Part I. Section B

Reduction of C–N Double Bond Using HCOOK and Catalytic $Pd(OAc)_2$: Development of a Simple Protocol for Direct Reductive Amination

IB.1 Introduction: Direct Reductive Amination–A Brief Review

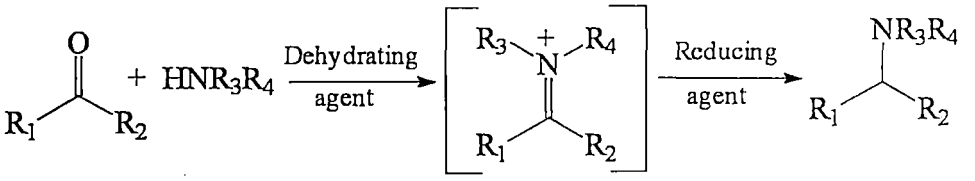
The amine functionality is one of the most ubiquitous in organic chemistry. Its importance is exemplified by the diverse nature of molecules that contain this functional group, which includes natural products and fine chemicals.[1] Amines are important synthetic targets as well as valuable synthons for a wide variety of medicinal agents and agrochemicals.[2] Secondary amines are important for the synthesis of various tertiary amines, as versatile ligands[3] in homogeneous asymmetric transformations, as fluorescence probes[4] in HPLC, as a modifier[5] in reversed-phase chromatography and as a buffer in sequential analysis of proteins and peptides. Tertiary amines, particularly triarylamines, are important structural elements of many organic materials, including dendrimers and polymers. They are of interest due to their electronic properties, particularly their ability to act as efficient hole conductors.[7] The triarylamine moiety is also a component of a nonlinear optical chromophores,[8] Xerox photoreceptors,[9] and holographic materials.[10]

Ketone-to-amine transformations could be of special utility in the construction of aminosugars. Such saccharides are important constituents of the glycolipids and glycoproteins which mediate cell-cell recognition and adhesion,[11] influence cellular growth and development, and act as receptors for hormones, vitamins and toxins at the cell membrane.[12] Biogenic amines are important nitrogen compounds of biological importance in vegetables, microbial and animal cells.[13]

For the important diversity of amines, carbon-nitrogen bond formation is of great interest, which is apparent from the number of methodologies that have been developed for this purpose. Various important methods for the synthesis of amines include alkylation of organic halides with amines, reductive amination of carbonyl compounds,[14] cross coupling reactions,[15] hydrocyanation of alkenes followed by reduction and hydroamination of olefins.[16] Among them, reductive amination of carbonyl compounds constitutes one of the most convenient and practical approaches.

The importance of the reductive amination process may be judged from the enormous number of its synthetic uses in various reaction schemes.[17] This reaction offers compelling advantages over other amine syntheses, including brevity, wide commercial availability of substrates, generally mild reaction conditions, and in some cases exceptionally high functional group tolerance.

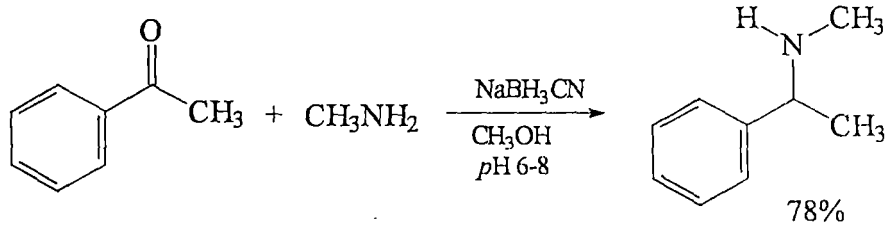
The reactions of aldehydes or ketones with ammonia, primary amines, or secondary amines in the presence of reducing agents to give primary, secondary, or tertiary amines, respectively, known as reductive aminations (of carbonyl compounds) or reductive alkylations (of amines) are among the most useful and important tool for the synthesis of different kinds of amines. The reaction involves the initial formation of an imine from the reaction of a carbonyl compound with an amine and its subsequent reduction to an alkylate amine. The process may be termed as direct or indirect depending upon the number of operational steps involved.[18]



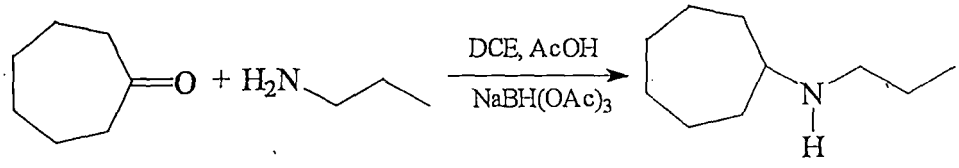
The reductive amination is described as a *direct* reaction when the carbonyl compound and the amine are mixed with the proper reducing agent without prior formation of the intermediate imine or iminium salt. A *stepwise* or *indirect* reaction involves the pre-formation of the intermediate imine followed by reduction in a separate step. A particular advantage of direct process is that no isolation of unstable intermediate imines is necessary.

The choice of the reductant is very critical since undesirable reduction of starting carbonyls must be suppressed for the predominant formation of intermediate imines. The two most commonly used direct reductive amination methods differ in the nature of the reducing agent. The first method is catalytic hydrogenation with platinum, palladium, and nickel catalysts.[19] This is an 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.[20] Moreover, hydrogenation is not compatible with a

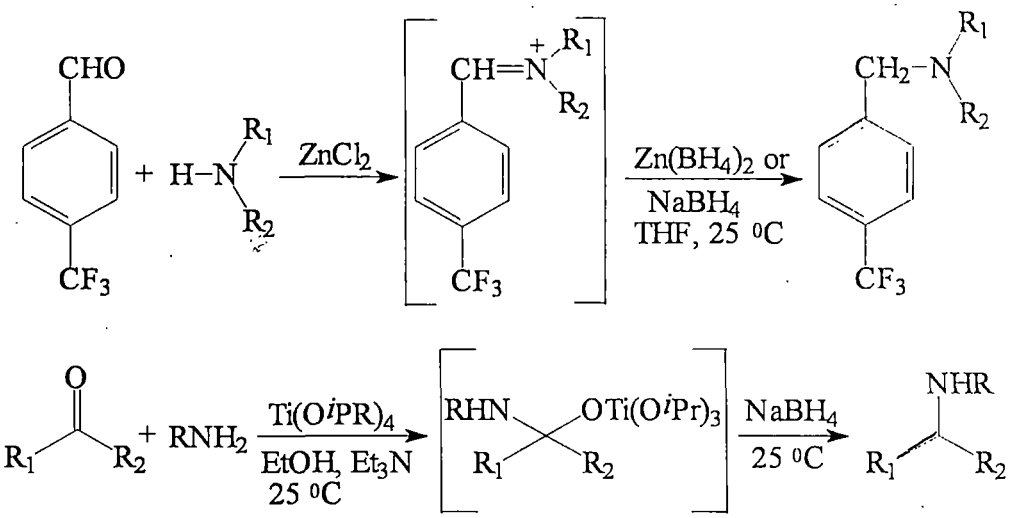
number of other wise reducible functional groups such as nitro, cyano and carbon-carbon double and triple bonds.[20] The catalyst may be inhibited by compounds containing divalent sulfur.[21] The second method utilizes hydride reducing agents for reduction. Among the hydride reagents used to effect this transformation, sodium cyanoborohydride ($NaBH_3CN$) has been used because of its applicability.[22]



The successful use of $NaBH_3CN$ is due to its stability in relatively strong acid solution (~*p*H 3), its solubility in hydroxylic solvents such as methanol, and its different selectivities at different *p*H values.[22] At *p*H 3-4 it reduces aldehydes and ketones effectively, but this reduction becomes very slow at higher *p*H values.[23] At *p*H 6-8, the more basic amines are protonated preferentially and reduced faster than aldehydes or ketones.[22] This selectivity allows for a convenient direct reductive amination procedure. Limitations are that the reaction may require up to 5-fold excess of the amine, is usually slow and sluggish with aromatic ketones,[22] and weakly basic amines,[24] and may result in the contamination of the product with cyanide.[25] Moreover, this reagent is highly toxic and generates toxic byproducts such as HCN and NaCN upon workup. To solve these problems, modified borohydride, such as sodium triacetoxyborohydride [$NaBH(OAc)_3$] has been developed.[26] This borohydride reagent is mild and exhibits remarkable selectivity as a reducing agent. 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.[27] Sodium triacetoxyborohydride has limitations with aromatic and unsaturated ketones.

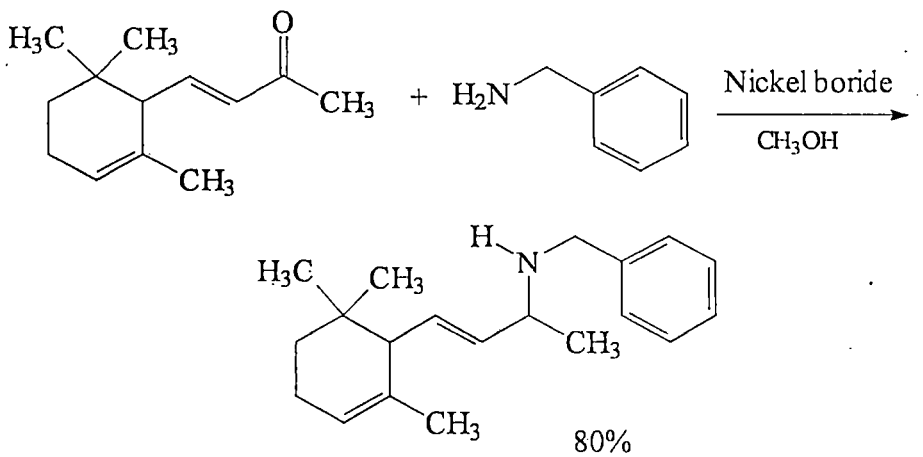


Recently, Bhattacharyya *et al.* developed $ZnCl_2$-$NaBH_4$[28] and $Ti(O^iPr)_4$-$NaBH_4$[29] for reductive amination of carbonyl compounds.

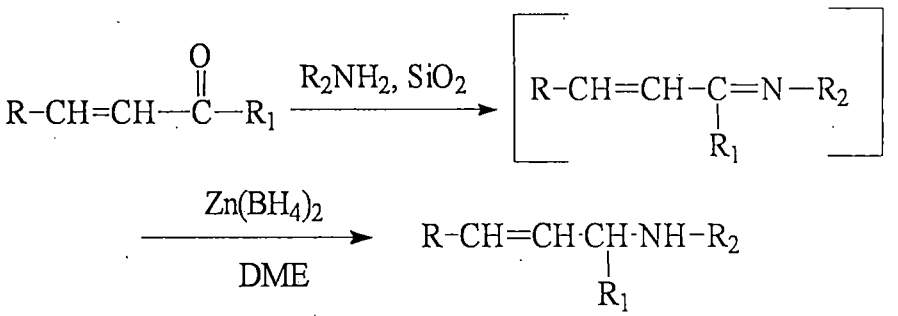


Titanium (IV) isopropoxide has been utilized[24b,30] as a mild Lewis acid compatible with a variety of potentially acid sensitive functional groups including acetal, acetonides, silyl ethers, and Boc derivatives.

Sarma and Sharma observed during their studies on *in situ* generated nickel boride[31] that a carbonyl group remains unaffected under appropriate reaction conditions. Since generation of nickel boride from sodium borohydride and nickel chloride is accompanied by a sufficient amount of hydrogen evolution,[32] it was argued that the system could be a suitable one for reductive amination of aldehydes and ketones. Based on this fact, Sharma *et al.*[33] carried out a series of reactions of aldehydes and ketones with amines. Although nickel boride is well suited to α,β-unsaturated ketones but remained unreactive to acetophenone and benzophenone with *n*-butylamine.

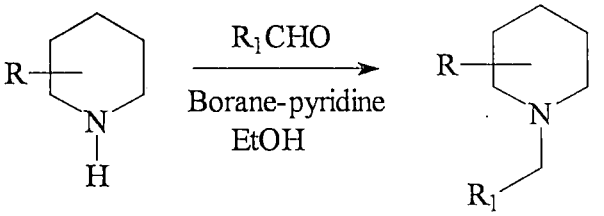


Ranu *et al.*[18] have discovered that reductive amination of conjugated aldehydes and ketone is achieved by treatment of the corresponding carbonyl compound with appropriate amine in the presence of silica gel followed by addition of $Zn(BH_4)_2$ in a one-pot operation.

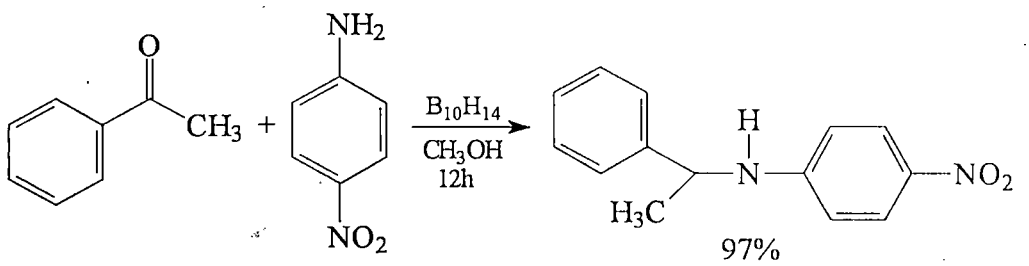


R, R_2 = alkyl or aryl, R_1 = H or alkyl

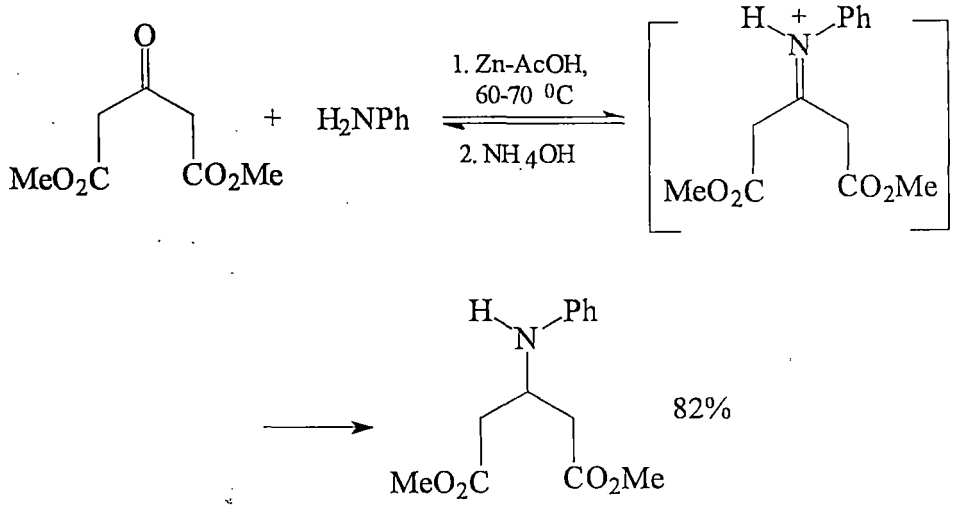
Borane-pyridine was introduced as a cheap and readily available alternative to sodium cyanoborohydride for the purpose of the reductive amination of a wide variety of carbonyl compounds.[24a,25,34] Although BH_3-pyridine works well for the reaction using aromatic amines, the reaction must be performed in acidic conditions.



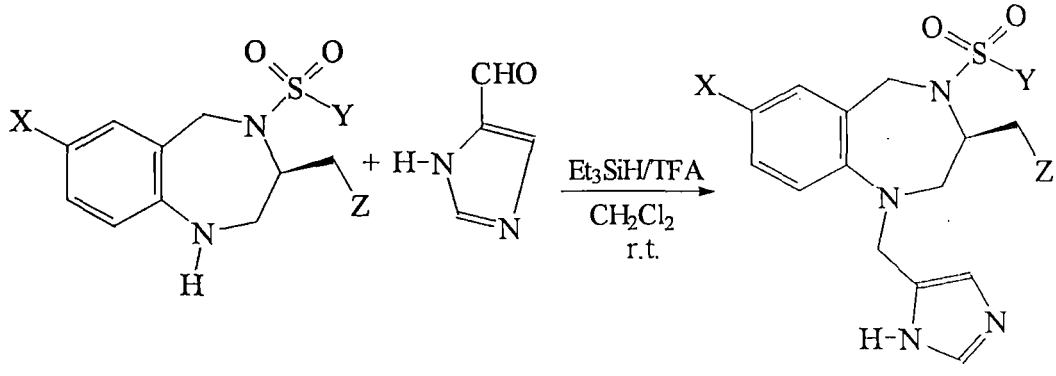
During the study of decaborane as a mild hydride reagent,[35] Yoon *et al.* found that carbonyls and amines undergo reductive amination in the presence of decaborane.[36] Decaborane in this case seemed to have a dual action: a catalyst for the imine formation as well as a mild reducing agent in the reduction of the imine.



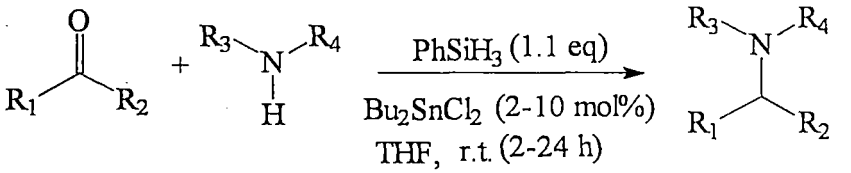
Beside borohydride derivatives, alternative metal hydride reagents such as Zn-AcOH[37] and Cl_3SiH[38] have also been developed. Zn-AcOH is more applicable than Zn-HCl, give better yields, and it is particularly well suited for preparation of β-arylamino esters. But it is not applicable to aldehydes or aliphatic amines.



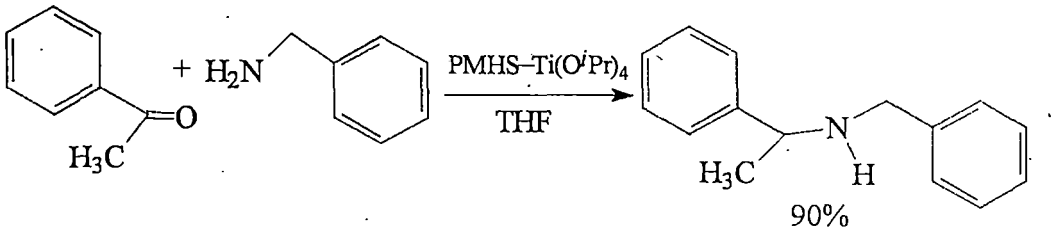
Hydrosilanes such as triethylsilane in the presence of Lewis acid are mild and useful reducing agent in the organic synthesis.[39] Chen *et al.*[40] developed a novel triethylsilane mediated reductive *N*-alkylation of amines to synthesize 1-(4-imidazolyl)methyl-4-sulfonylbenzodiazepines, new farnesyltransferase inhibitors.



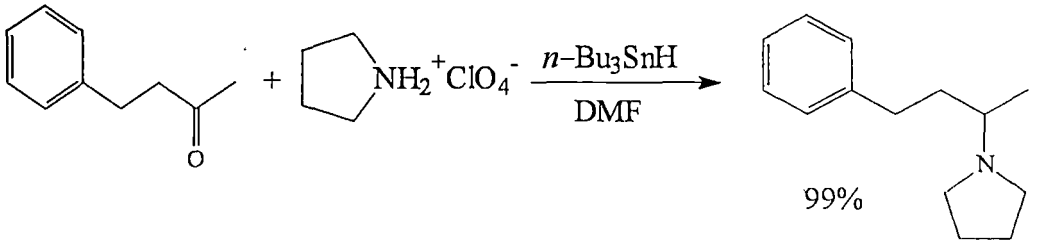
Apodaca and Xiao have developed[41] a simple direct reductive amination procedure which employs phenylsilane as a stoichiometric reductant and dibutyltin dichloride as a catalyst. Both aldehydes and ketones were reductively aminated with anilines and secondary alkyl amines by this method, but the reaction failed with primary alkylamines.



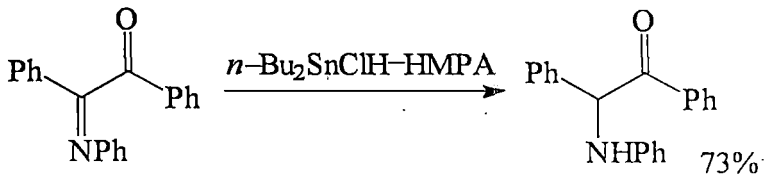
Polymethylhydrosiloxane (PMHS) is being pursued as a safe and environmentally friendly reagent for the reduction of organic functional groups.[42] This reagent is very inert on its own, making it safe to handle, but in the presence of a proper activator it proves itself as an excellent substitute for hydride reagents. Recently, Chandrasekhar *et al.* explored the utility of PMHS as a versatile reductant[43] and in this context they developed a method for direct conversion of carbonyl compounds to amines *via* reductive amination by using PMHS as reductant and $Ti(O^iPr)_4$ as activator.[44]



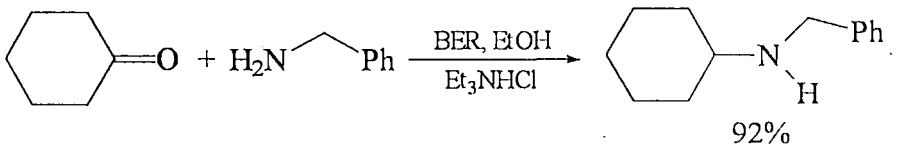
Organotin hydrides have been found to be a mild and chemoselective reductants.[45] Tributyltin hydride in DMF was reported as reducing agent for the reductive amination of carbonyl compounds with primary and secondary ammonium salts.[46]



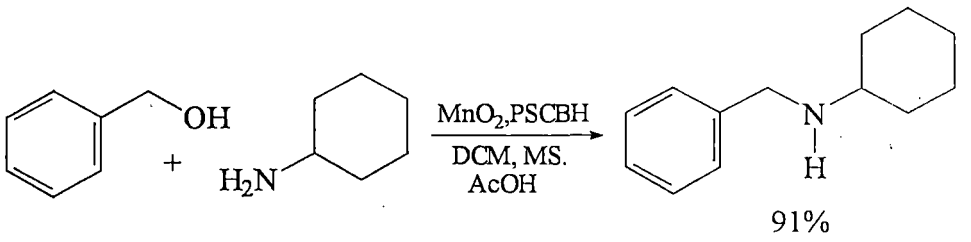
Baba *et al.* provided a set of organotin hydrides to achieve highly chemoselective reductions of functionalized substrates.[47] In particular, pentacoordinated tin hydride, Bu_2SnClH-HMPA,[48] formed *in situ* by simple mixing of Bu_2SnClH and HMPA, has been revealed to be a selective reductant of imines even in the presence of carbonyls.[49]



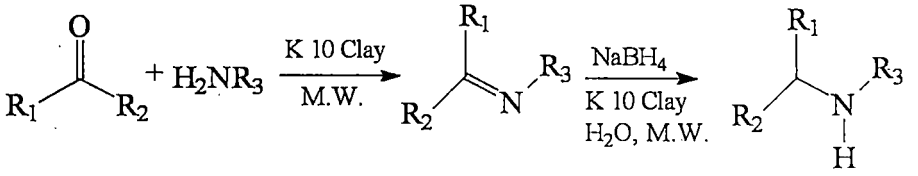
Due to recent trend in developing solid phase reactions for combinatorial chemistry, different solid supported reagents and reactions have also been developed for reductive amination.[50] Sometime ago Borohydride Exchange Resin (BER) was introduced by Gibson and Baily,[51] and Yoon *et al.* reported BER is an interesting chemoselective reducing agent for carbonyl compounds in alcoholic solvents.[52] Recently, Yoon *et al.* utilized BER successfully for the reductive amination of aldehydes and ketones.[53]



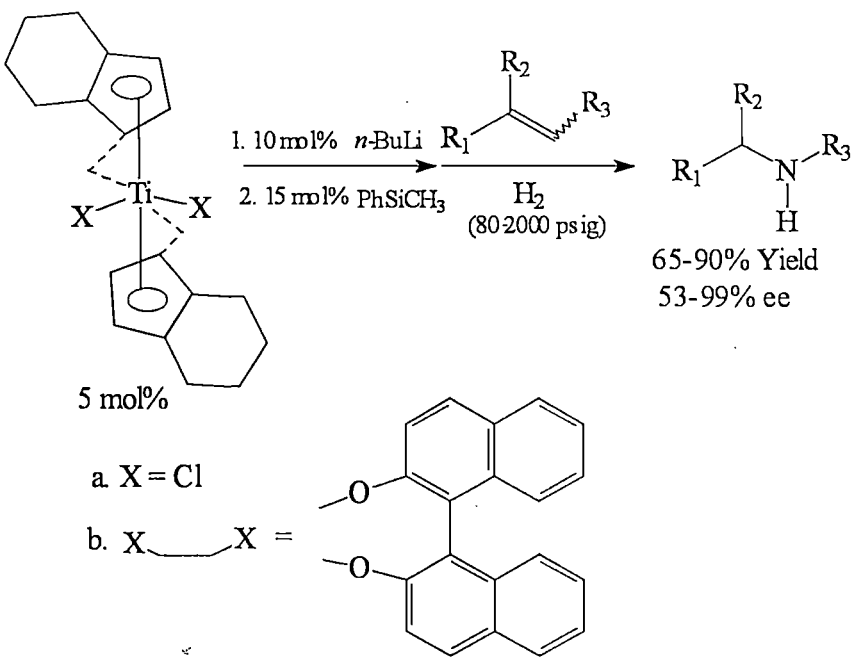
Blackburn and Taylor recently reported a new process for the conversion of alcohols into amines via an *in situ* oxidation-imine formation-reduction by using MnO_2 as oxidant and polymer-supported cyanoborohydride (PSCBH) as reductant.[54]



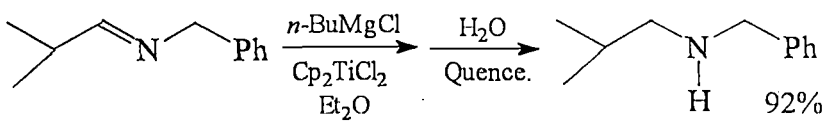
Wet montmorillonite K 10 clay supported $NaBH_4$ under microwave irradiation have also been reported for reductive amination.[55]



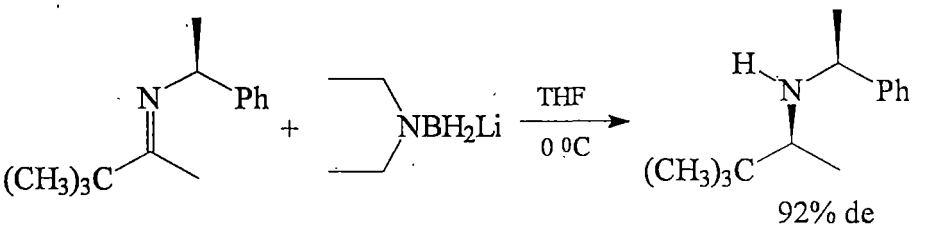
The development of asymmetric catalysts for the hydrogenation of achiral substrates to form enantiomerically enriched products represents a major area of research[56] with the growing importance of enantiomerically pure nitrogen containing compounds in the pharmaceutical and agrochemical industries. The asymmetric hydrogenation of imines to enantiomerically enriched amines has received much attention recently.[57] Processes have been developed using titanium,[58] ruthenium,[59] iridium[57b,60] and rhodium[57a,61] complexes as catalysts and hydrogen or silanes[62] as stoichiometric reducing agents. Titanocene was discovered as a catalyst for the asymmetric hydrogenation of imines.[62]



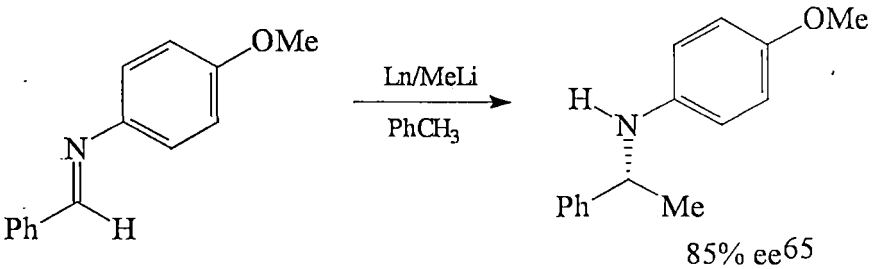
Amin and Crowe have discovered recently that imines can be reduced to amines *via* a titanium catalyzed hydromagnesation reaction using *n*-BuMgCl as the stoichiometric reducing agent.[63]



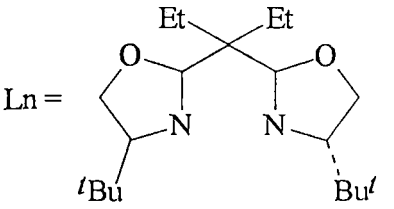
Beside late transition metal, organolithium reagents were also being employed for such transformation. Lithium diethylaminoborohydride and lithium diisopropyl-aminoborohydride reduce chiral aliphatic and aromatic imines, derived from α-methyl-benzylamines, to give the corresponding enantiomerically enriched secondary amines.[64]

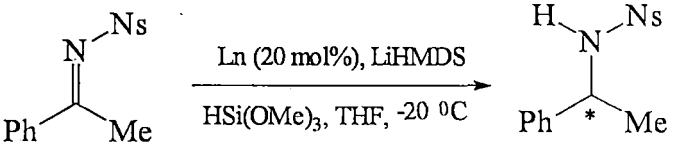


92% de



85% ee[65]





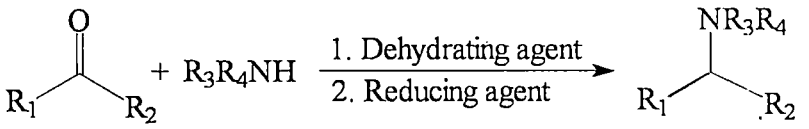
72% ee[66]

Ns = *p*-Nitrobenzenesulfonyl

Ln = (R)-1,1'-Bi-2-naphthol

IB.2.1 Present Work: Background, Objectives and strategy

In section A of this dissertation we described development of a mild and inexpensive reagent system [HCOOK-catalytic $Pd(OAc)_2$] for reduction of highly functionalized C–C double bond. The success of this methodology compounded with our continuous interests in developing novel reactions and methodology led us to investigate reduction of C–N double bond of imines using this reductant. The reduction of imines give rise to amines, which are important synthetic targets as well as valuable synthons for a wide variety of medicinal agents and agrochemicals. The imines can be prepared from a carbonyl compounds by reaction with ammonia or amine. If the overall reaction from ketone to amine is carried out in a one-pot protocol, the procedure is known as "direct reductive amination" of carbonyl compounds[18] (Scheme IV).



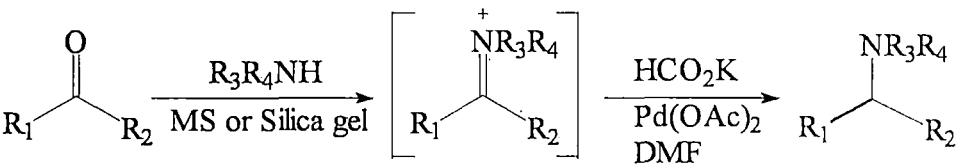
Scheme IV

Imines are reduced using a variety of reagents and applying different reaction conditions. For example, catalytic hydrogenation is one of the classical methods for carrying out this transformation. However, the reaction conditions are not compatible with a number of otherwise reducible functional groups such as, nitro, cyano, double and triple bonds.[19c,26b] Among the hydride reagents used for C–N double bond of imine, sodium cyanoborohydride[22,23] (the Borch reduction) has found considerable applications. Unfortunately, the use of this reagent is compromised by its cost and toxicity, which risks the presence of residual cyanide[25] in the product as well as in the work-up system. Alternative reducing systems currently include sodium triacetoxyborohydride (Gribble reduction) in neutral[67] or acidic media,[26] sodium borohydride in aqueous sulfuric acid and pyridine-borane.[34] Recently, Apodaca and

Xiao[41] reported a procedure for direct reductive amination of aldehydes and ketones which uses phenylsilane as stoichiometric reductant and dibutyltin dichloride as a catalyst. All these methods require either stoichiometric or excess quantities of hydrides and use of tin hydrides in some protocols is not recommended for large-scale preparation. On the other hand, use of formic acid as the source of hydrogen, called the Wallach reaction, or ammonium salts of formic acid, called the Leukart reaction, often yields the *N*-formyl derivative of the amine instead of the free amine. 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 procedure.

IB.2.2 Present Work: Results and Discussion

In this part, we describe our results for direct reductive amination, which constitute a mild, safe and efficient one-pot reductant system for conversion of various aldehydes and ketones, including conjugated ones, to *N*-alkyl/*N*-aryl secondary or tertiary amines (Scheme V).



R_1 = Alkyl or Aryl
R_2 = H, Alkyl
R_3 = H, Alkyl
R_4 = Alkyl

Scheme V

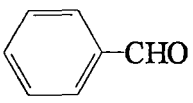
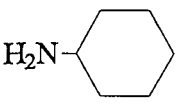
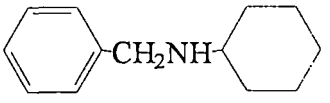
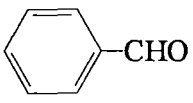
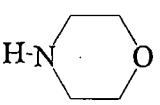
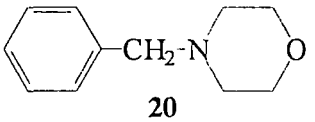
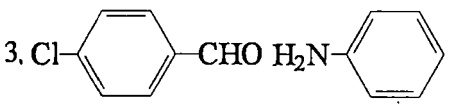
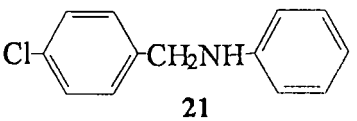
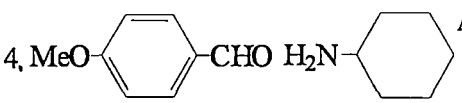
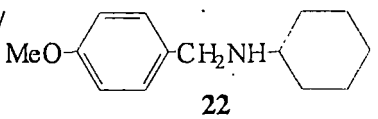
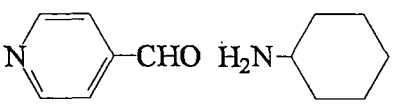
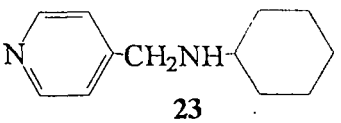
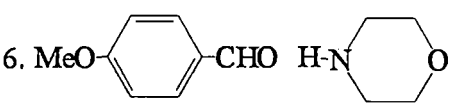
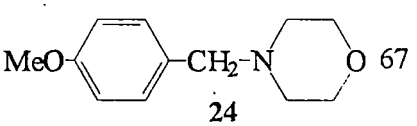
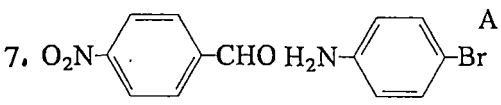
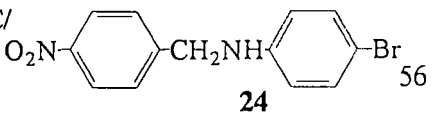
To examine the scope of this reaction, a variety of aldehydes and ketones were reductively aminated with aliphatic and aromatic amines (Table 2). Both primary and secondary amines such as morpholine (entries 2 and 6) have been used. Reactions with substrates bearing potentially reducible functional groups including choloro

(entry 3), bromo and nitro (entry 7) yielded anticipated products without detectable reductive side products. 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. The process is equally effective for heteroaromatic systems (entry 5). Thus pyridine-4-carboxyaldehyde and aniline underwent reductive amination to produce **23** in 86% yield. Reductive amination of cinnamaldehyde (entry 12) with cyclohexyl amine, however, proceeded with concomitant reduction of the C–C double bond. Unlike the Leukart 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 the 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.*[18] However the imines prepared by using either molecular sieves or silica gel were directly taken in dimethyl formamide (DMF) and subjected to reduction by adding palladium acetate (2-5 mol%) and potassium formate (2-3 equiv.) and heated at 40-60 ^{0}C for 3-6 hours. The products were obtained after purification on column chromatography. In general, the reaction procedure is very simple and the reaction condition appears to be mild.

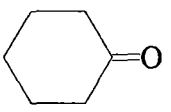
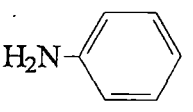
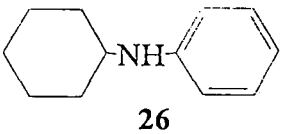
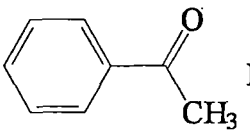
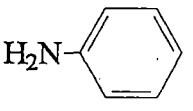
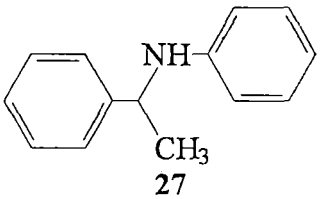
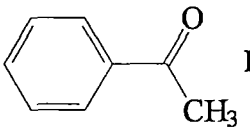
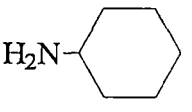
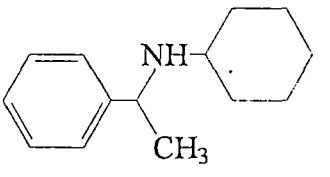
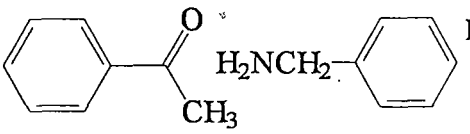
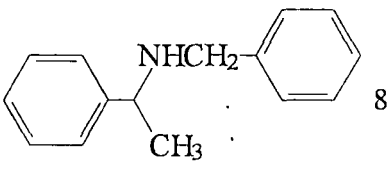
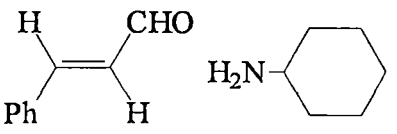
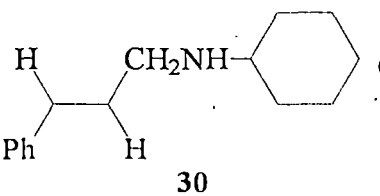
In summary, the method described here can be useful for preparing all classes of amines from suitable carbonyl compounds and the amines. Furthermore, the method can be of importance in view of cheap reducing agent, which decomposes to environmentally friendly chemicals. Since palladium catalyzed hydride 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 in future studies.

Table 2

Entry	Substrate	Amine	Condition a/ Temp./ Time	Product	%Yield b
1.			A /40 °C/ 3h	 **19**	68
2.			A /40 °C/ 4h	 **20**	62
3.			A /50 °C/ 5h	 **21**	67
4.			A /40 °C/ 3h	 **22**	75
5.			A /40 °C/ 3h	 **23**	86
6.			A /50 °C/ 5h	 **24**	67
7.			A /50 °C/ 5h	 **24**	56

Continued.....

Continued..... **Table 2**

Entry	Substrate	Amine	Condition[a]/ Temp./ Time	Product	%Yield[b]
8.			B /50 °C/ 5h	 **26**	70
9.			B /60 °C/ 6h	 **27**	76
10.			B /60 °C/ 6h	 **28**	83
11.			B /60 °C/ 6h	 **29**	80
12.			B /50 °C/ 5h	 **30**	69

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

IB.3 Experimental

General information regarding techniques and instrumentation used are the same as mentioned in the previous section. Molecular sieves (4Å) and silica gel (HF_{254}) SRL, India were activated by heating in an oven at 120 ^{0}C for 12 hours before use.

General procedure for aldehydes (except cinammaldehyde)

A solution of *p*-anisaldehyde (0.680g, 5 mmol) and cyclohexylamine (0.500g, 5 mmol) in dry DMF (5 mL) was magnetically stirred at room temperature for 4 hours, in presence of molecular sieves (4Å). To the resulting reaction mixture were added HCOOK (0.840g, 10 mmol) and palladium acetate (22mg, 0.1 mmol). The mixture was then heated at 40 ^{0}C for 3 hours to complete the reaction (TLC) and after cooling it was diluted with ice-cold water (15 mL). The mixture was extracted with ether (3×20 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) affording *N*-cyclohexyl-*p*-methoxybenzylamine (**22**).

Yield: 75% (0.815g), Liquid.

IR (neat): ν_{max} 2925, 2851, 1610, 1510, 1300, 1246 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): δ 158.4, 132.9, 129.2, 113.7, 56.0, 55.2, 50.3, 33.4, 26.2, 24.9.

Similarly compounds **19**, **20**, **21**, **23**, **24** and **25** were prepared from corresponding aldehydes and amines.

N-Cyclohexylbenzylamine (**19**)

Yield: 68% (0.644g), liquid.

IR (neat): ν_{max} 3400, 1600, 1450, 1321 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 (**20**)

Yield: 62% (0.550g), liquid.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.25-7.32 (m, 5H), 3.70 (t, 4H), 3.49 (s, 2H), 2.44 (t, 4H).

N-(4-Chlorobenzyl)aniline (**21**)

Yield: 67% (0.730g), liquid.

IR (neat): ν_{max} 3380, 1600, 1490, 1320 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 = 7.7 Hz), 6.71 (t, 1H, J = 7.2 Hz), 6.64 (d, 2H, J = 8.81 Hz), 4.29 (s, 2H), 3.97 (br, 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 (**23**)

Yield: 86% (0.818g), 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), 2.46 (br, 1H), 1.92-1.82 (m, 4H), 1.62-1.60 (m, 1H), 1.27-1.06 (m, 6H).

N-(4-Methoxybenzyl)morpholine (**24**)

Yield: 67% (0.694g), liquid.

IR (neat): ν_{max} 1612, 1514, 1246 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 (**25**)

Yield: 56% (0.860g), 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.

General procedure for ketones and cinammaldehyde

A mixture of acetophenone (0.601g, 5 mmol) and benzyl amine (0.535g, 5 mmol) was uniformly adsorbed on the surface of activated silica gel (5g) by dropwise addition under stirring, and the mixture was then stirred at room temperature (25 ^{0}C) under nitrogen for 4 hours to allow complete conversion imine. HCOOK (0.840g, 10 mmol), palladium acetate (22mg, 0.1 mmol) and DMF (5 mL) were added and the reaction mixture heated at 60 ^{0}C for 6 hours. After completion (TLC) the reaction mixture was cooled, diluted with ice-cold water and extracted with ether (3×20 mL). The extract was washed with brine, dried over anhydrous Na_2SO_4 and evaporated the 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 (**29**).

Yield: 80% (0.845g), 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 **26**, **27**, **28** and **30** were prepared from the corresponding carbonyls and amines.

N-Cyclohexylaniline (**26**)

Yield: 70% (0.614g), liquid.

IR (neat): ν_{max} 3400, 1602 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 (**27**)

Yield: 83% (0.844g), liquid.

IR (neat): ν_{max} 3416, 3053, 1603, 1506, 1450, 1322, 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 (**28**)

Yield: 76% (0.750g), 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 (**30**)

Yield: 69% (0.743g), 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.

IB.4 References

1. (a) Collman, J.P.; Trost, B.M.; Veroeven, T.R. In *Comprehensive Organometalic Chemistry*; Wilkinson, G.; Stone, P.G.A., Eds.; Pergamon Press: Oxford, 1982, *8*, 892. (b) Gibson, M.S. In *The Chemistry of Amino Group*; Patai, S., Ed.; Interscience, New York, 1968, 61.
2. (a) Krischbaum, J. In *Analytical Profiles of Drug Substances*; Florey, K., Ed.; Academic Press, New York, 1983, *12*, 1. (b) Main, B.G.; Tucker, H. In *Medicinal Chemistry;* Genellin, C.R.; Roberts, S.M., Eds.; 2nd Edn., Academic Press, New York, 1993, 187.
3. (a) Swamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857. (b) Togni, A.; Venanzi, L.M. *Angew. Chem., Int. Ed. Eng.* **1994**, *33*, 497.
4. (a) Sango, C.; Zimmerson, E. *J. Liq. Chromatogr.* **1980**, *3*, 971. (b) Kormos, L.H.; Sandrige, R.L.; Killer, J. *Anal. Chem.* **1981**, *53*, 1122.
5. Wahlund, K.G.; Solkolowski, A. *J. Chromatogr.* **1978**, *151*, 299,
6. Hermodson, M.A.; Ericsson, L.H.; Titani, K.; Neurath, H.; Walsh, K. A. *Biochemistry* **1972**, *11*, 4493.
7. Sakanoue, K.; Motoda, M.; Sugimoto, M.; Sakaki, S. *J. Phys. Chem. A* **1999**, *103*, 5551.
8. Thayumanavan, S., Mendez, J., Marder, S.R. *J. Org. Chem.* **1999**, *64*, 1125.
9. Law, K.-Y. *Chem. Rev.* **1993**, *93*, 449.
10. Schloter, S.; Schreiber, A.; Grasruck, M.; Leopold, A.; Kol'chenko, M.; Pan, J.; Hohle, C.; Strohriegee, P.; Zilker S.J.; Haarer, D. *Appl. Phys. B.* **1999**, *68*, 899.
11. Costerton, J.W.; Geesey, G.G.; Cheng, K.-J. *Sci. Am.* **1978**, *238*, 86.
12. Recent advances are described in annual chapters of amino sugars in "Carbohydrates" (*Specialist Periodical Reports*, The Chemical Society) Vol. 1, 1968 to present.
13. Santos, M.H.S. *Int. J. Food Microbiol.* **1996**, *29*, 213.
14. Smith, M.B.; March, J. In *March's Advanced Organic Chemistry;* 5th Edn., John Wiley and Sons, New York, 2001, 1187.
15. (a) Wolfe, J.P.; Wagaw, S.; Marcoux , J.F.; Buchwald, S.L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J.F. *Acc. Chem. Res.* **1998**, *31*, 852.

16. (a) Muller, T.E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Nobis, M.; Driessen; Holscher, B. *Angew. Chem., Int. Ed. Eng.* **2001**, *40*, 3983.

17. (a) Lewin, G.; Schaeffer, *Heterocycles* **1998**, *48*, 171. (b) Tahmassebi, D.C.; Sasaki, T. *J. Org. Chem.* **1998**, *63*, 728. (c) Rowlands, G.J.; Craig, D.; Jones, P.S. *Chem. Commun.* **1997**, 2141.

18. Ranu, B.C.; Majee, A.; Sarkar, A. *J. Org. Chem.* **1998**, *63*, 370.

19. (a) Emerson, W.S. *Org. React.* **1948**, *4*, 174. (b) Klyuev, M.V.; Khidekel, M.L. *Russ. Chem. Rev.* **1980**, *49*, 14. (c) Rylander, P.N. In *Catalytic Hydrogenation over Platinum Metal*, Academic Press, New York, 1967, 118.

20. Skita, A.; Keil, F. *Chem. Ber.* **1928**, *61B*, 1452.

21. Ref. 20, page 21.

22. (a) Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. (b) Lane, C.F. *Synthesis* **1975**, 135.

23. Borch, R.F.; Durst, H.D. *J. Am. Chem. Soc.* **1969**, *91*, 3996.

24. (a) Pelter, A.; Rosser, R.M.; Mills, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 717. (b) Mattson, R.J.; Pham, K.M.; Leuck, D.J.; Cowen, K.A. *J. Org. Chem.* **1972**, *37*, 1673.

25. Moormann, A.E. *Synth. Commun.* **1993**, *23*, 789.

26. (a) Gribble, G.W.; Lord, P.D.; Skotnicki, J.; Deitz, S.E.; Eaton, J.T.; Johnson, J.L. *J. Am. Chem. Soc.* **1974**, *96*, 7812. (b) Abdel-Magid, A.F.; Crson, K.G.; Hrris, B.D.; Maryanoff, C.A.; Shah, R.D. *J. Org. Chem.* **1996**, *61*, 3849. (c) Abdel-Magid, A.F. Maryanoff, C.A. *Tetrahedron Lett.* **1990**, *31*, 5595.

27. Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* **1985**, *17*, 317.

28. Bhattacharyya, S.; Chatterjee, A.; Williamson, J.M. *Synth. Commun.* **1997**, *27*, 4265.

29. (a) Bhattacharyya, S.; Neidigh, K.A.; Avery, M.A.; Williamson, J.M. *Synlett* **1999**, 1781. (b) Neidigh, K.A.; Avery, M.A.; Williamson, J.M.; Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2527.

30. (a) Bhattacharyya, S. *Tetrahedron Lett.* **1994**, *35*, 2401 (b) Bhattacharyya, S. *Synlett* **1994**, 1029. (c) Bhattacharyya, S.; Chatterjee, A.; Williamson, J.M. *Synlett* **1995**, 1079. (d) Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928. (e) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zueger, M. *Synthesis* **1982**, 138.

31. Sarma, J.C.; Sharma, R.P. *Chem. Ind.* (London) **1987**, 764.

32. Brown, H.C. Brown, C.A. *J. Am. Chem. Soc.* **1962**, *84*, 1493.

33. Saxena, I.; Borah, R.; Sarma, J.C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 503.

34. Bomann, M.D.; Guch, I.C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995.

35. Lee, S.H.; Park, Y.J.; Yoon, C.M. *Tetrahedron Lett.* **1999**, *40*, 6049.

36. Bae, J.W.; Lee, S.H.; Cho, Y.J.; Yoon, C.M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 145.

37. Micovic, I.V.; Ivanovic, M.D.; Piatak, D.M.; Bojic, V.D. *Synthesis* **1991**, 1043.

38. Koboyashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407.

39. Kursanov, D.N.; Parnes, Z.N.; Loim, N.M. *Synthesis* **1974**, 633.

40. Chen, B.-C.; Sundeen, J.E.; Guo, P.; Bednarz, M.S.; Zhao, R. *Tetrahedron Lett.* **2001**, *42*, 1245.

41. Apodaca, R.; Xiao, W. *Org. Lett.* **2001**, *3*, 1745.

42. Lawrence, N.J.; Drew, M.D.; Bushell, S.M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381.

43. (a) Chandrasekhar, S.; Chandraiah, L.; Reddy, Ch. R.; Reddy, M.V. *Chem. Lett.* **2000**, 780. (b) Chandrasekhar, S.; Ahmed, M. *Tetrahedron Lett.* **1999**, *40*, 2325. (c) Chandrasekhar, S.; Reddy, M.V.; Chandraiah, L. *Synth. Commun.* **1999**, *29*, 3981.

44. Chandrasekhar, S.; Reddy, Ch. R.; Ahmed, M. *Synlett* **2000**, 1655.

45. Pereyre, M.; Quintard, P.J.; Rahm, A. In *Tin in Organic Synthesis*; Butterworths: London, 1987.

46. Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synlett* **2000**, 556.

47. (a) Kawakami, T.; Shibata, I.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1993**, *58*, 7608. (b) Kawakami, T.; Shibata, I. Baba, A. *J. Org. Chem.* **1996**, *61*, 82. (c) Kawakami, T.; Miyatake, M.; Shibata, I.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1996**, *61*, 376.

48. Kawakami, T.; Sugimoto, T.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *J. Org. Chem.* **1995**, *60*, 2677.

49. Shibata, I.; Suwa, T.; Kawakami, T.; Tanizawa, D.; Sugiyama, E.; Matsuda, H.; Baba, A. *J. Org. Chem.* **1998**, *63*, 383.

50. (a) Bui, C.T.; Rasoul, F.A.; Ercole, F.; Pham, Y.; Maeji, N.J. *Tetrahedron Lett.* **1998**, *39*, 9283. (b) Brown, E.G.; Nass, M.J.; *Tetrahedron Lett.* **1997**, *38*, 8457.

51. Gibson, H.W.; Baily, F.C.; *J. Chem. Soc., Chem. Commun.* **1977**, 815.

52. (a) Yoon, N.M.; Park, K.B.; Gyound, Y.S. *Tetrahedron Lett.* **1983**, *24*, 5367. (b) Gyound, Y.S.; Yoon, N.M.; Jeon, D.H. *Bull. Korean Chem. Soc.* **1987**, *8*, 62.

53. Yoon, N.M.; Kim, E.G.; Son, H.S.; Choi, J., *Synth. Commun.* **1993**, *23*, 1595.

54. Blackburn, L.; Taylor, R.J.K. *Org. Lett.* **2001**, *3*, 1637.

55. Varma, R.S.; Dahiya, R. *Tetrahedron* **1998**, *54*, 6293.

56. Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; VCH, New York, 1993, 1.

57. (a) Burk, M.J.; Feaster, E.J. *J. Am. Chem. Soc.* **1992**, *114*, 6266. (b) Splinder, F.; Pugin, B.; Blaser, H.U. *Angew. Chem., Int. Ed. Eng.* **1990**, *29*, 558.

58. (a) Willoughby, C.A.; Buchwald, S.L. *J. Am. Chem. Soc.* **1994**, *116*, 8952. (b) Willoughby, C.A.; Buchwald, S.L. *J. Am. Chem. Soc.* **1994**, *116*, 11703. (c) Verdaguer, X.; Lange, U.E.W.; Reding, M.T.; Buchwald, S.L. *J. Am. Chem. Soc.* **1996**, *118*, 6784.

59. (a) Fogg, D.E.; James, B.R.; Kilner, M. *Inorg. Chim. Acta* **1995**, *222*, 85. (b) Cho, C.S.; Park, J.H.; Kim, T.-J.; Shim, S.C. *Bull. Korean Chem. Sci.* **2002**, *23*, 23.

60. Tani, K.; Onouchi, J.; Yamagata, T.; Kataoka, Y. *Chem. Lett.* **1995**, 985.

61. (a) Burk, M.J.; Martinez, J.P.; Feaster, E.J.; Cosford, N. *Tetrahedron* **1994**, *50*, 4399. (b) Kang, G.-J.; Cullen, W.R.; Fryzuk, M.D.; James, B.R.; Kutney, J.P. *J. Chem. Soc., Chem. Commun.* **1988**, 1466.

62. (a) Willoughby, C.A.; Buchwald, S.L. *J. Am. Chem. Soc.* **114**, *114*, 7562. (b) Willoughby, C.A.; Buchwald, S.L. *J. Org. Chem.* **1993**, *58*, 7627.

63. Amin, Sk. R.; Crowe, W.E. *Tetrahedron Lett.* **1997**, *38*, 7487.

64. Fuller, J.C.; Belisle, C.M.; Goralski, C.T.; Singaram, B. *Tetrahedron Lett.* **1994**, *35*, 5389.

65. Denmark, S.E.; Nakajima, N.; Nicaise, O.J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797.

66. Nishikori, H.; Yoshihara, R.; Hosomi, A. *Synlett* **2003**, 561.

67. Verado, G.; Giumanini, A.G.; Strazzolini, P.; Poina, M. *Synthesis* **1993**, 121.