Part - II: Section - A

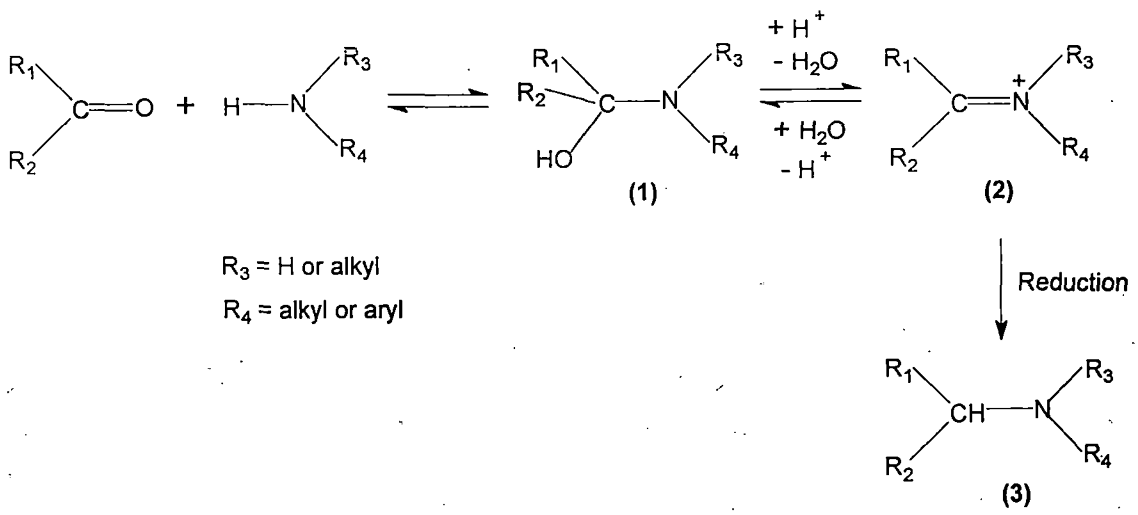
II-A: Direct Reductive Amination of Aldehydes and Ketones Using Potassium Formate and Catalytic Palladium Acetate: Development of a New and Simple Protocol

II-A.1: Reductive Amination: A Brief Review

The synthesis of amines and their derivatives has long been of interest because of their versatile utility as medicinal agents and agrochemicals.[1] Alkyldiarylamines are common structural elements found in many biologically active compounds. Examples include the antipsychotic agent mosapramine, the coronary vasodilator pretiadil, and the anti-inflammatory agent mepheclocine.[2] Tertiary amines are an extremely important class of compound from the drug discovery perspective. Indeed no less than a quarter of registered drugs contain tertiary amines.[3] The *N,N*-dimethylalkylamines are particularly useful as ligands[4] in homogeneous catalytic asymmetric transformation, as a modifier[5] for reversed phase chromatography, and as a buffer[6] in sequential analysis of proteins and peptides.[7]

In both biological systems and chemical synthesis the reductive amination of aldehydes and ketones is an important transformation which allows the direct conversion of carbonyl compounds into amines. The reductive amination reaction is described as a direct reaction when the carbonyl compound and the amine are mixed with proper reducing agent in a single operation (Scheme 1). The reaction involves the initial formation of the intermediate carbinol amine (**1**), which dehydrates to form an imine (**2**). Under the reaction conditions, which are usually weakly acidic to neutral, the imine is protonated to form an iminium ion (**2**),[8] which is subsequently reduced to produce the alkylated amine (**3**). However, there are some reports that provide evidence suggesting a direct reduction of the carbinol amine as a possible pathway leading to alkylated amine (3).[9] A stepwise or indirect reaction involves the pre-formation of the intermediate imine followed by reduction in a separate step.

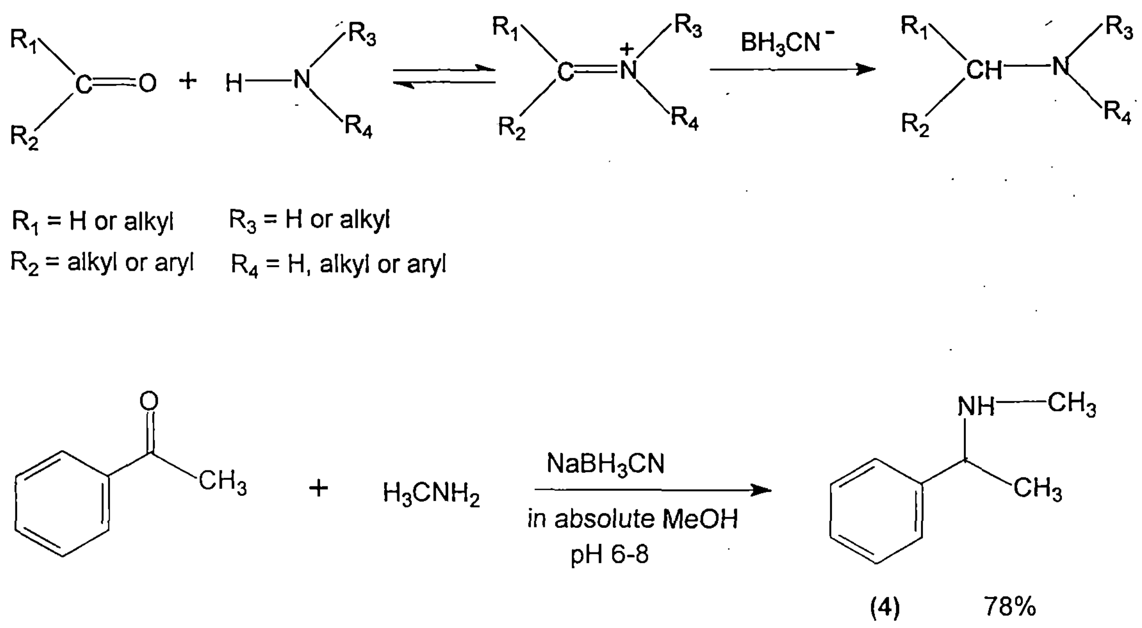
Scheme 1

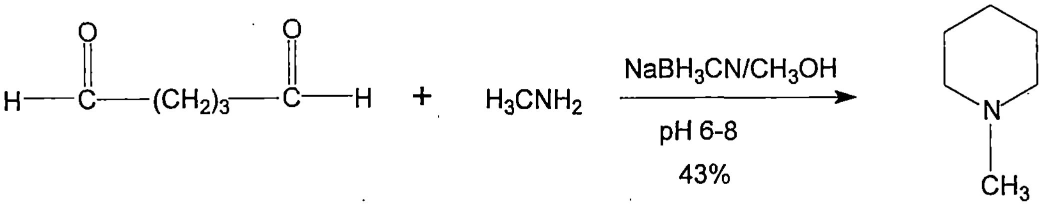


Since the iminium ion (**2**) is reduced much faster than a carbonyl group, it is possible to reductively aminate an aldehyde or ketone by simply reacting the carbonyl compound with an amine at pH 6-8 in the presence of a reducing agents. Several reagents which effect direct reductive amination have been recently developed, include the following: Hydrogen in presence of metal catalyst (catalytic hydrogenation),[8a,10] sodium cyanoborohydride,[11] titanium(IV) isopropoxide-sodium cyanoborohydride,[12] sodium borohydride-magnesium perchlorate,[13] zinc-acetic acid,[14] borohydride exchange resin (BER),[15] zinc bororohydride-zinc chloride,[16] borane-pyridine,[17] sodium triacetoxyborohydride,[18] silica gel-zinc borohydride,[19] zinc chloride-sodium borohydride,[20] titanium(IV) isopropoxide-sodium borohydride,[21] nickel chloride-sodium borohydride,[22] titanium(IV) isopropoxide-polymethylhydrosiloxane,[23] decaborane,[24] tributyltin hydride,[25] dibutyltin chloride hydride and dibutyltin iodide hydride,[26] dibutyltin dichloride-phenylsilane,[27] Et_3SiH-trifluoroacetic.[28] In addition, there are some reports of electrochemical reductive amination reactions.[29] Reductive *N*-alkylation of amides with carbonyl compounds using Et_3SiH-trifluoroacetic acid has also been described.[30]

The catalytic hydrogenation of C-N double bond with platinum, palladium or nickel catalysts[10] is economical and effective reductive amination method, particularly in large scale reactions. However, the reaction may give a mixture of products and low yields depending on the molar ratio and the structure of the reactants[31]. Hydrogenation has limited use with compounds containing C-C multiple bonds and in the presence of reducible functional groups such as nitro[32,33] and cyano[33] groups. The catalyst may be inhibited by compounds containing divalent sulfur.[34] The Borch reduction,[35a] using sodium cyanoborohydride [$NaBH_3CN$] has been the most popular and general method to carry out reductive amination of aldehydes and unhindered ketones with ammonia, primary and secondary amines (Scheme 2). Hindered and diaryl ketones fail to react and aromatic amines react somewhat sluggishly. Reductive amination of acetophenone and methylamine with sodium cyanoborohydride afforded *N*-methyl-1-phenylethylamine (**4**) in 78% yield. Due to its different selectivities at different pH values sodium cyanoborohydride is allowed for a convenient direct reductive amination procedure. At pH 3-4 it reduces aldehydes and ketones effectively, but this reduction becomes slow at higher pH values.[35b] At pH 6-8, the more basic imines are protonated preferencially and reduced faster than aldehydes or ketones.[35a] It has also been successfully used due to its stability in relatively strong acid solutions (~pH 3), its solubility in hydroxylic solvents such as methanol. The reaction of a dicarbonyl compound with an amine in the presence of sodium cyanoborohydride provided an interesting synthesis of nitrogen-heterocycles, as illustrated by the preparation of **5**, **6**.

Scheme 2





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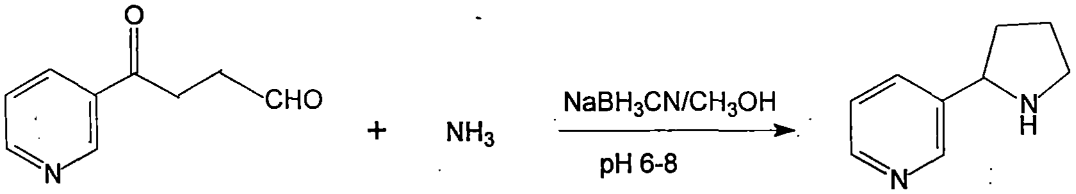
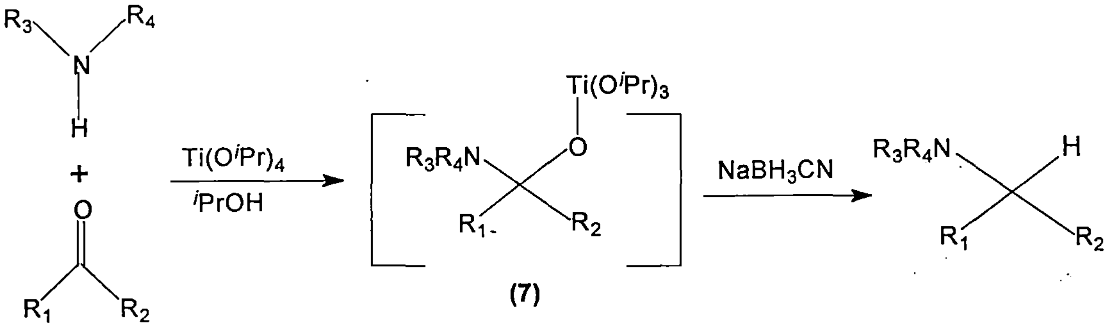


(6)

Limitations are that the reaction may require up to a fivefold excess of the amine,[35] is usually slow and sluggish with aromatic ketones[35] and with weakly basic amines,[36] and may result in the contamination of the product with cyanide.[17b] The reagent is highly toxic[37] and produces toxic byproducts such as HCN and NaCN upon workup.

The Borch reductive alkylation method[35a,c,d] works well provided the intermediate iminium adduct forms readily. For this reason the Borch procedure usually requires an excess of amine to favor the formation of iminium intermediates. When both the ketone and amine starting materials are valuable or the iminium intermediate is difficult to form, the Borch method can be less than satisfactory. Titanium(IV) chloride has been used as a Lewis acid catalyst in cases when the formation of enamines has proven to be difficult,[38] however, an excess of amine is still needed[39] and the presence of acid-sensitive functionality is limited. Titanium(IV) isopropoxide has been used as a trans-esterification catalyst compatible with variety of functional groups, such as lactam, acetonide, and *tert*-butyl dimethylsilyl ether.[40] The research group of Mattson[13] reported that titanium(IV) isopropoxide is a mild and effective Lewis acid catalyst for the reductive alkylation of amines with ketones and aldehydes in the presence of acid-sensitive functional groups (Scheme 3). This one-pot procedure proved to be compatible with carbamate, urea, acetal, ketal, ester, and amide groups. After studying IR spectra of the amine/ketone/titanium(IV) isopropoxide mixtures they suggested that an iminium species is, at most, a transient

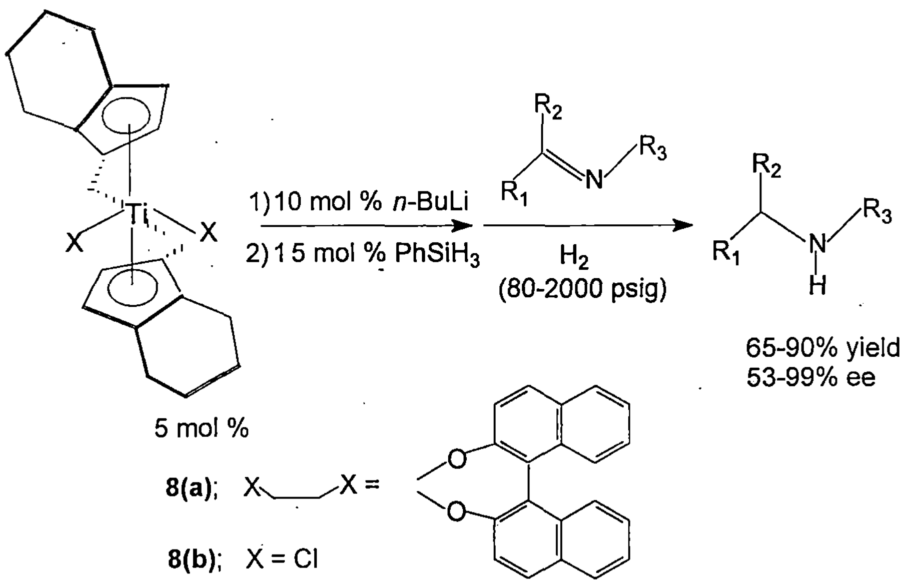
Scheme 3



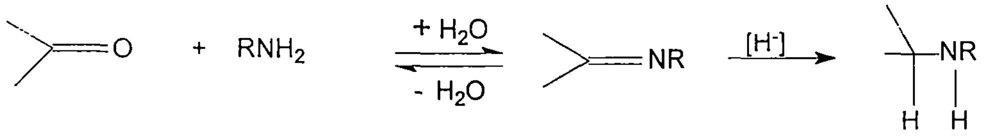
intermediate in this reaction. In one possible mechanism, the stable complex (7) is formed, which then is reduced either directly or via a transient iminium species.

The development of asymmetric catalysts for the hydrogenation of achiral substrates to form enantiomerically enriched products represents a major area of research[41]. With the growing importance of enantiomerically pure nitrogen containing compounds in the pharmaceutical and agrochemically enriched amines has received much attention recently[42]. Processes have been developed using titanium,[43] ruthenium,[44] iridium[45] and rodium[46] complexes as catalysts and hydrogen or silanes[47] as stoichiometric reducing agents. Virtually all of the systems employed for this reaction have been derived from late transition metals and in general substrates must possess a coordinating ligand such as a carbonyl group for high levels of reactivity and selectivity to be realized. As part of an ongoing study of the viability of titanium catalysts for the reduction of unsaturated organic compounds,[48] Buchwald et al have discovered a titanocene catalyst (8) system for the asymmetric hydrogenation of imine (Scheme 4).[49] A feature of this system is that no coordinating group is necessary for high levels of enantioselectivity to be achieved. The catalyst (8) is particularly effective for the reduction of cyclic imines. For these substrates enantiomeric excesses were observed. The reason for this is likely due to the fact that the acyclic imines are mixtures of anti and syn isomers which interconvert during the reaction. The system exihibits tolerance to several common organic functional groups including trisubstituted olefines, acetals and alcohols.

Scheme 4

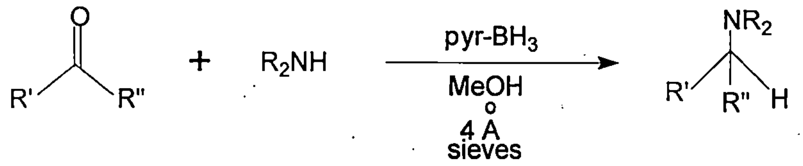


The *in situ* reductive amination of ketones or aldehydes has been an important part of the synthetic chemist's repetoire since the introduction of a procedure based on cyanobohydride,[35b,d,36] yet the toxicity and disposal problems associated with this material has led to a continuing search for alternative reductants.[11c,15,16,50] A successful reductive amination procedure for ketones and aldehydes hinges on rapid imine formation and imine selective reductants. As imine formation is usually rate-determining for *in situ* reductive aminations, catalyzing this reaction is desirable.[51] Typical catalysts are harse, for example, PCl_5,[52] $BF_3{\cdot}OEt_2$,[53] and $ZnCl_2$,[54] with at least one exception - molecular sieves. The *in situ* application of molecular sieves to imine synthesis is logical given the equivalent of water generated during imine formation.[55] Westheimer, however, recognized that molecular sieves display a catalytic role,[56] although the origin of this effect has been contested.[57]

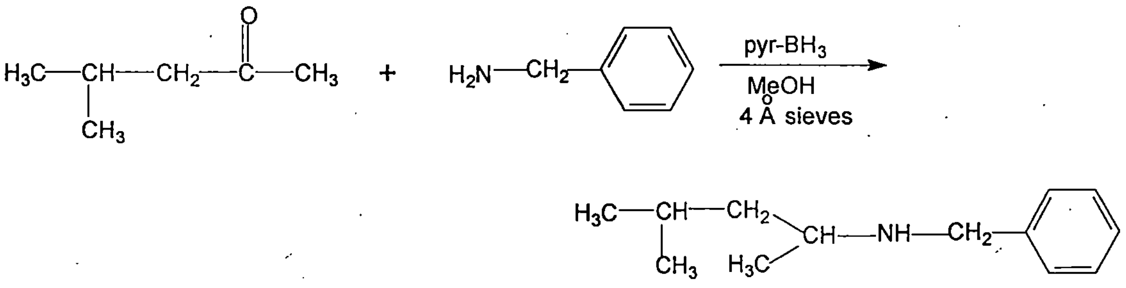


A member of the amine-borane family of reducing agents,[58] pyridine-borane has the selectivity necessary for reductive aminations. Two applications of pyridine-borane to direct reductive amination have appeared. The study of Moormann was limited to reductive amination of piperidines with aldehydes.[17b] The older and broader study of Pelter exploited an unusual two-phase reaction medium of acetic acid, presumably a catalyst for imine formation, and petroleum ether (2:7).[17a] DiMare et al[17c] reported that *in situ* reductive aminations of aldehydes and ketones with methanolic pyridine-borane in the presence of 4 Å molecular sieves offer a mild, convenient and effective alternative to cyanoborohydride-based procedures (Scheme 5).

Scheme 5



This procedure works well in case of aliphatic ketones. For example, the reaction of 4-methyl-2-pentanone and benzylamine under this condition afforded the amine (9) in 67% isolated yield. Secondary amines give consistently low yields with ketones.

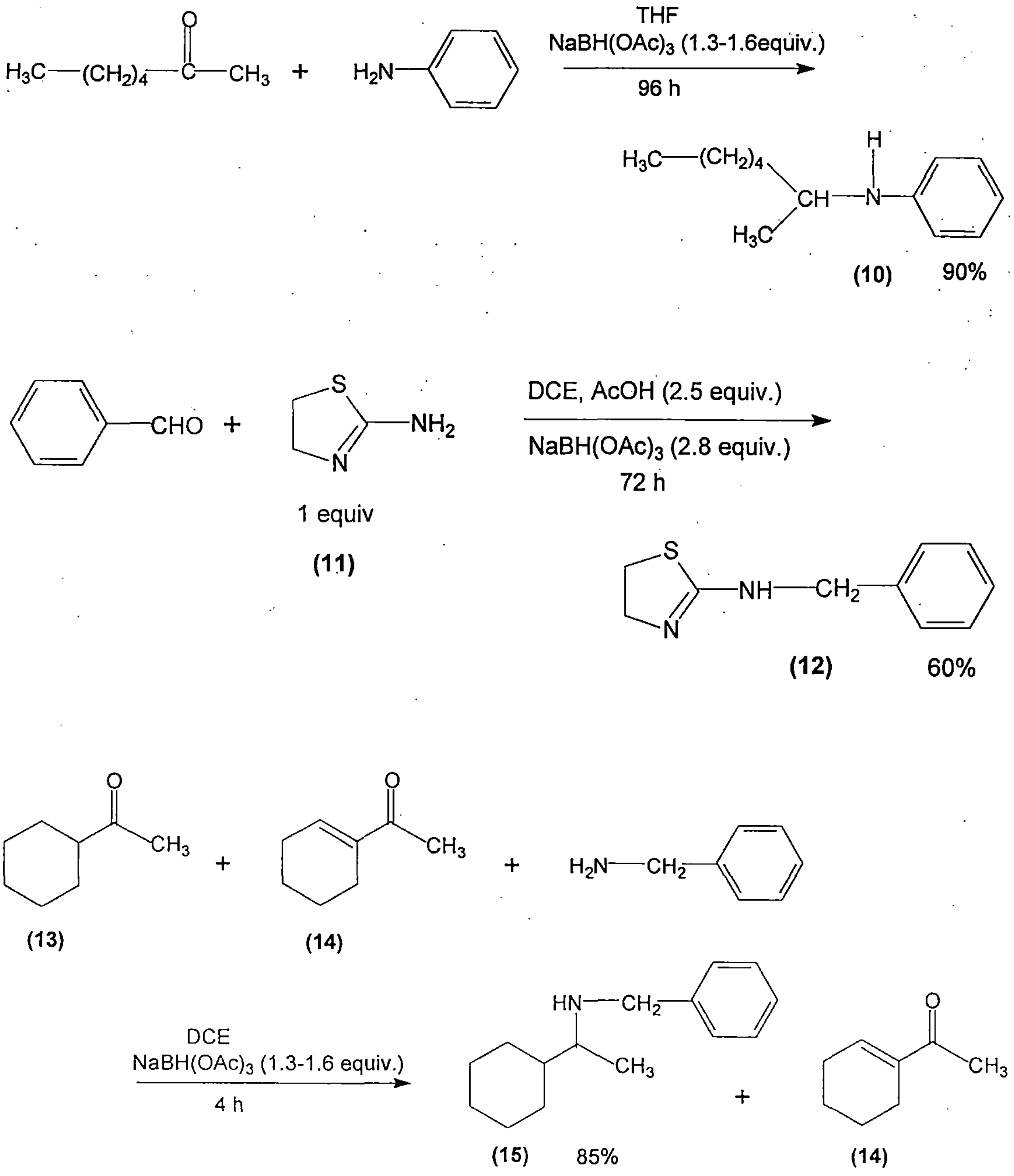


(9) 67%

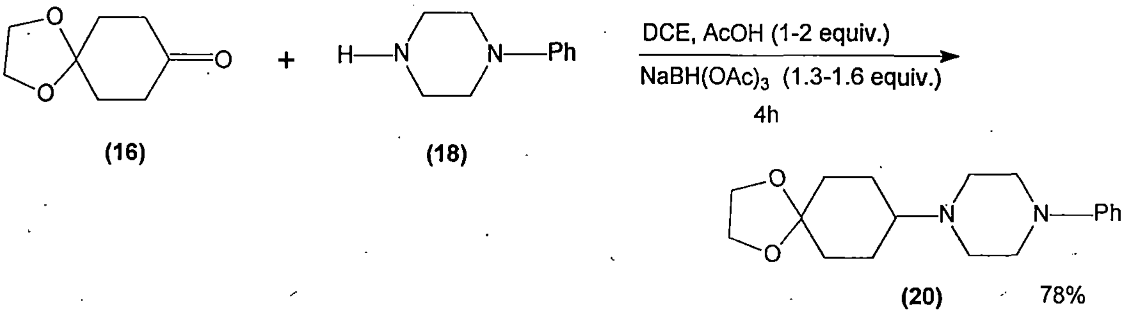
The research group of Abdel-Magid[18] discovered that sodium triacetoxyborohydride is synthetically useful reagent for reductive amination of aldehydes and ketones. Procedures for using this mild and selective reagent have been developed for a wide variety of substrates. The reaction of acyclic ketone 2-heptanone and aniline for 96 h in the presence of sodium triacetoxyborohydride afforded 90% isolated yield of *N*-phenyl-2-aminoheptane (**10**) as outlined in Scheme 6. The scope of the reaction includes aliphatic acyclic and cyclic ketones, aliphatic and aromatic aldehydes, and primary and secondary amines including a variety of weakly basic and nonbasic amines. For example, the reductive amination of benzaldehyde and 2-aminothiazole

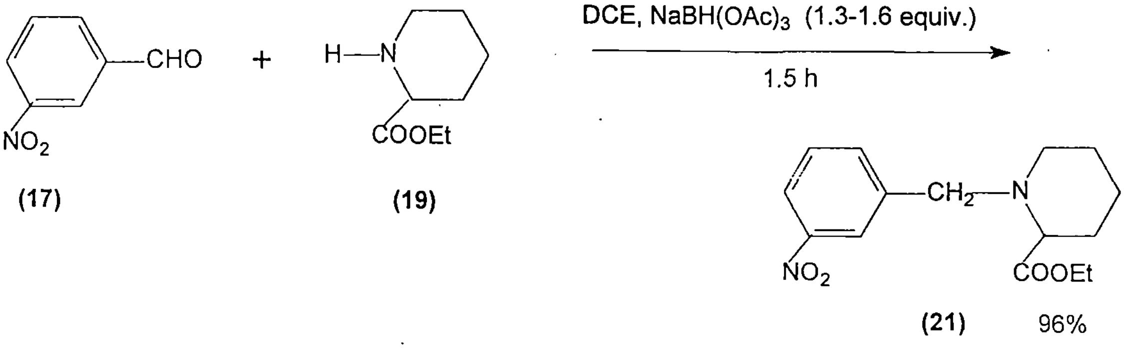
(**11**) using sodium triacetoxyborohydride gave compound (**12**) in 60% yield. Aliphatic ketones (and aldehydes) can be selectively reductively aminated in the presence of aromatic and α,β-unsaturated ketones. The mixture of 1-acetylcyclohexane (**13**) and 1-acetylcyclohexene (**14**) was reacted with benzylamine to give only *N*-[1-(cyclohexyl)-ethyl]benzylamine (**15**) without aminating 1-acetylcyclohexene (**14**). Acetic acid may be used as catalyst with ketone reactions, but it is generally not needed with aldehydes.

Scheme 6



This borohydride reagent is mild and exhibits remarkable selectivity as a reducing agent. This borohydride reduces aldehydes selectively over ketones,[59] except for β-hydroxy ketones which can be reduced selectively to give 1,3-trans diols.[60] The steric and the electron-withdrawing effects of the three acetoxy groups stabilize the boron-hydrogen bond and are responsible for its mild reducing properties.[61] The selection was also based on the results of reductive alkylation of amines using sodium borohydride in neat liquid carboxylic acids reported earlier by gribble et al.[62] The procedure is carried out in the presence of acid sensitive functional groups such as acetals and ketals; it can also be carried out in the presence of reducible functional groups such as C-C multiple bonds and cyano and nitro groups. Reductive amination of carbonyl compounds (**16** & **17**) with *sec*-amines (**18** & **19**) under the same condition afforded compounds **20** & **21** respectively. In comparison with other reductive amination procedures such as $NaBH_3CN$/MeOH, borane-pyridine and catalytic hydrogenation, $NaBH(OAc)_3$ gave consistently higher yields and fewer side products.

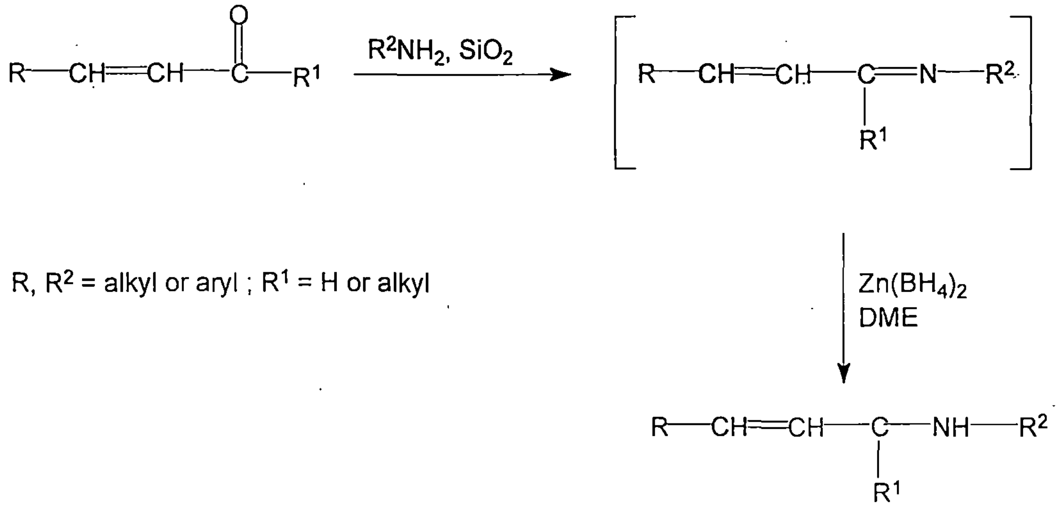


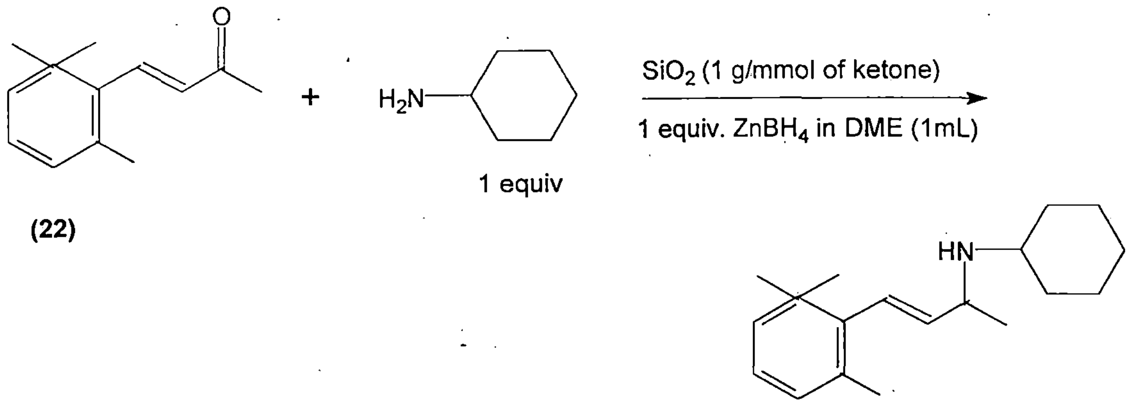


Limitations include reactions with aromatic and unsaturated ketones some sterically hindered ketones and amines.

In fact, reductive amination of conjugated carbonyl compounds has not been addressed in details in any of the reported methods–hydrogen in presence of metal catalysts, $NaBH_3CN$, BH_3-pyridine, borohydride exchange resin, Zn-AcOH, $NaBH_4$-$Mg(ClO_4)_2$, $ZnBH_4$-$ZnCl_4$, and $NaBH(OAc)_3$; only two exaples, 1-acetylcyclohexene and cinnalmaldehyde, have been included in $NaBH(OAc)_3$ procedure.[18] Although imines are, in general, prepared by the condensation of the carbonyl compound with an amine in the presence of a lewis or protic acid,[63] the research group of Ranu attempts to obtain the imines of conjugated carbonyl compounds, particularly ketones following reported procedures[63] using zinc chloride, boron trifluoride-etherate, *p*-toluenesulfonic acid, molecular sieves, failed. Ranu et al[19] have discovered that reductive amination of conjugated aldehydes ketone is achieved by treatment of the corresponding carbonyl compound with an appropriate amine in the presence of silica gel followed by addition of zinc borohydride in a one-pot operation (Scheme 7). This procedure does not affect nitro and cyano groups. Moreover, zinc borohydride is neutral in nature and, in general is compatible with many sensitive functionalities[19] like acetal[64a] and silyl ether.[64b] The reaction of compound (**22**) and cyclohexylamine under this condition afforded compound (**23**) in 85% yield.

Scheme 7





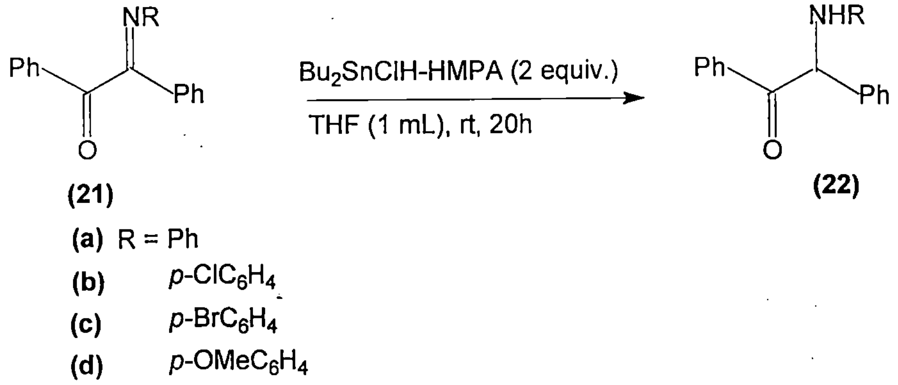
(22)

(23) 85%

The advantages of this procedure are (a) operational simplicity, (b) use of less costly or toxic chemicals, (c) low environmental pollution from waste, (d) mild conditions, (e) fast reaction, and (f) high yield.

Chemoselective reductions of imino groups are very important for the synthesis of multifunctionalized amines. Nevertheless, little attention has been paid to iminoselective reductions by metal hydrides in the presence of carbonyl groups because of the lower electrophilicity of imino groups.[65] Baba et.al. have developed a set of organotin hydrides that reduce polar multiple bonds such as C = O and C = N in an ionic manner,[66] and with which chemoselective reductions of bifunctional substrates could be achieved.[67] The introduction of a halogen substituent or a ligand onto the tin atom can change the character of the original tin hydrides[67c] to provide different chemoselectivities in the reduction of multifunctional substrates. For example, in the reaction with 2,3-epoxy ketones, Bu_2SnFH-HMPA selectively reduce the carbonyl group to furnish predominantely the *anti*-2,3-epoxy alcohol,[67a] whereas Bu_2SnIH-HMPA preferentially reduced the epoxy group to provide 3-hydroxy ketones.[67c] Baba et al[27c] have presented use of Bu_2SnClH-HMPA as a chemoselective reductant of imines in the presence of carbonyls (Scheme 8).

Scheme 8

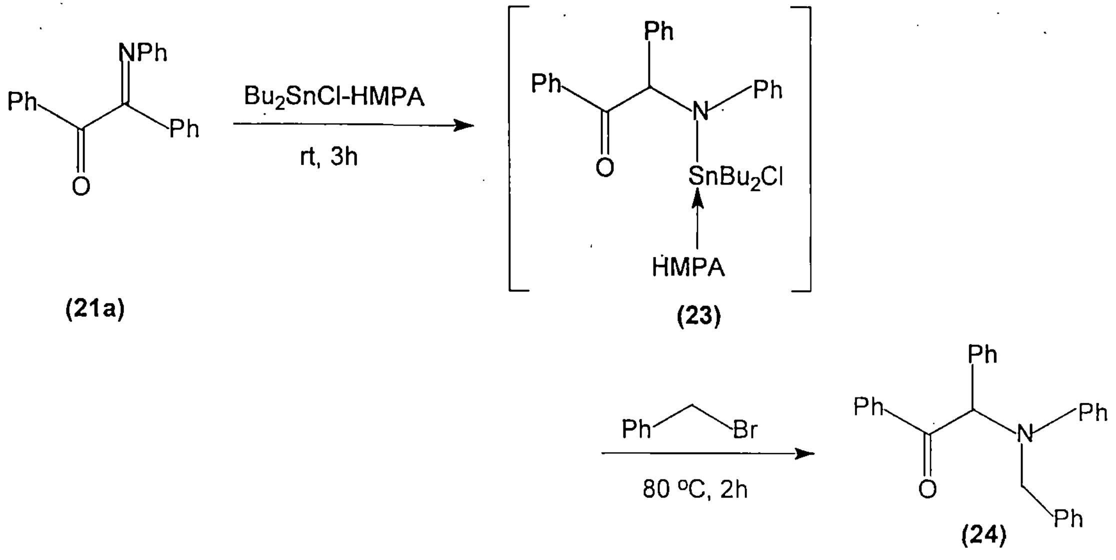


(21)

(22)

(a) R = Ph
(b) p-ClC_6H_4
(c) p-BrC_6H_4
(d) p-$OMeC_6H_4$

Further, Bu_2SnClH-HMPA possessed higher iminoselectivity compared with other conventional reductants such as $LiAlH_4$, DIBAL, and $NaBH_4$ which reduced the carbonyl group predominantly. 2-amino ketone (**22**) was obtained by the reduction of (**21**) with Bu_2SnCl-HMPA at room temperature followed by treating with methanol. The reduction progress stoichometrically, where the adducts bearing a nucleophilic Sn-N bond are generated in *situ* without protonation by tin hydride (Bu_2SnCl-HMPA). Moreover, the resulting tin amides from hydrostannation of imines subsequently react with organic halides to furnish unsymmetrical tertiary amines in a one-pot procedure. Multifunctionalized unsymmetrical amines (**24**) could be prepared directly by the subsequent *N*-alkylation of the tin amide (**23**) with benzyl bromide to afford unsymmetric tertiary amine (**24**).



(21a)

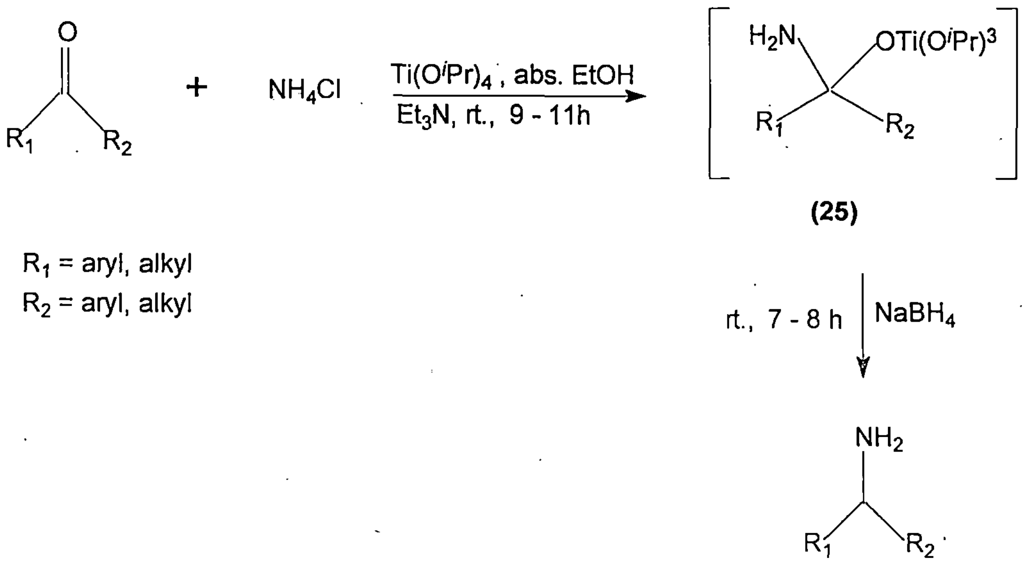
(23)

(24)

Noteworthly is that highly chemoselective reactions were achieved with the co-existence of other functionalities such as halogen, C-C double bond and hydroxy groups.

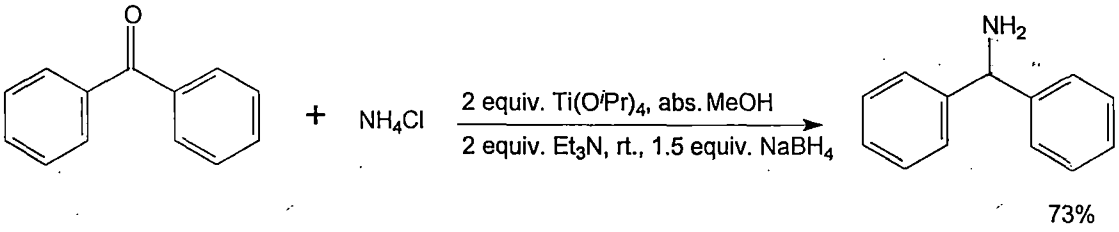
Though many of the reported protocols for reductive amination reactions work well for the preparation of tertiary and secondary amines, synthesis of primary amines by reductive alkylation of ammonia is mostly comprised by over alkylation reaction.[18,35b,36,68] The formation of variable amounts of secondary and tertiary amines along with primary amines is common. The synthesis of primary amines is, therefore, mostly addressed indirectly by using ammonia equivalents[69] such as tritylamine, diallylamine or allylamine. These protocols routinely require a subsequent deprotection step to get primary amines. Accordingly, development of a straightforward route for the synthesis of primary amines via selective monoalkylation of ammonia is an important objective. Bhattacharyya and coworkers[21] developed an efficient one-pot reagent system for the synthesis of primary amines by selective monoalkylation of ammonia with alkyl and aryl ketones using titanium(IV) isopropoxide and sodium borohydride (Scheme 9).

Scheme 9



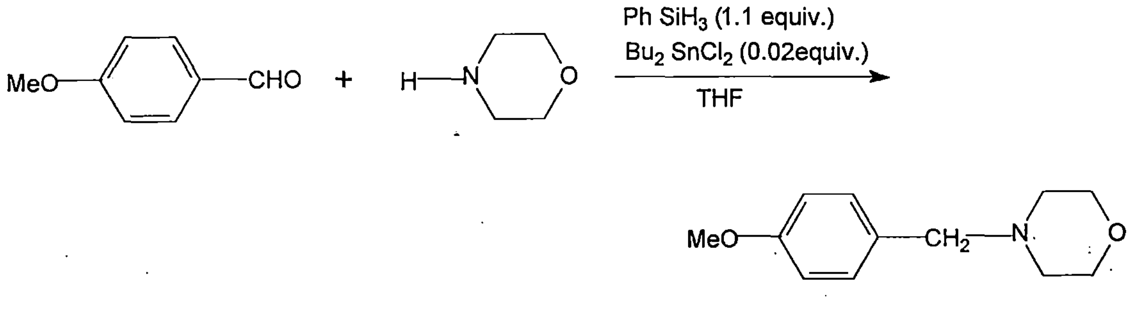
A mixture of ammonium chloride and triethylamine has been employed as the ammonia equivalent; this requires no special handling techniques and alleviates the use of excess gaseous ammonia. They used a combination of titanium(IV) isopropoxide and sodium borohydride in the reductive alkylations of primary and secondary amines.[70] Because this one-pot reagent system allows easy, direct access to diverse primary amines, it should find widespread application. Under these reaction conditions, only primary amines are formed - the traditional problem of over-alkylation of the product amines was not observed. The reaction may proceed through an intermediate aminocarbinolatotitanium(IV) complex (**25**), which is either reduced directly or via equilibration of **25** to form a transient iminium species.[71] The compatability[70,72] of titanium(IV) isopropoxide with a variety of acid- or base-sensitive groups provides an additional advantage for targeting the syntheses of amines with reagent-sensitive motifs.

The relevance of this protocol has been demonstrated on a structurally varied set of ketonic substrates. Benzophenone was allowed to react with a mixture of ammonium chloride, triethylamine and titanium (IV) isoproxide, followed by the treatment sodium borohydride at room temperature.



Apodaca et al[27] reported a direct reductive amination procedure which employs phenylsilane as a stoichiometric reductanrt and dibutyltin dichloride as a catalyst. Both aldehydes and ketones were reductively aminated with anilines and secondary alkylamines (acyclic, cyclic), although the reaction failed with primary alkylamines. Reductive amination of 4-methoxybenzyldehyde with morpholine in the presence of 2 mole % dibutyltin dichloride afforded 78% isolated yield of *N*-(4-methoxybenzyl) morpholine (**26**) (Scheme 10). Reactions with substrates bearing potentially reducible functional groups including aryl iodide, cinnamyl, nitro, benzyloxy gave the anticipated products, without detectable reduction side products. Potentially acid-labile groups were also well tolerated.

Scheme 10

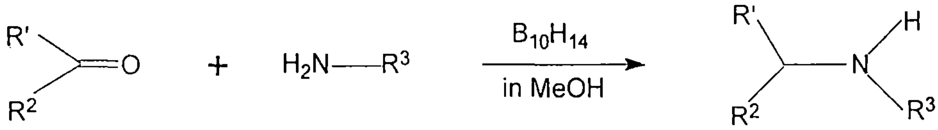


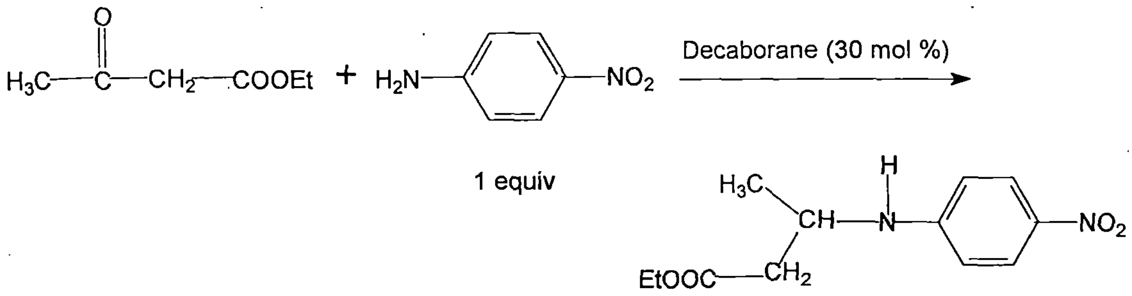
(26) 73%

This reported procedure offers some advantages over other methods. Because little, if any competitive carbonyl reduction was observed in these reactions, the use of excess aldehyde or ketone is unnecessary. Because of its catalytic nature, reaction rates can be increased by simply adding more catalyst or through the potential development of more active catalysts.

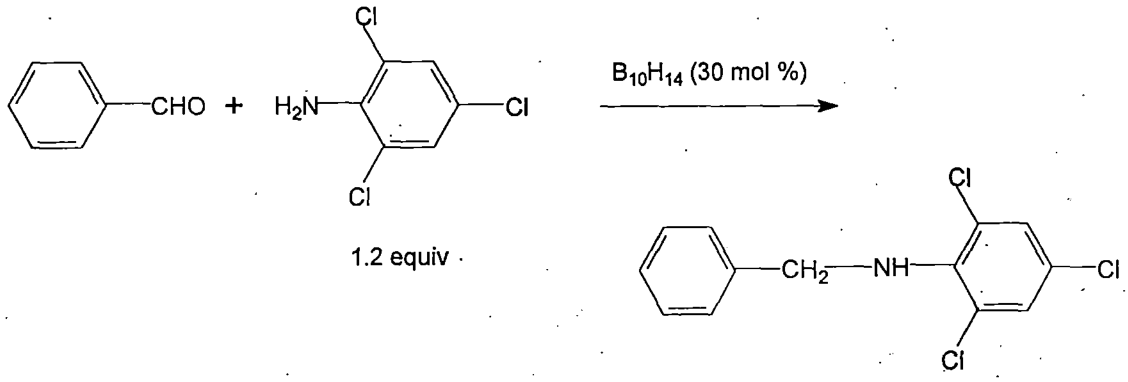
During the study of decaborane as a mild reducing reagent,[73] Yoon et al[24] found that carbonyls and amines undergo reductive amination in the presence of decaborane (Scheme 11). The treatment of ethyl acetoacetate with 4-nitroaniline usings decaborane in methanol at room temperature under nitrogen, gave the corresponding amines (**27**) in 93% yield. This reaction is efficient, even with a relatively poor nucleophilic amine and is compatible with other functional groups such as nitro groups, olefins and halogen groups. The reaction benzaldehyde with 2,4,6-trichloroaniline under this condition the amine (**28**) in 39% yield, a reaction known to fail using sodium triacetoxyborohydride.[19]

Scheme 11





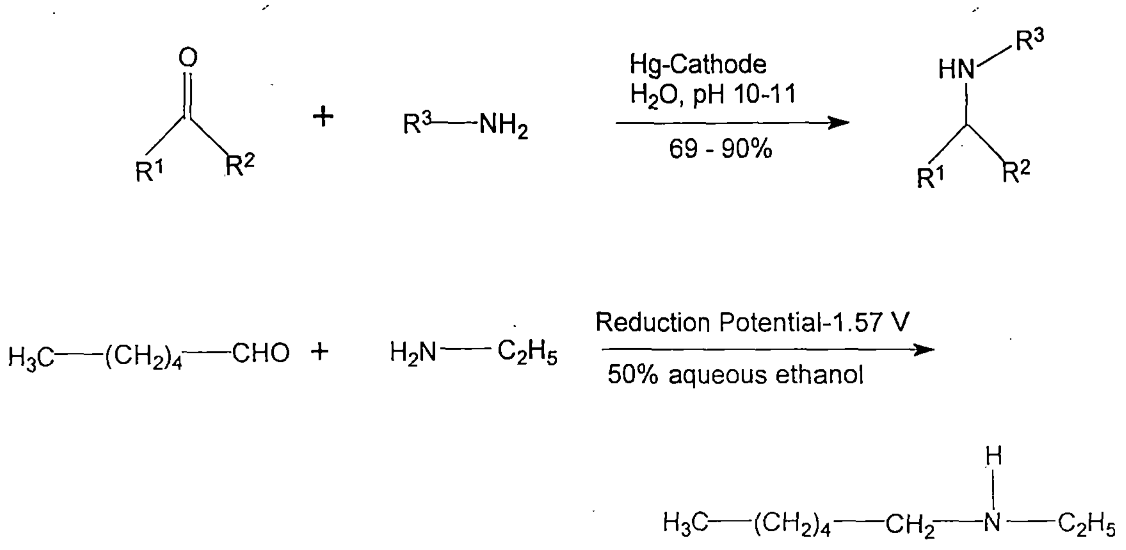
(27) 93%



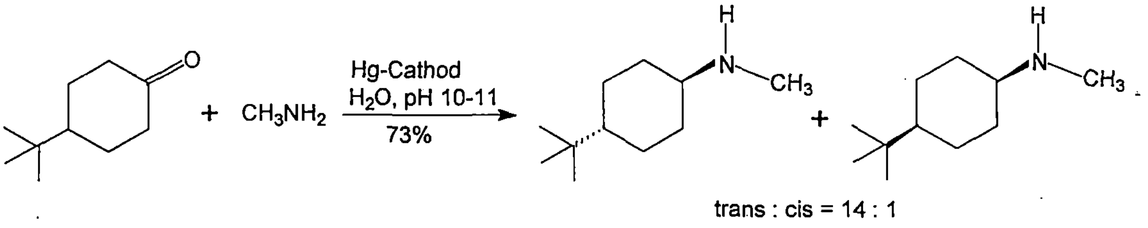
(28) 39%

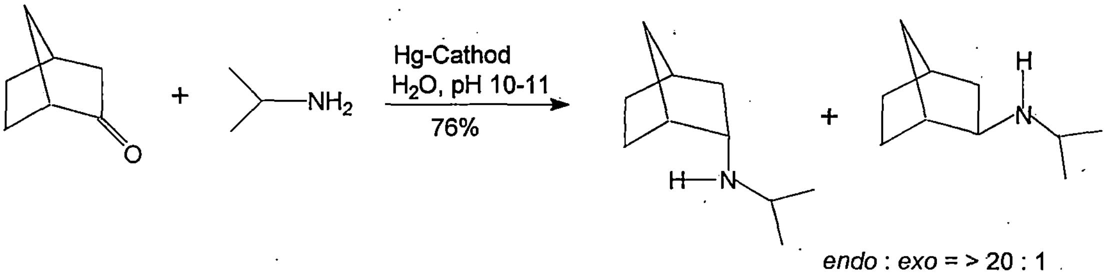
Schäfer et al[29b] have found that secondary amines may be prepared in good yields by potential-controlled reduction of aldehydes or ketones at a mercury cathode in an aqueous solution containing a primary amine (Scheme 12).

Scheme 12



In aqueous medium, an aldehyde or ketone and a primary amine equilibrate to the corresponding schiff base. Because of its lower reduction potential compared with the aldehyde or ketone, the schiff base may be reduced selectively to yield a secondary amine after electron- and proton-transfers. For cyclic ketones, high diastereoselectivities are obtained in some cases.

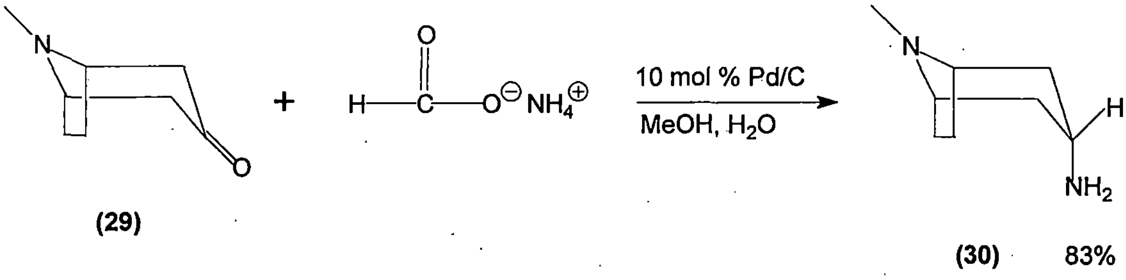




Cathodic reductive amination may be considered as a good alternative of existing methods for the preparation of secondary amines, because of its high chemoselectivity, good yields, simple work-up and low reagent costs.

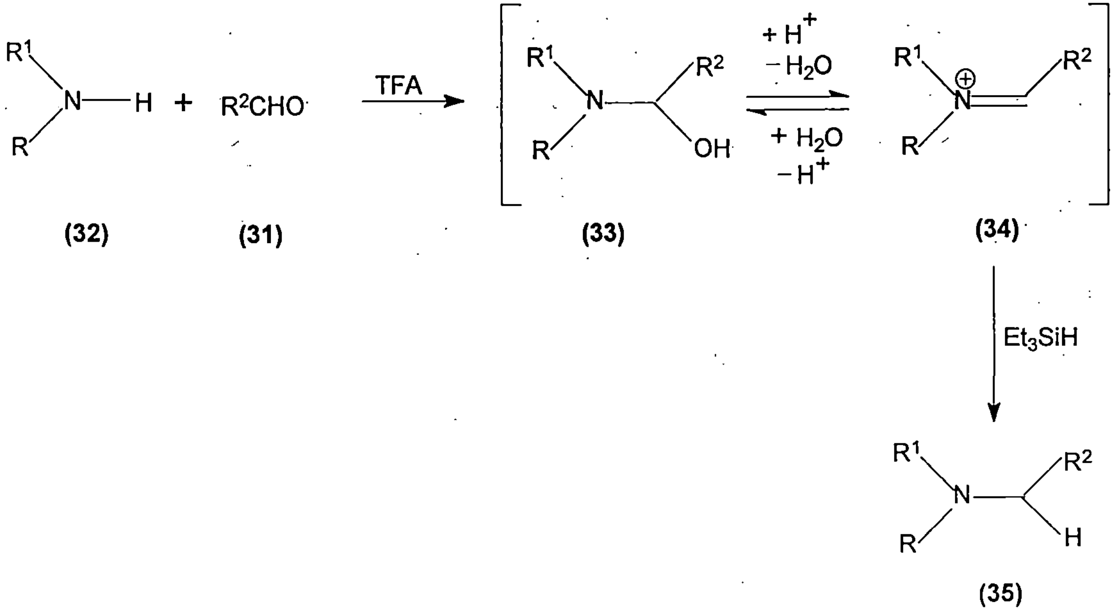
The research group of Allgrette[74] first reported a new versatile method for the reductive amination of carbonyl compounds in which ammonium salts are employed together with a palladium catalyst .The use of a cheap and versatile hydrogen source coupled with the catalyst in an aqueous medium, advances the previous methods due to the mild conditions and to the handy and cheap reagents required. This method advances the usual reductive amination processes in terms of yield and shows high stereoselectivity whether applied to constrained carbonyl compounds. This is a new method for the synthesis of a wide range of primary, secondary and tertiary amines. The reaction of 8-methyl-8-azabicyclo-[3.2.1]octa-3-one (**29**) was treated with ammonium formate in the presence 10% Pd/C catalyst to give 3-endo-amino-8-methyl-8-azabicyclo-[3.2.1]octane (**30**) in 83% yield (Scheme 13).

Scheme 13

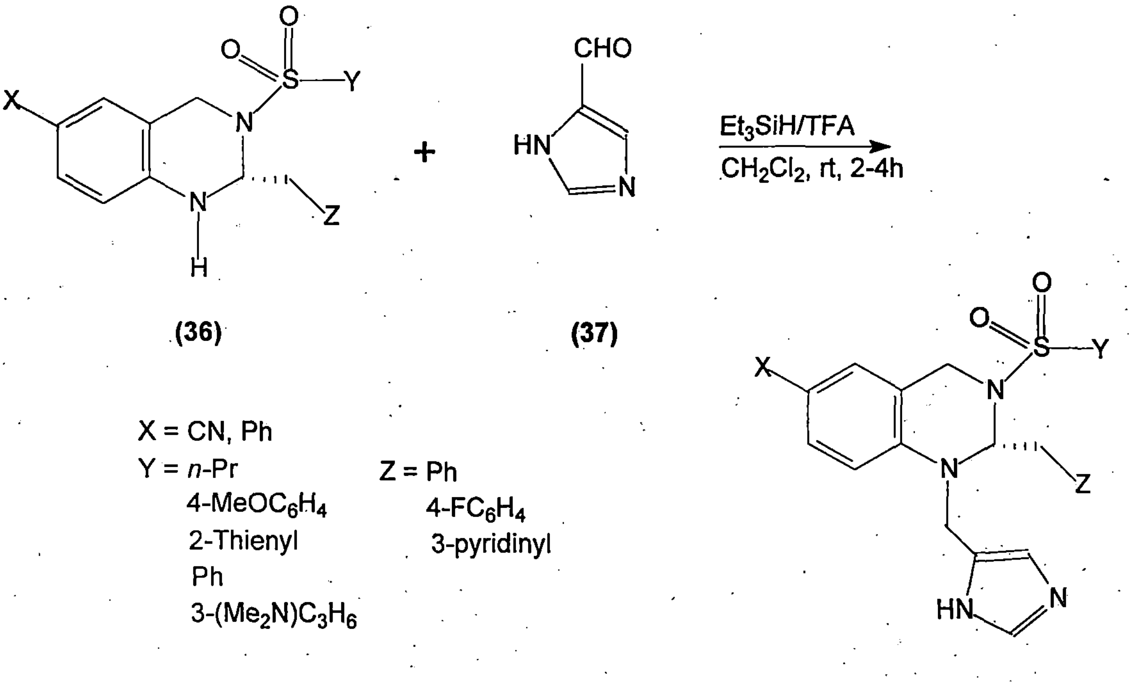


Hydrosilanes such as triethylsilane in the presence of Lewis acid are mild and useful reducing reagents in organic synthesis.[30,75-79] They have been used in the reduction of imines to secondary amines,[76] In the reductive N-methylation of amino acids via oxazolidines,[77] In the N-alkylation of anthranilamides via oxazolidines,[78] and recently in the *N*-alkylation of amides, carbamates and ureas.[79] The research group of Chen envisioned[28] that a secondary amine **32** would react with an aldehydes **31** to give a hemiaminal **33** (scheme 14). This in hemiaminal **33** may undergo reduction with triethylsilane and trifluoroacetic acid through an iminium ion **34** affording the *N*-alkylated product **35**.

Scheme 14



An improved synthesis of 1-(imidazolyl)methyl-4-sulfonylbezodiazapines (**38**), new farnesyltransferase inhibitors, from the corresponding carbonyl compound (**36**) and amine (**37**) was developed using this novel reductive N-alkylation method.



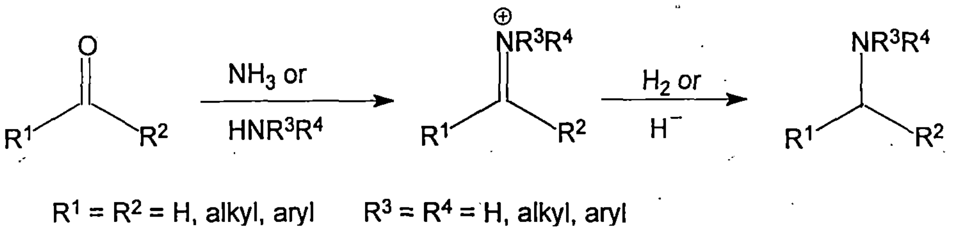
(36) **(37)** **(38)**

X = CN, Ph
Y = *n*-Pr, 4-$MeOC_6H_4$, 2-Thienyl, Ph, 3-$(Me_2N)C_3H_6$
Z = Ph, 4-FC_6H_4, 3-pyridinyl

II-A.2.1: Present Work: Background, Objectives and Strategy

As described in the introduction, the reductive amination is a useful organic transformation for preparing primary, secondary and tertiary amines. The carbonyl compounds initially react with ammonia or amine to form an imine, which then undergoes reduction in presence of hydrogen or hydride ion (Scheme 15). when the overall two-step procedure is performed in a one-pot operation, such protocol is described as "direct reductive amination".

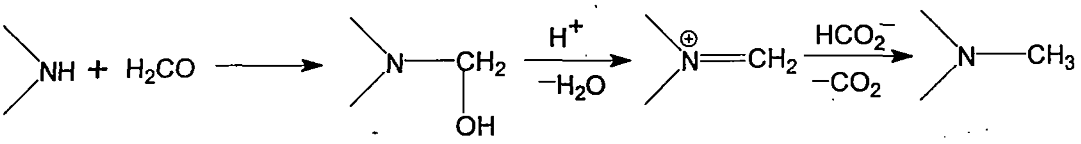
Scheme 15



Several reductive systems are known to effect the reduction of C-N double bond of the imine. Use of molecular hydrogen in presence of a metal-catalyst is one of classical methods to perform this reduction. However, the reaction conditions are not compatible with a number of otherwise reducible groups such as nitro, cyano, double or triple bonds. Secondly, such reduction requires a special set of apparatus and is always associated with usual risks of using hydrogen gas.

On the other hand, several hydride containing reagents are much common to have been employed in imine reduction. A few of them are: [$NaBH_3CN$];[11] $ZnCl_2$-$Zn(BH_4)_2$;[16] pyridine-BH_3;[17] [$NaBH(OAc)_3$];[18] silica gel-$Zn(BH_4)_2$;[19] $Ti(^iPrO)_4$-$NaBH_4$;[21] $NiCl_2$-$NaBH_4$;[22] $Ti(^iPrO)_4$-polymethylhydro-siloxane;[23] decaborane;[24] Bu_3SnH;[25] Bu_2SnClH and Bu_2SnIH;[26] phenylsilane-dibutyltin dichloride;[27] Et_3SiH-trifluoroacetic acid.[28] All these methods require stoichiometric or excess quantities of the hydrides, which are generally highly reactive and expensive as well. Furthermore, use of tin hydrides in some protocols are not recommended for large-scale preparation as the residual insoluble tin comopounds pose a great risk in its elimination. There are some well-known organic reactions which appear to proceed via transfer of hydrogen as hydride species, although the reagents themselves are not immediately obvious hydride donors. Formic acid and formates are recognized as hydride donors in such reactions as the methylation of amines using formaldehyde/ammonium formate (Scheme 16; Leuckart reaction).[80] The reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst is known as hydrogen-transfer reaction or transfer hydrogenation (H-transfer).[81] The process entails hydrogen abstraction from the reagent (hydrogen donor) by means of the catalyst, followed by (or in concert with) hydrogen addition to the unsaturated functional group of the substrate (hydrogen acceptor). This can be generalized as in eq. 1. In hydrogen-transfer reactions the hydrogen source must be different from dihydrogen. Formic acid and its salts have been successfully used for this purpose. The use of hydrogen donors had some advantages over the use of molecular hydrogen since it avoids the risks and the constraints associated with this reagent as well as the necessity of pressure vessels. Additionally, rate and selectivity of the reaction can be favorably affected by selecting the most appropriate hydrogen donor.

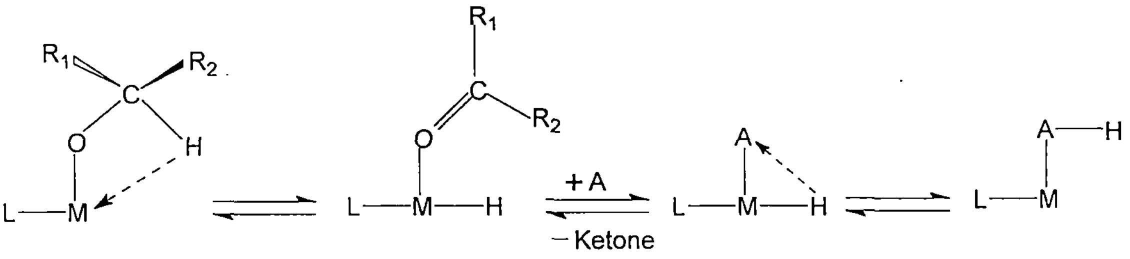
Scheme 16



$$DH_2 + A \overset{cat}{\rightleftharpoons} D + AH_2 \tag{1}$$

DH_2 = hydrogen donor ; A = hydrogen acceptor

From a mechanistic point of view, two general reaction paths cans be envisaged for hydrogen transfer:[82] a step-wise process, called "hydridic route", and a concerted process, called "direct hydrogen transfer" (Figure 1). The "hydridic route" involves



"hydridic route"

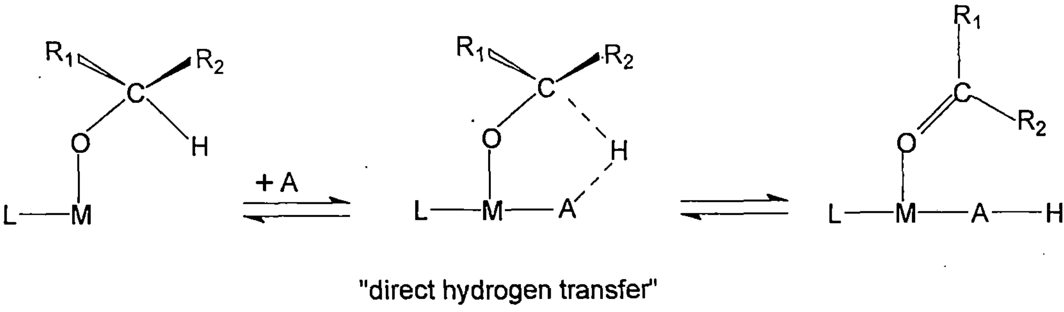
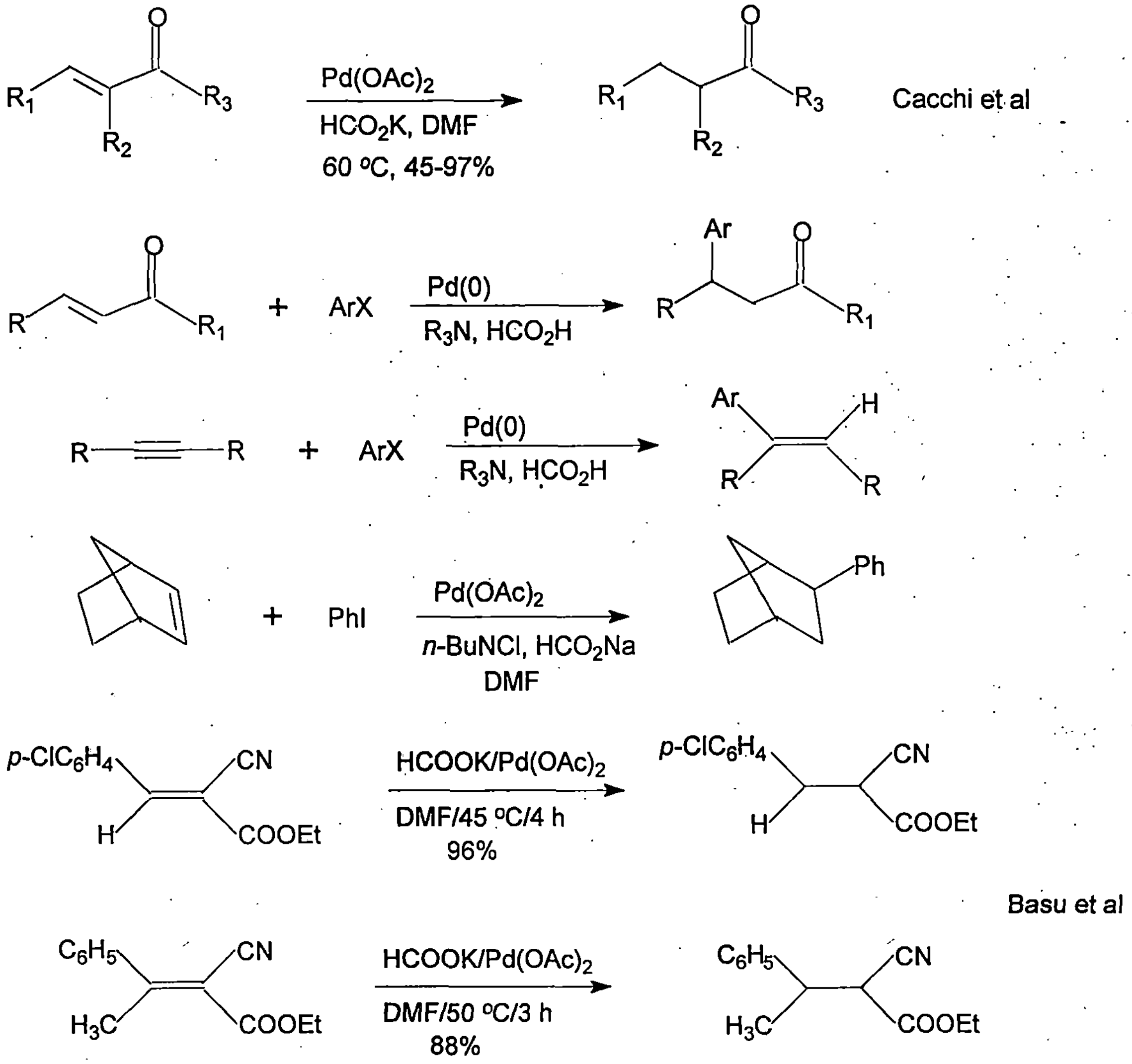


Figure 1. Possible paths for the hydrogen-transfer reactions.

the intermediate formation of a metal hydride derivative by interaction of the catalyst with the hydrogen donor, followed by hydride transfer from the metal to the substrate. The "direct hydrogen transfer" implies that hydrogen is transferred to the substrate in a concerted process where both the H-donor and the H-acceptor are held together in close proximity by the catalyst. A cyclic transition state such as the one proposed for Meerwein-Pondorf-Varely reduction is possibly involved.

The most popular H-donors are alcohols, including chiral ones, and formic acid.[83] More recently, alkyl-ammonium formates, in particular triethylammonium formate (TEAF), have proven to be useful sources of hydrogen, due to their solubility in organic solvents.[84] Since dehydrogenation of formic acid derivatives is an irreversible and exothermic process,[85] this usually overwhelms the energetic requirement of the reduction process. The use of such H-donors is recommended in reactions where unfavorable energetic balances are expected. The use of formic acid as hydrogen donor appears to have advantages over cyclohexene, cyclohexadiene and hydrazine. A further elaboration in the use of formate anion as a donor has been reported. During the early nineties, Cacchi[86a] and others[87] reported use of different combinations of formic acid and its salts such as, $HCOOH/NaHCO_3/n\text{-}Bu_4NCl$; $HCOOH/n\text{-}Bu_3N$; HCOOK in palladium-catalyzed reduction of electron-deficient alkenes and reductive arylation of alkenes (Scheme 17). They also observed that differences in the nature of formate salt and of the reaction medium can significantly affect the course of reaction.[87] Use of formic acid as the source of hydrogen, called the Wallach reaction, or ammonium salts of formic acid, called the Leuckart reaction, often yields the *N*-formyl derivative of the amine instead of the free amine.[68b] On the other hand, we[86b] and other groups[86a] have recently shown that potassium formate promoted by palladium acetate can reduce

Scheme 17

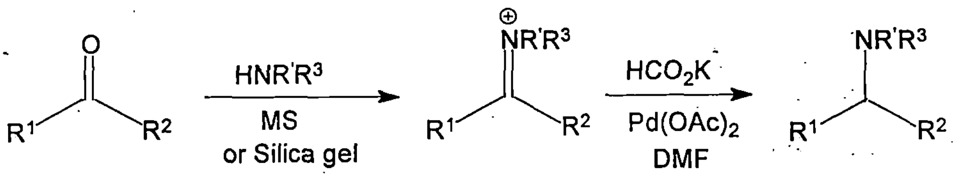


efficiently the conjugated C-C double bond. It therefore appeared reasonable to investigate whether potassium formate, which is soluble in polar organic solvents and in water, with activation by palladium salt could significantly reduce the C-N double bond of the imine formed in the direct reductive amination reaction.

II-A.2.2: Present Work: Results and Discussion

We report herein our observation, which finally constitutes a one-pot reductive amination protocol for aldehydes and ketones, including conjugated ones, with the aid of potassium formate and catalytic palladium acetate (Scheme 18).

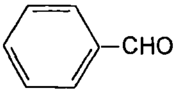
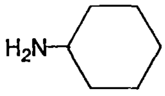
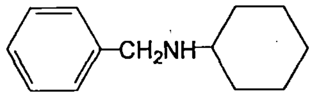
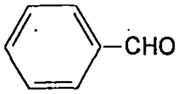
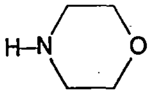
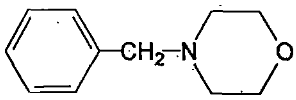
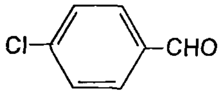
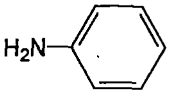
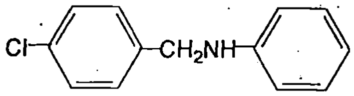
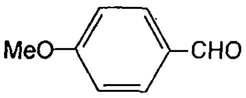
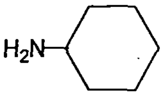
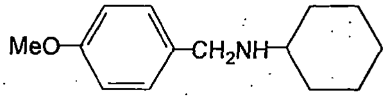
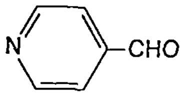
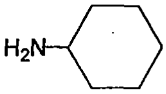
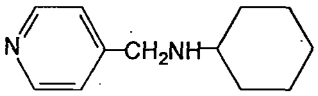
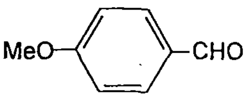
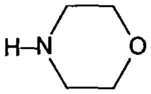
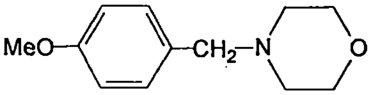
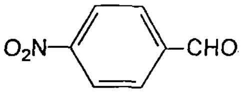
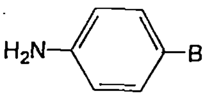
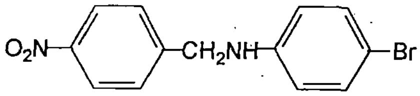
Scheme 18



R^1 = alkyl or aryl
R^2 = H, alkyl
R^3 = H, alkyl
R' = alkyl

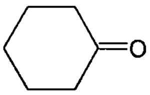
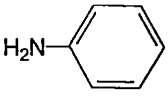
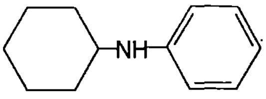
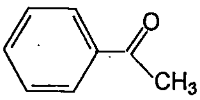
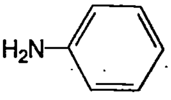
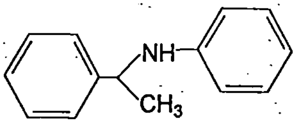
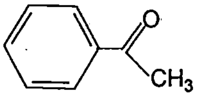
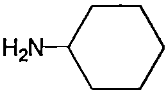
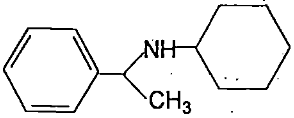
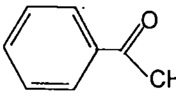
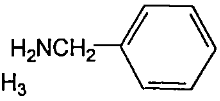
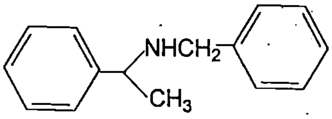
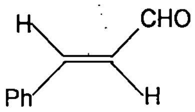
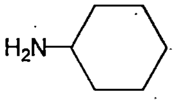
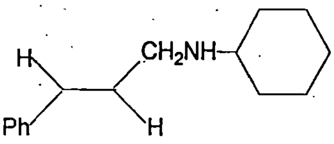
To examine the scope of this reaction, a variety of aldehydes and ketones were reductively aminated with aliphatic and aromatic amines (Table 1). Both primary and secondary amines, such as morpholine (entries 2 and 6) have been used. Reactions with substrates bearing potentially reducible functional groups including chloro (entry 3), bromo and nitro (entry 7) yielded anticipated products without detectable reductive side products. The reaction of pyridine-4-aldehyde with cyclohexylamine was reductively at 40 °C for 3 h and the desired product (**43**) was isolated after column chromatogric purification in 86% yield. Similarly, *p*-methoxybenzaldehyde underwent reductive amination (entries 4 and 6) efficiently with both primary and secondary aliphatic amines affording the desired products (**42**) and (**44**) in 75% and 67% yields respectively. The reaction of *p*-nitrobenzaldehyde with aromatic amine (*p*-bromoaniline) was also studied (entry 7). The reaction also proceeded under fairly mild condition to furnish the compound (**45**) in 56% yield. Among the ketones, we first studied the reaction of cyclohexanone with aniline (entry 8). The desired product, *N*-cyclohexylaniline (**46**) was isolated as colourless oil (70%). Although acetophenone is a difficult case for some reductive amination protocols, use of excess potassium formate (2-4 mmol) and a slight excess of palladium acetate (5 mol %) gave reductive amination of the ketones at a rate comparable to that of other substrates. Thus, acetophenone was subjected to reaction with both aliphatic and

Table 1. Direct reductive amination of aldehydes and Ketones with HCO_2K and Catalytic $Pd(OAc)_2$

Entry	Substrate	Amine	Condition [a]/Temp Time	Product	%Yield [b]
1.			A / 40 °C/ 3 h	 **(39)**	68
2.			A / 40 °C/ 4 h	 **(40)**	62
3.			A / 50 °C/ 5 h	 **(41)**	67
4.			A / 40 °C/ 3 h	 **(42)**	75
5.			A / 40 °C/ 3 h	 **(43)**	86
6.			A / 50 °C/ 5 h	 **(44)**	67
7.			A / 50 °C/ 5 h	 **(45)**	56

Continued……

Continued......... **Table 1**

Entry [b]	Substrate	Amine	Condition [a]/Temp Time	Product	%Yield
8.			B / 50 °C/ 5 h	 (46)	70
9.			B / 60 °C/ 6 h	 (47)	76
10.			B / 60 °C/ 6 h	 (48)	83
11.			B / 60 °C/ 6 h	 (49)	80
12.			B / 50 °C/ 5 h	 (50)	69

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[a] Conditions A: Aldehyde + Amine in DMF with MS (4Å) and stirred at room temparature for 3-5 h; B: Ketone + Amine intimately mixed on activated silica gel and stirred at room temperature for 5-6 h.

[b] Yields are reported after chromatographic purification (2-3 runs). Satisfactory spectral data were obtained for all the amines (products) and given in the experimental section.

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aromatic primary amines (entries 9-11) to afford the desired *N*-aryl or *N*-alkyl amines in 76-83% yields. Reductive amination of cinnamaldehyde (entry 12) with cyclohexyl amine, however, proceeded with concomitant reduction of the C-C double bond. Unlike the Leuckart reaction or the Wallach reaction, no *N*-formyl derivatives were formed in this protocol.

It is well known that aldehydes generally form imines faster than ketones. In this protocol, separate conditions were employed for imine preparation prior to addition of reducing agent. Whereas the aldehydes (except cinnamaldehyde) were reacted with amines in presence of activated molecular sieves (4 Å), the imines from the ketones were prepared on a surface of silica gel following the procedure of Ranu et al.[19] However, the imines prepared by using either molecular sieves or silica gel were directly taken in dimethyl formamide and subjected to reduction by adding palladium acetate (2-5 mol %) and potassium formate (2-3 equiv) and heated at 40-60°C for 3-6 h (see experimental section). The products were obtained after purification on column chromatography. In general, the reaction procedure is very simple and the reaction procedure appears to be mild.

II-A.3: Conclusion:

In summary, the method described here can be useful for preparing all classes of amines from suitable carbonyl compounds and the amines. Furthermore, the method can be of importance in view of cheap reducing agent, which decomposes to environmentally friendly chemicals. Since palladium-catalyzed hydride addition is probably the cause of the C-N double bond reduction, the possibility for asymmetric reductive amination in presence of a chiral ligand might be explored.

II-A.4: Experimental

II-A.4.1: Preparation of activated Silica Gel (HF_{254})

Silica gel (HF_{254}) was purchased from SRL, India, and was activated by heating at 150 °C under vacuo (0.5 Hg) for 1 h and then cooled under N_2 before use.

II-A.4.2: *General procedure for Aldehydes (except Cinammaldehyde)*

A solution of *p*-anisaldehyde (0.680 g, 5 mmol) and cyclohexylamine (0.500 g, 5 mmol) in dry DMF (5 mL) was magnetically stirred at room temperature for 4 h, in presence of molecular sieves (4 Å). To the resulting reaction mixture were added HCOOK (0.840 g, 10 mmol) and palladium acetate (22 mg, 0.1 mmol). The mixture was then heated at 40 °C for 3 h to complete the reaction (TLC) and after cooling it was diluted with ice-cold water (15 mL). The mixture was extracted with diethyl ether (3 x 20 mL). The combined extract was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to leave the crude product, which was purified by column chromatography over silica gel using EtOAc : hexane (1 : 19; R_f 0.26) affording *N*-cyclohexyl-*p*-methoxybenzylamine (**42**).

Yield: 75% (0.815 g), liquid

IR (neat): ν_{max} 2925, 2851, 1610, 1510, 1456, 1300, 1246, 1178, 1035, 821 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.22 (d, 2H, J = 8.3 Hz), 6.85 (d, 2H, J = 8.3 Hz), 3.78 (s, 3H), 3.73 (s, 2H), 2.47 (br.s, 1H), 1.92-1.70 (m, 4H), 1.62-1.59 (m, 1H), 1.31-1.05 (m, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 158.4, 132.9, 129.2, 113.7, 56.0, 55.2, 50.3, 33.4, 26.2, 24.9.

Similarly compounds **39**, **40**, **41**, **43**, **44** and **45** were prepared from corresponding aldehydes and amines.

N-Cyclohexylbenzylamine (**39**)

Yield: 68% (0.644 g), liquid

IR (neat): ν_{max} 3400 (N-H), 1600, 1450, 1321 (C-N) cm^{-1}

^{1}H-NMR (CDCl$_3$, 300 MHz): δ 7.31-7.06 (m, 5H), 3.80 (s, 2H), 2.48 (br, 1H), 1.92-1.70 (m, 1H), 1.61-1.54 (m, 4H), 1.31-1.07 (m, 6H)

N-Benzylmorpholine (**40**)

Yield: 62% (0.550 g), liquid.

^{1}H-NMR (CDCl$_3$, 300 MHz): δ 7.32-7.25 (m, 5H), 3.70 (t, 4H), 3.49 (s, 2H), 2.44 (t, 4H).

N-(4-Chlorobenzyl)aniline (**41**)[88]

Yield: 67% (0.730 g), liquid

IR (neat): ν_{max} 3380 (N-H), 1600, 1490, 1320 (C-N), 1095 cm^{-1}

^{1}H-NMR (CDCl$_3$, 300 MHz): δ 7.54 (d, 2H, *J* = 7.9 Hz), 7.32 (d, 2H, *J* = 7.9 Hz), 7.15 (t, 2H, *J* = 7.2 Hz), 6.71 (t, 1H, J = 7.2 Hz), 6.64 (d, 2H, *J* = 8.81 Hz), 4.29 (s, 2H), 3.97 (br s, 1H)

^{13}C-NMR (CDCl$_3$, 75 MHz): δ 147.8, 138.0, 133.0, 129.3, 128.7, 128.2, 117.8, 112.8, 47.6.

N-(Pyridin-4-yl-methyl)cyclohexylamine (**43**)

Yield: 86% (0.818 g), liquid.

IR (neat): ν_{max} 2940, 1603, 1547, 1455, 1383 cm^{-1}

^{1}H-NMR (CDCl$_3$, 300 MHz): δ 8.52 (d, 2H, *J* = 4.8 Hz), 7.26 (d, 2H, *J* = 4.8 Hz), 3.83 (s, 2H), 2.86 (br, 1H), 1.92-1.82 (m, 4H), 1.62-1.60 (m, 1H), 1.27-1.06 (m, 6H).

N-(4-Methoxybenzyl)morpholine (**44**)

Yield: 67% (0.694 g), liquid.

IR (neat): ν_{max} 2954,2852, 1612, 1514, 1456, 1245, 1116, 1033 cm^{-1}

^{1}H-NMR (CDCl$_3$, 300 MHz): δ 7.22 (d, 2H, *J* = 8.34 Hz), 6.85 (d, 2H, *J* = 8.34 Hz), 3.78 (s, 3H), 3.69 (t, 4H), 3.43 (s, 2H), 2.42 (t, 4H)

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 158.7, 130.4, 129.5, 113.6, 66.9, 62.8, 55.2, 53.4.

4-Bromo-*N*-(4-nitrobenzyl)aniline (**45**)

Yield: 56% (0.860 g), liquid.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.19 (d, 2H, *J* = 8.5 Hz), 7.50 (d, 2H, *J* = 8.5 Hz), 7.23 (d, 2H, *J* = 8.6 Hz), 6.44 (d, 2H, *J* = 8.6 Hz), 4.45 (s, 2H), 4.22 (br, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 146.8, 146.2, 132.1, 127.6, 123.9, 114.5, 114.4, 109.8, 47.5.

Anal. Calcd. for $C_{13}H_{11}BrN_2O_2$ (307.15): C, 50.84; H, 3.61.

Found: C, 50.66; H, 3.69.

II.-A.3.3: *General Procedure for Ketones and Cinnamaldehyde*

A mixture of acetophenone (0.601 g, 5 mmol) and benzyl amine (0.535 g, 5 mmol) was uniformly absorbed on the surface of activated silica gel (5 g) by dropwise addition under stirring, and the mixture was then stirred at room temperature (25 °C) under nitrogen for 4 h to allow complete conversion of the corresponding imine. HCOOK (0.840 g, 10 mmol), palladium acetate (22 mg, 0.1 mmol) and DMF (5 mL) were added and the reaction mixture was then heated at 60 °C a for 6 h. After completion (TLC) the reaction mixture was cooled, diluted with ice-cold water and extracted with diethyl ether (3 x 20 mL). The extract was washed with brine, dried over anhydrous Na_2SO_4 and evaporated with solvent to leave the crude product, which was purified by column chromatography over silica gel using EtOAc : hexane (1 : 9) affording *N*-(1-phenylethyl)benzylamine (**49**).

Yield: 80% (0.845 g), liquid.

IR (neat): ν_{max} 3380, 1602, 1452, 1305 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.34-7.23 (m, 10H), 3.79 (q, 1H, *J* = 6.57 Hz), 3.60 (q, 2H, *J* = 13.1 Hz), 1.86 (br, 1H), 1.35 (d, 3H, *J* = 6.57 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 145.4, 140.5, 128.3, 127.3, 125.5, 57.4, 51.5, 24.4.

Anal. Calcd. for $C_{15}H_{17}N$ (211.31): C, 85.26; H, 8.11.

Found: C, 85.11; H, 8.43.

Using the same method compounds 46, 47, **48 and 50** were prepared from the corresponding carbonyls and amines.

N-Cyclohexylaniline **(46)**[14]

Yield: 70% (0.614 g), liquid.

IR (neat): ν_{max} 3400, 3085, 3055, 1602, 1560, 1462, 1450,1367, 1321 (C-N), 1255, 1179,1148 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.22-7.14 (m, 2H), 6.71-6.61 (m, 3H), 3.27 (m, 1H), 1.81-1.62 (m, 5H), 1.45-1.10 (m, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 147.1, 129.2, 117.0, 113.3, 51.9, 33.4, 25.9, 25.0.

N-(1-Phenylethyl)aniline **(47)**

Yield: 76% (0.844 g), liquid.

IR (neat): ν_{max} 3416 (N-H), 3053, 1603, 1506, 1450, 1322 (C-N), 1260 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.36-7.31 (m, 5H), 7.06 (t, 2H, *J* = 7.3 Hz), 6.6 (t, 1H, *J* = 7.3 Hz), 6.48 (d, 2H, *J* = 1.92 Hz), 4.46 (q, 1H, *J* = 6.7 Hz), 3.81 (s, 1H), 1.47 (d, 3H, *J* = 6.7 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 147.2, 145.2, 129.0, 128.2, 126.8, 125.8, 117.1, 113.2, 53.3, 24.9.

N-(1-Phenylethyl)cyclohexylamine **(48)**

Yield: 83% (0.750 g), liquid.

IR (neat): ν_{max} 3380, 1640 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.35-7.20 (m, 5H), 3.96 (q, 1H, *J* = 6.6 Hz), 2.28 (br, 1H), 1.72-1.65 (m, 4H), 1.55 (m, 1H), 1.33 (d, 3H, *J* = 6.6 Hz), 1.14-1.01 (m, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 146.0, 128.3, 126.6, 125.4, 54.3, 53.5, 34.4, 33.0, 26.0, 24.8.

N-(3-Phenylpropan-1-yl)cyclohexylamine **(50)**

Yield: 69% (0.743 g), liquid.

IR(neat): ν_{max} 3320, 2930, 1629, 1496, 1440, 1378, 1127 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.35-7.16 (m, 5H), 2.8-2.62 (m, 1H), 2.64 (t, 4H, *J* = 7.4 Hz), 2.38 (m, 1H, NH), 1.87-1.59 (m, 8H), 1.30-1.02 (m, 4H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 142.1, 128.3, 128.2, 125.6, 56.8, 46.4, 34.2, 33.6, 31.9, 26.1, 25.0.

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