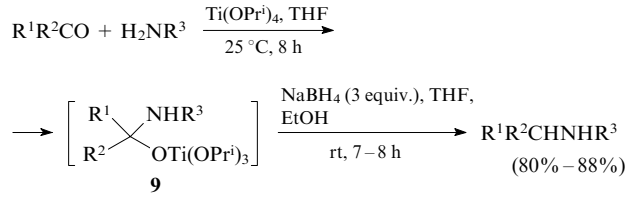


R^1 = H: R^2 = Bu^n, Ph; $R^1 - R^2$ = $(CH_2)_5$

Efficient reductive alkylation catalysts are Lewis acids — $Ti(OPr^i)_4$,[55 – 59] $Fe(OTf)_3$ (OTf is trifluoromethanesulfonate),[60] $CeCl_3 \cdot 7H_2O$[61] and $NiCl_2$.[31] It should be noted that Lewis acids efficiently inhibit the side process of alcohol formation.

When the reaction is carried out in the presence of $Ti(OPr^i)_4$, amine and carbonyl compounds are taken in equimolar amounts, and the reducing agent is introduced into the system only after the formation of adduct **9**, which allows one to avoid the undesirable reduction of functional groups (Scheme 9). The reaction of dimethylamine with substituted benzaldehydes (R^1 = H: R^2 = 4-ClC_6H_4, 4-$AcHNC_6H_4$, 3-$MeOC_6H_4$, 3-$O_2NC_6H_4$) and phenylacetaldehyde (R^1 = H, R^2 = Bn) affords high-purity amines in yields of up to 96%.[55]

Scheme 9



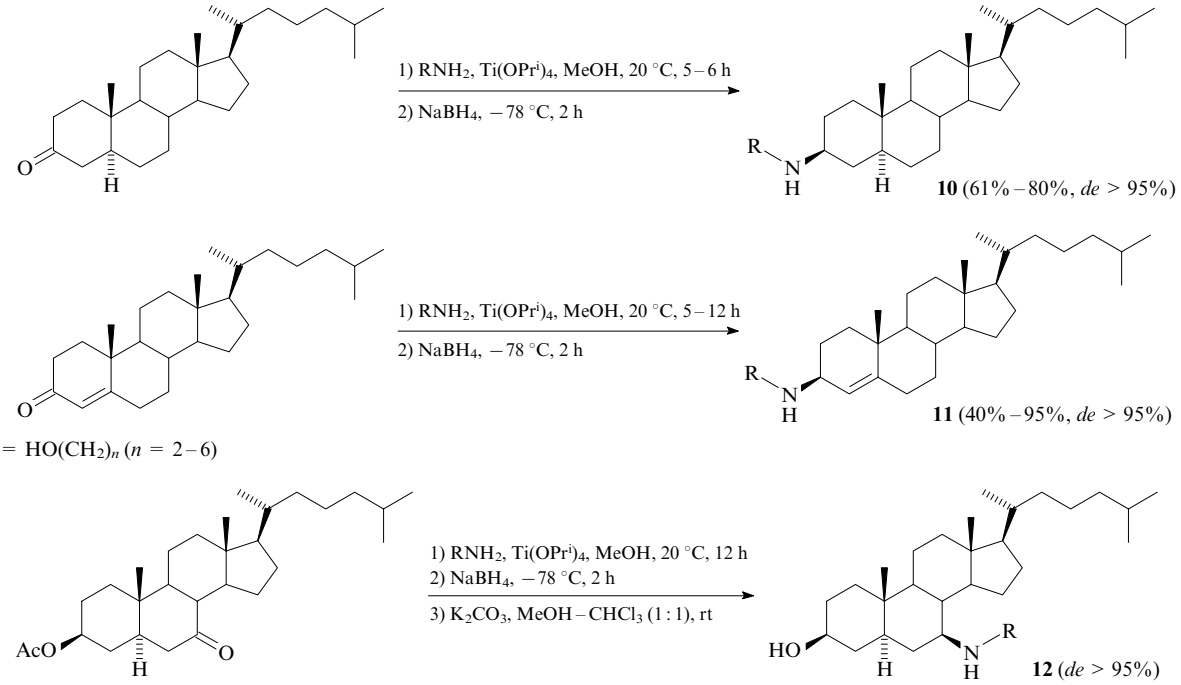
R^1 = H: R^2 = Et, cyclo-C_6H_{11}, 4-MeC_6H_4, 4-$O_2NC_6H_4$, *etc.*;
R^1 = Me: R^2 = Et, Ph, 2-Fu, 3-Py; $R^1 - R^2$ = $(CH_2)_4$;
R^3 = $HO(CH_2)_2$, 2-morpholinoethyl, 3-$PyCH_2$, $(EtO)_2CHCH_2$,
3-(2-pyrrolidinon-1-yl)propyl; Py is pyridyl

The use of the $Ti^{IV} - NaBH_4$ reductive system leads to the synthesis of 3β-*N*-(hydroxyalkyl)aminocholestanes **10** and -cholestenes **11**, as well as 7β-amino-3β-hydroxycholestanes **12**, from 5α-cholestan-3-one, 4-cholesten-3-one and 3β-acetylcholestan-7-one, respectively, in preparative yields (Scheme 10).[58, 59] For many amines, the reaction is highly diastereoselective. It should be noted that the efficiency of direct reductive amination depends on the order of introduction of the catalyst and reducing agent and that some period of time is necessary for the formation of a complex of the intermediate imine with the catalyst.

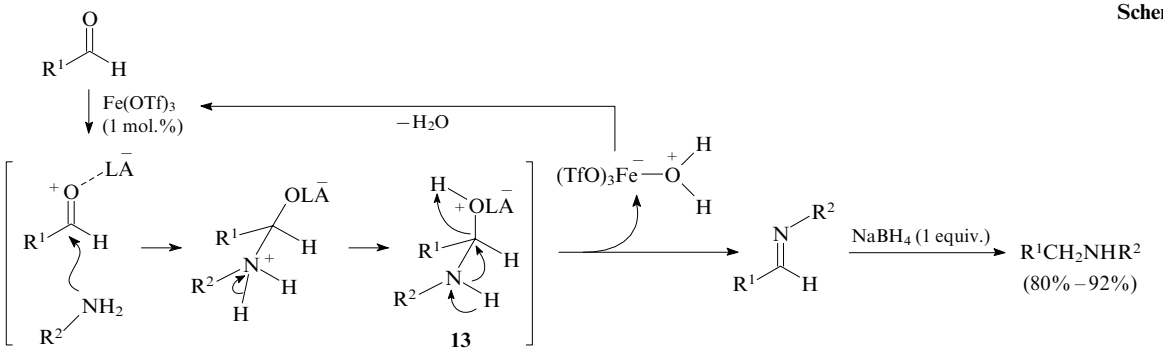
To minimize the presence of toxic metals in catalytic processes of reductive alkylation used for synthesis of active pharmaceutical substances, iron triflate has been suggested as a catalyst since it is a compound of the least toxic and most suitable metal from the standpoint of requirements for pharmaceutical industry.[60]

The mechanism of reductive alkylation of primary amines with carbonyl compounds and $NaBH_4$ with participation of $Fe(OTf)_3$ implies activation of the carbonyl group by a Lewis acid (LA), the reaction of amine with activated aldehyde to form intermediate (hemiaminal) **13** analogous to adduct **9**, dehydration of **13** to give imine and the *in situ* reaction of the latter with $NaBH_4$ (Scheme 11). At the stage of dehydration, the catalyst is released.[60] The developed protocol has been used to synthesize the active principle of

Scheme 10



Scheme 11



R^1 = Ph, 3-ClC_6H_4, 2-FC_6H_4, 3-$F_3CC_6H_4$, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 2-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 2-HO-5-$O_2NC_6H_3$, 3-$F_3CC_6H_4(CH_2)_3$; R^2 = Ph, Bu^n, Bn, PhCHMe, (1-Naph)CHMe

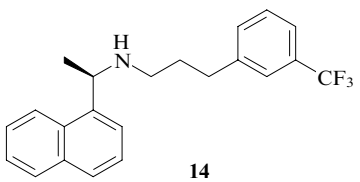
drug cinacalcet (**14**, yield 80%) and key intermediate **15** in the synthesis of the active principle of antihypertensive drug aliskiren (88%).[60]

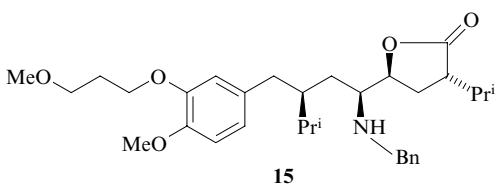
The reductive alkylation of substituted anilines with arylaldehydes with participation of $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ proceeds under solvent-free conditions at room temperature. Due to the high selectivity of the reaction of cinnamaldehyde with aniline derivatives, the reaction is an alternative green route to the synthesis of *N*-cinnamylanilines.[61]

Early studies by Gribble *et al.*[62,63] demonstrating the potential of sodium triacetoxyhydroborate obtained from $NaBH_4$ in an acetic acid medium led to interest in the use of $NaBH(OAc)_3$ in reductive alkylation of amines as a mild selective reducing agent.

As in the case of reduction by the $NaBH_4-H_3BO_3$ system, the yield of benzylamines in reductive alkylation in the presence of acetic acid depends on the order of mixing of the reactants and the time of contact of the aldehyde and amine before the introduction of the reducing

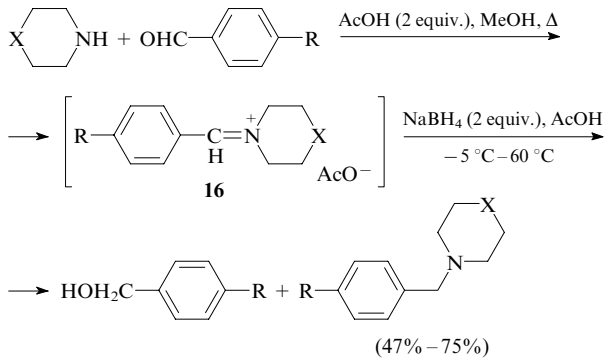
Structures 14, 15





agent.[40, 41, 64 – 67] The optimal reactant molar ratio carbonyl compound : amine : sodium borohydride is 1 : 1.1 : 1.1; acetic acid is used as both a reactant and the solvent for the preparation of a solution of the initial carbonyl compound.[64] The simultaneous introduction of sodium borohydride, aldehyde and amine into the reaction increases the yield of benzyl alcohol, which reaches 90% in the reaction of morpholine and 4-methoxycarbonylbenzaldehyde; therefore, $NaBH_4$ is added after the intermediate imine is stabilized in the form of iminium salt **16** (Scheme 12).[40]

Scheme 12

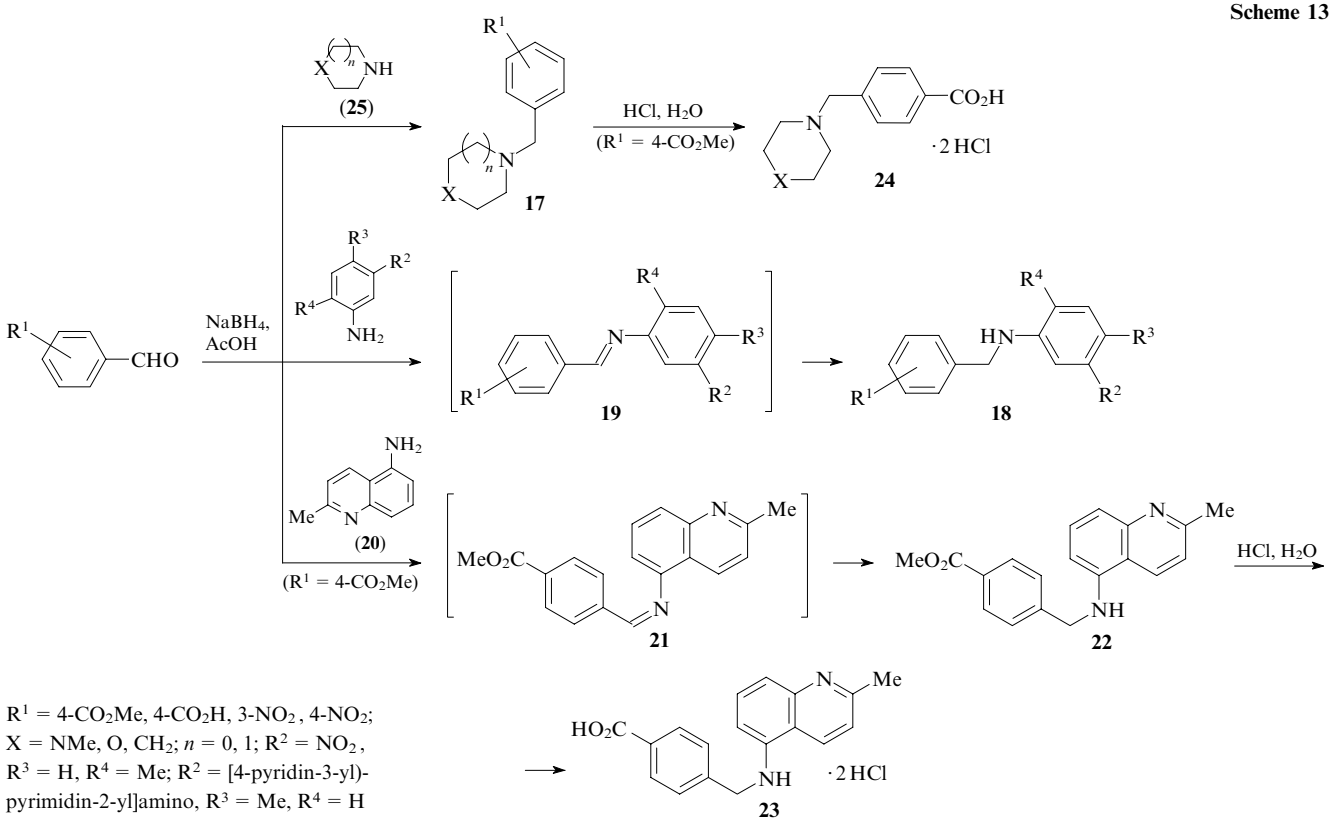


X = NMe: R = CO_2H, CO_2Me, NO_2;
R = CO_2Me: X = O or none

As already mentioned, $NaBH_4$ reacts with 3 equiv. of acetic acid to form sodium triacetoxyhydroborate, and its participation in reductive amination has been experimentally demonstrated for the reaction of cyclohexanone and aniline as an example.[64] Since the reduction of imine to the target amine with sodium borohydride in acetic acid was only 20% complete after 10 h, and the reductive amination of cyclohexanone with aniline and sodium borohydride under the same conditions was completed in 1.5 h, it has been suggested [64] that the reaction mechanism in acetic acid is somewhat different from the conventional scheme, and it is likely that imine is not the only intermediate. At the same time, for the reaction of substituted benzaldehydes with aniline derivatives, 80% – 85% of the intermediate imines are reduced at room temperature to benzylamines in 10 – 20 h.[41]

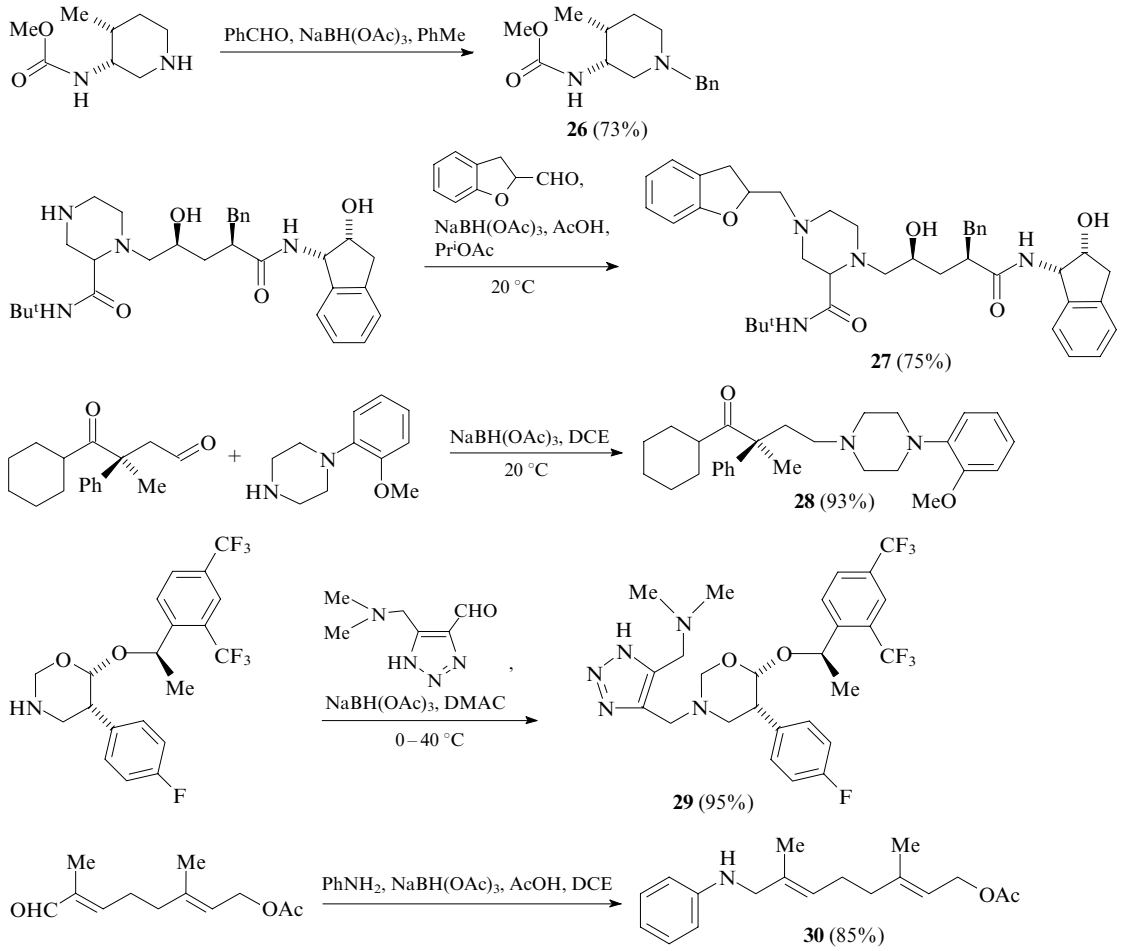
Since the $NaBH_4$ – AcOH system is able to reduce, in addition to the exocyclic C=N bond, multiple bonds in heterocyclic molecules, as well as carbonyl, nitro and nitrile groups,[68] conditions for selective synthesis of target amines should be carefully selected. An efficient protocol of synthesis of benzyl-substituted cyclic amines has been developed on the basis of the reductive alkylation of amines with functionalized aromatic aldehydes in the presence of the sodium borohydride – acetic acid reductive system, generating active $NaBH(OAc)_3$.[69] Sodium triacetoxyhydroborate *in situ* is a milder reducing agent as compared to $NaBH_4$, and, hence, it ensures the high reaction selectivity. In particular, in synthesis of benzylpiperazines **17** with the use of the $NaBH_4$ – AcOH system, no alcohol formation as the product of reduction of the initial aldehyde was observed, as distinct from the reductive alkylation with $NaBH_4$ in methanol. 4-Methoxycarbonylbenzyl derivatives **17** (R^1 = 4-CO_2Me) of 4-methylpiperazine, morpholine and pyrrolidine have been obtained in 86% – 98% yields, and 3- and 4-nitrobenzylpiperazines (R^1 = NO_2) have been synthesized in 84% – 90% yields (Scheme 13).[69, 70] Direct reductive alkylation has been used to synthesize secondary amines **18** from primary aromatic amines and methyl 4-for-

Scheme 13



R^1 = 4-CO_2Me, 4-CO_2H, 3-NO_2, 4-NO_2;
X = NMe, O, CH_2; n = 0, 1; R^2 = NO_2,
R^3 = H, R^4 = Me; R^2 = [4-pyridin-3-yl)-pyrimidin-2-yl]amino, R^3 = Me, R^4 = H

Scheme 14



DCE is dichloroethane, DMAC is dimethylacetamide

mylbenzoate (R^1 = 4-CO_2Me). The reaction of amines with aldehyde proceeds through intermediate imines **19** in the $NaBH_4$–AcOH system to give benzylamines **18** in 95%–98% yields (see Scheme 13).[69]

From 5-aminoquinaldine (**20**), the 'one-pot' process involving the reduction of the initially forming methyl 4-[(2-methylquinolin-5-ylimino)methyl]benzoate (**21**) with the $NaBH_4$–AcOH system at 0–5 °C and subsequent acid (HCl) hydrolysis of derivative **22** leads to 4-[(2-methylquinolin-5-ylamino)methyl]benzoic acid dihydrochloride (**23**) in 83% yield (see Scheme 13). It should be noted that in this temperature range, the reduction of the azomethine bond in the molecule of imine **21** proceeds selectively, whereas at 20 °C, the quinoline ring is partially hydrogenated along with the exocyclic C=N bond.[41]

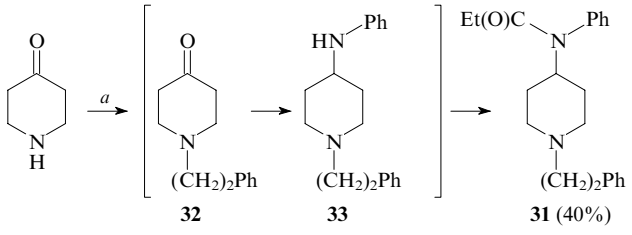
This protocol has been used to synthesize 4-[(4-methylpiperazino)methyl]benzoic acid (**24**, X = NMe) — the key intermediate in the synthesis of anti-leukemia drug imanitib — in up to 96% yield in two stages involving the synthesis of methyl 4-[(4-methylpiperazino)methyl]benzoate from 1-methylpiperazine (**25**, X = NMe, n = 1) and 4-methoxycarbonylbenzaldehyde (R^1 = 4-CO_2Me) and its acid (HCl) hydrolysis.[70] 4-Morpholinomethylbenzoic acid dihydrochloride (**24**, X = O) has been synthesized in 85% yield in the same way (see Scheme 13).

The use of $NaBH(OAc)_3$ as a selective reducing agent is most preferable for reductive alkylation in nonaqueous solvents and at moderate temperatures.[71–81] Above 50 °C, the reducing agent can decompose into ethanol and acetaldehyde, and the latter can give imines and then other by-products, ethylamine derivatives.

The products of reductive amination of different aldehydes and ketones (aromatic, heterocyclic, *etc.*) with the participation of $NaBH(OAc)_3$ — compounds **26**–**30** — have been synthesized in high yields, including large-scale syntheses in the production of drug substances (Scheme 14).[73]

The three-stage one-pot synthesis of the active principle of analgesic (narcotic) drug fentanyl — *N*-(1-phenetylpiperidin-4-yl)-*N*-phenylpropanamide (**31**) — involves two reductive alkylation reactions with the participation of $NaBH(OAc)_3$: (1) the phenylethylation of the 4-piperidone

Scheme 15

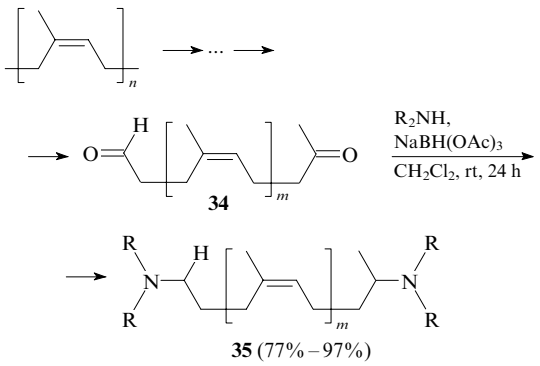


(*a*) 1) $PhCH_2CHO$, Et_3N, $NaBH(OAc)_3$, DCE, rt, 24 h; 2) $PhNH_2$, $NaBH(OAc)_3$, DCE, rt, 24 h; 3) EtC(O)Cl

NH group with phenylacetic aldehyde and (2) the alkylation of aniline with formed ketoamine **32**; these reactions precede the final stage — acylation of diamine **33** (Scheme 15).[80]

The reductive alkylation of amines with carbonyl telechelate oligoisoprenes **34** with the participation of $NaBH(OAc)_3$ leads to new functionalized oligoisoprenes **35** in high yields (Scheme 16).[74]

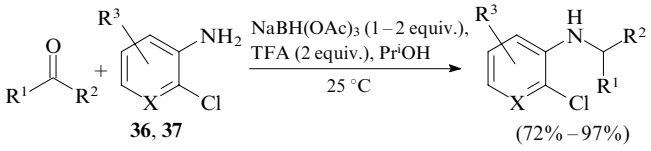
Scheme 16



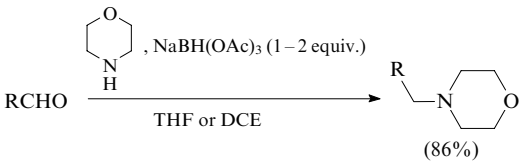
R = H, $(CH_2)_2Cl$, CH_2CO_2Et, $(CH_2)_2OH$

Efficient protocols of using $NaBH(OAc)_3$ for amination of carbonyl compounds with weakly basic amines, for example, with *ortho*-chloro derivatives of aniline **36** (X = CH) and aminopyridine **37** (X = N) (Scheme 17),[75] morpholine, and 2-ethoxycarbonylpiperidine[72,73] have been suggested. In the case of weakly basic initial amines, the yield of the desired amine often decreases because of the competing aldehyde reduction; therefore, acetic, trifluoroacetic or trifluoromethanesulfonic acid is added to the reaction mixture for protonation of the intermediate imine or enamine, and molecular sieves are used to promote imine formation.

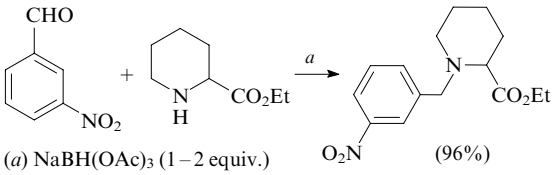
Scheme 17



R^1 = H: R^2 = Ph, 4-$MeOC_6H_4$; $R^1–R^2$ = $(CH_2)_4$, $(CH_2)_5$; X = N, R^3 = H; X = CH: R^3 = H, 4-Me, 4-F, 4-NO_2, 5-NO_2 (relative to NH_2); TFA is trifluoroacetic acid

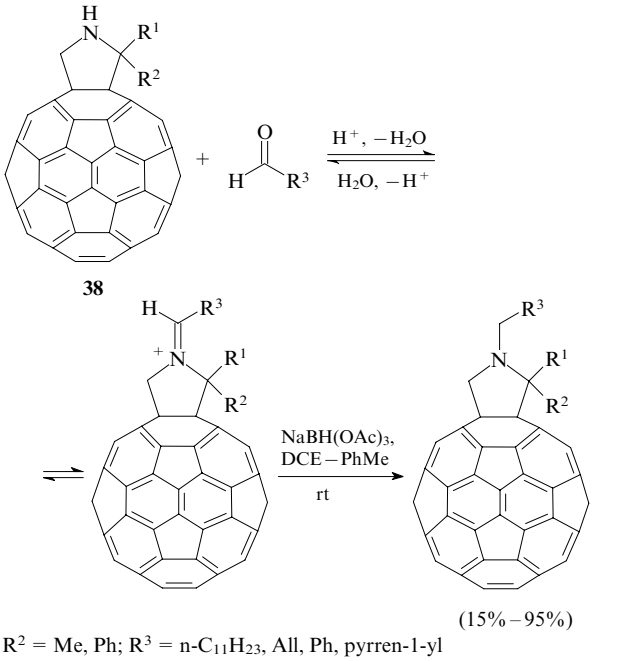


R = cyclo-C_6H_{11} (86% yield), 3-$MeOC_6H_4$ (88%)



The reductive alkylation of low-basicity fulleropyrrolidines **38** in the presence of $NaBH(OAc)_3$ proceeds most efficiently (the yield of the product is 93%–95%) with aliphatic aldehydes, whereas a bulky aromatic substituent in the pyrrene-1-carbaldehyde molecules decreases the yield of the reaction product to 15% (Scheme 18).[81]

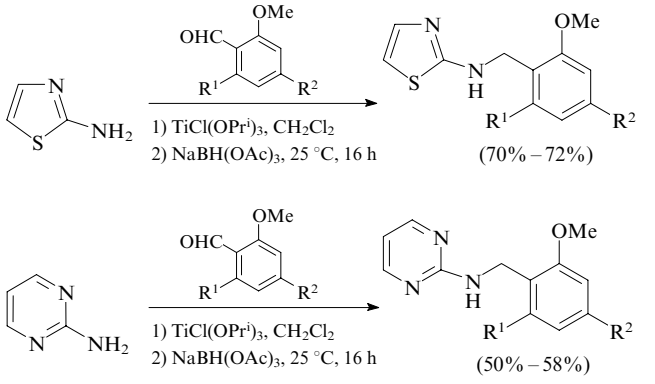
Scheme 18



R^1, R^2 = Me, Ph; R^3 = n-$C_{11}H_{23}$, All, Ph, pyrren-1-yl

Electron-deficient 2-amino-1,3-thiazole and 2-aminopyrimidine have been alkylated with substituted benzaldehydes and $NaBH(OAc)_3$ in the presence $TiCl(OPr^i)_3$ (Scheme 19).[82] The presence of the Cl^- ion rather than the isopropoxide ligand in the catalyst increases the acidity of the reagent and, thus, the yield of the target product.

Scheme 19



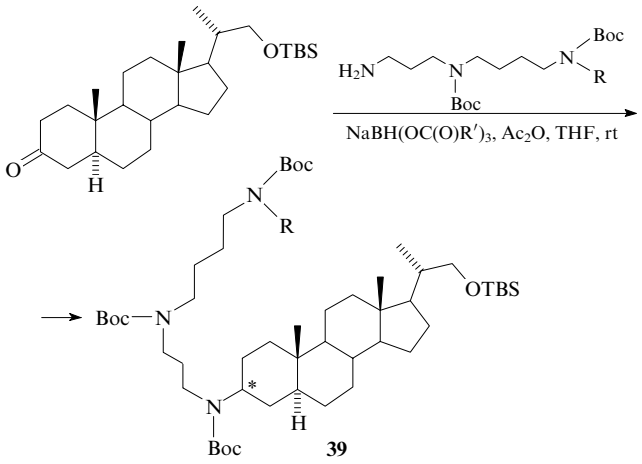
R^1 = R^2 = OMe; R^1 = H: R^2 = OMe, $O(CH_2)_3C(O)NHBn$

In the presence of the $NaBH(OAc)_3–TiCl(OPr^i)_3$ system, the reductive alkylation of arylamines with 1,1′-diacetylferrocene occurs successfully.[83]

The stereoselectivity of reductive alkylation with *in situ* generated acyloxyborohydrides in the synthesis of 3α-aminosteroids **39** is dictated by the structure of the amine component and the steric environment of the carbonyl group in the acyloxyborohydride molecule. The best result [yield 96%–97%, the ratio of stereoisomers 3α : 3β = (19–23) : 1] for spermine and spermidine has

been achieved using tris(2-ethylhexanoyloxy)borohydride (the product of the reaction of $NaBH_4$ with 2-ethylhexanoic acid, R′ = Bu^{n}EtCH) as the reducing agent (Scheme 20).[84]

Scheme 20



TBS = Bu^{t}Me$_2$Si; Boc = Bu^{t}OC(O);R = H, $(CH_2)_3$NHBoc; R′ = Me, Pr^n, Pr^i, Bu^i, Bu^t, Et$_2$CH, Bu^{n}EtCH

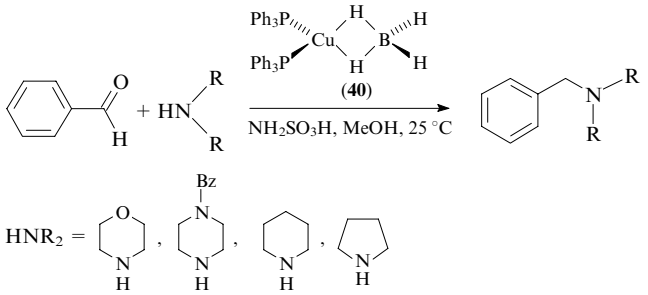
The use of $NaBH_3CN$ or $LiBH_3CN$ as a reducing agent is caused by their stability in acid media (pH ~3), good solubility in a polar solvent, selectivity and stability of many functional groups of substrates under synthetic conditions.[34,85,86] Reductive alkylation with the participation of $NaBH_3CN$ or $LiBH_3CN$ proceeds efficiently at pH 6–8, and the resulting iminium ion is reduced much faster than the carbonyl group.

Reduction with $NaBH_3CN$ is performed in the presence of $Ti(OPr^i)_4$, which, as in the above cases, plays the role of the dehydrating agent at the stage of imine formation and catalyzes the reaction in the required direction. However, both sodium and lithium cyanoborohydrides are toxic: cyanide ion (through acid hydrolysis) and directly HCN can form as by-products. Therefore, modified cyanoborohydride reductive systems have been suggested. In such systems, $NaBH_3CN$ is combined with transition metal (M) salts; in the reaction media, they form an equilibrium mixture of $Na[MCl(BH_3CN)_2]$, $Na_2[MCl_2(BH_3CN)_2]$, $Na[M(BH_3CN)_3]$ and $M(BH_3CN)_2$ complexes.

Special attention should be paid to tetra-n-butylammonium cyanoborohydride (TBACB) — a rather convenient and mild reducing agent used in protic and aprotic media. Since $NaBH_3CN$ is insoluble in solvents commonly used in the laboratory, such as CH_2Cl_2, $CHCl_3$ and diethyl ether, its reactivity is very low, so that the syntheses require about 70 h. Even in the presence of Aliquat 336, the reaction lasts for ~48 h. The use of TBACB and trialkylmethylammonium has reduced the reaction time to 2.5–20 h; the corresponding yields of the target products of benzylation of secondary cyclic amines were 60%–89%.[87]

An efficient reagent in reductive alkylation is bis(triphenylphosphine)copper borohydride $[Cu(PPh_3)_2BH_4]$ (**40**). Unlike the syntheses with the participation of $NaBH_4$, this reaction does not require an excess of the borohydride reagent; borohydride **40** is inert to many functional groups and multiple C—C bonds. Noteworthy is the availability of the reducing agent itself, its high reactivity and stability upon prolonged storage in air. The reductive alkylation of cyclic amines (morpholine, piperazine, pyrrolidine etc.) with benzaldehyde with the use of borohydride **40** proceeds in the presence of sulfamic acid in methanol and gives target benzylamines in >90% yields (Scheme 21). The copper complex is highly reactive precisely in the solvent where it is insoluble, in particular, in methanol. In the solvents most frequently used for reduction (chloroform and THF), $Cu(PPh_3)_2BH_4$ is readily soluble, and the reaction is absent.[88]

Scheme 21

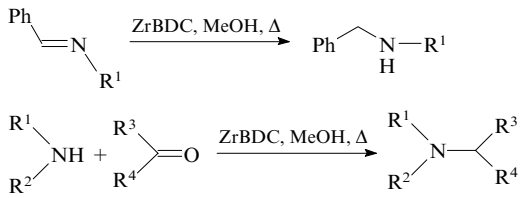


Among the latest advances in this field are organoborohydride complexes: zinc borohydride complexes with *N*-methylpyrrolidine[89,90] and *N*-methylpiperidine,[91] zirconium borohydride complexes with piperazine $[(Pipz)Zr(BH_4)_2Cl_2]$[92,93] and 1,4-diazabicyclo[2.2.2]octane (DABCO) (ZrBDC).[94]

Reductive alkylation with zinc borohydride complexes is carried out in common organic solvents at room temperature or on cooling; the target amines are formed in 80%–95% yields.[89] The reaction with the zirconium complex with piperazine (Pipz), $Zr(Pipz)(BH_4)_2Cl_2$ is catalyzed by lithium perchlorate; in the absence of the catalyst the initial carbonyl compound is reduced. The alkylation of functionalized benzaldehydes provides the yields of the products of 75%–95%. To obtain amines in high yields, it is necessary to introduce trimethylsilyl chloride as a catalyst into the system.[92,93] It should be noted that Lewis acids not only catalyze the *in situ* amine reduction but also activate the carbonyl substrate.

The ZrBDC complex has been successfully used for imine reduction and reductive alkylation with aldehydes and ketones under mild aqueous acid conditions (pH 4–6) (Scheme 22). The reagent persists in H_2O for several days without losing its reductive activity.[94]

Scheme 22

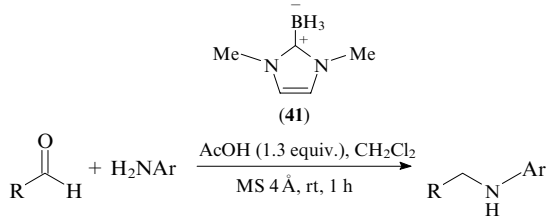


ZrBDC = $Zr(DABCO)_2Cl_2(BH_4)_2$; R^1 = Alk, Ar; R^2, R^3 = H, Alk; R^4 = H, Alk, Ar

Metal organoborohydride complexes are especially suitable when the use of amine excess is not recommended (for example, under acid hydrolysis conditions) or when the substrates introduced into the reaction are acid sensitive.

Among neutral organoboron reducing agents are N-heterocyclic carbene boranes, in particular, dimethylimidazolium borohydride **41**, similar in nucleophilicity (nucleophilicity parameter $N = 12$) to $NaBH_3CN$ and providing high yields of the products of reductive alkylation with aromatic aldehydes of substituted anilines (Scheme 23).[95]

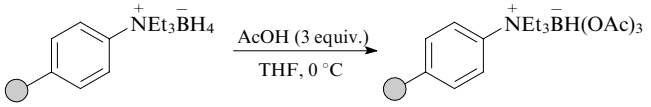
Scheme 23



R = Ar, CH_2=CH

In recent years, reducing agents immobilized on polymer supports have been widely used.[96 – 98] When immobilized $NaBH(OAc)_3$ is used (Scheme 24), the procedure of removal of by-products is reduced to the purification of the polymer support; removal of the support from the reaction system is not difficult, and the reaction occurs at room temperature. An advantage of this method is chemical selectivity, which is responsible for relatively high yields of pure reaction products. Among the weaknesses of the method are the loss of activity of the immobilized reagent in a few days after carrying out the reaction and the necessity to preliminarily synthesize imines since immobilized $NaBH(OAc)_3$ also efficiently reduces carbonyl compounds.[96]

Scheme 24

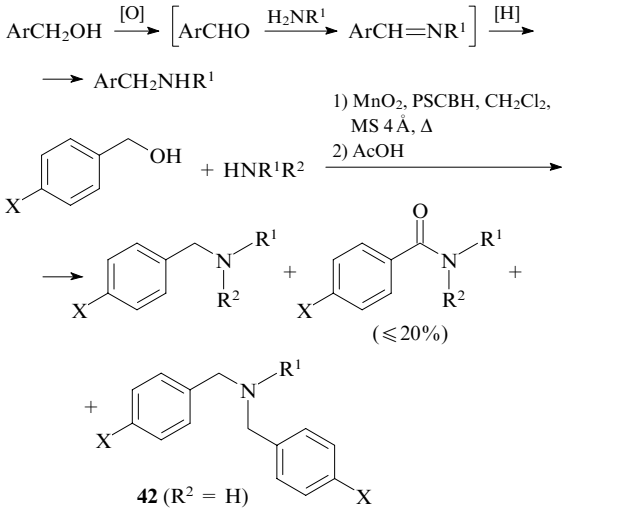


is polymer support

For direct synthesis of amines from alcohols, polymer-supported cyanoborohydride (PSCBH) has been suggested. The starting alkylating reagents were substituted benzyl alcohols, and simultaneously with the reducing agent, an oxidant (MnO_2) was introduced into the reaction system to oxidize alcohols to carbonyl derivatives. Under the chosen conditions, the reducing agent starts acting only when aldehyde and then imine is formed in the reaction system, *i.e.*, at the stage of reductive alkylation (Scheme 25). For imine reduction, acetic acid is necessary; to improve the yield of the target product, acetic acid is added after nearly complete (as shown by thin-layer chromatography) oxidation of the alcohol. Amides (in up to 20% yields) and minor amounts of dibenzyl derivatives **42** have been identified as by-products.[99] It should be noted that the sequence oxidation – imine formation – reduction is rather rare in classical organic synthesis.

In the reductive alkylation of amines with the participation of $NaBH_4$ and $NaBH_3CN$, Amberlyst 15 ion exchange resin,[100] silica gel[86, 101, 102] and HZSM-5 zeolite[103] have been used as supports. Almost all researchers note high yields of reaction products (70% – 95%) and neutral conditions (THF, room temperature); in some cases, the reactions proceed under solvent-free conditions.[100]

Scheme 25



X = Alk, NO_2, Hal; R^1, R^2 = H, Alk, Ar

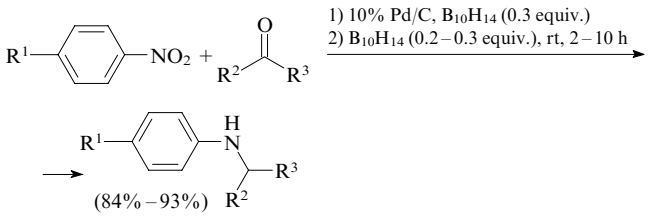
The conversion of the starting substances in the reactions with participation of silica gel-supported cyanoborohydride is 25% higher than that with $NaBH_3CN$.[86]

III. Boranes and silanes in synthesis of amines

The use of boranes and silanes in the reductive alkylation reaction is caused by their lower reductive activity as compared to metal borohydrides and, hence, by higher selectivity. In particular, aldehydes and ketones are readily converted into the corresponding amines (90% – 98% yield) in methanol with the use of decaborane ($B_{10}H_{14}$) at room temperature in a nitrogen flow.[104]

Efficient synthesis of *N*-alkylaminobenzenes through a one-pot, two-step protocol involving reduction of nitrobenzenes and subsequent reductive alkylation with aldehydes and ketones in the presence of decaborane and 10% Pd/C catalyst has been suggested (Scheme 26).[105]

Scheme 26

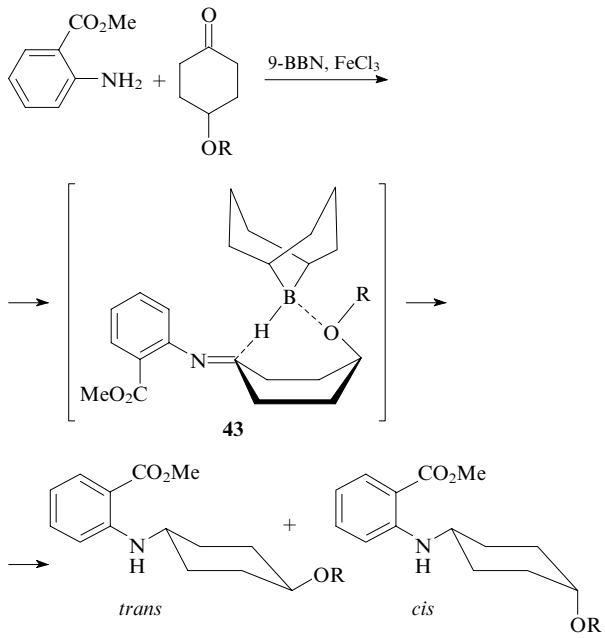


R^1 = Me, CO_2Me, CH_2OH; R^2 = H: R^3 = Et, 4-HOC_6H_4;
R^2 = Me: R^3 = Et, 4-HOC_6H_4; R^2 = OEt, R^3 = CH_2Ac

The use of sterically crowded catalysts ensures the stereoselective result of the reaction. The reductive alkylation of aniline derivatives with substituted cyclohexanone with 9-borabicyclo[3.3.1]nonane (9-BBN) in the presence of $FeCl_3$ is controlled by chelation through the formation of intermediate **43** with high *trans*-diastereoselectivity (Scheme 27). 4-Substituted cyclohexylamines form as a mixture of the *cis* and *trans* isomers in the ratio 18 : 82 (R = Me) and 22 : 78 (R = H).[106] At the same time, if Me substituent is present in the ketone instead of the OR group,

the selectivity of the process is changed: the reaction gives 91% of *cis* and 9% of *trans* isomer.

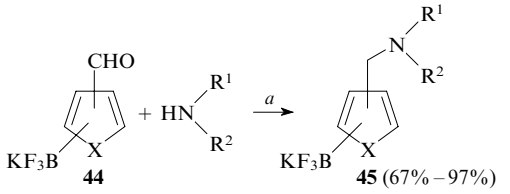
Scheme 27



R = H, Me

As alternative reducing agents, amine borane systems have been suggested, which have advantages over borohydride reducing agents.[107–114] For example, pyridine borane ($Py \cdot BH_3$) is a more chemoselective reducing agent with respect to the imine forming in the reaction.[107] The reaction is carried out in the presence of molecular sieves (4 Å) in CH_2Cl_2, THF, $CHCl_3$ or Et_2O, and the reaction rate increases considerably when methanol is used as a solvent. Pyridine borane, along with the hydride systems $HCO_2K-Pd(OAc)_2$ and $NaBH(OAc)_3-AcOH$, has been efficiently used for transformation of (hetero)aromatic aldehydes **44**, containing the trifluoroborate substituent, into corresponding amines **45** (Scheme 28).[109] However, $Py \cdot BH_3$ is unstable to heating (explosive!) and, therefore, unsuitable for industrial use.

Scheme 28



X = S, O, CH=CH; R^1 = H: R^2 = Bu^n, cyclo-C_3H_5, cyclo-C_6H_{11}; R^1-R^2 = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_2NMe(CH_2)_2$, $(CH_2)_2O(CH_2)_2$; *a* — $Pd(OAc)_2$, HCO_2K, or $NaBH(OAc)_3$, or $Py \cdot BH_3$ (4 equiv.), KHF_2, MeOH, rt, 16 h

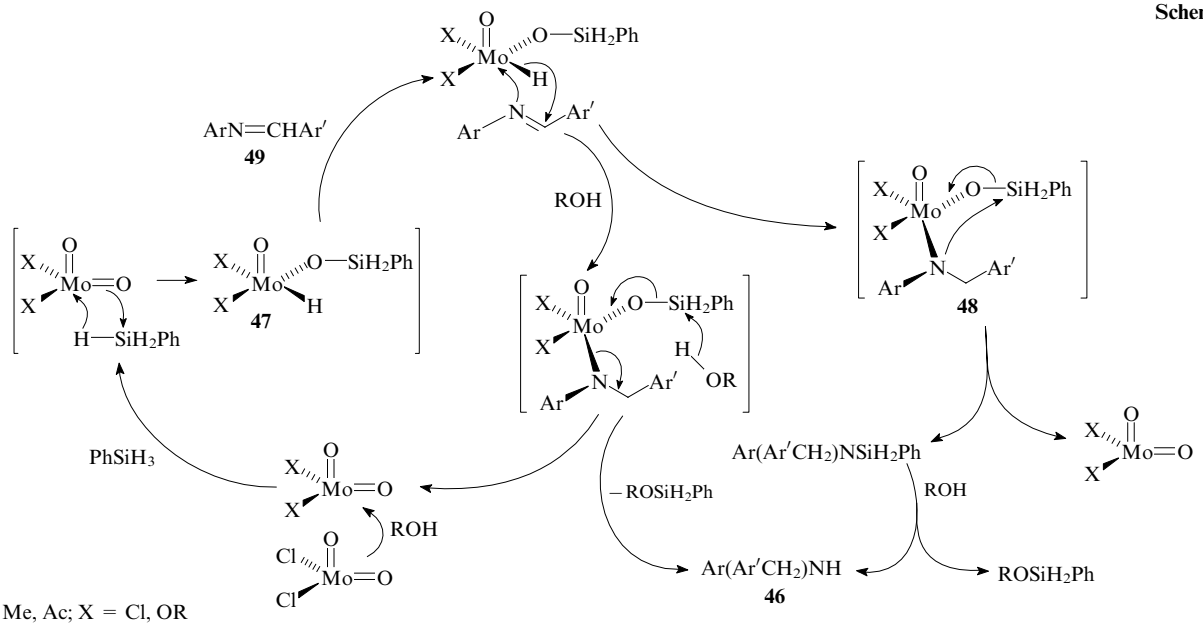
α-Picoline borane ($Pic \cdot BH_3$) has advantages over pyridine borane: it is a crystalline substance stable to heating and can be stored for a long time. Picoline borane has been suggested as an efficient and mild reagent for reductive alkylation of aniline derivatives and cyclic amines in water, methanol, as well as without solvent, in the presence of small amounts of AcOH.[110] The possibility of carrying out the reaction in water and under solvent-free conditions makes the use of $Pic \cdot BH_3$ promising for green chemistry.

Silanes readily soluble in organic solvents are also efficient reagents of reductive alkylation.[115–123] As a rule, silanes are used with catalysts, which are halogen derivatives and(or) Lewis acids; they form a complex involved in hydride transfer in the reaction mixture.

The reductive properties of phenylsilane have been studied for reductive alkylation of functionally substituted anilines, morpholine, *N*-phenylpiperazine and piperidine with 4-methoxybenzaldehyde. The reaction is carried out with a small excess of a reducing agent in the presence of a catalyst — di-n-butyldichlorostannane ($Bu^n_2SnCl_2$) — in a concentrated solution of THF.[115]

In synthesis of arylbenzylamines **46**, the complex of phenylsilane and MoO_2Cl_2 has been used as a catalyst (Scheme 29).[116] It has been demonstrated that the $PhSiH_3-MoO_2Cl_2$ reductive system is tolerant to some

Scheme 29

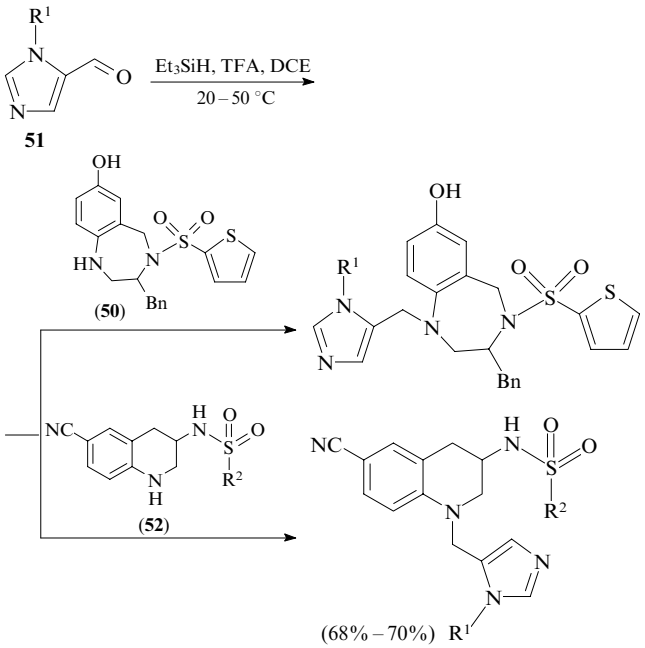


R = H, Me, Ac; X = Cl, OR

functional groups (F, Cl, I, OMe, NO_2, CO_2Me and CN) and unsaturated heterocycles. The putative mechanism of the reaction involves [2+2] addition of the metal oxide (Mo=O) to the Si–H bond to form active reducing agent **47**. Then, hydride transfer to the iminium carbon atom occurs, and either the iminium nitrogen atom of intermediate **48** captures silane, releasing the catalyst, or the intermediate is attacked by a nucleophile from the reaction medium ROH (R = Ac, Me, H) with catalyst recovery (see Scheme 29). The reaction proceeds in a polar medium: in MeOH at room temperature or in EtOH under reflux. The introduction of small amounts of water (1.0 equiv.) and acetic acid into the reaction mixture promotes the formation of imine **49**.[116]

Efficient reducing systems based on triethylsilane (Et_3SiH) and *tert*-butyldimethylsilane have been suggested for reductive alkylation.[117–121] The alkylation of sulfonated derivatives of benzodiazepines **50** with imidazole-5-carbaldehydes **51** with the participation of Et_3SiH is carried out in the presence of trifluoroacetic acid in dichloroethane at room temperature (Scheme 30).[117] Analogous reductive alkylation of sulfones **52** of the tetrahydroquinoline series is carried out in an argon medium at 50 °C.[118]

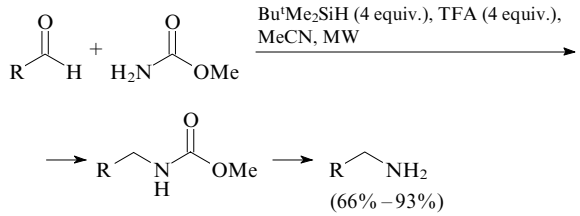
Scheme 30



R^1 = H, Me; R^2 = 4-$FC_6H_4CH_2$, 2-Py, 1-methylimidazol-4-yl

The reductive alkylation of methyl carbamate with aldehydes with the participation of Bu^tMe_2SiH in the presence of trifluoroacetic acid under microwave (MW) exposure leads, after alkaline treatment, to a wide range of primary amines (Scheme 31).[119]

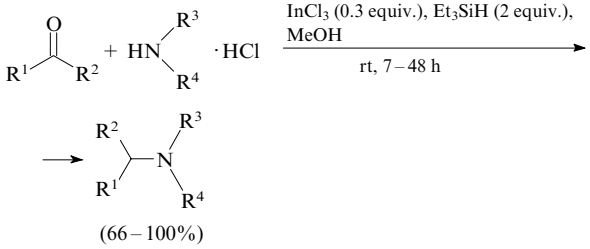
Scheme 31



R = 4-MeC_6H_4, 2-$F_3CC_6H_4$, PhCH=CH, $Ph(CH_2)_2$

The reductive alkylation of amines with unsaturated and aromatic aldehydes promoted by the $InCl_3-Et_3SiH-MeOH$ reducing system shows high selectivity in synthesis of cyclic, acyclic, aromatic and aliphatic amines; hydroxyl, ester, carboxyl and olefin functionalities are found to be stable under the reaction conditions (Scheme 32). Mass spectrometric studies have demonstrated the existence of methanol-coordinated indium(III) species which are presumably responsible for the gentle *in situ* generation of indium hydride [In–H] through the reaction of $InCl_3$ and Et_3SiH and, thus, for mild reaction conditions.[120]

Scheme 32

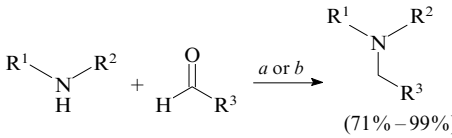


R^1 = H: R^2 = PhCH=CH, $Me(CH_2=)C$, $Me_2C=CH$, n-$C_5H_{11}CH=CH(CH_2)_2$, n-C_5H_{11}, 4-$MeOC_6H_4$, *etc.*;
R^1-R^2 = $(CH_2)_n$ (n = 4–6); R^3 = R^4 = Bn; R^3 = Me, R^4 = Ph;
R^3-R^4 = $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$, $(CH_2)_2C(O)(CH_2)_2$, *etc.*

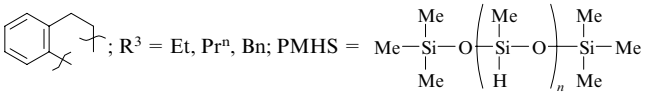
Reductive alkylation of primary amines with aldehydes and ketones promoted by the $InCl_3-Et_3SiH$ system has also been carried out in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$.[121]

An efficient protocol of reductive alkylation of secondary amines with aldehydes and Et_3SiH in the presence of an iridium complex — (cycloocta-1,5-diene)chloroiridium dimer ($[IrCl(cod)]_2$) — on heating in dioxane or n-octane has been developed. When polymethylhydrosiloxane (PMHS) is used instead of Et_3SiH, the reaction is carried out in THF (Scheme 33).[122] Polymethylhydrosiloxane, a by-product of silicone industry, is cheap, easy to handle, promising from the standpoint of environmental protection and more stable in a humid environment than silanes and persists for a long period of time without loss of activity.

Scheme 33



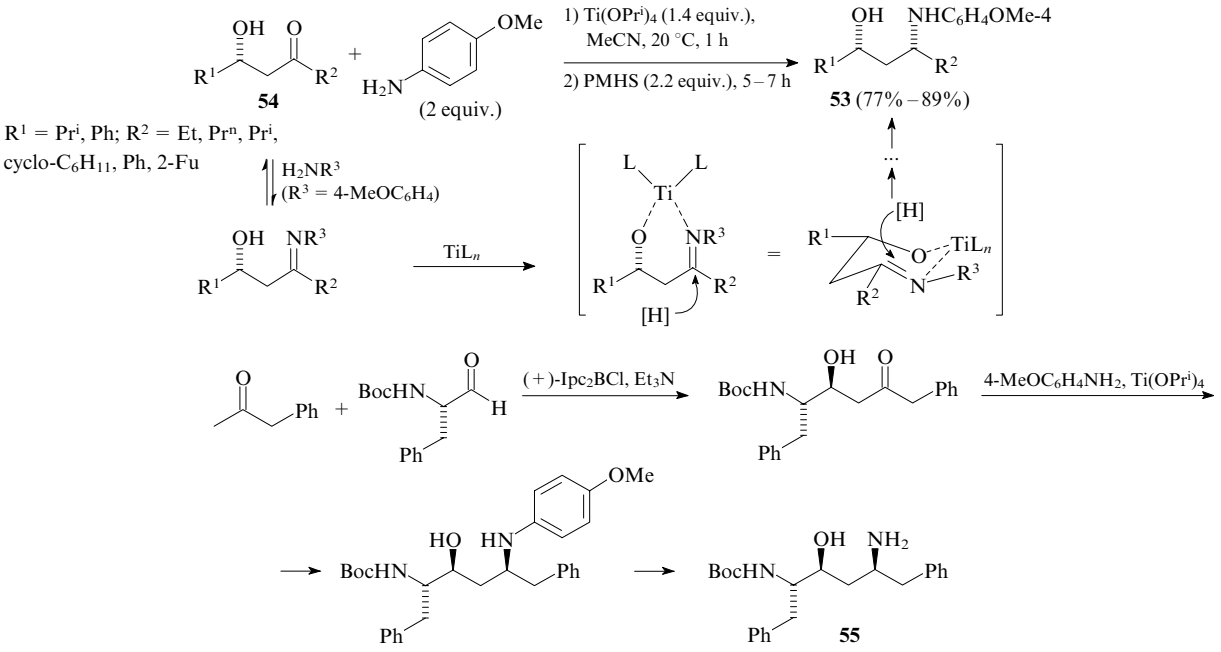
R^1 = R^2 = Bu^n, Bu^i, Bn; R^1-R^2 = $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$,



; R^3 = Et, Pr^n, Bn; PMHS =

(*a*) Et_3SiH (1 equiv.), $[IrCl(cod)]_2$ (0.5 mol.%), 1,4-dioxane, 75 °C, 8 h;
(*b*) PMHS (5 mol.%), $[IrCl(cod)]_2$ (0.5 mol.%), THF, 50 °C, 5 h

Scheme 34



Ipc$_2$BH is diisopinocampheylborane

PMHS activated with trifluoroacetic acid has been used for alkylation of various aryl- and (het)arylamines with aldehydes and ketones. The reaction is carried out in methylene chloride at room temperature; the yields of alkylated products are 40%–92%.[123]

Reactions with PMHS are also catalyzed by Zn and Ga triflates and iron-containing catalysts. Reductive alkylation of aniline derivatives with substituted benzaldehydes in the presence of PMHS and $Zn(OTf)_2$, $Ga(OTf)_3$ or $FeCl_3$ occurs under mild conditions, giving the products in nearly quantitative yield (to 99%).[124–126]

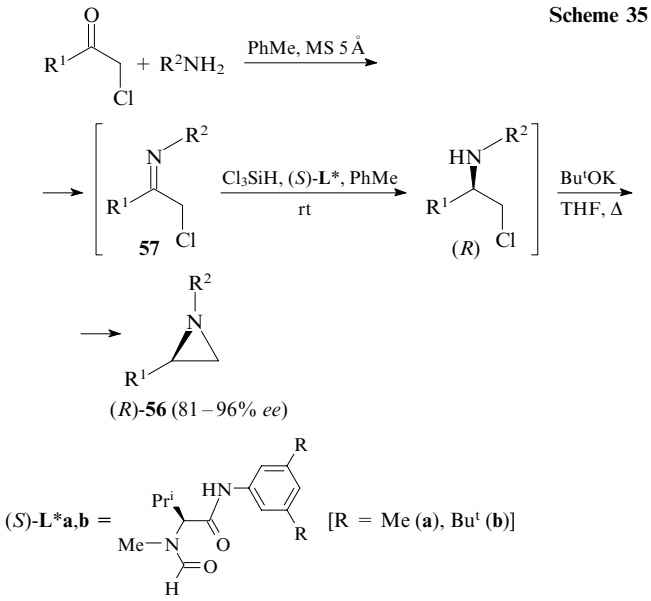
With the use of the PMHS–Ti(OPr^i)$_4$ reductive system, two-step stereoselective synthesis of 1,3-*syn*-amino alcohols **53** has been developed. At the first stage, chiral β-hydroxyketones **54** are synthesized through the enantioselective aldol reaction; the reductive amination of them with *p*-anisidine catalyzed by tetra(isopropoxy)titanium occurs with 72%–86% *cis*-diastereoselectivity (Scheme 34).[127] This protocol represents the shortest known method of preparation of key building blocks in synthesis of lopinavir and ritonavir (**55**), HIV-protease inhibitors.

A protocol for enantioselective synthesis of aziridines **56** in two stages has been developed. The method involves reductive alkylation of aniline derivatives with α-chloroketones with the participation of Cl_3SiH catalyzed by chiral L-valine amide [(*S*)-**L***]. The key stage is *in situ* enantioselective reduction of unstable α-chloroimines **57** and cyclization of the resulting amines into 1,2-substituted aziridines (Scheme 35).[128]

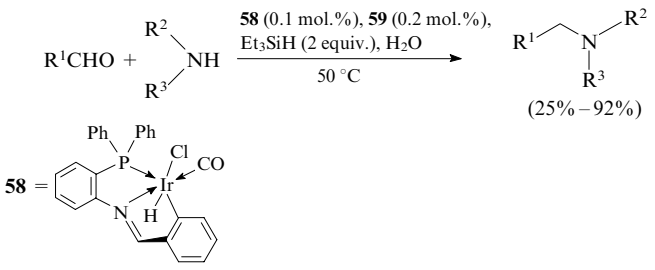
It should be noted that even relatively simple catalytic complexes (titanium triflates and alkoxides) can lead not only to chemo- but also to stereoselective result.[12, 58–60, 84, 107]

When a combination of iridium complex **58** with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (**59**) and triethylsilane is used, the reductive alkylation of amines with aldehydes is carried out in water (Scheme 36).[129]

Scheme 35

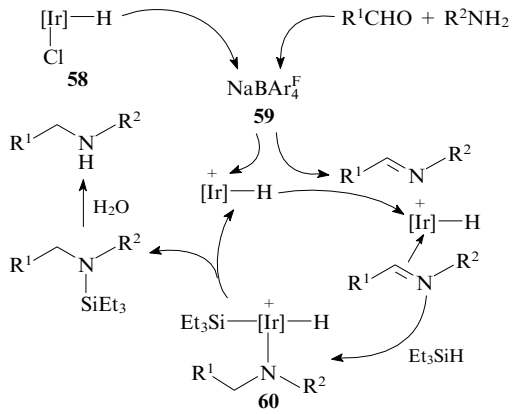


Scheme 36



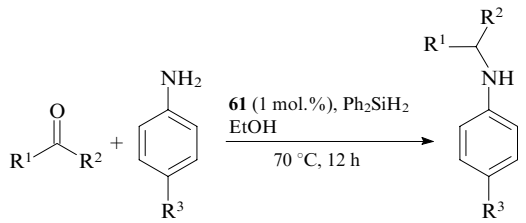
The reaction with the participation of an intermediate Ir^{III} complex involves the coordination of the catalyst to the imine substrate with the reduction of the imino group in imine silane complex **60** and subsequent hydrolysis to give the target amine (Scheme 37).

Scheme 37

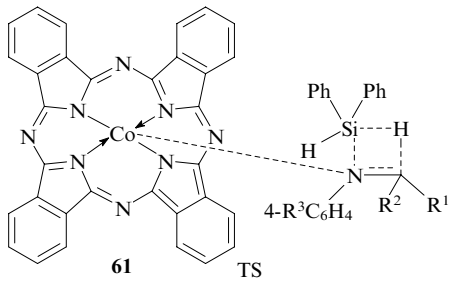


Cobalt phthalocyanine complex **61** in combination with diphenylsilane has been used for reductive alkylation of aniline derivatives and alicyclic and aliphatic amines in ethanol at 70 °C.[130] It has been suggested that complex **61**, being a Lewis acid, activates the intermediate imine through the Lewis acid – Lewis base interaction. The reaction presumably proceeds through transition state (TS). The protocol affords the products in high yields (75% – 93%) for all the amines except the reaction of acetophenone with nitroaniline, benzylaniline, benzylamine and morpholine (yields 0% – 14%) (Scheme 38). Functional groups, such as nitro, hydroxy, alkoxy, nitrile, carbonyl, alkene and heterocyclic rings, persist under the reaction conditions.[130]

Scheme 38

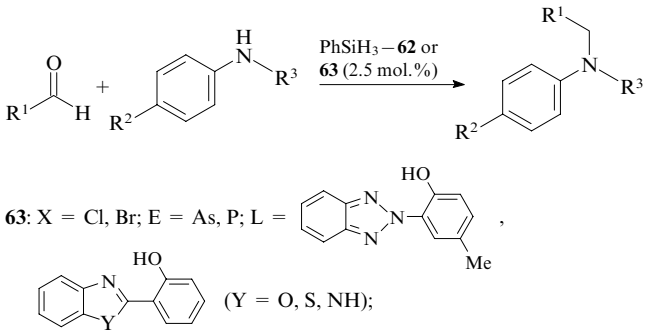


R^1 = H, Me; R^2 = Ph, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 4-NCC_6H_4, 4-MeC_6H_4, 2-HOC_6H_4, 2-HO-3-$MeOC_6H_3$, 4-$MeOC_6H_4$;
$R^1 - R^2$ = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_2CHMe(CH_2)_2$
R^3 = H, F, I, NO_2, OMe, CO_2H, CO_2Me, $C(O)NH_2$, OBn, NHBn



Rhenium oxo complexes $ReIO_2(PPh_3)_2$ (**62**) and $ReOX_2(L)(EPh_3)$ (**63**) turned out to be efficient catalysts of reductive alkylation with the participation of $PhSiH_3$ (Scheme 39). Double bonds and a wide range of functional groups (NO_2, CF_3, SO_2R, CO_2Alk, F, Cl, Br, I, CN, OH, OMe, SMe, NC(O)Alk etc.) are stable under the reaction conditions.[131, 132]

Scheme 39



63: X = Cl, Br; E = As, P; L =

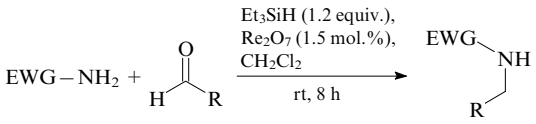
,

(Y = O, S, NH);

R^1 = 4-XC_6H_4 (X = NO_2, SO_2Me, Br, OMe, SMe, NHAc, *etc.*);
R^3 = H: R^2 = F, Cl, Br, OMe; R^2 = H, R^3 = Me, *etc.*

Selective reductive alkylation of amines containing electron-withdrawing groups (EWG) with aldehydes proceeds with the participation of Et_3SiH and Re_2O_7 as a catalyst (Scheme 40).[133]

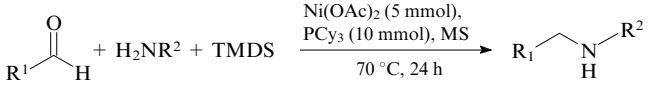
Scheme 40



EWG = Boc, Cbz, Fmoc, $ArS(O)_2$, $Ar_2P(O)$, EtOC(O), Bz;
Cbz is benzyloxycarbonyl; Fmoc is 9-fluorenylmethyloxycarbonyl

Reductive alkylation of amines with aldehydes in the presence of tetramethyldisiloxane (TMDS) under hydrosilylation conditions catalyzed by nickel compound prepared *in situ* from $Ni(OAc)_2$ and tricyclohexylphosphine gives secondary amines in moderate to good yields (Scheme 41).[134]

Scheme 41



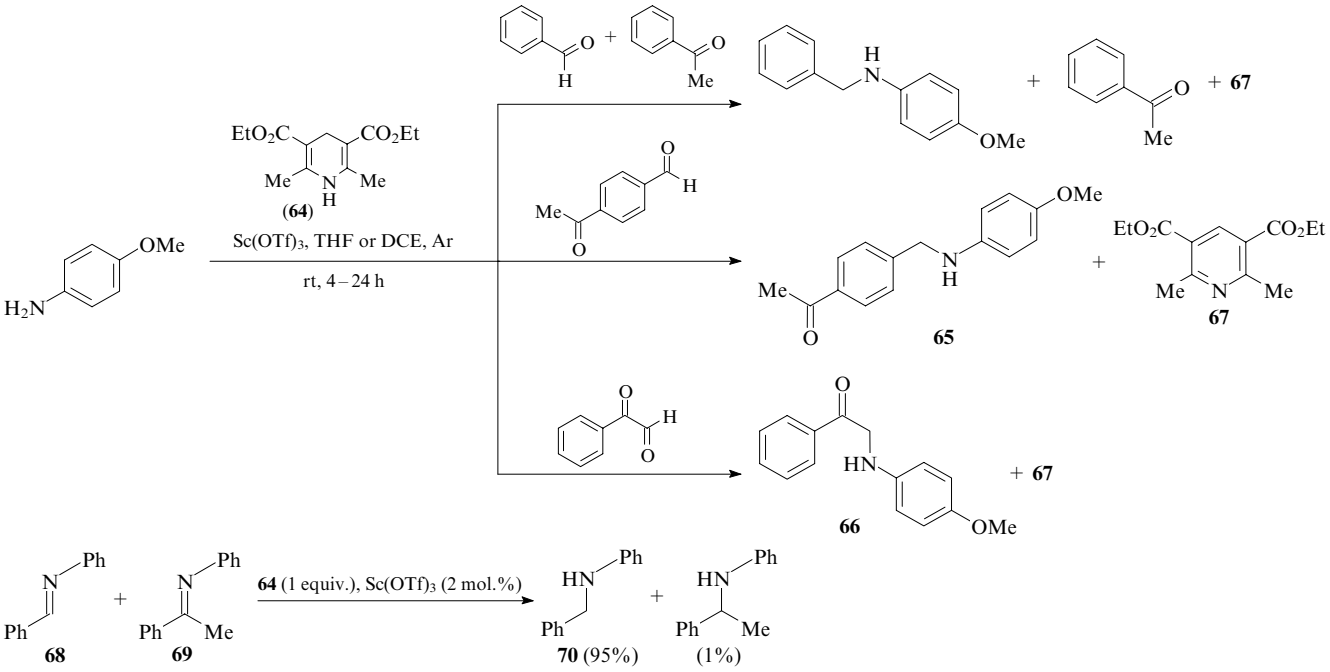
R^1, R^2 = Ar, Alk

Direct reductive alkylation of amines with aldehydes in the presence of Me_2PhSiH has also been carried out with the use of a hybrid catalyst — carbon nanotubes modified with gold nanoparticles.[135]

IV. Organic reagents and chiral catalysts in enantioselective synthesis of amines

In early protocols of enantioselective synthesis of amines through the reductive alkylation with carbonyl compounds, hydrogen was used as a reducing agent. The procedure of synthesis of herbicide metolachlor catalyzed by an iridium complex has been developed with the use of such protocols.[136] Kadyrov and Riermeier[3] suggested synthesizing α-chiral amines by the Leuckart – Wallach reaction with the use of catalytic rhodium and ruthenium complexes. In

Scheme 42



the past decade, a new strategy of enantioselective synthesis of amines (direct asymmetric reductive amination, DARA) has been formulated where organic compounds are used as reducing agents in combination with chiral catalysts.

Itoh *et al.*[137, 138] have pioneered the use of Hantzsch dihydropyridine (or ester) (DHP, **64**) — the product of condensation of ammonia, formaldehyde and acetoacetic ester — as a hydrogen source in this reaction. Reductive alkylation of *p*-anisidine in the presence of the Lewis acid $Sc(OTf)_3$ occurs with high chemoselectivity to give amines **65** and **66**; in the reaction, the reducing agent converts into pyridine derivative **67** (Scheme 42).[137, 138]

Hantzsch ester is highly selective and reduces neither aldehyde nor ketone even in the absence of imine. In a mixture of aldehyde and ketone (benzaldehyde and acetophenone), aldehyde is considerably more reactive in the direct reductive alkylation, while ketone does not react. At the same time, reductive amination of ketone in the absence of aldehyde leads to the corresponding amine in high yield. In joint reduction of benzaldehyde and acetophenone imines (**68** and **69**, respectively), the reduction proceeds with 99% selectivity in sterically unhindered benzylideneaniline (**68**) to give amine **70** (see Scheme 42).[138]

Major reagents, including Hantzsch ester, were borrowed from imine reduction methods. Reduction of the imine bond is a necessary stage of reductive alkylation of amines, and precisely this stage determines the outcome of this reaction. However, in the DRA method, imine is an intermediate; therefore, this method of amine synthesis is most preferable and sometimes the only possibly one, especially for alkyl substrates when imine is unstable and poorly isolated from the reaction mixture. This fact accounts for the evident advantage of DRA over a two-stage procedure involving synthesis and reduction of imines.

Currently, Hantzsch ester is widely used as a hydrogen source in the reductive alkylation reaction in combination with different catalysts. Weakly basic amines, such as aniline derivatives with electron-withdrawing substituents and heteroaromatic amines, are alkylated with the use of the $ZrCl_4$–DHP combination.[139] In the presence of the TMSCl–DHP system, the alkylation of halogen-substituted anilines, pyrrolidine, piperidine and diethylamine with benzaldehyde derivatives and furan-2- and thiophene-2-carbaldehydes at room temperature gives the products in high yield (75%–95%).[140]

Application of Hantzsch ester in combination with chiral catalysts as an efficient strategy for the formation of the asymmetric carbon atom bonded to the nitrogen atom and development of catalysts for enantioselective synthesis of amines have been the focus of research in recent years.[141–147]

The idea of using bound hydrogen for stereoselective reduction of imine was borrowed from the natural process of enantioselective synthesis of essential amino acids. Such an *in vivo* chemical reaction is transferase-activated selective hydride transfer from the NADH coenzyme (a dihydropyridine derivative — nicotinamide adenine dinucleotide) to ketimines formed in the course of biosynthesis, responsible for the enantiocontrolled synthesis of a natural amino acid. In the *in vitro* enantioselective amination protocol, Hantzsch dihydropyridine (**64**) is treated as a chemical equivalent of NADH, and a chiral organophosphoric acid, like an enzyme, catalyzes hydride transfer (Fig. 1).[141, 146]

A protocol for direct enantioselective organocatalytic alkylation of amines based on this biomimetic reaction makes it possible to combine complex fragments of achiral carbonyl derivatives and amines into chiral amine derivatives by means of chiral catalysis (Scheme 43 shows two possible catalysts as an example).

Direct catalytic alkylation with carbonyl compounds as a method of formation of a C–N bond with the asymmetric carbon atom involves several stages, the rate-limiting stage being the C–N bond formation. Enantioselectivity is realized at the stage of reduction of the intermediate imine (formed in the cascade of reactions beginning with the protonation of imine with a catalyst — chiral Brønsted acid **71**) with Hantzsch ester (**64**). Asymmetric induction is

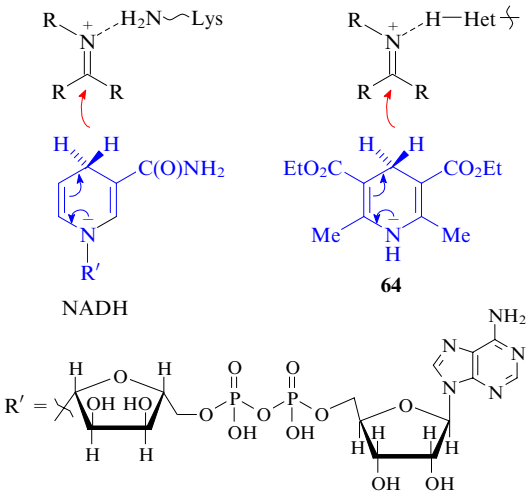
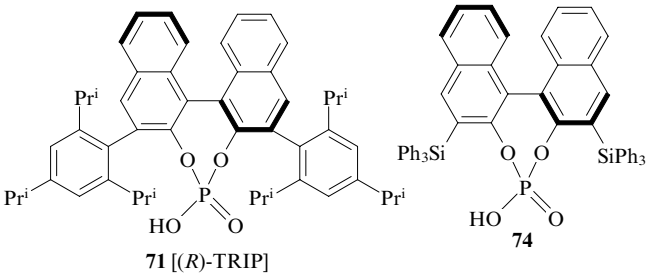


Figure 1. Hantzsch dihydropyridine (**64**) as an NADH analogue in enantioselective amination of ketones.

provided through the formation of the catalyst phosphate anion – iminium cation ion pair.

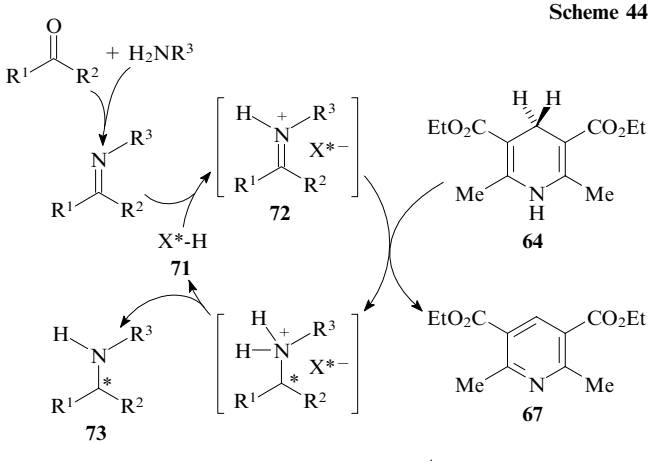
Structures 71, 74



This ion pair **72**, which is evidently H-bond stabilized, is chiral, and its reaction with Hantzsch ester gives enantioenriched product **73** and pyridine derivative **67** (Scheme 44).[141] It is necessary to add molecular sieves for binding water released in the course of imine formation.[146, 147]

The catalyst structure is of crucial importance for achieving the enantioselective result.[3] Screening of catalysts

Scheme 44



based on chiral derivatives of phosphoric acid (binols) like **71** and **74** has shown that the increase in the volume of the catalyst molecule through the introduction of aromatic substituents in the 3- and 3′-positions of the binaphthol molecule leads to a significant increase in enantioselectivity. The most efficient catalyst is 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrophosphate (TRIP, **71**).[141, 142] It should be noted the catalyst molecule volume is crucial in the above reaction; however, the catalyst is selected separately for a specific pair of substrates.[143 – 146]

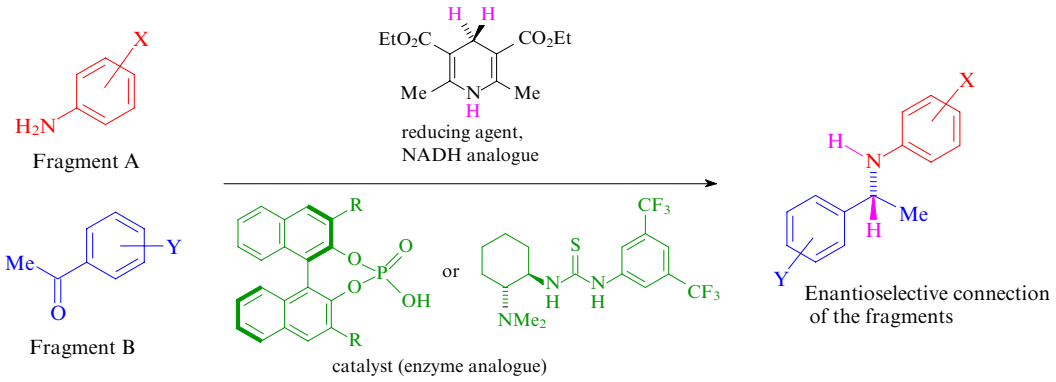
Great progress in the application of organocatalysts has been made by the research teams of List, MacMillan and Antilla.[141, 143 – 146] The development of new chiral catalysts — phosphoric acid derivatives like **71** — has provided a general and effective way to the formation of stereogenic C – N bond in synthons for natural and modified amine derivatives. Selective catalysts have been designed, which block (do not stimulate) the side process of reduction of carbonyl substrates to alcohols.

In 2005 – 2006, a protocol for the DARA of prochiral ketones with the use of Hantzsch ester has been suggested. The procedure is distinguished by the use of the organic (metal-free) catalytic process and occurs with high yield and enantioselectivity for a wide range of amines and ketones.[141 – 147]

For acetophenone derivatives containing aryl substituents with different electronic effects in different positions, for cycloalkyl ketones and α-CF_3-substituted ketones, the reaction with *p*-anisidine and bis(*o*-triphenylsilyl) derivative of binol phosphoric acid (the Terada – Akiyama catalyst,

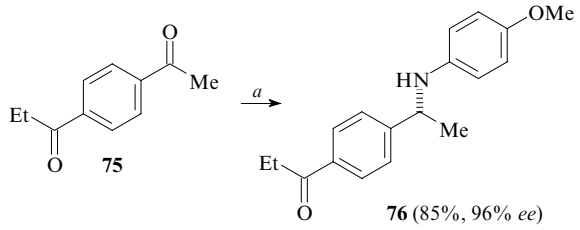
Scheme 43

Direct enantioselective organocatalytic alkylation



74) occurs in 70%–90% yield and high enantioselectivity. The yield of the products is determined by the ketone structure. The reaction rate for alkyl and cycloalkyl ketones is lower than for aryl ketones; dialkyl ketones and cycloalkyl ketones alkylate *p*-anisidine in lower yield (50%–70%) but with high enantioselectivity (80%–95%). The chemoselectivity depends on the structure of the alkyl substituent: the alkylation of *p*-anisidine with diketone **75** occurs chemoselectively (18 : 1) to give amine **76** at the methyl keto group (Scheme 45).[146]

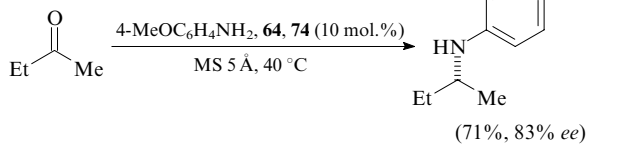
Scheme 45



(*a*) 4-MeOC$_6$H$_4$NH$_2$, **64**, **74** (10 mol.%), MS 5 Å, 40 °C, 72 h

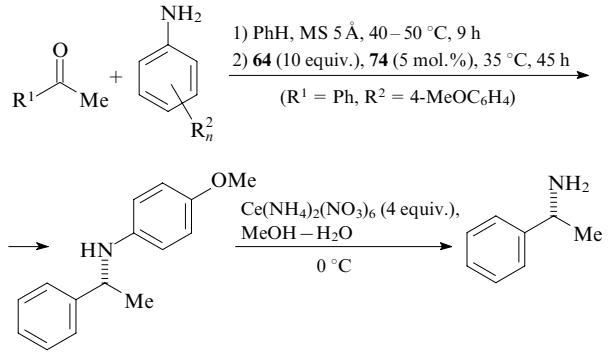
Since the reduction of the imine intermediate plays a key role in enantioselectivity control, the enantioselectivity of the reductive amination of methyl ethyl ketone with *p*-anisidine (Scheme 46) decreases insignificantly, which shows that enantioselectivity is independent of the structure of the alkyl substituent at the reaction centre. Reductive alkylation of aromatic and heteroaromatic amines with Hantzsch ester (**64**) occurs with high enantioselectivity and high yield of target derivatives **77** (55%–94%) (Scheme 47).[146] In these reactions, *p*-anisidine is used as the amine functionality translator to complex functionalized carbonyl compounds; the *p*-methoxyphenyl substituent is readily eliminated under the action of an oxidant (see Scheme 47).[143]

Scheme 46



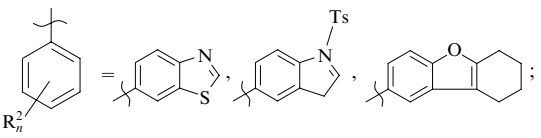
(71%, 83% *ee*)

Scheme 47



77 [77%–96%, (83%–97%) *ee*]

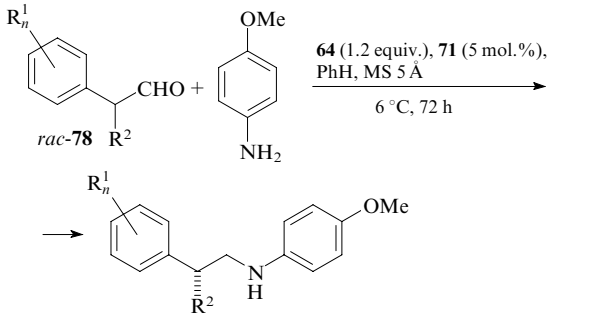
R^1 = Ph, 4-XC$_6$H$_4$ (X = Me, MeO, O$_2$N, Cl), 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 2-Naph, Et, n-C$_6$H$_{13}$, Ph(CH$_2$)$_2$, cyclo-C$_6$H$_{11}$, BzOCH$_2$, CH$_2$=CH(CH$_2$)$_2$; R^2_n = 4-MeO;



Ts = 4-MeC$_6$H$_4$SO$_2$

Organocatalytic asymmetric reductive amination of racemic α-branched aldehydes **78** with *p*-anisidine in the presence of chiral phosphoric acid **71** as a catalyst leads to β-branched secondary amines **79** in high yields (Scheme 48). It is assumed that, under the reaction conditions, aldehyde **78** can undergo rapid racemization in the presence of amine and acid catalyst through imine–enamine tautomerization **A** → **B** → **C**. Reduction of one of the enantiomers should occur faster than that of the other to give an enantioenriched product. The enantioselectivity of the reaction is 94%–99%, but decreases to 89%–90% in the case of aliphatic and carbocyclic aldehydes (Scheme 49).[143]

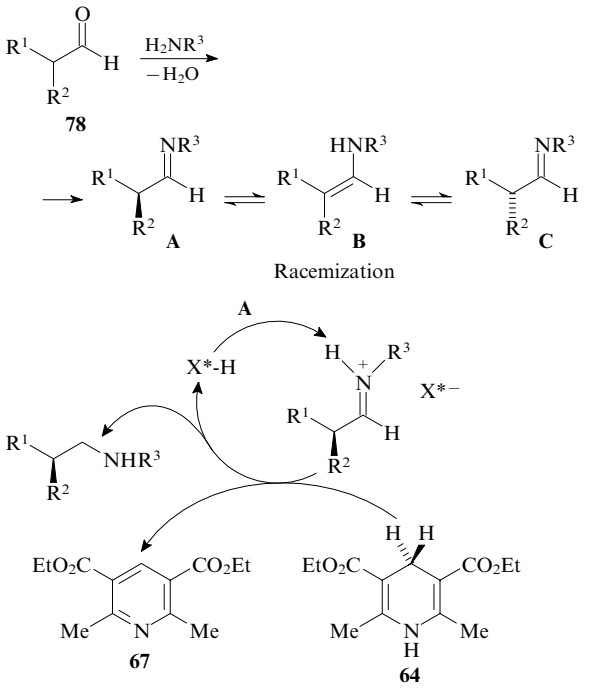
Scheme 48



79 [92%, (90%–99%) *ee*]

R^2 = Me: R^1_n = H, 4-Me, 4-MeO, 4-Br, 2-F, 3-F, 2,3-benzo, 3,4-benzo, *etc.*; R^2 = Et, R^1_n = H

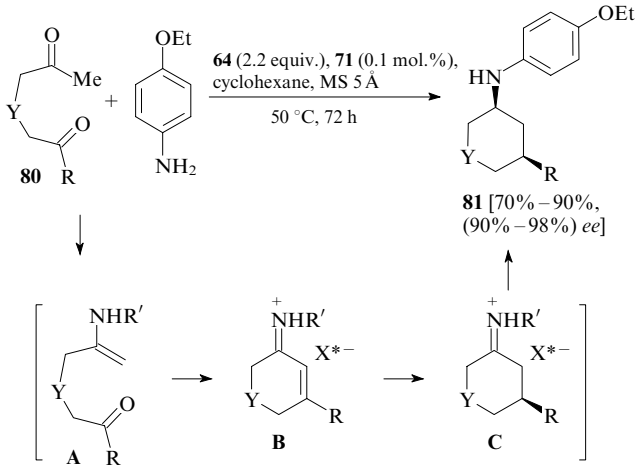
Scheme 49



X*-H = **71**

A cascade process involving aldol addition, dehydration and reduction has been developed for synthesis of cyclohexylamine derivatives. The protocol is based on the known ability of an amine salt to catalyze aldol formation. Achiral *p*-ethoxyaniline in combination with a catalytic amount of chiral Brønsted acid **71** reacts with 2,6-diketones **80** to give cyclohexylamines (and their heteroanalogues) **81** in excellent yields and enantioselectivity (Scheme 50).[144] The first stage of addition (aldolization) through the formation of intermediate **A** occurs very rapidly (according to chromatography – mass spectrometry) and is presumably a kinetically controlled process since no regioisomers have been detected. In the chain of transformations **B** → **C** → reaction product **81**, catalyst **71** is responsible for the observed *cis*-stereoselectivity since other phosphoric acid derivatives lead to the *trans* isomer.

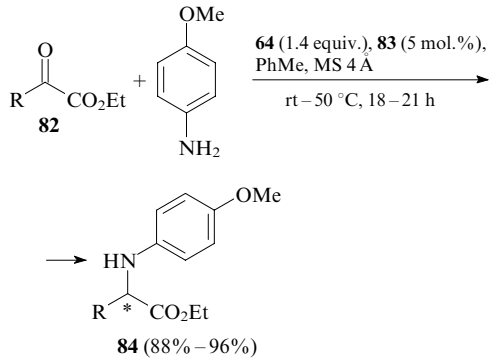
Scheme 50



Y = CH_2, O, S; R = Bu^n, Bn, (cyclo-C_5H_9)CH_2, (cyclo-C_6H_{11})CH_2, 2-Naph; R′ = 4-$EtOC_6H_4$

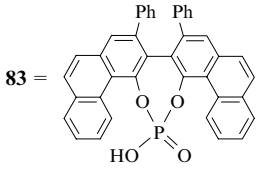
The use of DARA in synthesis of natural and unnatural α-amino acids has enabled the production of these compounds widely necessary in pharmaceutics and bioengineering. The reaction of Hantzsch ester (**64**) with α-imino esters derived from aryl or alkyl keto esters **82** and *p*-anisidine in the presence of chiral phosphoric acid **83** as a catalyst leads to α-amino esters **84** in high yield and 96% *ee* (Scheme 51). An analogous direct process without isolation of the imino ester prepared *in situ* also leads to high yield and enantioselectivity.[145] The most efficient catalyst in synthesis of α-amino esters **84** is phosphoric acid derivative **83** [(*S*)-VAPOL-PA].

Scheme 51



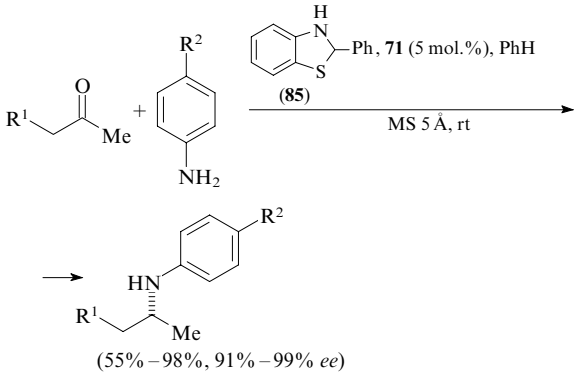
R = 4-$MeOC_6H_4$, 4-BrC_6H_4, 3,5-$F_2C_6H_3$, Me, n-C_6H_{13};

83 =



Hantzsch ester long remained the only organic reducing agent used in such reactions. In the past few years, the Akiyama group has proposed aryl derivatives of benzothiazoline which, in comparison with Hantzsch ester, show better enantioselectivity and reactivity. Enantioselective reductive alkylation of aromatic amines with aliphatic and cycloaliphatic ketones catalyzed by chiral phosphoric acid **71** have been successfully carried out using benzothiazoline **85** as the hydrogen source (Scheme 52).[147] The reaction occurs at room temperature; the yield of alkylated amine depends on the ketone structure, while enantioselectivity is determined by the catalyst structure.

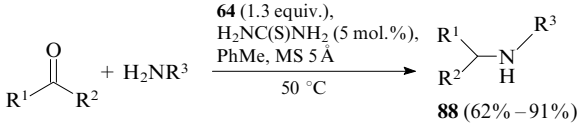
Scheme 52



R^1 = Et, Bu^n, Bu^i, cyclo-C_6H_{11}, $Ph(CH_2)_2$, $PhCO_2CH_2$, 3,4-$OCH_2OC_6H_3(CH_2)_2$, $CH_2{=}CH(CH_2)_2$; R^2 = H, MeO, Br

Menche *et al.*[148 – 151] have suggested using thiourea or its derivatives as catalysts in the reaction with Hantzsch ester (Scheme 53). Mild conditions and high chemoselectivity of such a procedure free of acid agents and metal derivatives makes it preferable for acid-sensitive and sterically hindered substrates, including those that contain functional groups labile to reduction.[152]

Scheme 53

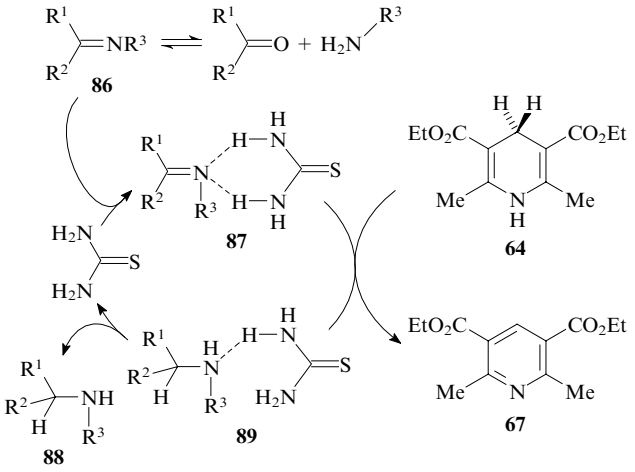


R^1 = H: R^2 = Pr^i, Ph, 3-AcC_6H_4, 4-$O_2NC_6H_4$, 1-Naph, 2-Naph, *etc.*;
R^1 = Me: R^2 = Pr^i, Bn, Ph, 3-Th, 2-Fu, $PhCH{=}CH$, XC_6H_4 (X = 4-Me, 4-MeO, 4-CF_3, 3-Me, 2-Me, 2-Cl, *etc.*);
R^1 = Et, R^2 = Bu^n; $R^1 - R^2$ = $(CH_2)_5$; R^3 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$HO_2CCH_2C_6H_4$, 2-Cl-5-MeC_6H_3, 3-O_2N-4-MeC_6H_3, 2-Py; Th is thienyl

The reaction can be catalyzed through the formation of hydrogen bonds with imine due to the protonation of the amino group and(or) formation of hydrogen bonds between

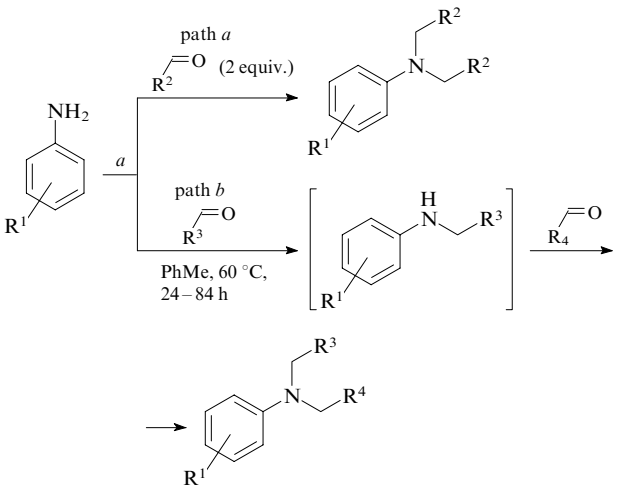
the catalyst and both substrates before imine formation.[153] Thiourea selectively catalyzes the reduction of imine **86**, which is in equilibrium with the carbonyl and amine substrates in the reaction mixture. The enantioselectivity of the process is determined by the mode of binding of reaction substrates to the catalyst.[151, 154] Once reaction complex **87** of thiourea with imine has formed, hydrogen transfer occurs in the course of reduction of imine to amine **88** through transition complex **89** (Scheme 54).

Scheme 54



This method has been successfully used in synthesis of tertiary amines (Scheme 55).[149, 150] In this case, 2 equiv. of a carbonyl compound can be used (see Scheme 55, path *a*)[149] or two different aldehydes can be introduced successively without isolation of an intermediate compound (path *b*).[150]

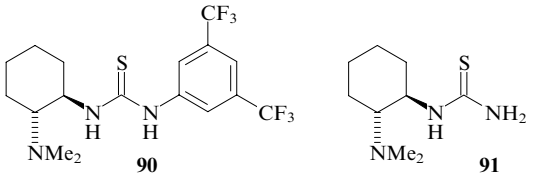
Scheme 55



R^1 = 4-Me, 4-MeO; R^2 = Pr^i, Ph, 3-AcC_6H_4; R^3 = Pr^i, n-C_8H_{17}, Ph, 4-$O_2NC_6H_4$, 2-$MeOC_6H_4$; R^4 = Pr^i, Ph, 4-$O_2NC_6H_4$;
(*a*) **64** (1.5 equiv.), $(NH_2)_2CS$ (0.1 equiv.), MS 5 Å

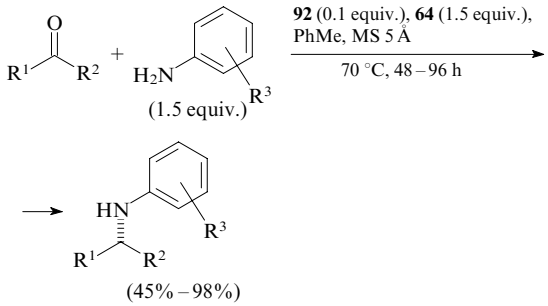
For the asymmetric variant of the method, thiourea derivatives **90** and **91** with chiral electron-withdrawing substituents have been suggested.[146, 153, 155] The use of such catalysts significantly increased the reaction enantioselectivity.

Structures 90, 91

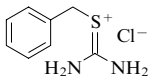


S-Benzylisothiuronium chloride (**92**) as an organic catalyst for enantioselective synthesis has been recently suggested for direct reductive alkylation with the use of Hantzsch ester (**64**); the reaction has been carried out for a wide range of ketones and arylamines (Scheme 56).[156]

Scheme 56



R^1 = Alk, Ar; R^2 = Alk; R^3 = 4-MeO, 3-Cl, 4-HO, 4-Me

92 = 

* * *

Significant progress has been achieved in the past decade in synthesis of amines by reductive alkylation. The use of new complex catalysts of reductive alkylation makes it possible to carry out the reactions under mild conditions and with high selectivity and realize environmentally safe processes. With the use of new reagents and catalysts, complex functionalized derivatives of heterocyclic amines have been synthesized. Development of methods of direct asymmetric (enantioselective) reductive alkylation enables the synthesis of compounds widely demanded in chemical and pharmaceutical industry and bioengineering.

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