SYNTHETIC ORGANIC REACTIONS–NEW METHODOLOGY AND APPLICATIONS

Thesis submitted for the Degree of Doctor of Philosophy in Science of the University of North Bengal

by
Md. Mosharef Hossain Bhuiyan

under the supervision of
Dr. Basudeb Basu

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NORTH BENGAL
DARJEELING – 734 430
WEST BENGAL
INDIA

August 2003

Md. Mosharef Hossain Bhuiyan
Assistant Professor of Chemistry
University of Chittagong
Chittagong 4331
Bangladesh

Research Scholar (ICCR)
Department of Chemistry
University of North Bengal
Darjeeling, India
E-Mail: mosharef65@yahoo.com

DECLARATION

I do hereby solemnly declare that the thesis entitled "SYNTHETIC ORGANIC REACTIONS – NEW METHODOLGY AND APPLICATIONS" is the outcome of my empirical research work pursued under Govt. of India Scholarship scheme. I have accomplished this study as an ICCR sponsored research scholar under the supervision of Dr. B. Basu, Reader, Department of Chemistry, University of North Bengal, India. It is affirmed that this thesis or any part of it has not been submitted before any University or Institution for Ph.D. or any other degree.

Md. Mosharef Hossain Bhuiyan

Date: NBU
18-08-2003

(Md. Mosharef Hossain Bhuiyan)

UNIVERSITY OF NORTH BENGAL

Name : Dr. Basudeb Basu, Reader
DEPARTMENT OF CHEMISTRY
Email : basu_nbu@indiatimes.com

Ph. : (0353) 2581 425
Fax : (0353) 2581 546
P.O. NORTH BENGAL UNIVERSITY,
RAJA RAMMOHUNPUR, DIST. DARJEELING.
PIN -734 430
Dated : 18-08-2003.

To Whomsoever It May Concern

This to certify that Md. Mosharef Hossain Bhuiyan has carried out his work under my supervision. His thesis entitled "SYNTHETIC ORGANIC REACTIONS–NEW METHODOLOGY AND APPLICATIONS" is based on his original work and is being submitted for the award of Doctor of Philosophy (Science) Degree in Chemistry in accordance with rules and regulations of the University of North Bengal.

(Dr. B. Basu)

Dedicated to
my beloved Parents
&
Parents-in-Law

Acknowledgment

I have great pleasure in expressing my deep sense of gratitude to my honourable supervisor Dr. B. Basu, Reader, Department of Chemistry, University of North Bengal, Darjeeling, India for his inspiring guidance, parental attitude, solicitude behaviour and constant encouragement through out the entire course of study. Without his profound help, sincere supervision and perspicacious directions the work might not have been completed. I am grateful to him for sparing his valuable time in solving my problems and allowing me to share the benefit of his research experience and academic acumen.

I wish to express my sincere thanks to Prof. B.C. Ranu, Prof. A. Dey, Prof. S. Ghosh, Prof. S. Lahiri, Indian Association for the Cultivation of Science, Kolkata; Dr. R. Mukherjee, Indian Institute of Chemical Biology, Kolkata; Dr. A.T. Khan, IIT, Guwahati and Prof. S. Chandrasekaran, IISc, Bangalore for their help in recording NMR spectra, and other spectral and element analyses.

Thanks are also due to all teachers, staff members and scholars of the Department of Chemistry, NBU, and Mr. M.M. Matin, University of Punne for their continuous help, cooperation, encouragement and suggestions.

I am grateful to the ICCR, India for award of the Fellowship, to the NBU authority for allowing me to complete my research studies; Bangladesh Govt. and Chittagong University authority to allow me study leave for the completion of the course.

I am also grateful to my wife, Zafreen for her inspiration and constant encouragement during the course of the research. With a sense of moral liability I would like to record the name of my sons, Mahdee and Muttaqee, sources of inspirations but became deprived of pleasing paternal love and affection during the period I was wholeheartedly engaged in research work.

Md. Mosharef Hossain Bhuiyan

(Md. Mosharef Hossain Bhuiyan)
Assistant Professor
Department of Chemistry
University of Chittagong
Chittagong 4331
Bangladesh

Contents

Part I. Section C

Solid Phase Organic Synthesis: Development of a New Method for Reduction of C–C and C–N Double Bonds Using Polymer Supported Formate and Catalytic $Pd(OAc)_2$

Part II

Pd-Catalyzed C–N Hetero Cross Coupling Reactions: Synthesis of Amino Pyridines

Annexure: List of Publications

Paper I

Basu, B.; Bhuiyan, M.M.H.; Jha, S. "Palladium mediated chemoselective reduction of α,β-unsaturated cyano esters with potassium formate," *Synth. Commun.* **2003**, *33*(2), 291-296.

Paper II

Basu, B.; Jha, S.; Bhuiyan, M.M.H.; Das, P. "A simple protocol for direct reductive amination of aldehydes and ketones using potassium formate and catalytic palladium acetate," *Synlett* **2003**, (4), 555-557.

Paper III

Basu, B.; Jha, S.; Mridha, N.K.; Bhuiyan, M.M.H. "Palladium-catalyzed amination of halopyridines on a KF-alumina surface," *Tetrahedron Lett.* **2002**, *43*(44), 7967-7969.

Paper IV

Bhuiyan, M.M.H.; Basu, B. "Catalytic transfer reduction of alkenes and imines using polymer supported formates," Manuscript attached.

Poster

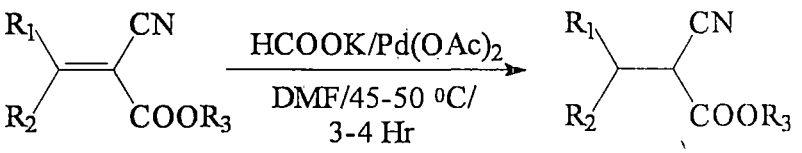
Bhuiyan, M.M.H.; Basu, B. "Palladium mediated chemoselective reduction of enamides on a solid supported reducing agents," 5th National Symposium in Chemistry, Chennai, 2003, Abstract No. P303, p341.

SUMMARY

Investigations embodied in this thesis entitled "**SYNTHETIC ORGANIC REACTIONS – NEW METHODOLOGY AND APPLICATIONS**" are primarily concerned with studies on the development of new methodology, reagents and conditions for organic reactions and its applications. The thesis has been divided into two parts: **Part–I** and **Part–II**. **Part–I** comprises three sections: **Section–A**, **Section–B** and **Section–C**.

Section–A starts with a brief introduction on catalytic transfer hydrogenation (CTH) reactions. Several aspects of CTH including possible mechanistic pathways have been discussed.

In the present work it is reported that α,β-unsaturated cyanoesters possessing other sensitive functional groups can be smoothly converted into the corresponding saturated cyanoacetates using a combination of potassium formate and catalytic palladium acetate (Scheme I). The reduction is chemoselective to C–C double bond and appeared to be mild and efficient as the nitrile, ester (alkyl and tri-*n*-butyl stannyl), and halogen functions remain unaffected.

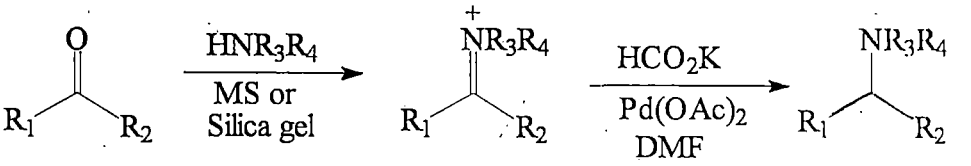


R_3 = Et, Sn(*n*-Bu)$_3$

Scheme I

The present study constitutes a useful condition for chemoselective reduction of C–C double bond of α,β-unsaturated cyanoesters using potassium formate and catalytic palladium acetate as simple and inexpensive reductant. The reaction possibly involves "hydride transfer" ***in situ*** at the β-carbon and proceeds without any concomitant reduction of cyano, ester, or halogen groups. The ability of this reductant to perform conjugate reduction on functionalized alkylidenecyanoacetate in a controlled fashion is noteworthy. The homogeneous catalytic condition offers further use of chiral ligands to promote asymmetric induction. Future studies may be attempted in this direction. This work has been published in *Synth. Commun.* **2003**, *33*(2), pp. 291-296.

Section–B deals with the development of a simple protocol for direct reductive amination of aldehydes and ketones using potassium formate and catalytic palladium acetate (Scheme II).



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

Scheme II

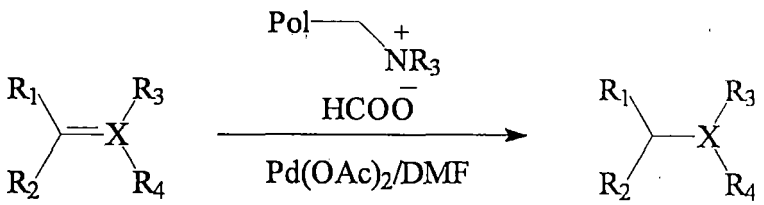
The direct reductive amination of carbonyl compounds is a useful organic transformation for preparing primary, secondary and tertiary amines. The reaction offers compelling advantages over other amine syntheses, including brevity, wide commercial availability of substrates, generally mild reaction conditions, and in some cases exceptionally high functional group tolerance.

The 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. This work has been published in *Synlett* **2003**, (4), pp.555-557.

Section–C delineates studies on the development of formic acid–based stable H–donors in solid phase CTH reactions.

The growing need for atom efficient reactions, clean and green technology and combinatorial chemistry compounded with environmental constraints has led to undertake this study.

The functionalized polymers have been emerged as versatile tools for solution-phase chemistry and automated parallel synthesis. The polymeric supports have been used for anchoring several reducing agents such as, borohydrides, tin hydrides etc. These hydrides are either expensive, reactive or the residue poses a risk in its elimination. Therefore, the design of ideal support with suitable reagents has been a subject of research for many synthetic chemists. A method for catalytic transfer hydrogenation of C–C and C–N double bonds with the aid of polymer supported formate (PSF) as the hydrogen donor and palladium acetate as the catalyst is described in this section (Scheme III).



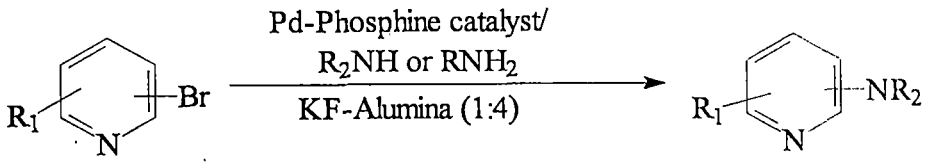
$R_1 = R_2 =$ Ph, Ar, H, X = C, N

R_3 and R_4 = CN, COOEt, COOMe, NHBoc, H, Ph

Scheme III

The method is operationally simple and applicable to a range of unsaturated organic compounds. The use of palladium catalyst showed some substrate selectivity. Other advantages are: clean work-up, high yields and environmentally benign. (A manuscript on a brief preliminary account, to be submitted, is under preparation).

Part–II of this dissertation deals with palladium catalyzed amination of halopyridines on a KF–alumina surface (Scheme IV).



P(*o*-tolyl)$_3$, DPPF, BINAP; Pd sources: $PdCl_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(acac)_2$, $Pd[PPh_3]_4$

Scheme IV

Aminopyridines are versatile intermediates for synthetic transformations to biologically active compounds and are known to act as central nervous system stimulants. Their derivatives are often used as ligands in coordination and organometallic chemistry, and have found industrial applications as fluorescent dyes. The recent development of palladium-catalyzed C–N hetero cross coupling reactions disclosed independently by Buchwald and Hartwig involves use of strong base such as sodium *t*-butoxide, which is not desirable and remains associated with problems such as in the case of direct amination using NaNHR or $NaNR_2$.

In this part, we have described the development of a convenient and efficient heterogeneous method for C–N coupling by palladium-catalyzed amination of halopyridines on KF–alumina surface, thus negating the use of strong bases such as sodium *t*-butoxide. The reaction conditions are optimized with reference to catalytic system, solvents and the surface. This method represents a significant improvement and useful extension relative to Buchwald's procedure using the strong base. Future work may include studies with more base-sensitive functionalities or the heterocyclic nucleus as well as chiral amines. A preliminary account of the work has been published in *Tetrahedron Lett.* **2002**, *43*(44), pp.7967-7969.

Part I. Section A

Transfer Hydrogenation of Highly Functionalized Alkenes by Potassium Formate and Catalytic Palladium Acetate

IA.1 Introduction: Transfer Hydrogenation–A Brief Review

Reduction of organic compounds is important synthetically both in the laboratory and in industry.[1] Reduction is used in the sense of addition of hydrogen to an unsaturated group such as a carbon-carbon double bond, a carbonyl group or an aromatic nucleus, or addition of hydrogen with concomitant fission of a bond between two atoms, as in the reduction of a disulfide to a thiol or an alkyl halide to a hydrocarbon. Reductions are generally effected either chemically or by catalytic hydrogenation. Though reduction of an isolated functional group can be carried out conveniently with a number of reagents, selective reduction of one functionality in presence of other such functional groups with a minimum damage to the sensitive portions of a molecule is a frequent problem in organic synthesis. Thus, developments of selective, mild and effective reducing agents still an area of considerable interests. Conventional hydrogenation procedure although often offers selective reduction under mild conditions, it requires a special set of apparatus and is always associated with the usual risks of using hydrogen gas. Of the many methods of effecting reduction of organic compounds or more specifically the organic functional groups, catalytic hydrogenation offers the advantages of widespread applicability and experimental simplicity to a unique degree.[2] The reduction of multiple bonds using molecular hydrogen and a metal catalyst is a familiar to all organic chemists. Far less well known is the possibility of achieving reduction of multiple bonds with the aid of an organic molecule as the hydrogen donor in the presence of a catalyst, a process known as catalytic transfer hydrogenation (CTH) or hydrogen-transfer reaction (H-transfer).[3] 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 equation (1).

$$DH_X + nA \xrightarrow{\text{Catalyst}} D + nAH_X \quad \text{---------- (1)}$$

DH_X = hydrogen donor; A = hydrogen acceptor.

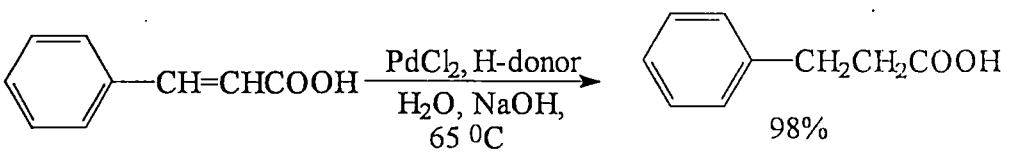
As a result of the transfer, unsaturated groups in *A* may be reduced and/or susceptible bonds may be cleaved by hydrogenolysis. This process is but one of several possible hydrogen transfer reactions which were classified by Braude and Linstead[4] as i) hydrogen migrations, taking place within one molecule; ii) hydrogen disproportionation, transfer between identical donor and acceptor units; iii) transfer hydrogenation-dehydrogenation, occurring between unlike donor and acceptor units. Such of these reaction types in turn can be realized in principle by thermal means, homogeneous catalysis, heterogeneous catalysis, photochemical means, or with biological processes.

In comparison with catalytic reduction using molecular hydrogen, transfer reduction using hydrogen donors has real and potential advantages. Molecular hydrogen, a gas of low molecular weight and therefore high diffusibility, is easily ignited and presents considerable hazards, particularly on the large scale; the use of hydrogen donors obviates these difficulties in that no gas containment is necessary, no pressure vessels are needed, and simple stirring of solutions is usually all that is required. Potentially, transfer methods could afford enhanced selectivity in reduction. With a catalyst and molecular hydrogen, changes of catalyst, solvent, and temperature are possible variants of reaction conditions but, with hydrogen donors, a new dimension is opened up because the choice of hydrogen donor can effect the reaction through its competitive adsorption onto the catalyst surface. Thus, rate and specificity of reduction are amenable to control through choice of hydrogen donor. Most transfer hydrogenation mechanisms are poorly understood and there are a few direct comparisons of products of reaction following the use of molecular hydrogen or a hydrogen donor. Research in these areas is needed not only to unravel details of mechanism, but also to provide a proper appraisal of the advantages or disadvantages of the two methods.

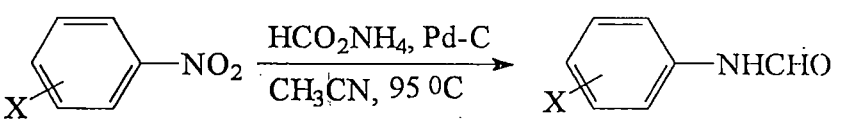
In 1952, Braude *et al.*[5] made the suggestion that the catalytic hydrogen transfer from an organic donor molecule to a wide variety of organic acceptors might be possible under mild conditions. In fact, sporadic use had been made in the past of unsaturated compounds as hydrogen acceptors in catalytic hydrogenation reactions. Reviews of reactions of this type by Brieger and Nestrick[3] and by Johnstone, Wilby and Entwistle[6] show that a wide variety of unsaturated groups can be reduced using an almost equally wide variety of donor compounds and catalysts. In the early work in

this field the donor compound-catalyst combination used most frequently was cyclohexene in the presence of 5% or 10% palladium supported carbon (Pd/C). However as noted by Johnstone and his coauthors,[6] the indifferent yields and long reaction times associated with many of the reactions investigated mediated against the acceptance of CTH as a generally useful synthetic technique.

CTH can be made an effective method for reducing a variety of organic substrates, which avoids some of the technical and safety concerns associated with using compressed hydrogen gas. The heterogeneous mixture of Pd-C and ammonium formate in alcohol solvent has proven to be a particularly effective reagent in organic synthesis. Replacing organic solvent with water offers economic advantages, improves safety, reduces the environmental impact in the waste stream, and in combination with the development of catalytic processes offers great opportunities for 'green chemistry'. Arterburn *et al.*[7] reported a convenient, effective method for reducing unsaturated carboxylic acids using the non-pyrophoric catalyst $PdCl_2$, HCOOH, and NaOH base in water.

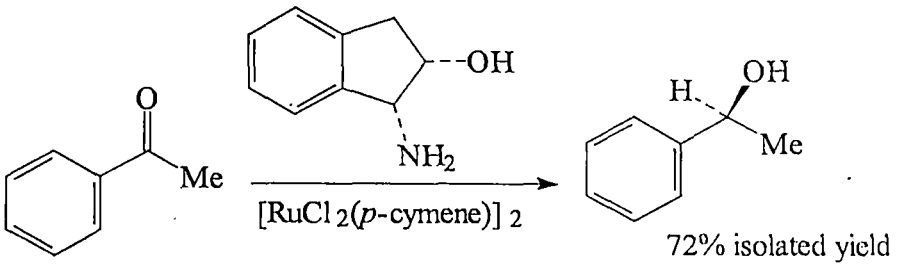


During the course of the study on the catalytic transfer hydrogenation (CTH) of arylnitro compounds with the ammonium formate/Pd-C system,[8] Baskaran *et al.* recently made the interesting observation that ammonium formate in an aprotic solvent like acetonitrile can function as a formylating agent[9] apart from being a source of hydrogen. Based on this observation, Pratap and Baskaran[10] have developed a novel and highly selective procedure for the direct conversion of arylnitro compounds to formanilides in acetonitrile under CTH conditions.



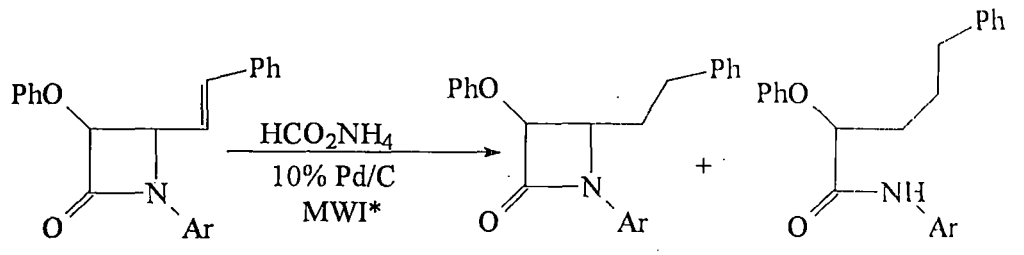
The asymmetric transfer hydrogenation also becomes synthetically very useful. Chiral nonracemic hydrogen donors can be profitably employed as chirality sources for inducing enantioselectivity in the product, thus providing new routes to accomplish an asymmetric process. This expands the potential of asymmetric H-transfer and makes it more versatile than asymmetric catalytic H_2-hydrogenation.

Catalytic asymmetric reduction of ketones to form chiral secondary alcohols is an important transformation in organic synthesis.[11] The enantioselective transformation can be accomplished by hydride reduction using the oxazaborolidine catalyst,[12] by hydrogenation with for example chiral BINAP and DuPHOS ligands,[13] and by transfer hydrogenation.[14] The later has been studied extensively during recent years because of the low cost, operational simplicity and favorable properties of the hydrogen donor-usually secondary alcohols and formic acid.[15] Asymmetric transfer hydrogenation with ruthenium complexes has recently emerged as an effective approach to asymmetric carbonyl reduction,[14b,16] although other metal complexes of samarium,[17] rhodium,[18] and iridium[19] have been used successfully. Recently, Noyori *et al.* developed an efficient and highly enantioselective ruthenium catalyst using diamines as chiral ligands.[20] Other types of chiral phosphorous and/or nitrogen ligands have also been used with varying levels of rate, yield and selectivity.[14c,16b,21] Wills *et al.*[22] reported that (1R,2S)-(+)(R,R)-DIOP is an excellent ligand for asymmetric transfer hydrogenation of ketones.



72% isolated yield
91% ee

Catalytic transfer hydrogenation has also been conducted under microwave irradiation using high boiling solvents such as ethylene glycol as the microwave energy transfer agent. Derivatives of β-lactam[23] underwent CT hydrogenation as well as the cleavage of the ring by hydrogenolysis of N-C_4 bond.



In the following pages, CTH reactions are described according to the nature of substrates, hydrogen donors, catalysts, promoters and ligands.

IA.1.1 Substrates

Several different substrates have been successfully reduced by transfer hydrogenation in the presence of both heterogeneous and homogeneous catalysts.[3,6] The list of hydrogen acceptors (H-acceptors) includes alkenes, alkynes, nitriles, azides, azo compounds, aldehydes, ketones, α,β-unsaturated carbonyl compounds, α,β-unsaturated acids, esters, and imines and nitro compounds. Particular attention has been paid to the chemoselectivity in the case of α,β-unsaturated carbonyl derivatives, which can give rise to scalemic products upon reductions both at the carbon-oxygen and at the carbon-carbon double bond.[24] It is well recognized that the reduction of carbon-carbon double bonds by alcohols and formic acid is thermodynamically favoured proceeds to completion under a great variety of conditions. In contrast, the reduction of carbonyl groups by alcohols suffers from unfavourable thermodynamics[25] and it can be anticipated that the equilibrium of H-transfer reduction of ketones by means of alcohols lies to the left side, particularly when primary alcohols are employed. Well-suited hydrogen donors and appropriate reaction conditions are necessary in order to attain high conversions in this case.

IA.1.2 Hydrogen Donors

In hydrogen transfer reactions the hydrogen donor must be different from dihydrogen. Most of the reagents employed are alcohols, including chiral ones, and formic acid,[15] cyclohexene[3,4] or cyclohexadiene,[26] ammonium formate,[27] triethyl or tri-*n*-butyl ammonium formate,[28] phosphinic acid,[29] sodium hypophosphite,[30] hydrazine,[6,31] *n*-Bu_3SnH,[32] $Ph_2SiH_2/ZnCl_2.H_2O$,[33] and triethoxysilane.[34]

According to their relative oxidation potentials, secondary alcohols are better H-donors than primary ones and can be successfully employed even in the reduction of ketones, provided they are present in great excess.[25] Among secondary alcohols, propan-2-ol is the reagent of choice because it is inexpensive and readily available, has an appropriate boiling point and solubility properties, and upon dehydrogenation gives acetone, which can be easily removed from the reaction mixture, if shifting an unfavourable equilibrium is necessary.

Generally, these donors are used with noble-metal catalysts, particularly Pd, Pt, Rh, and give up hydrogen to the substrate under mild conditions with reaction temperatures rarely exceeding 100 ^{0}C. After giving up their hydrogen, the oxidized products from the hydrogen donors are frequently easily removable from the reaction system. Thus, formic acid exhibits two modes of decomposition and may CO_2 or CO as its non-hydrogen containing side products, depending on the catalyst used.

IA.1.3 Catalysts

Transition metal-catalyzed transfer hydrogenation of hydrogen acceptors by hydrogen donors has been recognized to be the importance in reduction chemistry.[3,6,14,35] Both salts and complexes of Pd, Pt, Ru, Ir, Rh, Fe, Ni, and Co have been used as catalysts for the transfer of hydrogen from hydrogen donors to organic substrates. Chiral complexes containing an Ir(I),[19,36] Rh(I),[19,36] or Ru(II)[37] have been successfully employed to catalyze asymmetric reduction of certain prochiral ketones to afford chiral secondary alcohols of high enantiomeric purity.[17,38]

According to Braude *et al.*[4] palladium catalysts are the most effective. The exceptional role of palladium in hydrogen transfer reactions appears to be due, at least in part, to its general mobilizing action for hydrogen-carbon bonds. Palladium is the catalyst of choice for the most catalytic transfer hydrogenations.

As an interface between homogeneous and heterogeneous catalysts, dendritic catalysts have received attention,[39] however, the application of chiral organometallic dendrimers in asymmetric synthesis is a field still in its infancy.[40] Recently Deng *et al.*[41] reported the synthesis of chiral TsDPEN analogue enclosed dendritic ligands and the application of their Ru(II) complexes in the asymmetric transfer hydrogenation of acetophenone.

IA.1.4 Promoters

Strong bases like KOH or NaOH or sodium alkoxides are frequently added as promoters in H-transfer reactions since often they exert a beneficial effect on reaction rates.[42] In 1991, Backvall had discovered that the use of catalytic amount of NaOH in the $[RuCl_2(PPh_3)_3]$-catalyzed transfer hydrogenation of ketones by propan-2-ol

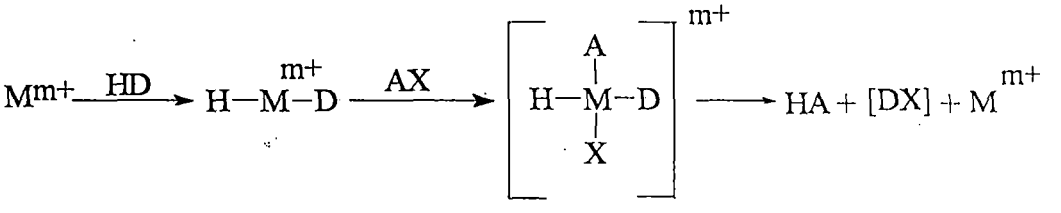
dramatically increased the activity of the catalyst.[15a] Without having added NaOH, or other bases such as K_2CO_3, no transfer hydrogenation occurred. This observation was important, as previously ruthenium-catalyzed transfer hydrogenation of ketones had frequently been performed at high temperatures.[43] The role of the base is considered to be increasing the concentration of 2-propoxide ion, which co-ordinates with the metal and then β-eliminates forming an M-H reducing species and acetone.[44]

IA.1.5 Mechanism

The actual mechanism of transfer reduction is not clear,[3] but it is not simply an alternative to reduction by molecular hydrogen.[45] Usually, if significant evaluation of hydrogen is observed during transfer reduction, the yield of reduction product is low. Conversely, when evaluation of hydrogen is not readily apparent, reduction may be rapid and high yielding. Further, transfer reduction shows different selectivity towards functional groups from that shown in catalytic reduction with molecular hydrogen.

From a mechanistic point of view, two general reaction paths can be envisaged for hydrogen transfer:[43] a step-wise process called "hydridic route", and a concerted process, called "direct hydrogen transfer."

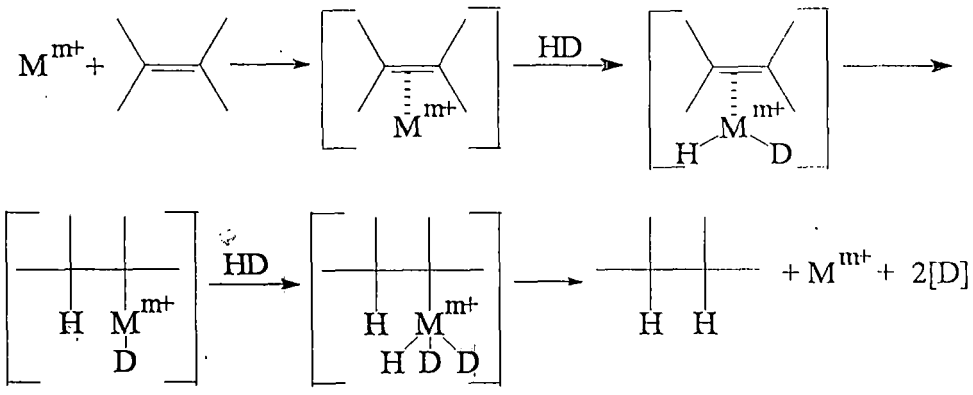
The "hydridic route" involves the intermediate formation of a metal hydride derivative by interaction of the catalyst with the hydrogen donor, followed by hydride transfer from the metal to the substrate.



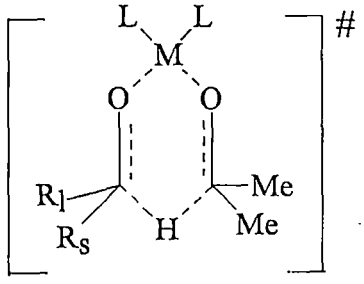
[HD = hydrogen donor; AX = hydrogen acceptor]

Elimination of HA and the elements of X, D from the complex, $HAXDM^{m+}$, give back the metal, M^{m+}, ready for the next catalytic cycle.

This is a typical hydrogenolysis reaction, which needs only slight modification in the mechanism to account for reduction of unsaturated systems such as alkenes.



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 the Meerwein-Pondorf-Verley reduction is possibly involved.



The exact mechanism operating in a given system depends on the metal catalyst and hydrogen donor. Main group elements are reported to undergo the direct hydrogen transfer route preferentially, as in MPV reduction.[46] In contrast, transition metal complexes, as stated by Noyori, "prefer the hydride mechanism".[16a] Such metal hydrides species have been reported in various systems. $[RhH(bipy)_2]$ is implicated in the mechanism of $[Rh(bipy)_2Cl]$-catalyzed dehydrogenation of ethanol in the presence of a base.[47] Also, Backvall has suggested the involvement of ruthenium dihydride species in a $[RuCl_2(PPh_3)_3]$ and NaOH catalyst system for the transfer hydrogenation of ketones.[15a]

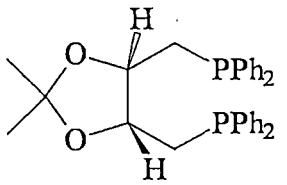
IA.1.6 Ligands

Asymmetric hydrogenation reactions are important in practical organic synthesis ranging from laboratory scale research to large scale production.[48] Chiral phosphine ligands play a significant role in various metal catalyzed asymmetric reductions.[49] Over the past three decades, most effort on asymmetric hydrogenation has been focused on the use of Rh, Ru and Ir catalysts complexing with chiral phosphine ligands. Besides a few tertiary monophosphines,[50] chelating bidentate diphosphines like DIOP, CHIRAPHOS, NORPHOS, and BINAP have been mainly used. Recently, it has been shown that some of the results obtaining with phosphinite,[51] phosphite,[52] phosphine-phosphite with xylofuranoside backbone,[53] phosphonite,[54] or phosphoramide[55] ligands can match those obtained by using phosphines. Rhodium catalysts bearing aminophosphine ligands also have shown good to excellent enantioselectivity and high reactivity in asymmetric hydrogenation.[56] Since many effective phosphine ligands are quite difficult to prepare, the search for easily prepared and highly effective new chiral ligands is still of high interest. Schmid,[57] Pregosin,[58] and RajanBabu[51a,59] reported that in asymmetric hydrogenation, the enantioselectivities of transition metal phosphine/phosphinite catalyst were significantly influenced by the substituents on the phosphorous atoms. Chan *et al.* found that the Rh catalyst containing bidentate aminophosphine, 2,2'-bis[diphenylphosphinoamino]-1,1'-binaphthyl (BDPAB),[60] to be effective in the hydrogenation of enamides,[56b] and dehydroaminoacid derivatives.[61]

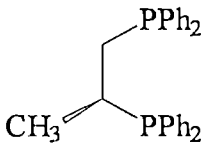
Rh(I) and Ir(I) complexes containing chelating bidentate nitrogen ligands such as 2,2'-bipyridine(bipy), 1,10-phenanthroline (phen), and their substituted derivatives also displayed high catalytic activity in the H-transfer reactions.

A chiral Rh complex, (R)-Cp*RhCl[(1S,2S)-*p*-TsNCHPhCHPhNH$_2$], (S,S)-Cp*RhClTsDPEN), generated from [Cp*RhCl$_2$]$_2$ and (1S,2S)-N-*p*-Ts-1,2-diphenylene diamine [(S,S)-TsDPEN], and its enantiomer provide superior catalysts[62] for the rapid high yielding, asymmetric transfer hydrogenation of some heterocyclic imines, using an HCO_2H-Et_3N azeotrope as the H-source.

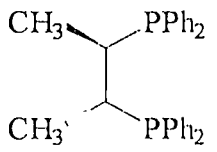
Structures of some ligands:



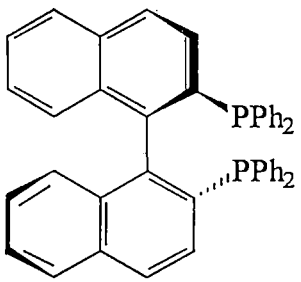
(R,R)-(-)-DIOP



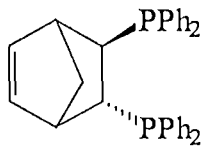
(R)-(+)-PROPHOS



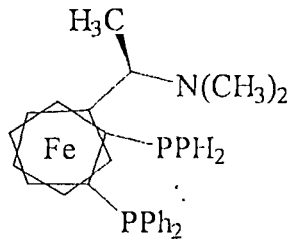
(R,R)-(+)-CHIRAPHOS



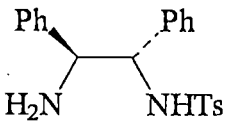
(S)-(-)-BINAP



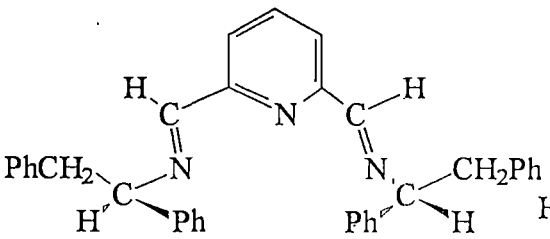
(R,R)-(-)-NORPHOS



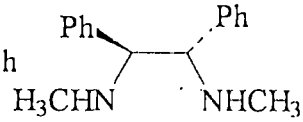
(R,S)-(-)-BPFA

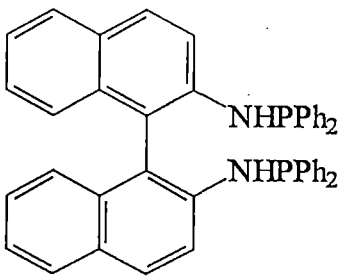


TsDPEN

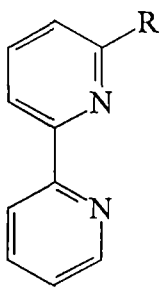


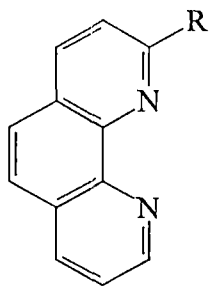
(R,R)-(+)-PDPBI

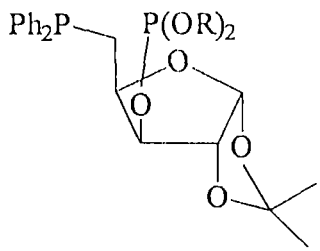


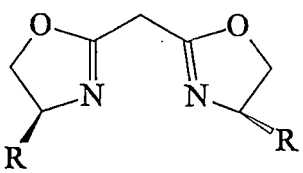


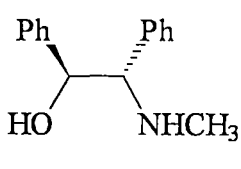
BDPAB

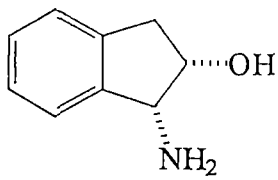


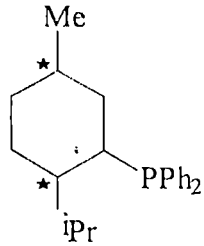












MDPP

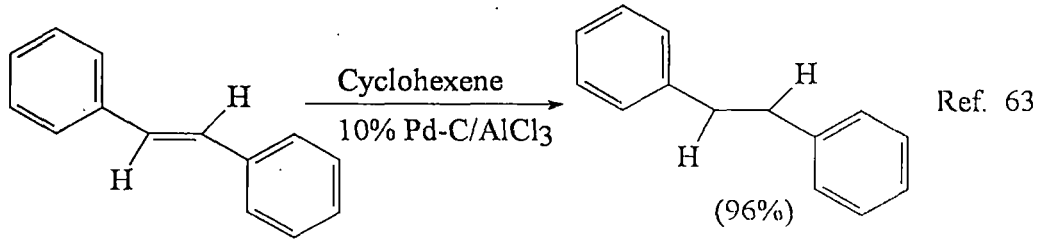
IA.1.7 Catalytic transfer reduction of specific functional groups

A wide range of donors and catalysts has been deployed in various combinations to carry out heterogeneous hydrogen-transfer reductions of most of the major functional groups attached to or part of both aromatic and aliphatic structures. Several important functional groups have received little study, in particular, carboxylic acids, their esters, and their amides. All of them are frequently reduced efficiently by hydride reagents, but are usually found not to be reduced under catalytic transfer conditions.

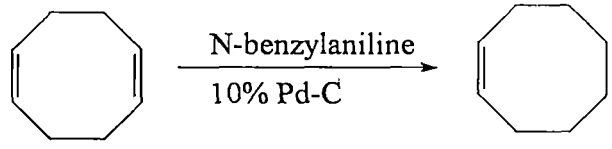
IA.1.7.1 Alkenes

A number of different olefins have been reduced by catalytic transfer hydrogenation. For simple alkenes, palladium on charcoal (Pd/C) appears to effect reduction using either hydrocarbon hydrogen donors, such as cyclohexene, or amines such as *N*-benzyl aniline.

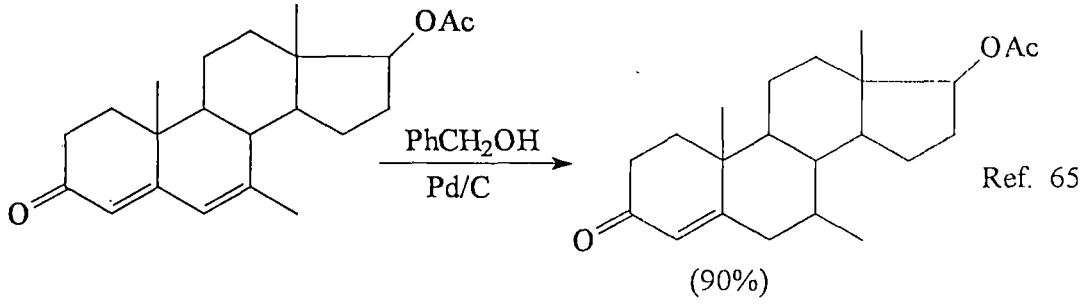
For example,



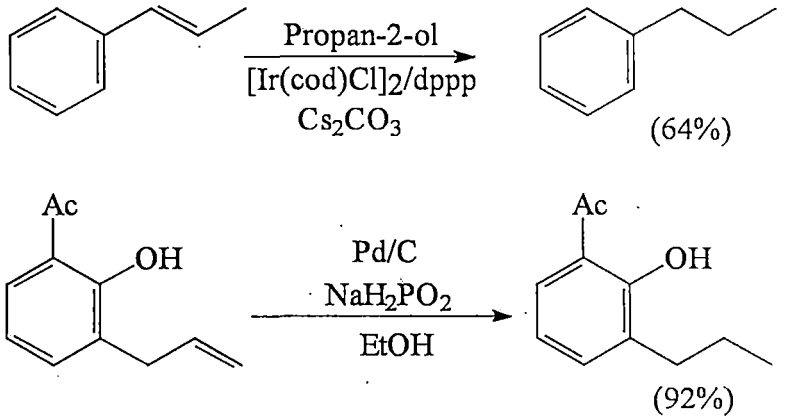
Ref. 63



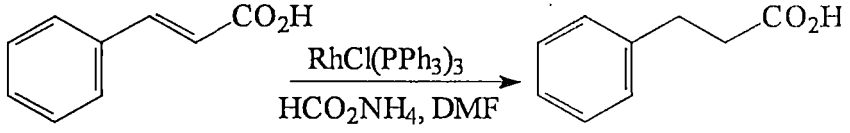
Ref. 64



Ref. 65



Transfer hydrogenation of alkenes using ammonium formate as source of hydrogen has been well established as a synthetic procedure for the reduction of alkenes and the removal of *O*- and *N*-benzyl groups for many years.[2b,66] When cinnamic acid for example is treated with ammonium formate and Wilkinson's catalyst in a solvent such as DMF at 70 ^{0}C for 3 h high yields of the saturated acid are produced.



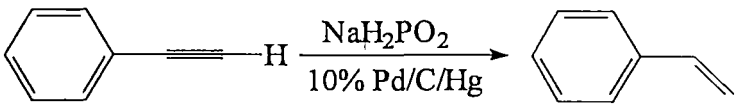
The application of microwave irradiation to these reactions results in a significantly reduced reaction times and solvents volumes, which are environmentally attractive.[23]

IA.1.7.2 Alkynes

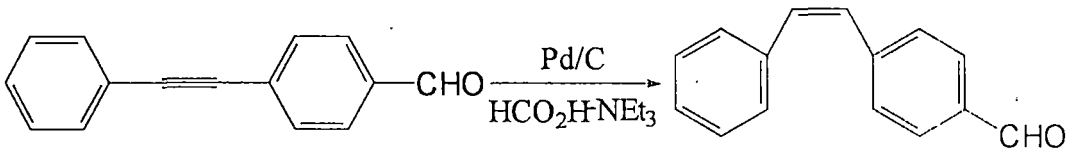
The reduction of alkynes to alkenes is an important reaction in synthetic organic chemistry because the alkyne grouping can be introduced readily into organic molecules[67] and reduction to *cis*- or *trans*-alkenes can be affected stereoselectively.[68]

When Pd/C was used as a catalyst, complete conversion of 1,2-diphenylethyne into 1,2-diphenylethene was observed when sodium phosphinate was the hydrogen donor.[69]

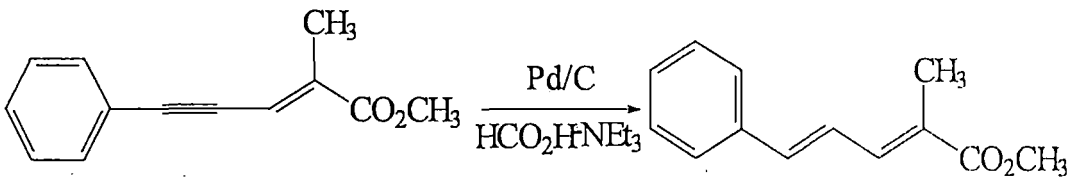
Some representative examples are given below:



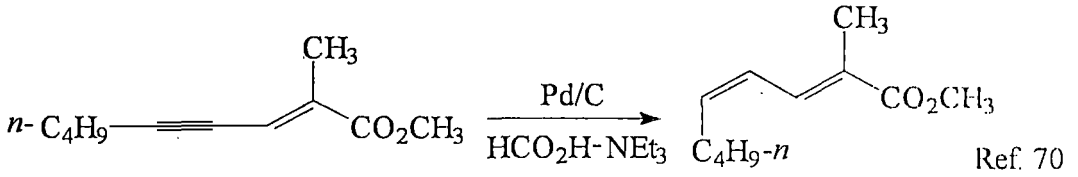
Ref. 69



Ref. 70



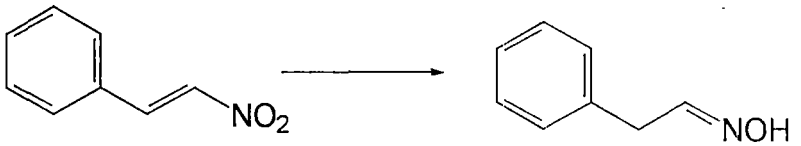
Ref. 70



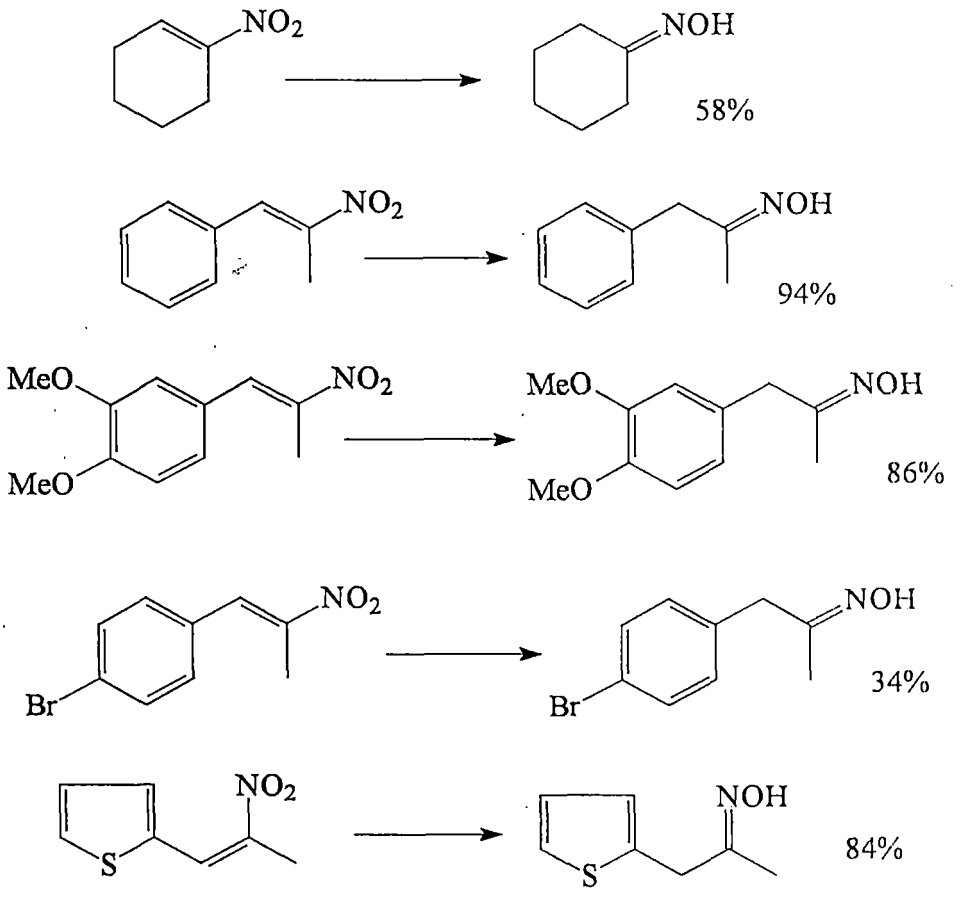
Ref. 70

IA.1.7.3 Nitroalkenes

Reduction of β-nitrostyrene with formic acid and palladium gave the amine of phenylacetaldehyde, presumably following rearrangement of an intermediate (β-nitrosoethyl)benzene.[45]

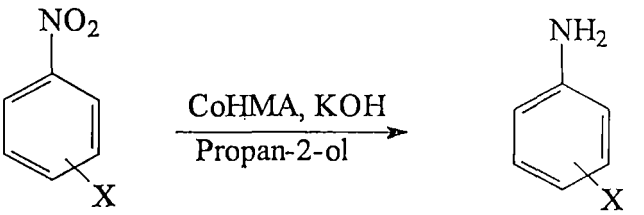


α,β-Unsaturated nitroalkenes are readily reduced to the corresponding oximes in good yields using ammonium formate in the presence of palladium.[71] The reactions occur rapidly at room temperature in a solvent system of methanol and tetrahydrofuran. A series of nitro alkenes are subjected to this procedure and the results are summarized in the following table.

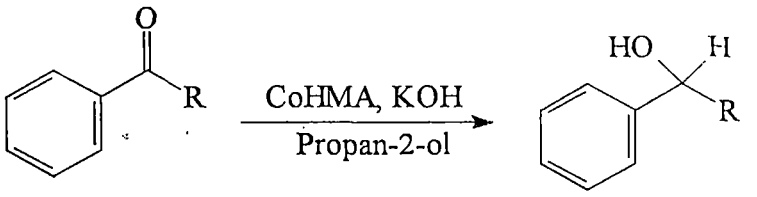


IA.1.7.4 Nitroarenes

The reduction of nitro and carbonyl compounds is a very important in organic synthesis both from the academic and industrial view points.[72] A wide variety of soluble metal complexes have reported for this purpose.[73] Selvam *et al.*[74] reported a very efficient and highly selective method for the CTH of aromatic nitro and carbonyl compounds using a newly developed mesoporous based heterogeneous catalyst, viz, Co(III) substituted hexagonal mesoporous aluminophosphate (CoHMA) molecular sieves, using potassium hydroxide and propan-2-ol.



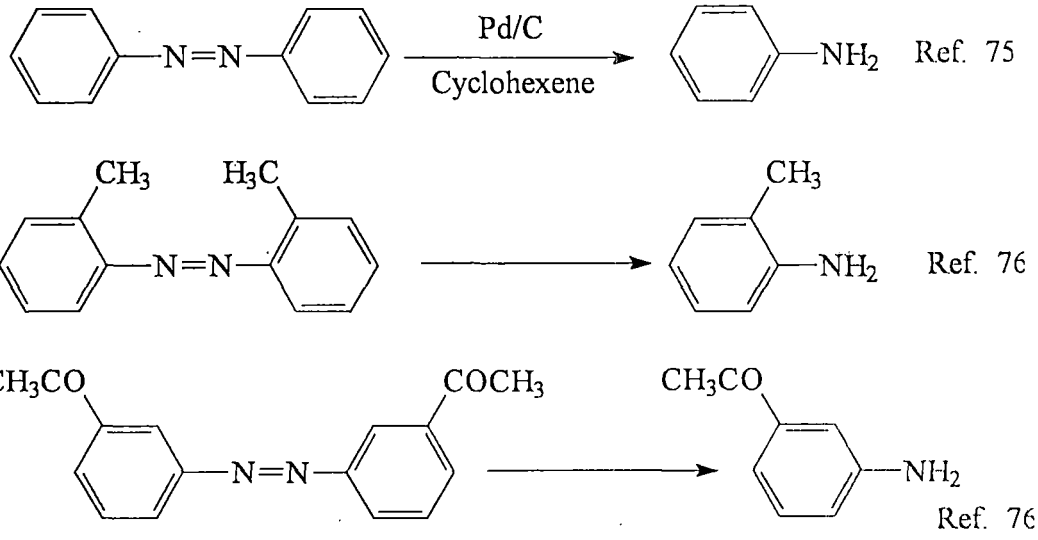
X = H, Me, Cl, OMe, NO_2, CHO, NH_2.



R = H, CH_3

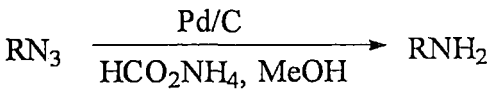
IA.1.7.5 Azo compounds

The N–N double bond in azo compounds can be reduced readily to give hydrazo compounds, but the latter are readily hydrogenolyzed. Catalytic hydrogen-transfer reduction of azo benzene was reported earlier to give aniline in 97% yield.[75]



IA.1.7.6 Azides

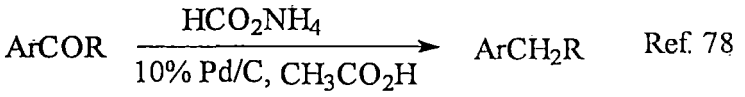
Insertion of amino group in the organic molecule *via* azide is a well-known procedure. In past years a number of reagents have been developed for the reduction of azides to amino derivatives. Latterly alkyl azides were successfully reduced to the corresponding primary amines in the presence of Pd-C, using ammonium formate as the hydrogen source.[77]



IA.1.7.7 Carbonyl compounds

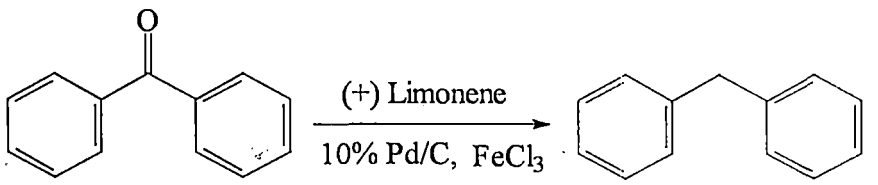
Reduction of carbonyl functionality is widely used in organic synthesis. Although there are numerous reagents available for reduction, reagent for selective reduction in the presence of other groups is well appreciated.

Ram and Spicer demonstrate a rapid, mild and selective reduction of a wide variety of aromatic aldehydes and ketones to methylene derivatives under moderate CTH reaction conditions[78] and can be an attractive alternative for Wolf-Kishner or Clemmensen reduction.



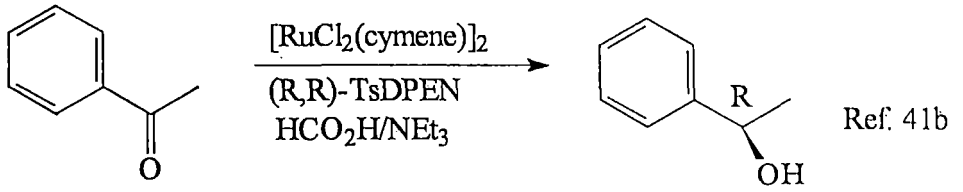
Ref. 78

R = H, alkyl, aryl, heteroaryl.



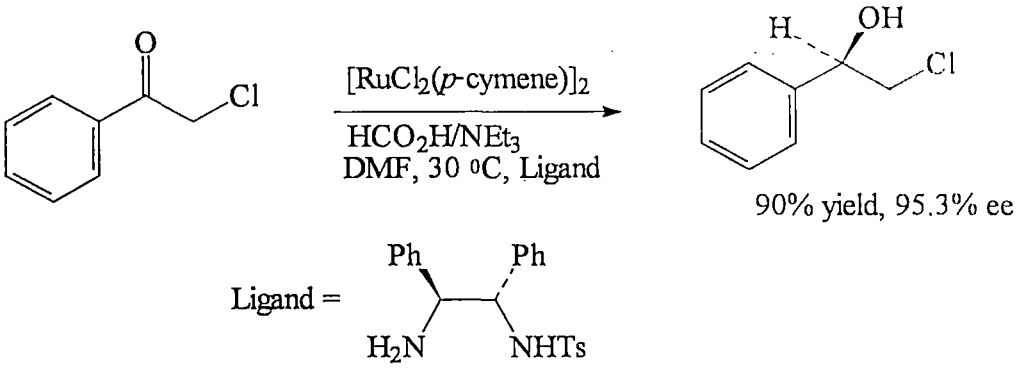
Ref. 79

The asymmetric reduction of ketones to enantiomerically enriched alcohols remains a pivotal transformation in organic synthesis.[11a] Acetophenone was reduced to corresponding alcohol maintaining high enantioselectivity and yield.

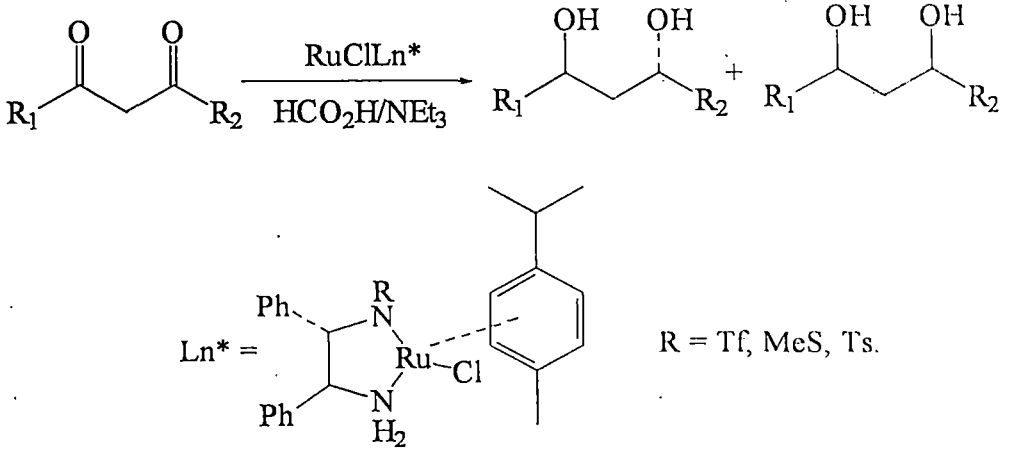


Ref. 41b

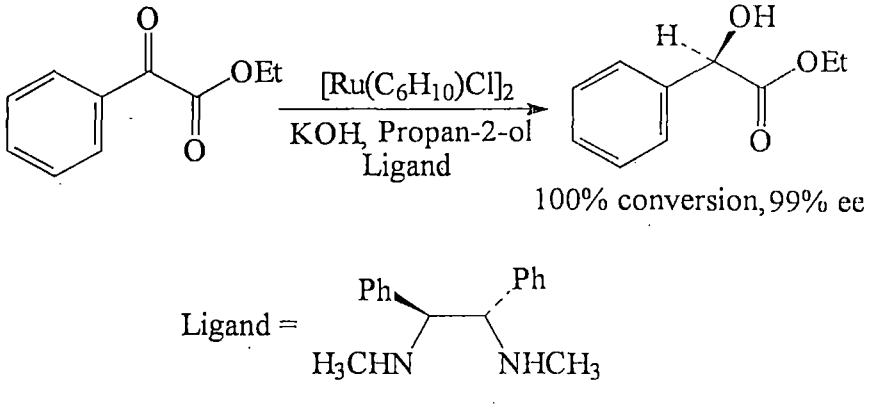
Substituted substrates such as 2-chloroacetophenone are valuable substrates for asymmetric reduction, since their products may be converted to epoxides and other valuable synthetic intermediates. Using a polymer-supported ligand with the formic acid/triethylamine system, this process has been used to give (R)-2-chloro-1-phenethanol of 95.3% ee.[37b]



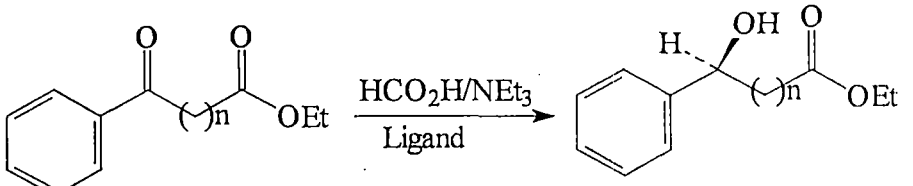
Cossy *et al.*[80] reported a practical asymmetric reduction of 1,3-diketones to the corresponding 1,3-diols with good diastereo- and enantioselectivities using a catalytic amount of RuCl[(*N*-arylsulfonyl)-1,2-diamine(*p*-cymene)] complexes in the presence of Et_3N and HCOOH.



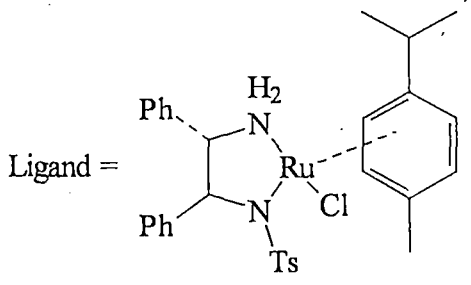
The α-keto ester on reduction gives the product in 99% ee.[81]



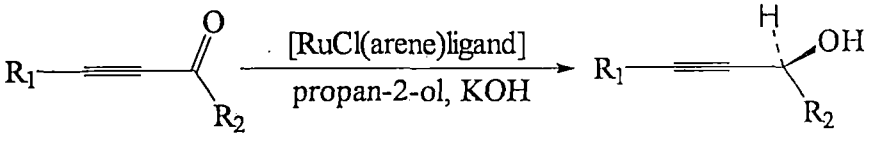
The asymmetric transfer hydrogenation of β-keto esters and higher homologues has also been reported.



n = 3, 99% yield, 95% ee [82]
n = 1, 94% yield, 93% ee [16a]

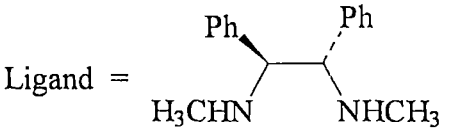


Although the transfer hydrogenation of the carbonyl group of enones appears underdeveloped,[83] the asymmetric reduction of acetylenic ketones provides a valuable method for the synthesis of functionalized target molecules.[20a]

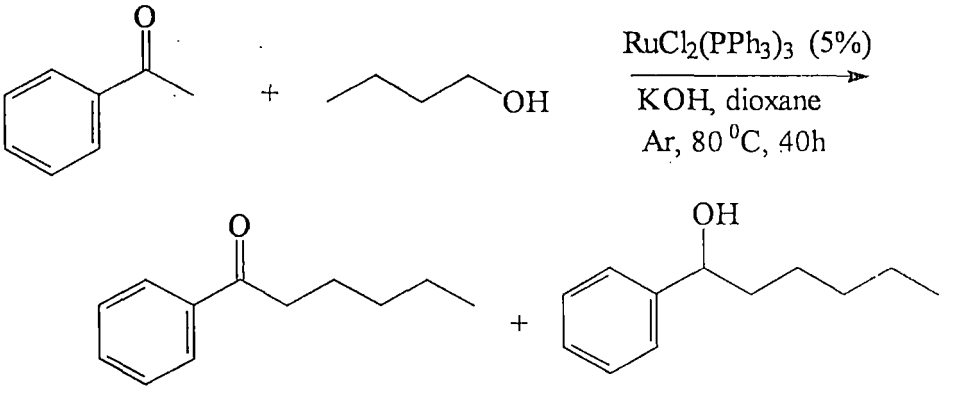


R_1 = Ph, n-Bu, TMS
R_2 = Me, Et, i-Pr, t-Bu, cHex, n-Pent.

yields 90->99%
ee.s typically 97-99%



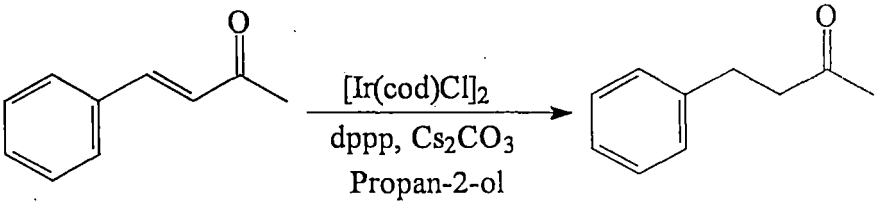
Cho *et al.*[37e] reported an unusual type of ruthenium-catalyzed transfer hydrogenation of ketones with alcohols accompanied by C–C coupling. They observed during transfer hydrogenation of acetophenone with butanol, the reaction gives rise to unconventional alkylated products, 1-phenylhexan-1-ol and 1-phenyl-hexan-1-one, rather than the expected direct transfer hydrogenation product 1-phenyl-ethanol, the yield which remains less than 5%.



Yield 92%
Products ratio (97:3)

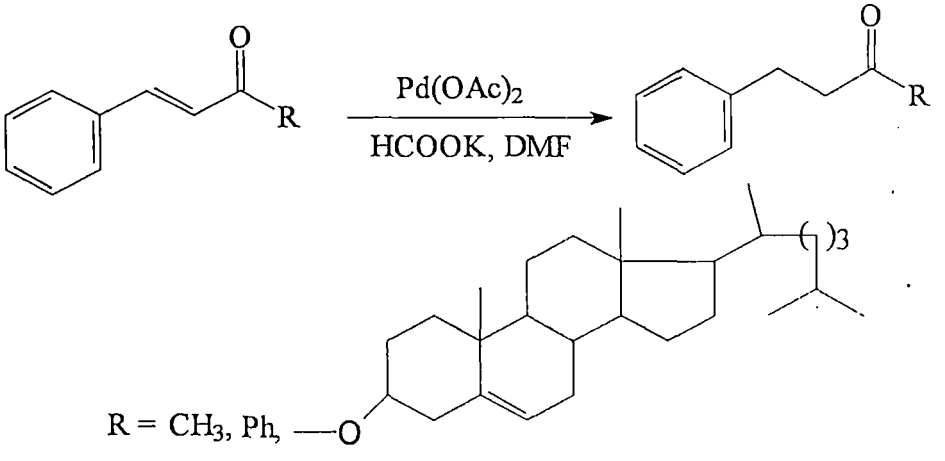
IA.1.7.8 α,β-Unsaturated carbonyl compounds

Chemoselective reduction of α,β-unsaturated carbonyl compounds using an alcohol as hydrogen source has been widely studied, since the reaction is easily carried out under mild conditions using an environmentally benign and safe reagent like propan-2-ol.

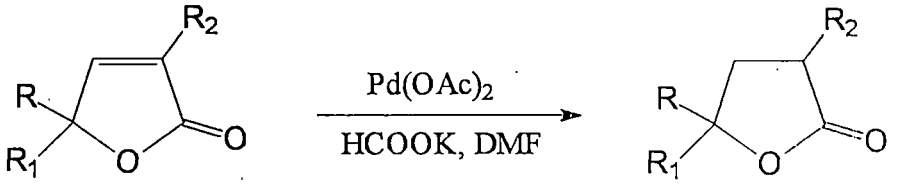


Ref. 36e

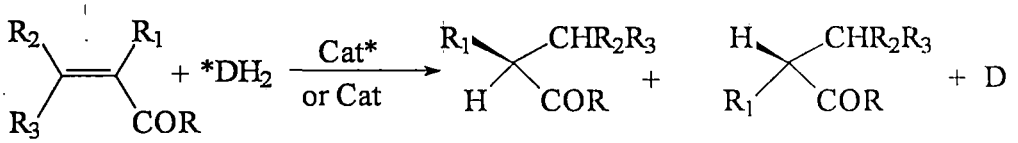
Cacchi *et al.*[84] reported such conversion using HCOOK as hydrogen source and catalytic $Pd(OAc)_2$.



Cacchi *et al.*[84] also reported the CTH reduction of trisubstituted 2-buten-4-olides to γ-butyrolactone ring, a structural unit of many natural substances[85] and a useful synthetic intermediate.[86]



Enantioface discriminating H-transfer reduction of conjugated carbon-carbon double bond has been accomplished by means of optically active H-donors and in the presence of both achiral and chiral ruthenium catalysts.[87]

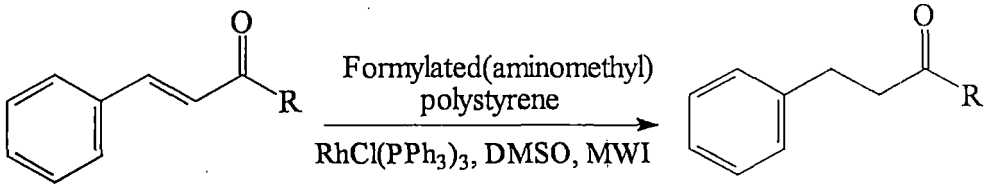


1) $*DH_2$ = optically active glucides
   Cat = $RuCl_2(PPh_3)_3$, Cat* = $RuCl_4(DIOP)_3$
2) R = OH, OCH_3, CH_3, Ph

Optically active glucides were employed with fair success in the reduction of α,β-unsaturated ketones to saturated ones in the presence of $[RuCl_2(PPh_3)_3]$.[87a] The highest ee (34%) was obtained with 3,5,5-trimethyl-2-cyclohexene-1-one. Stereoselectivities up to 8.9% were reported by Ohkubo *et al.*[87b] in the reduction of tiglic acid with the same catalyst and similar optically active H-donors. Higher optical yields were obtained by the same author when the reaction was carried out in the presence of $[Ru_2Cl_4((-)\text{-DIOP})_3]$.[87b]

IA.1.7.9 α,β-Unsaturated acids and esters

Desai and Danks reported the hydrogenation of α,β-unsaturated acids and esters under microwave conditions in excellent yields using a hydrogen donor supported on a polymer and Wilkinson's catalyst.[88]



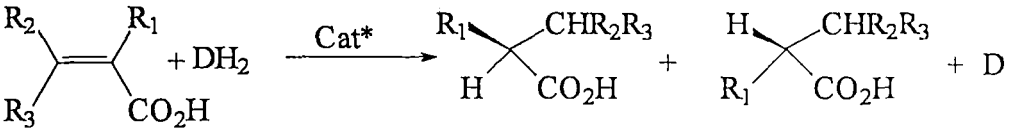
R = OH, OCH_3, OCH_2CH_3

Ram and Spicer[89] reported the reduction of double bond in conjugated carboxylic ester with ammonium formate in combination with 5% Pd on charcoal in acetic acid at 110 ^{0}C. Conjugated nitriles are also reduced to the corresponding saturated compounds by this procedure.

$$R_1CH = CHR_2 \xrightarrow[CH_3CO_2H,\ 100\ ^0C]{Pd/C,\ HCO_2NH_4} R_1CH_2CH_2R_2$$

$R_1 = CH_3$, Ph
$R_2 = CO_2Et$, $CONH_2$, CN

Asymmetric transfer hydrogenation of α,β-unsaturated carboxylic acids has been accomplished for the first time using benzyl alcohol as H-donor and chiral ruthenium phosphine catalysts.[90] The highest ee (16.4%) was obtained with tiglic acid (R_1=R_2=CH_3, R_3=H).[90]

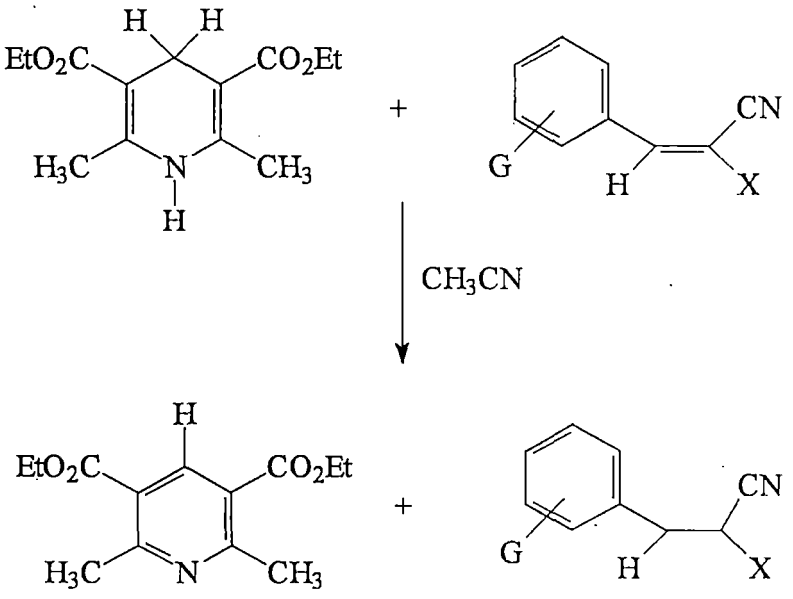


DH_2 = alcohols; $HCOOH/NEt_3$

Much better results have been obtained subsequently by Brunner *et al.*[28b] in the same process using the azeotropic mixture of formic acid-triethylamine (5:2) as the hydrogen source. Preformed catalysts of general formula [Ru(acac-F_6)(η^3-C_3H_5)(P-P)] (P-P= (-)-DIOP, (-)-BPPM, (-)-BINAP, BPPFA) have been employed, the best result always being obtained with the BINAP chelating complex. A very high enantioselectivity has been recorded with this ligand (93.5% ee) in the reduction of itaconic acid (R_2=R_3=H; R_1=CH_2COOH).

IA.1.7.10 α,β-Unsaturated cyano ester

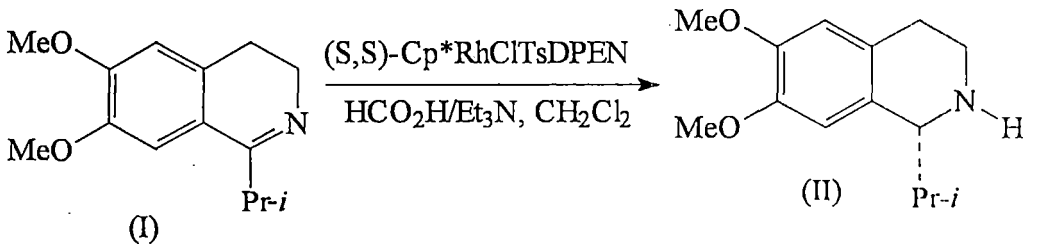
Very recently, Hantzsch 1,4-dihydropyridine (HEH) has been employed for selective reduction of α,β-unsaturated cyanoesters.[91] This procedure, however, involves specific reagent (Hantzsch 1,4-dihydropyridine, HEH) and after the reaction the redox products require separation.



X = CO_2Et, CN
G = *p* - OCH_3, *p* - CH_3, *p* - Cl, *p* - CN

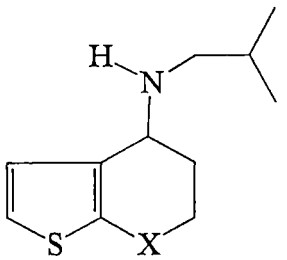
IA.1.7.11 Imines

In contrast to ketones, imines have seldom been reported as viable substrates for enantioselective transfer hydrogenation. For example, dihydroisoquinoline (I) underwent asymmetric hydrogenation to give 96% tetrahydroisoquinoline (R)-(II) (99% ee) when the hydrogenation was conducted at a substrate/catalyst (S/C) molar ratio of 200:1 using a 5:2 formic acid-triethylamine azeotrope as the hydrogen source.[62]

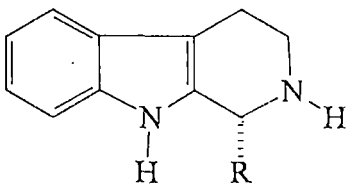


(I) (II)

This highly enantioselective reaction opens a new route for the synthesis of natural and unnatural isoquinoline alkaloids. This reaction was applied to the synthesis of (III), an intermediate for MK-0417 (a carbonic anhydrase inhibitor). Certain chiral indoles, such as (IV), are also obtainable by this method.[44]



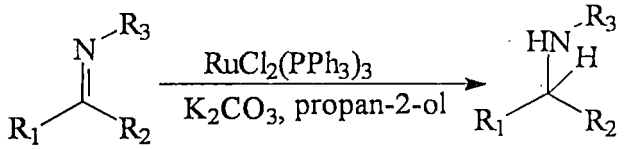
(III) X = S, SO_2



(IV) R = CH_3, C_6H_5

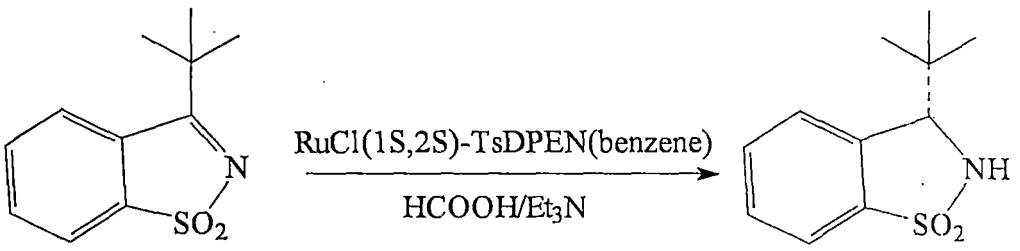
Unlike the reaction in propan-2-ol, imines are more reactive than ketones under such conditions using an aprotic polar solvent such as DMF, DMSO, CH_3CN and CH_2Cl_2.

Backvall had earlier reported the ruthenium-catalyzed (racemic) transfer hydrogenation of imines by propan-2-ol in the presence of an appropriate base such as K_2CO_3.[92]



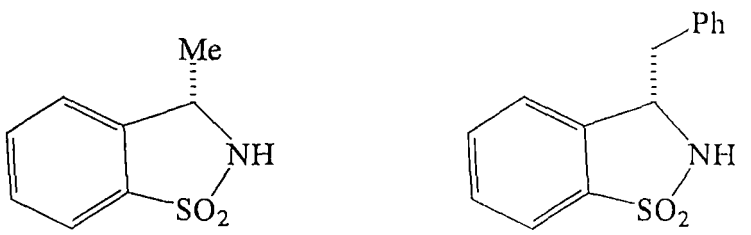
Interestingly, useful chiral sultam auxiliaries (VI), particularly for the 1,3-dipolar cycloaddition of nitrile oxides, could be obtainable quantitatively from imines

(V) catalyzed by the dendritic catalyst in 98.3% ee[41b] or with Ru(II) complex of (S,S)-TsDPEN in 91% ee.[93]



(V) (VI) 91% ee

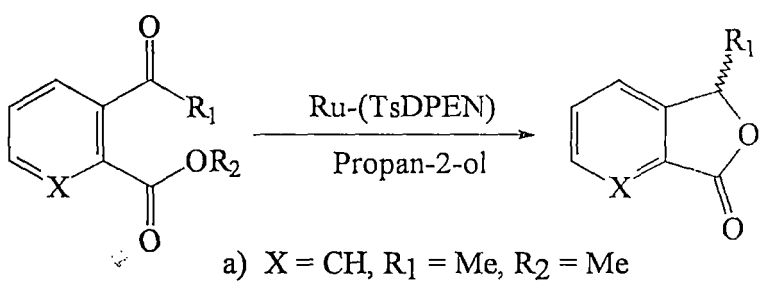
Ahn *et al.*[93] also reported a practical synthesis of the sultam auxiliaries (VII) and (VIII) in high enantiomeric excess which is also applicable to the synthesis of other structural analogs.



(VII) (VIII)

IA.1.7.12 Acylbenzoates

The asymmetric transfer hydrogenation of methyl 2-acylbenzoates and 2-propyl 3-acetylpyridine-2-carboxylate in propan-2-ol, in the absence of a base, with presynthesized Ru-{β-amino alcohol} or Ru-{TsDPEN} true catalysts provides 3-alkylphthalides in high yields and 92-97% ee.[94]

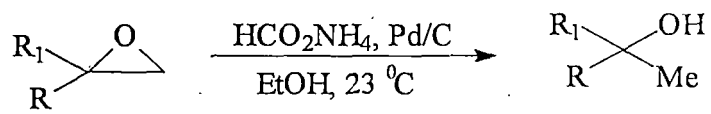


a) X = CH, R_1 = Me, R_2 = Me

b) X = N, R_1 = Me, R_2 = ^{i}Pr

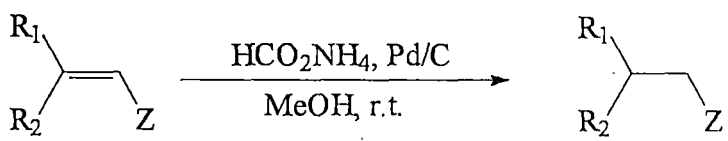
IA.1.7.13 Epoxides

The reduction of unsymmetrically substituted epoxides can produce either a more-substituted or less-substituted alcohol depending on the mode of attack at less-substituted or more-substituted carbon atom respectively. 1,2-Epoxides are regioselectively reduced at the less-substituted end by ammonium formate in the presence of a palladium on charcoal to provide the corresponding more-substituted alcohol in high yield.[95]



IA.1.7.14 α, β-Unsaturated sulfones and phosphonates

Chemoselective reduction of α,β-unsaturated sulfones and phosphonates to the corresponding saturated analogues constitutes a useful process as these compounds are of great importance in the studies of biological systems as well as in synthetic strategy. Ranu *et al.*[96] developed a simple method of this reduction using ammonium formate and palladium-charcoal (10%) in methanol at room temperature in high yields.



a) R_1 = Ph, R_2 = Me, Z = SO_2-*p*-Tol

b) R_1 = Ph, R_2 = Ph, Z = $PO(OEt)_2$

IA.1.7.15 Deprotection of functional groups

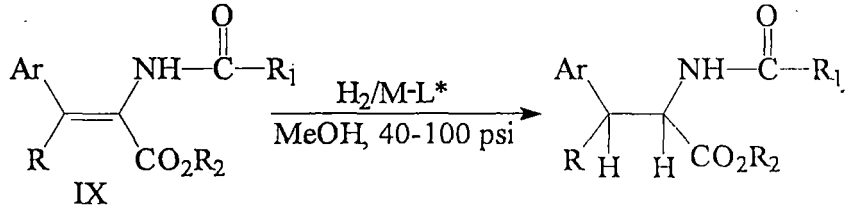
Rapid and selective removal of protecting groups under moderate reaction conditions is often a necessary step in the area of peptide chemistry. Ammonium formate has been used several stages in the synthesis of leucine-enkephalin[97] for reductive cleavage of the benzoyloxycarbonyl group.

Z-Leu-OC_4H_9-*t* $\xrightarrow{Pd/C/HCO_2NH_4}$ H-Leu-OC_4H_9-*t*

Z-Gly-Gly-phe-Leu-OC_4H_9-*t* $\xrightarrow{Pd/C/HCO_2NH_4}$ H-Gly-Gly-phe-Leu-OC_4H_9-*t*

IA.2.1 Present Work: Background, Objectives and Strategy

This laboratory is interested in preparing phenylalanine and phenylalanine-based amino acids by selective reduction of carbon-carbon double bond of suitably substituted and functionalized enamides (IX). Such natural and non-natural amino acids and their derivatives are important in different fields of chemistry. The reduction of functionalized enamides has been achieved using molecular hydrogen (H_2) in presence of homogeneous transition metal catalysts[11a,56b,98] (scheme I).



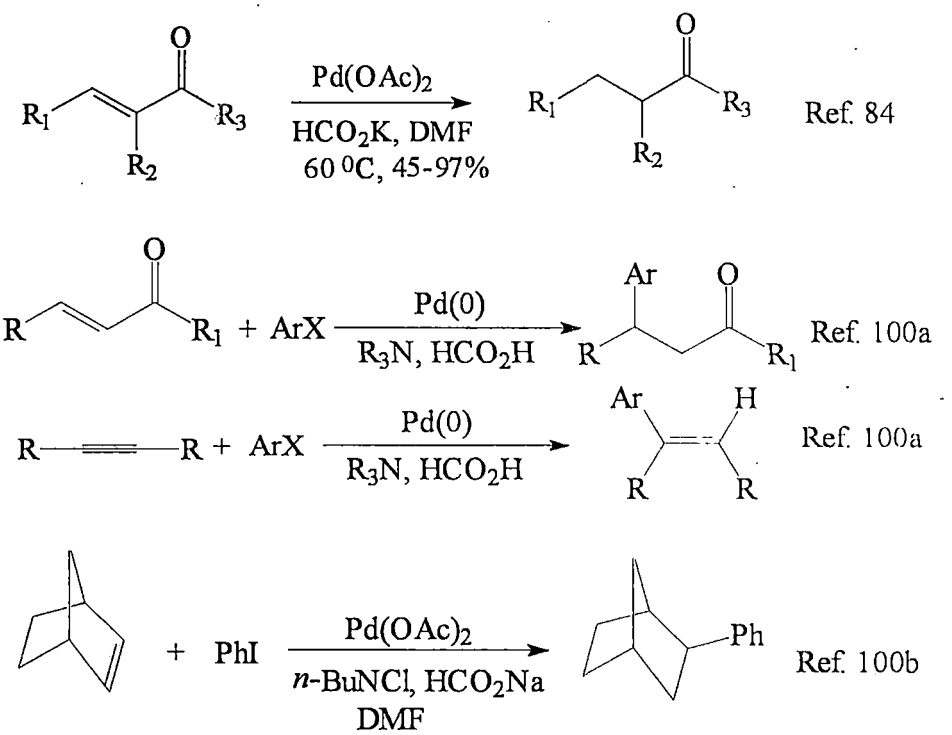
Scheme I

The reduction has also been accomplished in presence of chiral homogeneous catalyst to obtain optically pure alanine-based amino acid derivatives.[99] The reductions are carried out under high pressure (40-100 psi) using high quality of hydrogen gas (99.9% purity). The air in the hydrogenator has to be completely removed either by flushing the system for several minutes with hydrogen, or, by repeatedly pumping the system down to a low pressure and refilling with hydrogen. Some hydrogenation processes are more effective under high pressure (100 psi or more) and thus require more elaborate equipment. Considerable amounts of hydrogen are wasted during flushing of such equipment. Hydrogen and air mixtures are potentially hazardous if flames or sparks are produced in the neighbourhood of hydrogenators.

Our laboratory is unfortunately not equipped with this type of high pressure hydrogenators and its elaborate equipment. The simplification of this operation is therefore necessary providing the total process being safe and ecologically friendly. In the recent years a few laboratories have started to employ an alternative reduction procedure known as catalytic transfer hydrogenation (CTH).[23] As mentioned in the introduction, the reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst is usually known as hydrogen transfer reduction.

Several organic/inorganic molecules have been used as hydrogen donor such as cyclohexene,[3,4] hydrazine,[6,31] formic acid,[15] ammonium formate,[28] cyclohexadiene,[28] phosphinic acid[29] and sodium hyphophosphite.[30] In presence of a metal catalyst, this type of hydrogenation is usually conducted in a flask fitted with a magnetic stirrer and sometimes a reflux condenser.

One of the major limitations of CTH is the problem associated with the removal of dehydrogenated donors. For example, use of unsaturated hydrocarbons as the donor lead to formation of aromatic hydrocarbons as the byproducts, which may cause problems at the time of purification. Some of the hydrogen donors are very prone to hydrogenolyses of carbon-hydrogen or carbon-sulfur bonds.[6] 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[84] and others[100] reported use of different combinations of formic acid and its salts such as, HCOOH/$NaHCO_3$/*n*-Bu_4NCl; HCOOH/*n*-Bu_3N; HCOOK in palladium catalyzed reduction of electron-deficient alkenes and reductive arylation of alkenes (Scheme II). They also observed that differences in the nature of formate salt and of the reaction medium can significantly affect the course of reaction.[100]



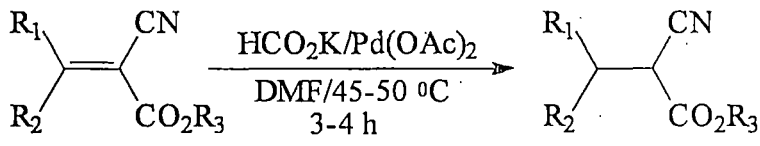
Scheme II

The use of cheap HCOOK and lack of any toxic residues in the waste stream had attracted our interest to explore the reagent for reduction of enamides (IX). However, prior to carrying out reduction of enamides, we initially planned to develop the appropriate conditions at our hands. Therefore we undertook a detailed study on CTH of highly functionalized electron-deficient alkylidenecyano esters (Scheme III) using a combination of potassium formate (as the source of hydrogen) and catalytic palladium acetate.

This section will describe our observations which constitute a method for reduction of highly functionalized alkenes.

IA.2.2 Present Work: Results and Discussion

In the present work, a series of α,β-unsaturated cyano esters (**1-9**) have been prepared from their carbonyl substrates condensed with ethyl cyanoacetate under Knoevenagel condition[101] (for purification and characterization see Experimental Part, page 32). The unsaturated cyano esters were dissolved in DMF and added $Pd(OAc)_2$ (2 mol%), HCOOK (2 equivalent) and stirred at 45-50 ^{0}C for 3-4 h in a screw-cap sealed tube under N_2. After usual workup, the products were purified by column chromatography over silica gel to afford the reduced products (**10-18**) in good to excellent yields (Scheme III, Table 1).



R_3 = Et, Sn(*n*-Bu)$_3$

Scheme III

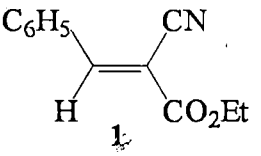
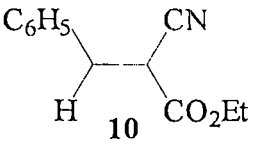
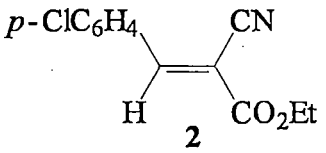
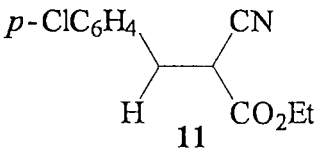
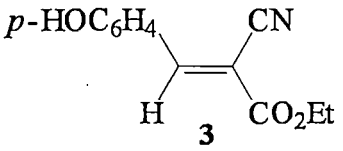
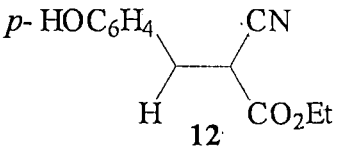
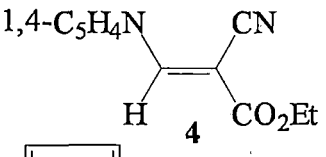
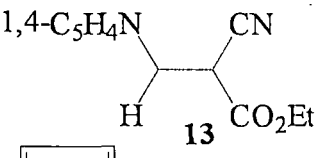
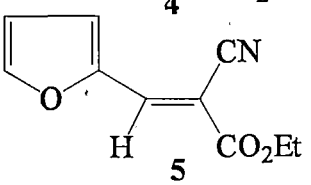
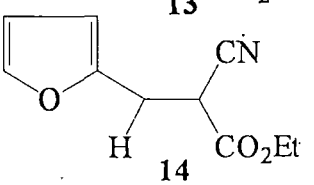
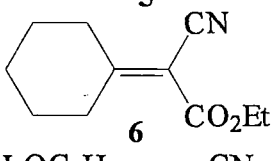
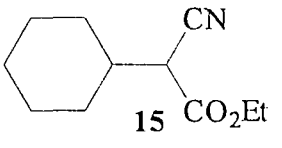
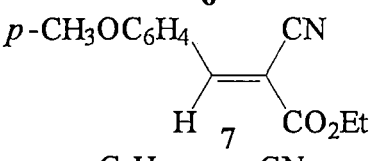
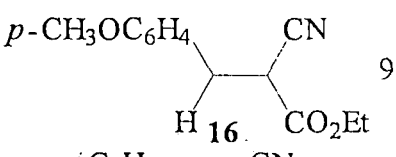
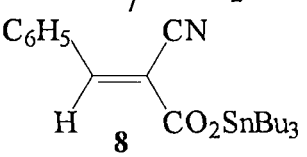
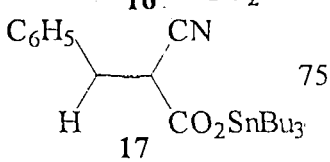
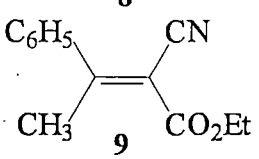
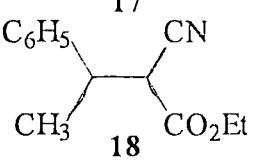
The present study is important with reference to several aspects. Some of the salient features of the present work are delineated below.

- Reduction of α,β-unsaturated cyano esters in the presence of Pd/C and *p*-menthene (as hydrogen donor) led to reduction of not only the C-C double bond, but also the nitrile function to a methyl group.[3,89] Moreover, reduction of nitrile using a combination of Pd/C and formic acid seemed to be very variable in many other examples.[6] The present method, however, did not affect any changes of the nitrile function.
- The dehalogenation of halo-aromatics is known under transfer reduction using heterogeneous catalyst,[43,45] the present method did not proceed with cleavage of carbon-halogen bond (entry 1b).
- The stannyl ester (entry 1h), prepared from its ethyl ester by transesterification with *bis*-tri-*n*-butyltin oxide,[102] also survived demetallation under the reaction condition.[103]
- To observe any effect of ligand participation in the catalytic process, the reduction was carried out in the presence of various ligands, such as PPh_3, P(*o*-tolyl)$_3$ and TMEDA (entry 1i). In all the experiments, a smooth conversion to the reduced product with excellent yield was obtained. Studies directed towards any participation of ligands and their effects in terms of stereoselectivity of the reduced products are under active pursuit.
- Choice of solvent is an important factor governing the activity of soluble catalyst in transfer reduction.[6] As most soluble catalysts are often coordinated to solvent, DMF was found to be superior in comparison to non-polar solvents like toluene or carbon tetrachloride.

Between the two discrete mechanisms proposed for the CTH (discussed in the Introduction Part, page 7), "the hydridic route" seems to be involved in homogeneous

catalytic hydrogenation. Early studies for reduction of alkenes conjugated with strong electron-withdrawing groups such as, esters, nitriles, sulfonates esters, or nitro groups has been accomplished with borohydrides or cyanoborohydrides, acetoxyborohydrides or lithium aluminium hydride. The hydrides are reactive, expensive and sometimes toxic in addition to causing further reduction of substituted functional groups. In the recent years the application of Hantzsch 1,4-dihydropyridine (HEH) as a reducing agent in reduction of electron-deficient alkenes has been reported.[91] The latter procedure, however, involves specific reagent and after the reaction the redox product requires separation. The present study thus constitutes a useful condition for selective reduction of C–C double bond of α,β-unsaturated cyano esters using HCOOK/$Pd(OAc)_2$ as simple and inexpensive reductant. The reaction possibly involves 'hydride transfer' *in situ* at the β-carbon and proceeds without any concomitant reduction of cyano, ester, or halogen groups. The ability of this reductant to perform conjugate reduction on functionalized alkylidenecyanoacetate in a controlled fashion is noteworthy. The homogeneous catalytic condition offers further use of chiral ligands to promote asymmetric induction. Future studies will be attempted in this direction.

Table 1. Reduction of α,β-unsaturated cyano esters by using HCOOK and catalytic $Pd(OAc)_2$.

Entry	Olefin	Temp./time	Product	%Yield [a]
1a.	 **1**	45 °C/ 3h	 **10**	92
1b.	 **2**	45 °C/ 4h	 **11**	96
1c.	 **3**	50 °C/ 4h	 **12**	95
1d.	 **4**	50 °C/ 3h	 **13**	87
1e.	 **5**	45 °C/ 4h	 **14**	79
1f.	 **6**	50 °C/ 4h	 **15**	76
1g.	 **7**	45 °C/ 4h	 **16**	95
1h.	 **8**	50 °C/ 3h	 **17**	75
1i. [b]	 **9**	50 °C/ 3h	 **18**	88

[a] Yields refer to single runs and are pure, isolated products: all compounds were fully characterized by IR, UV, and ^{1}H- and ^{13}C-NMR spectra and given in the Experimental Section.

[b] The reaction was also carried out in presence of PPh_3, P(*o*-tolyl)$_3$, and TMEDA.

IA.3 Experimental

All melting points and boiling points are uncorrected. M.P.s were determined in open capillary in silicone oil bath. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} coated aluminium sheets (Merck, Germany) and spots were detected by UV-fluorescence and/or using iodine vapour. Silica gel G 60 (60-120 mesh) was used for column chromatography. All evaporations were conducted under reduced pressure with bath temperature below 50 ^{0}C. IR spectra were recorded on Shimadzu FTIR 8300 spectrometer. For recording UV spectra, a Shimadzu UV-240 spectrometer was used. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker spectrometer (operating at 300 MHz and 75 MHz respectively) using $CDCl_3$ as solvent. Tetramethylsilane (TMS) was used as an internal standard and chemical shifts are expressed in ppm (δ units). The peaks are characterized by s (singlet), d (doublet), t (triplet), m (multiplet). Solvents and commercial reagents were purified and dried by conventional methods before use. Petroleum ether refers to the fraction of b.p. 60-80 ^{0}C. Ether refers to diethyl ether.

IA.3.1 Preparation of α,β-unsaturated cyanoesters

A series of α,β-unsaturated cyanoesters have been prepared from their carbonyl substrates by condensing with ethyl cyanoacetate under Knoevenagel condition.[101]

General procedure

To a solution of ethyl cyanoacetate (50 mmol), aldehyde or ketone (55-60 mmol) in dry benzene (30 mL) was added ammonium acetate (10 mmol) and glacial acetic acid (40 mmol). The reaction mixture was then heated under reflux for 10-12 hours using Dean-Stark water separator. After cooling, the reaction mixture was successively washed with 10% sodium hydrogen carbonate, brine and water, and dried over anhydrous sodium sulphate. The solvent was then evaporated to dryness on a water bath under reduced pressure. The obtained solid was recrystallized from ether-light petroleum or oily residue was distilled under reduced pressure.

Ethyl 2-cyano-3-phenylacrylate (1)

Colourless crystals, m.p. 48-49 ^{0}C [Lit.[104] 49 ^{0}C].

UV (MeOH): λ_{max} 305 nm.

IR (Nujol): ν_{max} 3020, 2400, 2226, 1727, 1608, 1268, 1215, 1104, 754, 686 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.25 (s, 1H), 7.98 (dd, 2H, J = 7.32; 0.96 Hz), 7.56-7.48 (m, 3H), 4.39 (q, 2H, J = 7.12 Hz), 1.40 (t, 3H, J = 7.12 Hz).

Ethyl 2-cyano-3-(4-chlorophenyl)acrylate (2)

Colourless crystals, m.p. 89-90 ^{0}C [Lit.[104] 90 ^{0}C].

UV(MeOH): λ_{max} 311.6 nm.

IR (Nujol): ν_{max} 3019, 2400, 2226, 1726, 1609, 1591, 1492, 1269, 1214, 754, 670 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.20 (s, 1H), 7.93 (d, 2H, J = 8.6 Hz), 7.48 (d, 2H, J = 8.6 Hz), 4.39 (q, 2H, J = 7.14 Hz), 1.40 (t, 3H, J = 7.14 Hz).

Ethyl 2-cyano-3-(4-hydroxyphenyl)acrylate (3)

Colourless crystals, m.p. 165-166 ^{0}C.

UV (MeOH): λ_{max} 347.0 nm.

IR (Nujol): ν_{max} 3400, 2224, 1720, 1608 cm^{-1}.

Ethyl 2-cyano-3-(pyridin-4-yl)acrylate (4)

Pale brown crystals, m.p. 93-94 ^{0}C.

UV (MeOH): λ_{max} 271.6 nm.

IR (Nujol): ν_{max} 2222, 1715, 1605 cm^{-1}.

Ethyl 2-cyano-3-(furan-2-yl)acrylate (5)

Yellow crystals, m.p. 91-92 ^{0}C [Lit.[104] 93 ^{0}C].

UV (MeOH): λ_{max} 335.6 nm.

IR (Nujol): ν_{max} 2410, 2222, 2090, 1739, 1635, 779 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.02 (s, 1H), 7.75 (d, 1H, J = 1.6 Hz), 7.39 (d, 1H, J = 4.0 Hz), 6.67 (dd, 1H, J = 4.0; 1.6 Hz), 4.39 (q, 2H, J = 7.14 Hz), 1.38 (t, 3H, J = 7.14 Hz).

Ethyl 2-cyano-2-cyclohexylideneacetate (6)

Liquid, b.p. 117-121 ^{0}C/2 mm Hg.

IR (neat): ν_{max} 2220, 1710, 1598, 907, 732 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.27 (q, 2H, J = 7.14 Hz), 2.98 (t, 2H, J = 6.0 Hz), 2.66 (t, 2H, J = 6.2 Hz), 1.82-1.79 (m, 2H), 1.75-1.70 (m, 2H), 1.69-1.64 (m, 2H), 1.36 (t, 3H, J = 7.14 Hz).

Ethyl 2-cyano-3-(4-methoxyphenyl)acrylate (7)

Yellow crystals, m.p. 77-78 ^{0}C [Lit.[105] 79-80 ^{0}C].

UV (MeOH): λ_{max} 346.2 nm.

IR (Nujol): ν_{max} 2361, 1728, 1659, 1528, 757, 669 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.85 (s, 1H), 7.7 (d, 2H, J = 6.6 Hz), 6.7 (d, 2H, J = 6.6 Hz), 4.1 (q, 2H, J = 5.4 Hz), 3.6 (s, 3H), 1.1 (t, 3H, J = 5.4 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 164.1, 162.9, 154.6, 134.0, 124.7, 116.6, 115.1, 99.7, 62.7, 56.0, 14.6.

Tri-*n*-butylstannyl 2-cyano-3-phenylacrylate (8)

The title compound was prepared by transesterification method[102] from ethyl 2-cyano-3-phenylacrylate (**1**) and *bis*-tri-*n*-butyltin oxide in carbon tetrachloride using a Dean-Stark water separator as gummy syrup in 72% yield.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.15 (s, 1H), 7.95 (m, 2H), 7.47 (m, 3H), 1.70-1.65 (m, 6H), 1.39-1.31 (m, 12H), 0.94 (t, 9H, J = 7.2 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.6, 153.8, 133.6, 132.5, 131.0, 129.4, 116.7, 105.9, 27.5, 26.9, 17.0, 13.6.

Ethyl 2-cyano-3-phenyl-2-butenoate (9)

Liquid, b.p. 135-137 ^{0}C/2 mm Hg [Lit.[105] 136-138 ^{0}C/2 mm Hg].

UV (MeOH): λ_{max} 279.0 nm.

IR (neat): ν_{max} 2088, 1743, 1646, 1215, 756, 669 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.57-7.40 (m, 5H), 4.37 (q, 2H, J = 7.14 Hz), 2.59 (s, 3H), 1.39 (t, 3H, J = 7.14 Hz).

IA.3.2 Catalytic transfer hydrogenation of α,β-unsaturated cyanoesters

A representative procedure

Ethyl 2-cyano-3-(furan-2-yl)propionate (14)

To a solution of ethyl 2-cyano-3-furan-2-yl-acrylate (**5**) (0.191g, 1 mmol) in DMF (3 mL) was added $Pd(OAc)_2$ (5mg, 2 mol%), HCOOK (0.168g, 2 mmol) and stirred the reaction mixture in a sealed tube (Screw-cap) under N_2 at 45 ^{0}C for 4 h. The mixture was cooled, diluted with water and extracted with ether (3×15 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The oily residue was purified by column chromatography over silica gel and elution with ethyl acetate-light petroleum (1:9) afforded the desired product (**14**) as colourless oil in 79% (0.153g) yield.

UV (MeOH): λ_{max} 222.0 nm.

IR (neat): ν_{max} 2244, 1747 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.34 (s, 1H), 6.30 (s, 1H), 6.23 (s, 1H), 4.26 (q, 2H, J = 7.1 Hz), 3.79 (m, 1H), 3.28 (m, 2H), 1.31 (t, 3H, J = 7.1 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.4, 149.3, 142.8, 115.9, 110.9, 108.7, 63.3, 37.3, 36.1, 14.3.

Anal. Calcd. for $C_{10}H_{11}NO_3$ (193.20): C, 62.17; H, 5.74.

Found: C, 62.32; H, 5.96.

Similarly compounds (**10**), (**11**), (**12**), (**13**), (**15**), (**16**), (**17**) and (**18**) were prepared at corresponding temperature and time (as mentioned).

Ethyl 2-cyano-3-phenylpropionate (**10**)

Temp: 45 ^{0}C, Time: 3h, Column: EtOAc-light petroleum (1:19).

Yield: 92% (0.185g), Liquid,

UV (MeOH): λ_{max} 258.0 nm.

IR (neat): ν_{max} 2989, 2349, 2256, 1746, 1262, 1208, 701 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.36-7.25 (m, 5H), 4.21 (q, 2H, J = 9 Hz), 3.72 (dd, 1H, J = 9; 6 Hz), 3.29-3.13 (m, 2H), 1.24 (t, 3H, J = 9 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.5, 135.3, 129.1, 128.8, 127.8, 116.2, 62.9, 39.6, 35.7, 13.9.

Ethyl 2-cyano-3-(4-chlorophenyl)propionate (11)

Temp: 45 ^{0}C, Time: 4h, Column: EtOAc-light petroleum (1:9).

Yield: 96% (0.228g), Liquid.

UV (MeOH): λ_{max} 225.0 nm.

IR (neat): ν_{max} 2372, 2244, 1745, 1674, 1495 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.30 (d, 2H, J = 8.3 Hz), 7.20 (d, 2H, J = 8.3 Hz), 4.22 (q, 2H, J = 7.1 Hz), 3.68 (dd, 1H, J = 8.0; 5.9 Hz), 3.23-3.15 (m, 2H), 1.27 (t, 3H, J = 7.1 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.0, 133.7, 130.4, 128.9, 127.7, 115.7, 62.8, 39.3, 34.9, 13.9.

Ethyl 2-cyano-3-(4-hydroxyphenyl)propionate (12)

Temp: 50 ^{0}C, Time: 4h, Column: EtOAc-light petroleum (3:7).

Yield: 95% (0.208g), Liquid.

UV (MeOH): λ_{max} 242.0 nm.

IR (neat): ν_{max} 3338, 2244, 1742 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.10 (d, 2H, J = 7.9 Hz), 6.79 (d, 2H, J = 7.9 Hz), 4.25 (q, 2H, J = 7.2 Hz), 3.73 (dd, 1H, J = 8.1; 5.8 Hz), 3.08-3.22 (m, 2H), 1.26 (t, 3H, J = 7.2 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.7, 155.6, 133.9, 130.2, 126.6, 116.3, 63.0, 40.0, 34.8, 13.8.

Ethyl 2-cyano-3-(pyridin-4-yl)propionate (13)

Temp: 50 ^{0}C, Time: 3h, Column: EtOAc-light petroleum (2:3).

Yield: 87% (0.178g), Liquid.

UV (MeOH): λ_{max} 257.4 nm.

IR (neat): ν_{max} 2226, 1720 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.6 (d, J = 4.5 Hz, 2H), 7.23 (d, J = 4.5 Hz, 2H), 4.26 (q, 2H, J = 7.1 Hz), 3.77 (dd, 1H, J = 8.1; 5.9 Hz), 3.27-3.21 (m, 2H), 1.29 (t, 3H, J = 7.1 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 158.3, 150.2, 129.4, 124.1, 116.2, 63.4, 38.3, 34.7, 13.9.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$ (204.23): C, 64.69; H, 5.92.
Found: C, 64.34; H, 5.83.

Ethyl 2-cyano-2-cyclohexylacetate (15)

Temp: 50 ^{0}C, Time: 4h, Column: EtOAc-light petroleum (1:19).

Yield: 76% (0.148g), Liquid.

IR (neat): ν_{max} 2932, 2360, 2232, 1743, 1451 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.27 (q, 2H, J = 7.2 Hz), 3.4 (d, 1H, J = 5.7 Hz), 2.07-2.04 (m, 1H), 1.78-1.65 (m, 6H), 1.35 (t, 3H, J = 7.2 Hz), 1.29-1.20 (m, 4H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.8, 115.7, 62.5, 44.5, 38.8, 31.0, 29.3, 25.5, 14.5.

Ethyl 2-cyano-3-(4-methoxyphenyl)propionate (16)

Temp: 45 ^{0}C, Time: 4h, Column: EtOAc-light petroleum (1:9).

Yield: 95% (0.222g), Liquid.

UV (MeOH): λ_{max} 228.6 nm.

IR (neat): ν_{max} 2226, 1720 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.18 (d, 2H, J = 6.7 Hz), 6.86 (d, 2H, J = 6.7 Hz), 4.2 (q, 2H, J = 7.14 Hz), 3.78 (s, 3H), 3.68 (dd, 1H, J = 8.3; 6.06 Hz), 3.24-3.09 (m, 2H), 1.26 (t, 3H, J = 7.14 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.5, 159.0, 130.1, 127.2, 116.2, 114.1, 62.7, 55.1, 39.8, 34.9, 13.8.

Tri-*n*-butylstannyl 2-cyano-3-phenylpropionate (17)

Temp: 50 ^{0}C, Time: 3h, Column: EtOAc-light petroleum (1:4).

Yield: 75% (0.912g), highly viscous liquid.

UV (MeOH): λ_{max} 257.8 nm.

IR (neat): ν_{max} 2230, 1730 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.50-7.12 (m, 5H), 3.71-3.66 (m, 1H), 3.1-2.91 (m, 2H), 1.74-1.58 (m, 6H), 1.41-1.16 (m, 12H), 0.72 (t, 9H, J = 7.1Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.0, 135.7, 129.4, 128.4, 127.3, 116.3, 62.4, 47.9, 42.3, 27.4, 16.9, 13.3.

Ethyl 2-cyano-3-phenylbutanoate (18)

Temp: 50 ^{0}C, Time: 3h, Column: EtOAc-light petroleum (1:19).

Yield: 88 % (0.191g), Liquid.

UV (MeOH): λ_{max} 242.4 nm.

IR (neat): ν_{max} 2243, 1747, 1595, 1446, 1250 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.43-7.22 (m, 5H), 4.12 (q, 2H, J = 7.1 Hz), 3.70-3.61 (m, 1H), 3.55-3.48 (m, 1H), 1.50 (d, 3H, J = 7.0 Hz), 1.17 (t, 3H, J = 7.1 Hz).

IA.4 References

1. Augustine, R.L. (Ed.). In *Reduction*; Edward Arnold/Marcel Dekker, 1968.
2. (a) Augustine, R.L. In *Catalytic Hydrogenation*; Edward Arnold/Marcel Dekker, 1965. (b) Rylander, P.N. In *Hydrogenation Methods*; Academic Press, 1985. (c) Birch, A.J.; Williams, D.H. *Org. React.* **1976**, *24*, 1.
3. Brieger, G.; Nestrick, T.J. *Chem. Rev.* **1974**, *74*, 657.
4. Braude, E.A.; Linstead, R.P. *J. Chem. Soc.* **1954**, 3544.
5. Braude, E.A.; Linstead, R.P.; Jackman, L.M.; Mitchell, P.W.D.; Wooldridge, K.R.H. *Nature* (London) **1952**, *169*, 100.
6. Johnstone, R.A.W.; Wilby, A.H.; Entwistle, I.D. *Chem. Rev.* **1985**, *85*, 129.
7. Arterburn, J.B.; Pannala, M.; Gonzalez, A.M.; Chamberlin, R.M. *Tetrahedron Lett.* **2000**, *41*, 7847.
8. Ram, S.; Ehrenkaufer, R.E. *Tetrahedron Lett.* **1984**, *25*, 3415.
9. Reddy, P.G.; Kumar, G.D.K.; Baskaran, S. *Tetrahedron Lett.* **2000**, *41*, 9149.
10. Pratap, T.V.; Baskaran, S. *Tetrahedron Lett.* **2001**, *42*, 1983.
11. (a) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; John Wiley, NY, 1994. (b) Corey, E.J.; Helal, C.J. *Angew. Chem., Int. Ed. Eng.* **1998**, *37*, 1986.
12. Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475.
13. Noyori, R.; Takaya, H. *Acta Chem. Scand.* **1996**, *50*, 380.
14. (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051. (b) Palmer, M.J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (c) Nishibayashi, Y.; Takei, S.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291.
15. (a) Chowdhury, R.L.; Backvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1991**, 1063. (b) Fache, F.; Schilz, E.; Tommasino, M.L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159. (c) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.
16. (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (b) Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817. (c) Alonso, D.A.; Guijarro, D.; Pinho, P.; Temme, O.; Andersson, P.G. *J. Org. Chem.* **1998**, *63*, 2749. (d) Alonso, D.A.; Nordin, S.J.M.; Roth, P.; Tarnai, T.; Andersson, P.G. *J. Org. Chem.* **2000**, *65*, 3116. (e) Yamada, I.; Noyori, R. *Org. Lett.* **2000**, *2*, 3425.

17. Evans, D.A.; Nelson, S.G.; Gagne, M.R.; Muci, A.R. *J. Am. Chem. Soc.* **1993**, *115*, 9800.

18. (a) Gamez, P.; Dunjic, B.; Lemaire, M. *J. Am. Chem. Soc.* **1998**, *120*, 1441. (b) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **2000**, *65*, 2186.

19. (a) Bianchini, C.; Farnetti, E.; Glendenning, L.; Graziani, M.; Nardin, G.; Peruzzini, M.; Rocchinin, E.; Zanobini, F. *Organometallics* **1995**, *14*, 1489. (b) Inoue, S.; Nomura, K.; Hashiguchi, S.; Noyori, R.; Izawa, Y. *Chem. Lett.* **1997**, 957.

20. (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. (b) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119.

21. (a) Muller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. (b) Krasik, P.; Alper, H. *Tetrahedron* **1994**, *50*, 4347.

22. Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226.

23. Banik, B.K.; Barakat, K.J.; Wagle, D.R.; Manhas, M.S.; Bose, A.K. *J. Org. Chem.* **1999**, *64*, 5746.

24. Martin, S.D.; Zassinovich, G. Mestroni, G. *Inorg. Chim. Acta* **1990**, *114*, 9.

25. Adkins, H.; Elofson, R.M.; Rossow, A.G.; Robinson, C.C. *J. Am. Chem. Soc.* **1949**, *71*, 3622.

26. Bajwa, J.S. *Tetrahedron Lett.* **1992**, *33*, 2299.

27. (a) Ram, S.; Ehrenkaufer, R.E. *Synthesis* **1988**, 91. (b) Ranu, B.C.; Sarkar, A.; Guchhait, S.K.; Ghosh, K. *J. Indian Chem. Soc.* **1998**, *75*, 690.

28. (a) Cortese, N.A.; Heck, R.F. *J. Org. Chem.* **1978**, *43*, 3985. (b) Brown, J.M.; Brunner, H.; Leitner, W.; Rose, M. *Tetrahedron: Asymmetry* **1991**, *2*, 331.

29. Entwistle, I.D.; Gilkerson, T.; Johnstone, R.A.W.; Telford, R.P. *Tetrahedron* **1978**, *34*, 313.

30. (a) Sala, R.; Doria, G.; Passarotti, C. *Tetrahedron Lett.* **1984**, *25*, 4565. (b) Marques, C.A.; Selva, M.; Tundo, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 529.

31. Anwer, M.K.; Khan, S.A.; Sivanandaiah, K.M. *Synthesis* **1978**, 751.

32. Keinan, E.; Gleize, P.A. *Tetrahedron Lett.* **1982**, *23*, 477.

33. Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314.

34. Tour, J.M.; Cooper, J.P.; Pendalwar, S.L. *J. Org. Chem.* **1990**, *55*, 3452.

35. Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599.

36. (a) de Bellefon, C.; Tanchoux, N. *Tetrahedron: Asymmetry* **1998**, *9*, 3677. (b) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199. (c) Polborn, K.; Severin, K. *Eur. J. Inorg. Chem.* **2000**, 1687. (d) Higashino, T.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2000**, *2*, 4193. (e) Sakaguchi, S.; Yamaga, T.; Ishii, Y. *J. Org. Chem.* **2001**, *66*, 4710.

37. (a) Genet, J.-P.; Ratovelomanana-Vidal, V.; Pinel, C. *Synlett* **1993**, 478. (b) Bayston, D.J.; Treavers, C.B.; Polywka, M.E.C. *Tetrahedron: Asymmetry* **1998**, *9*, 2015. (c) Yamada, I.; Noyori, R. *Org. Lett.* **2000**, *2*, 3425. (d) Bied, C.; Moreau, J.J.E.; Man, M.W.C. *Tetrahedron: Asymmetry* **2001**, *12*, 329. (e) Cho, C.S.; Kim, B.T.; Kim, T.-J.; Shim, S.C. *J. Org. Chem.* **2001**, *66*, 9020.

38. Knauer, B.; Krohn, K. *Liebigs Ann.* **1995**, 677.

39. (a) Ropartz, L.; Morris, R.E.; Foster, D.F.; Cole-Hemilton, D.J. *Chem. Commun.* **2001**, 361. (b) Davis, A.V.; Driffield, M.; Smith, D.K. *Org. Lett.* **2001**, *3*, 3075.

40. (a) Kollner, C.; Pugin, B.; Togni, A. *J. Am. Chem. Soc.* **1998**, *120*, 10274. (b) Schmitzer, A.; Franceschi, S.; Perez, E.; Rico-Lattes, I.; Lattes, A.; Erard, M.; Vidal, C. *J. Am. Chem. Soc.* **2001**, *123*, 5956.

41. (a) Chen, Y.-C.; Wu, T.-F.; Deng, J.-G.; Liu, H.; Jiang, Y.-Z.; Choi, M.C.K.; Chan, A.S.C. *Chem. Commun.* **2001**, 1488. (b) Chen, Y.-C.; Wu, T.-F.; Deng, J.-G.; Liu, H.; Cui, X.; Zhu, J.; Jiang, Y.-Z.; Choi, M.C.K.; Chan, A.S.C. *J. Org. Chem.* **2002**, *67*, 5301.

42. Brunner, H.; Kunz, M. *Chem. Ber.* **1986**, *119*, 2868.

43. Sasson, Y.; Blum, J. *J. Am. Chem. Soc.* **1975**, *40*, 1887.

44. Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931.

45. Entwistle, I.D.; Jackson, A.E.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 443.

46. (a) Moulton, W.N.; van Att, R.E.; Ruch, R.R. *J. Org. Chem.* **1960**, *26*, 290. (b) Shiner, V.J.; Whittaker, D. *J. Am. Chem. Soc.* **1969**, *91*, 394.

47. Morton, D.; Cole-Hamilton, D.J.; Utuk, I.D.; Paneque-Sosa, M.; Lopez-Poveda, M. *J. Chem. Soc., Dalton Trans.* **1989**, 489.

48. Lin, G.Q.; Li, Y.M.; Chan, A.S.C. In *Principles and Applications of Asymmetric Synthesis*; John Wiley & Sons, NY, 2001.

49. (a) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062. (b) Pai, C.C.; Lin, C.W.; Chen, C.C.; Chan, A.S.C. *J. Am. Chem. Soc.* **2000**, *122*, 11513. (c) Li, W.; Xhang, X. *J. Org. Chem.* **2000**, *65*, 5871. (d) Seyden-Penne, J. In *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons, New York, 1995.

50. Krause, H.W.; Bhatnagar, A.K. *J. Organomet. Chem.* **1986**, *302*, 265.

51. (a) RajanBabu, T.V.; Ayers, T.A.; Halliday, G.A.; You, K.K.; Calabrese, J.C. *J. Org. Chem.* **1997**, *62*, 6012. (b) Chen, X.X.; Li, X.S.; Tong, S.K.; Choi, M.C.K.; Chan, A.S.C. *Tetrahedron Lett.* **1999**, *40*, 957.

52. (a) Reetz, M.T.; Neugebauer, T. *Angew. Chem., Int. Ed. Eng.* **1999**, *38*, 179. (b) Reetz, M.T.; Mehler, G. *Angew. Chem., Int. Ed. Eng.* **2000**, *39*, 3889.

53. Deerenberg, S.; Pamies, O.; Dieguez, M.; Claver, C.; Kamer, P.C.J.; van Leeuwen, P.W.N.M. *J. Org. Chem.* **2001**, *66*, 7620.

54. Reetz, M.T.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333.

55. van den Berg, M.; Minnaard, A.J.; Schudde, E.P.; van Esch, J.; de Veris, A.H.M.; de Veris, J.G.; Feringa, B.L. *J. Am. Chem. Soc.* **2000**, *122*, 11539.

56. (a) Fiorini, M.; Giongo, G.M. *J. Mol. Catal.* **1980**, *7*, 411. (b) Zhang, F.Y.; Pai, C.C.; Chan, A.S.C. *J. Am. Chem. Soc.* **1998**, *120*, 5808.

57. Schmid, R.; Broger, E.A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R.K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131.

58. Trabesinger, G.; Albinati, A.; Feiken, N.; Kunz, R.W.; Pregosin, P.S.; Tschoerner, M. *J. Am. Chem. Soc.* **1997**, *119*, 6315.

59. RajanBabu, T.V.; Radetich, B.; You, K.K.; Ayers, T.A.; Casalnuovo, A.L.; *J. Org. Chem.* **1999**, *64*, 3429.

60. (a) Miyano, S.; Nawa, M.; Hashimoto, H. *Chem. Lett.* **1980**, 729. (b) Miyano, S.; Nawa, M.; Mori, A.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2171.

61. Zhang, F.Y.; Kwok, W.H.; Chan, A.S.C. *Tetrahedron: Asymmetry* **2001**, *12*, 2337.

62. Mao J.; Baker, D.C. *Org. Lett.* **1999**, *1*, 841.

63. Olah, G.A.; Prakash, G.K.S. *Synthesis* **1978**, 397.

64. Parshal, G.W. In *Homogeneous Catalysis: The Application and Chemistry of catalysis by soluble Transition Metal Complexes*; Wiley-Interscience: N.Y. 1980.

65. Chiu, W.H.; Wolff, M.E. *Steroids* **1979**, *34*, 361.

66. James, B.R. In *Homogeneous Hydrogenation*; Wiley, New York, *1973.*

67. Patai, S. (ed), In *The Chemistry of Carbon-Carbon Triple bonds. Parts I, II*; Wiley, Chichester, 1978.

68. (a) Evans, R.F. In *Modern Reactions in Organic Synthesis*; Timmons, C.J. Ed.; Van Nostrand, 1970, *40*, 8. (b) Marvel, E.N.; Li, T. *Synthesis* **1973**, 457.

69. Johnstone, R.A.W.; Wilby, A.H. *Tetrahedron* **1981**, *37*, 3667.

70. Weir, J.R.; Patel, B.A.; Heck, F.R. *J. Org. Chem.* **1980**, *45*, 4926.

71. Kabalka, G.W.; Pace, R.D.; Wadgaonkar, P.P. *Synth. Commun.* **1990**, *20*, 2453.

72. Kabalka, G.W.; Verma, R.S. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I. Eds.; Pergamon Press, Oxford, 1991, *8*, 363.

73. Iyer, S.; Varghese, J.P. *J. Chem. Soc., Chem. Commun.* **1995**, 465.

74. (a) Mohapatra, S.K.; Selvam, P. *Top. Catal.* **2003**, *22*, 17. (b) Mohapatra, S.K.; Sonavane, S.U.; Jayaram, R.V.; Selvam, P. *Tetrahedron Lett.* **2002**, *43*, 8527.

75. Braude, E.A.; Linstead, R.P.; Mitchell, P.W.D.; Wooldridge, K.R.H. *J. Chem. Soc.* **1954**, 3595.

76. Ho, T.-L.; Olah, G.A. *Synthesis* **1977**, 169.

77. Gartiser, T.; Selve, C.; Depuech, J.-J. *Tetrahedron Lett.* **1983**, *24*, 1609.

78. Ram, S.; Spicer, L.D. *Tetrahedron Lett.* **1988**, *29*, 3741.

79. Brieger, G.; Fu, T.-H. *J. Chem. Soc., Chem. Commun.* **1976**, 757.

80. Cossy, J.; Eustache, F.; Dalko, P.I. *Tetrahedron Lett.* **2001**, *42*, 5005.

81. Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M. *Tetrahedron Lett.* **1993**, *34*, 6897.

82. Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.

83. Khai B.T.; Arcelli, A. *Tetrahedron Lett.* **1996**, *37*, 6599.

84. Arcadi, A.; Bernocchi, E.; Cacchi, S.; Marinelli, F. *Synlett* **1991**, 27.

85. Nagao, Y.; Dai, W.-M.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5221 and references cited therein.

86. Ruholl, H.; Schafer, H.-J. *Synthesis* **1987**, 408.

87. (a) Descotes, G.; Sinou, D. *Tetrahedron Lett.* **1976**, *17*, 4803. (b) Ohkubo, K.; Sugahara, K.; Terada, I.; Yoshinaga, K. *Inorg. Nucl. Chem. Lett.* **1978**, *14*, 297.

88. Desai, B.; Danks, T.N. *Tetrahedron Lett.* **2001**, *42*, 5963.

89. Ram, S.; Spicer, L.D. *Synth. Commun.* **1992**, *22*, 2683.

90. Yoshinaga, K.; Kito, T.; Ohkubo, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1786.

91. Zhu, X.-Q.; Zou, H.-L.; Yuan, P.-W.; Liu, Y.; Cao, L.; Cheng, J.-P. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1857.

92. Wang, G.-Z.; Bacvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1992**, 980.

93. Ahn, K.H.; Ham, C.; Kim, S.-K.; Cho, C.-W. *J. Org. Chem.* **1997**, *62*, 7047.

94. Everaere, K.; Scheffler, J.-L.; Mortreux, A.; Carpentier, J.-.F. *Tetrahedron Lett.* **2001**, *42*, 1899.

95. (a) Dragovich, P.S.; Prins, T.J.; Zhou, R. *J. Org. Chem.* **1995**, *60*, 4922. (b) Varghese, J.P.; Sudalai, A.; Iyer, S. *Synth. Commun.* **1995**, *25*, 2267.

96. Ranu, B.C.; Guchhait, S.K.; Ghosh, K. *J. Org. Chem.* **1998**, *63*, 5250.

97. Anwer, M.K.; Spatola, A.F. *Synthesis* **1980**, 929.

98. (a) Ojima, I.; Ed. In *Catalytic Asymmetric Synthesis*. VCH Publishers: Weinheim, 1993. (b) Knowels, W.S. *Acc. Chem. Res.* **1983**, *16*, 106. (c) Burk, M.J.; Gross, M.F.; Martinez, J.P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (d) Deereberg, S.; Pamies, O.; Dieguez, M.; Claver, C.; Kamer, P.C.J.; van Leeuwen, P.W.N.M. *J. Org. Chem.* **2001**, *66*, 7626.

99. (a) Basu, B.; Frejd, T. *Acta Chem. Scand.* **1996**, *50*, 316. (b) Basu, B.; Chattopadhyay, S.K.; Ritzen, A.; Frejd, T. *Tetrahedron: Asymmetry* **1997**, *8*, 1841. (c) Ritzen, A.; Basu, B.; Chattopadhyay, S.K.; Dossa, F.; Frejd, T. *Tetrahedron: Asymmetry* **1998**, *9*, 503. (d) Ritzen, A.; Basu, B.; Wallberg, A.; Frejd, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3491.

100. (a) Arcadi, A.; Bernocchi, E.; Cacchi, S.; Ortar, G. *J. Organomet. Chem.* **1989**, *368*, 249. (b) Laroc, R.C.; Johnson, P.L. *J. Chem. Soc., Chem. Commun.* **1989**, 1368.

101. Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. *Vogel's Textbook of Practical Oranic Chemistry*, 5th edn.; Addison Wesley Longman Limited: Harlow, 1989, 686.

102. Deb, C.; Basu, B. *Indian J. Chem.* **1992**, *31B*, 131.

103. Deb, C.; Basu, B. *J. Organomet. Chem.* **1993**, *443*, C24.

104. Cabello, J.A.; Campelo, J.M.; Garcia, A.; Luna, D.; Marinas, J.M. *J. Org. Chem.* **1984**, *49*, 5195.

105. Su, C.; Chen, Z.-C.; Zheng, Q.-G. *Synthesis* **2003**, 555.

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

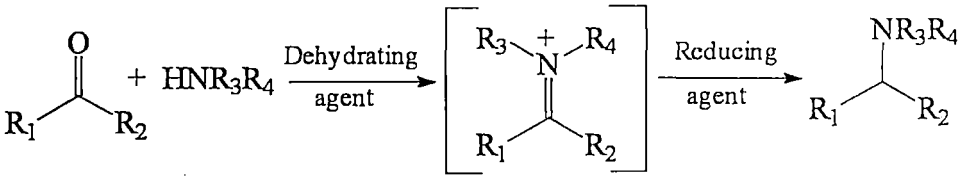
The amine functionality is one of the most ubiquitous in organic chemistry. Its importance is exemplified by the diverse nature of molecules that contain this functional group, which includes natural products and fine chemicals.[1] Amines are important synthetic targets as well as valuable synthons for 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.

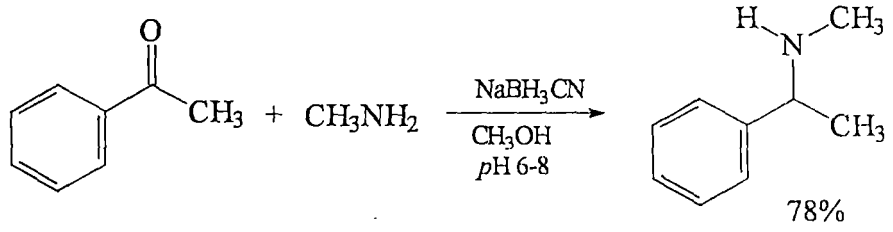
The reactions of aldehydes or ketones with ammonia, primary amines, or secondary amines in the presence of reducing agents to give primary, secondary, or tertiary amines, respectively, known as reductive aminations (of carbonyl compounds) or reductive alkylations (of amines) are among the most useful 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]



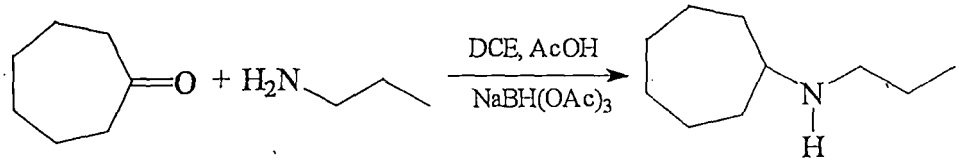
The reductive amination is described as a *direct* reaction when the carbonyl compound and the amine are mixed with the proper reducing agent without prior formation of the intermediate imine or iminium salt. A *stepwise* or *indirect* reaction involves the pre-formation of the intermediate imine followed 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

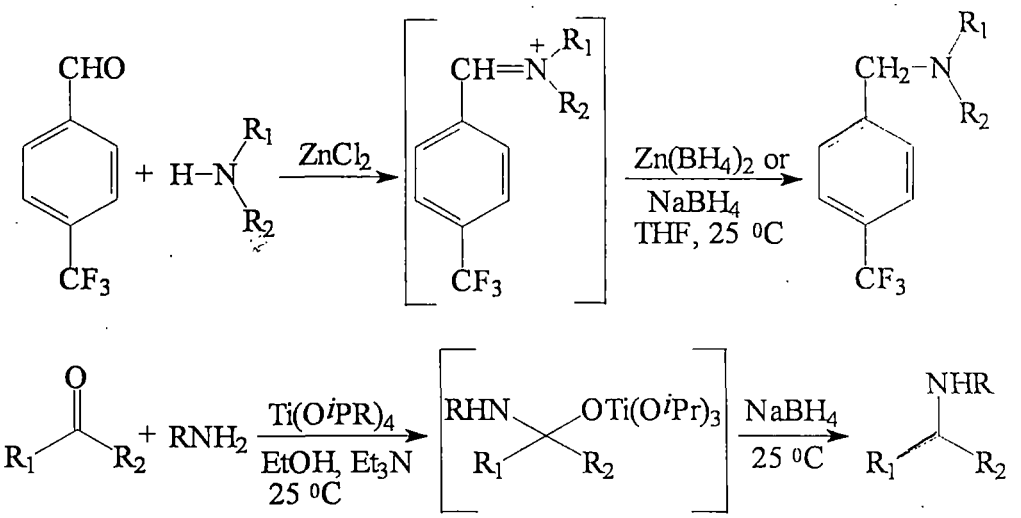
number of other wise reducible functional groups such as nitro, cyano and carbon-carbon double and triple bonds.[20] The catalyst may be inhibited by compounds containing divalent sulfur.[21] The second method utilizes hydride reducing agents for reduction. Among the hydride reagents used to effect this 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.

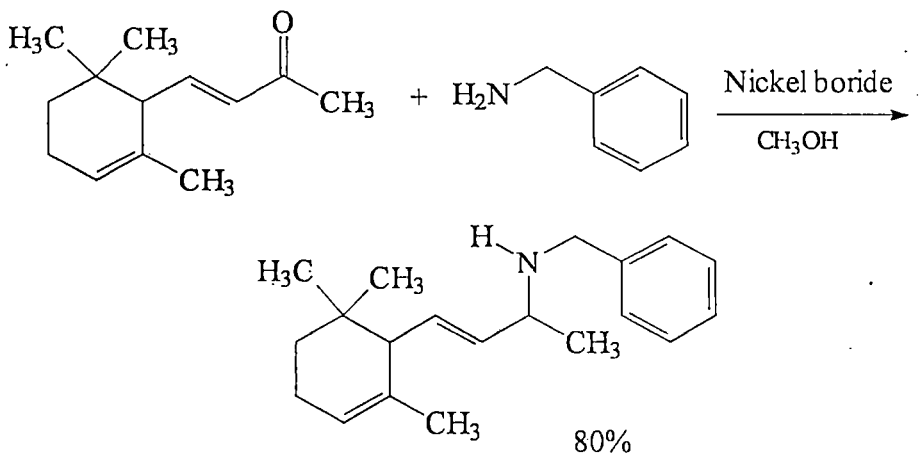


Recently, Bhattacharyya *et al.* developed $ZnCl_2$-$NaBH_4$[28] and $Ti(O^iPr)_4$-$NaBH_4$[29] for reductive amination of carbonyl compounds.

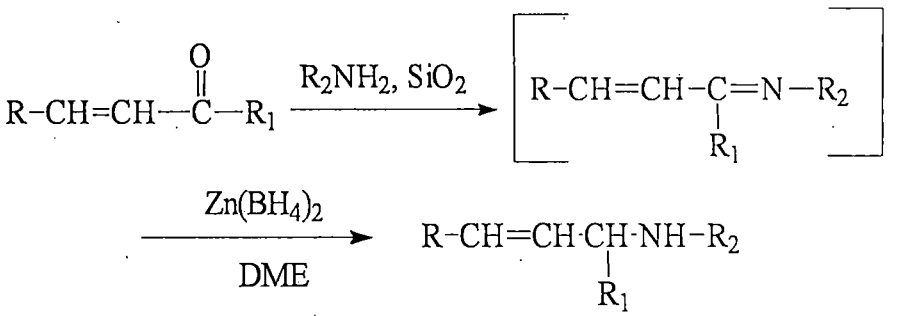


Titanium (IV) isopropoxide has been utilized[24b,30] as a mild Lewis acid compatible with a variety of potentially acid sensitive functional groups including acetal, acetonides, silyl ethers, and Boc derivatives.

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.

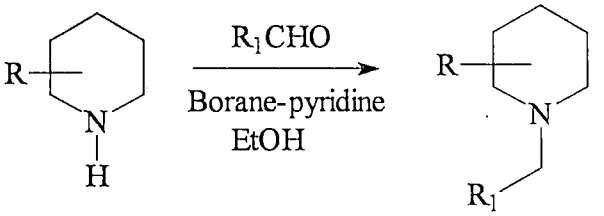


Ranu *et al.*[18] have discovered that reductive amination of conjugated aldehydes and ketone is achieved by treatment of the corresponding carbonyl compound with appropriate amine in the presence of silica gel followed by addition of $Zn(BH_4)_2$ in a one-pot operation.

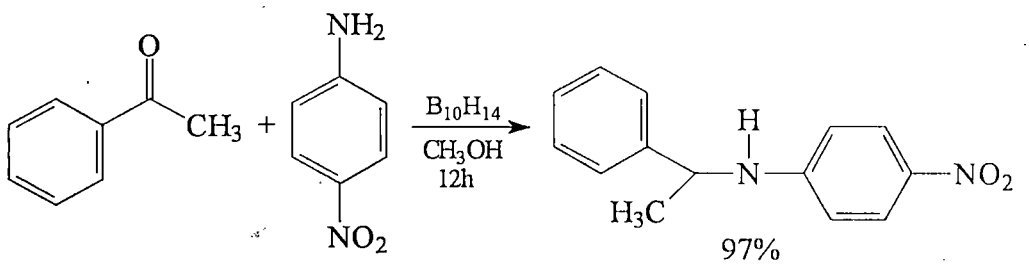


R, R_2 = alkyl or aryl, R_1 = H or alkyl

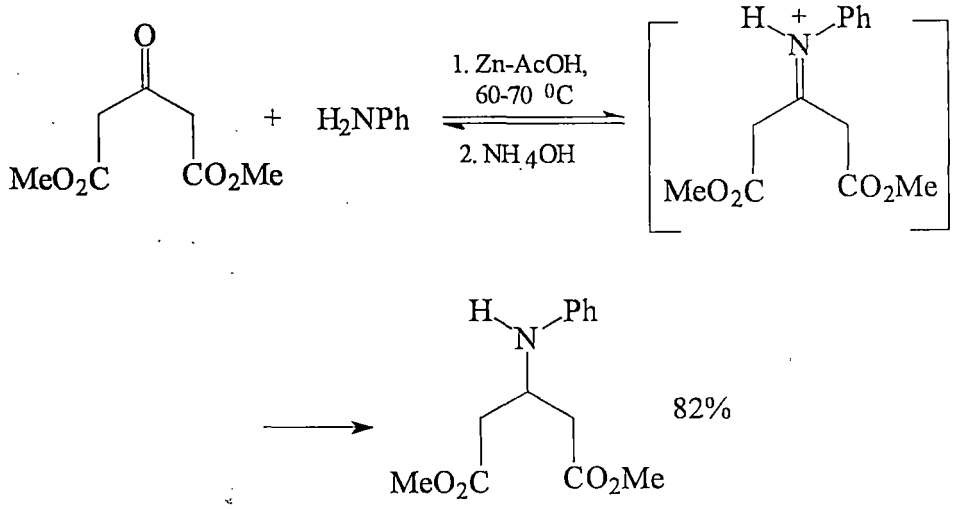
Borane-pyridine was introduced as a cheap and readily available alternative to sodium cyanoborohydride for the purpose of the reductive amination of a wide variety of carbonyl compounds.[24a,25,34] Although BH_3-pyridine works well for the reaction using aromatic amines, the reaction must be performed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



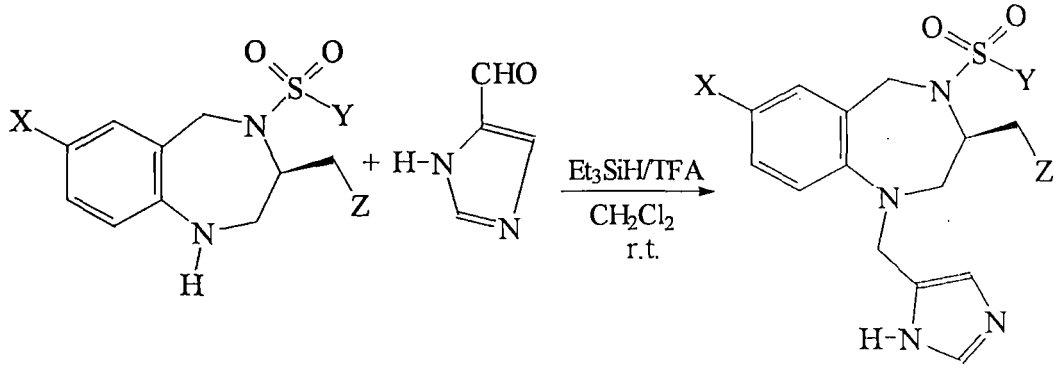
During the study of decaborane as a mild hydride reagent,[35] Yoon *et al.* found that carbonyls and amines undergo reductive amination in the presence of decaborane.[36] Decaborane in this case seemed to have a dual action: a catalyst for the imine formation as well as a mild reducing agent in the reduction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



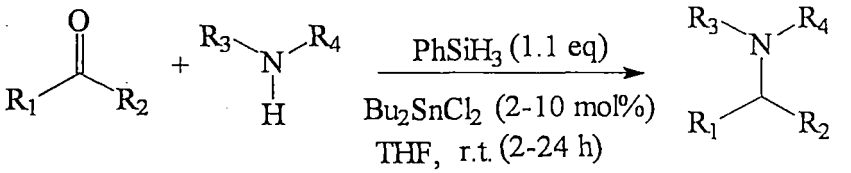
Beside borohydride derivatives, alternative metal hydride reagents such as Zn-AcOH[37] and Cl_3SiH[38] have also been developed. Zn-AcOH is more applicable than Zn-HCl, give better yields, and it is particularly well suited for preparation of β-arylamino esters. But it is not applicable to aldehydes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



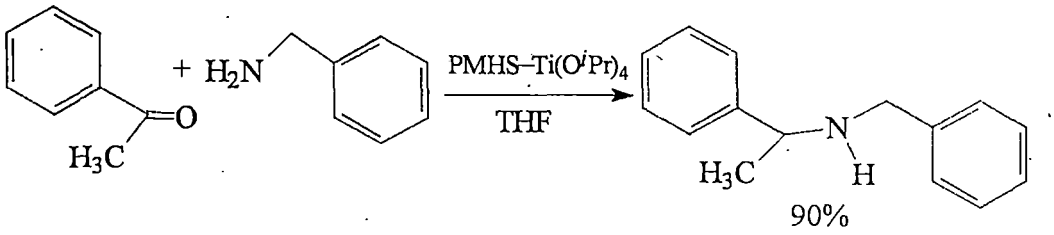
Hydrosilanes such as triethylsilane in the presence of Lewis acid are mild and useful reducing agent in the organic synthesis.[39] Chen *et al.*[40] developed a novel triethylsilane mediated reductive *N*-alkylation of amines to synthesize 1-(4-imidazolyl)methyl-4-sulfonylbenzodiazepines, new farnesyltransferase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



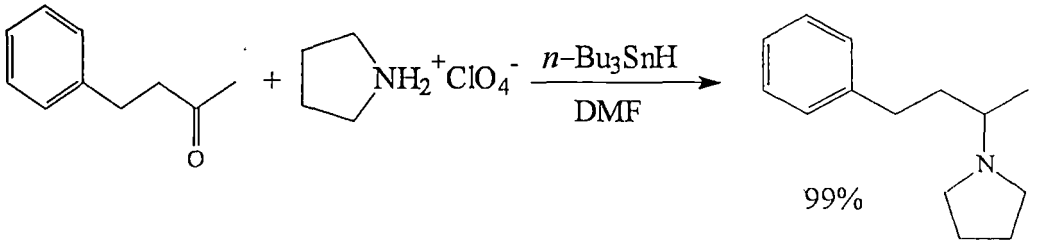
Apodaca and Xiao have developed[41] a simple direct reductive amination procedure which employs phenylsilane as a stoichiometric reductant and dibutyltin dichloride as a catalyst. Both aldehydes and ketones were reductively aminated with anilines and secondary alkyl amines by this method, but the reaction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



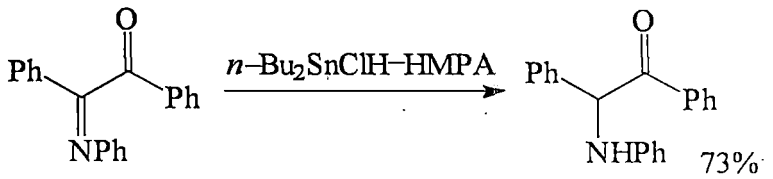
Polymethylhydrosiloxane (PMHS) is being pursued as a safe and environmentally friendly reagent for the reduction of organic functional groups.[42] This reagent is very inert on its own, making it safe to handle, but in the presence of a proper activator it proves itself as an excellent substitute for 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]



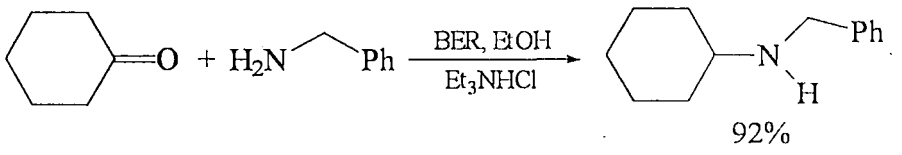
Organotin hydrides have been found to be a mild and chemoselective reductants.[45] Tributyltin hydride in DMF was reported as reducing agent for the reductive amination of carbonyl compounds with primary and secondary ammonium salts.[46]



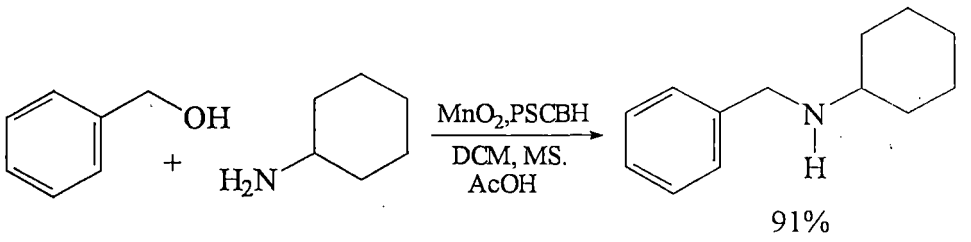
Baba *et al.* provided a set of organotin hydrides to achieve highly chemoselective reductions of functionalized substrates.[47] In particular, pentacoordinated tin hydride, Bu_2SnClH-HMPA,[48] formed *in situ* by simple mixing of Bu_2SnClH and HMPA, has been revealed to be a selective reductant of imines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



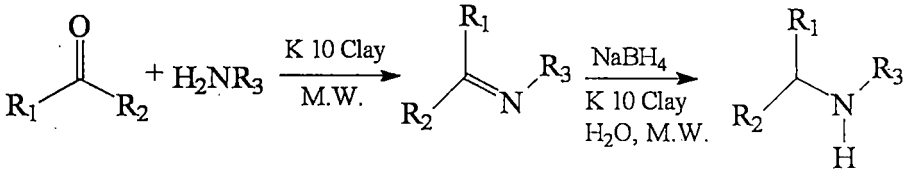
Due to recent trend in developing solid phase reactions for combinatorial chemistry, different solid supported reagents and reactions have also been developed for reductive amination.[50] Sometime ago Borohydride Exchange Resin (BER) was introduced by Gibson and Baily,[51] and Yoon *et al.* reported 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]



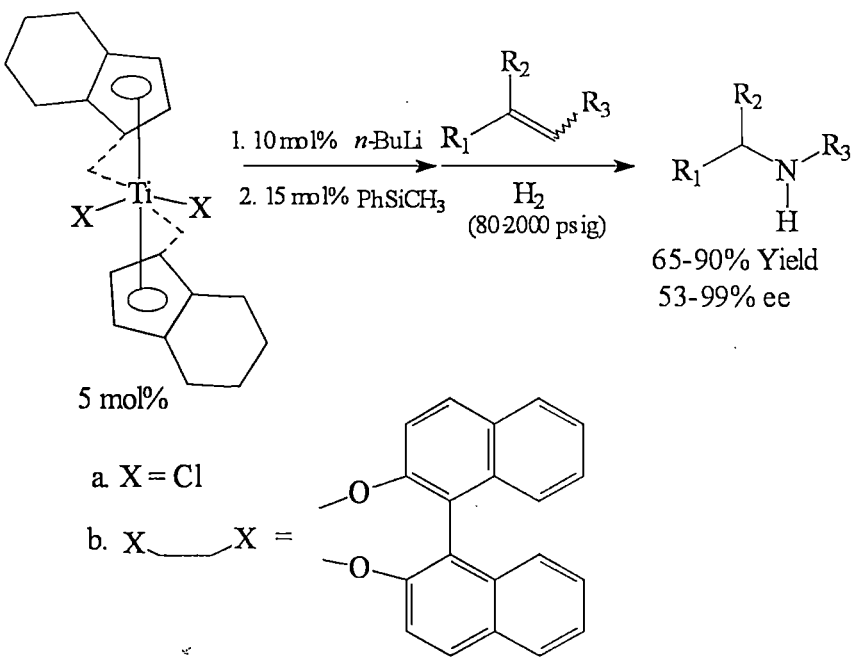
Blackburn and Taylor recently reported a new process for the conversion of alcohols into amines via an *in situ* oxidation-imine formation-reduction by using MnO_2 as oxidant and polymer-supported cyanoborohydride (PSCBH) as reductant.[54]



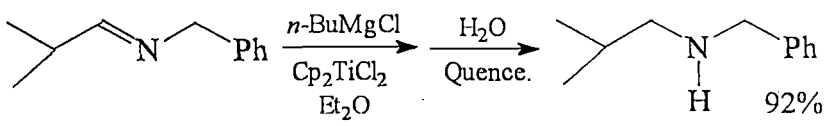
Wet montmorillonite K 10 clay supported $NaBH_4$ under microwave irradiation have also been reported for reductive amination.[55]



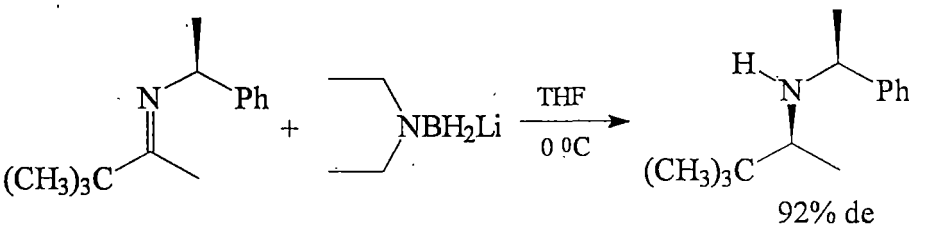
The development of asymmetric catalysts for the hydrogenation of achiral substrates to form enantiomerically enriched products represents a major area of research[56] with the growing importance of enantiomerically pure nitrogen containing compounds in the pharmaceutical and agrochemical industries. 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]



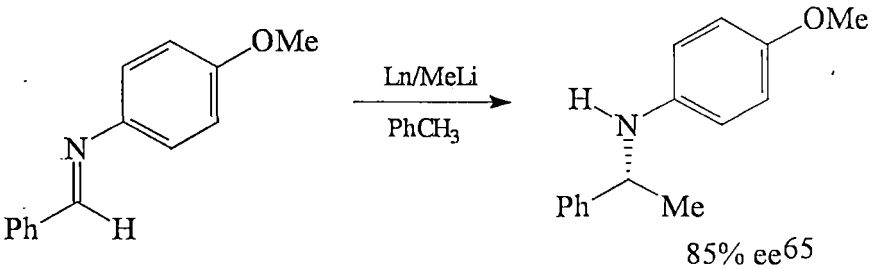
Amin and Crowe have discovered recently that imines can be reduced to amines *via* a titanium catalyzed hydromagnesation reaction using *n*-BuMgCl as the stoichiometric reducing agent.[63]



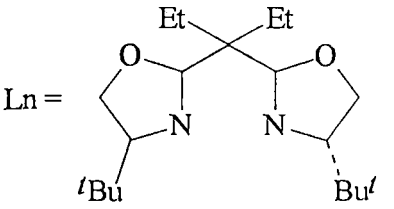
Beside late transition metal, organolithium reagents were also being employed for such transformation. Lithium diethylaminoborohydride and lithium diisopropyl-aminoborohydride reduce chiral aliphatic and aromatic imines, derived from α-methyl-benzylamines, to give the corresponding enantiomerically enriched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

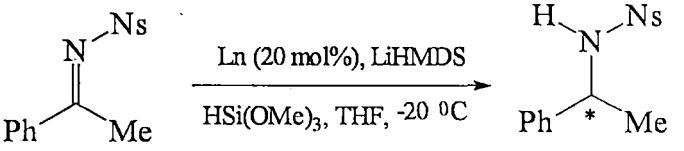


92% de



85% ee[65]





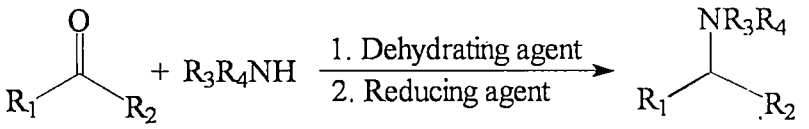
72% ee[66]

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).



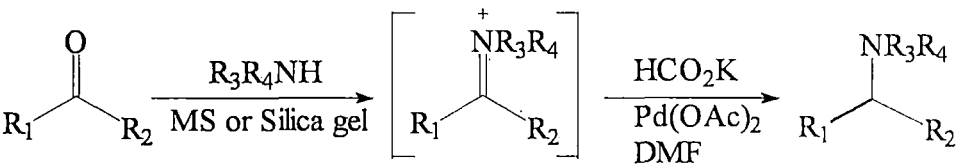
Scheme IV

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

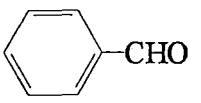
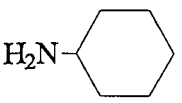
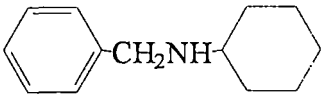
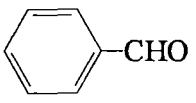
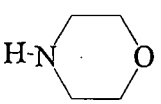
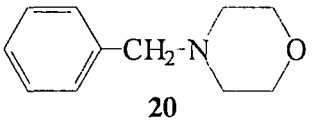
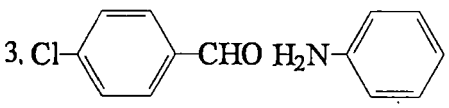
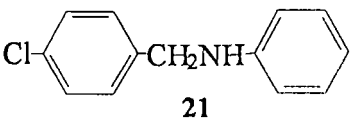
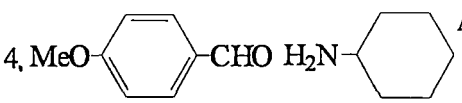
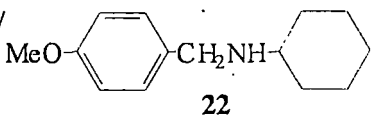
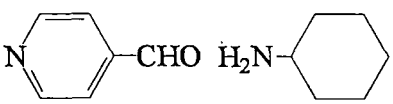
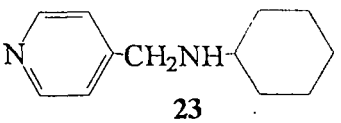
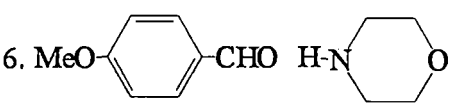
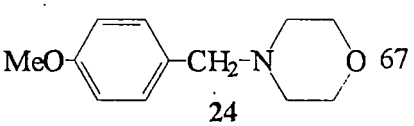
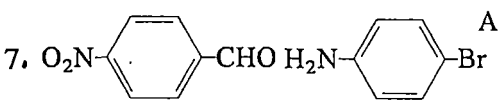
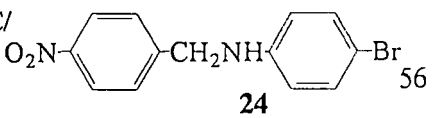
To examine the scope of this reaction, a variety of aldehydes and ketones were reductively aminated with aliphatic and aromatic amines (Table 2). Both primary and secondary amines such as morpholine (entries 2 and 6) have been used. Reactions with substrates bearing potentially reducible functional groups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

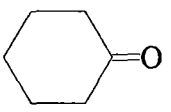
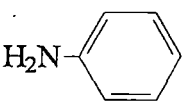
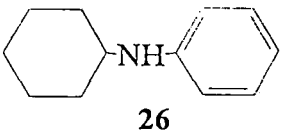
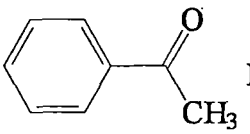
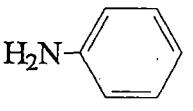
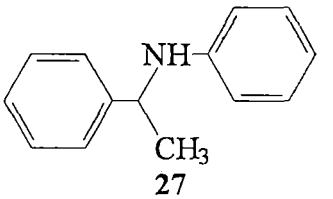
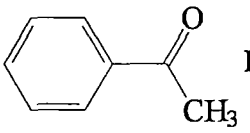
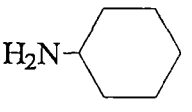
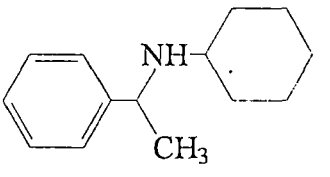
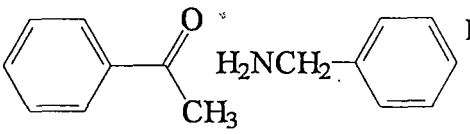
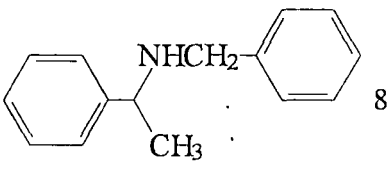
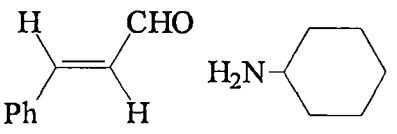
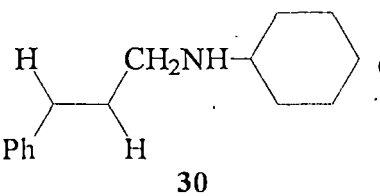
In summary, the method described here can be useful for preparing all classes of amines from suitable carbonyl compounds and the amines. Furthermore, the method can be of importance in view of cheap reducing agent, which decomposes to environmentally friendly chemicals. Since palladium catalyzed hydride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

Part I. Section C

Solid Phase Organic Synthesis: Development of a New Method for Reduction of C–C and C–N Double Bonds Using Polymer Supported Formate and Catalytic $Pd(OAc)_2$

IC.1 Introduction: A Brief Review on Solid Phase organic Reactions

There is need to develop new methods for organic synthesis which afford products free from contaminating by-products or excess reagents, but do not require the need for time consuming work-up and purification methods. Numerous applications can be envisaged for these methods in catalytic process, atom efficient reactions, clean and green technology and combinatorial chemistry.

The growing need for compound libraries, especially for biological evaluation, has led to an increasing demand for clean and efficient synthesis of complex organic molecules. Recent environmental constraints have led to the development of clean and easily recycled reagents for used in synthetic chemistry. This need has led to the development and use of reagents that are supported on a solid matrix. Also, because of the development of robotic systems for chemical synthesis in many industrial sectors, the need for solid supported reagents has increased considerably. Such supports facilitate easy removal of residues from the reaction mixture without release of residues into the environment.

Reactions on solid supports are significant for rapid and simultaneous synthesis of many new compounds required in the search for lead structures and their optimization for the preparation of novel pharmaceuticals. Solid-phase parallel synthesis is used worldwide to generate libraries of small organic compounds to accelerate the drug discovery process.[1] The widespread use of polypeptide[2] and oligonucleotide[3] synthesis highlights the benefits of carrying out a series of high yielding reactions whilst the target molecule remains tethered to an insoluble solid support. There are a growing number of classical organic reactions which have been successfully translated from solution onto the solid phase.[4]

The first formal expression of solid phase technique was introduced by Merrifield to facilitate polypeptide synthesis.[5] This technique was applied for other organic syntheses in which suitable functional polymer were chosen to solve specific synthetic problems.[6] Certainly, the invention by Merrifield of solid phase synthesis with its following automation is a classical example of scientific revolution. Traditional synthetic organic chemistry required isolation and characterization of intermediates as concrete evidence supporting the chemical structure of the product. By substituting the use of excess reagents to force chemical reactions to completion (or as close as possible), solid-phase chemistry was anathema to traditional synthetic practice of the time. Resistance to change by synthetic chemists in general, and peptides chemists in particular, was both vehement and vitriolic. In addition, solid-phase chemistry required careful purification and characterization of its product that did not depend on the history of the synthetic process. In reality, this was only possible with a concomitant improvement in both purification techniques and analytical methods of structural characterization. Without modern HPLC, capillary electrophoresis, NMR, mass spectroscopy, etc., solid-phase chemistry would not have been so feasible. The practical advantages in handling and automation offered a filterable, polymeric protecting group in automation of chemical synthesis for out way the increased needs for more effort in purification and characterization.

Not surprisingly, solid-phase synthesis was not limited to peptides only, and early contributions were made to its use for general organic synthesis, particularly by Leznoff,[7] Frechet[8] and Rapoport.[9] Solid-phase organic synthesis is attractive from the following perspectives:

i) it allows ease separation of synthetic intermediates from soluble components of a reaction mixture by simple filtration and washing of the resin-bound reaction product. A straight-forward consequence is the ability to use a high boiling reaction solvent such as DMF, DMSO, NMP, without the need to evaporate the solvent.

ii) A high concentration of reactants in solution facilitates driving reaction to completion without causing work-up problems.

iii) A simple repetitive process (adding reagent, mixing, washing) allows for integration and /or automation of solid-phase synthesis.

iv) Reducing toxicity and odor of supported species compared with low molecular weight unsupported analogues.

When Merrifield was looking for a suitable insoluble support for his solid-phase peptide synthesis, his choice ended up as a beaded form of copolymer of styrene and divinylbenzene.[10] Since then a variety of solid-phase support was introduced, a number of them claiming superior properties when compared to the original Merrifield resin. However, after almost 40 years, the copoly (styrene-1% divinylbenzene) is still the most commonly used resin. The polymeric matrix surrounds the synthesized compound and it behaves as a solvent. Thus, synthesis on copoly (styrene-divinylbenzene) resembles performing the reaction in toluene.[11] However, there is no single polymer support that favours all reactions, and the need to use polar or nonpolar media should influence the choice of support.[12]

Until the early 1990s, solid-phase organic synthesis was not widely used, and its domains remained principally peptides, nucleic acids, and, later, carbohydrates. Subsequently the potential for generating molecular diversity in a non-peptide environment were greatly increased. Ureas,[13] oligonucleotides[14] benzodiazepines,[15] hydantoins,[16] γ-butyrolactones[17] and β-mercapto ketones[18] have been prepared successfully *via* polymer-supported synthesis. Very recently, catalytic hydrogenations,[19] [3+2] cycloadditions,[20] and Suzuki, Heck and Stille reactions[21] with polymer-bound substrates have been reported.

The renaissance of solid-phase organic synthesis was triggered by the advent of combinatorial chemistry techniques.[22] The groundwork for combinatorial chemistry had already been set in peptide chemistry by Geysen with his pin approach[23] and Houghten with his "teabag" approach to epitope mapping.[24] Both approaches used physical separation of polymers to control reaction sequences and thus peptide products. Lam[25] and Furka[26] conceived independently of the "one bead, one product" split-and-mix approach that has been so powerful. Houghten has shown that synthesis of large mixtures followed by screening and deconvolution to identify

the active components is a viable and efficient technique.[27] In many ways, it is analogous to isolation of active natural products from fermentation broths. Nevertheless, the pressure from the medicinal chemistry community in the pharmaceutical industry has focused on combinatorial synthesis of single compounds, partial due to perceived problems with false positives in the deconvolution process. The flood of recognition by the medicinal chemistry community of the advantages of filterable, polymeric protecting groups was catalyzed by a paper in 1992 by Bunin and Ellman[28] on synthesis of a combinatorial library of benzodiazepines, a privileged class of structure thought to mimic turns. The generation of a compound library of direct interest to the pharmaceutical interest because of the many biological activities found with benzodiazepines was a turning point in acceptance of the overall approach. It has become difficult to find a chemical reaction, or class of compound, that has not been adapted to solid-phase chemistry. Traceless supports[29] for SPS and on heterocyclic chemistry[6a] have recently appeared for examples of the pervasiveness of the approach in the synthetic organic chemistry. Synthesis of complex natural products as diverse as sarcodictylins, chalcones and epothilones[30] utilizing solid-phase organic chemistry are becoming more commonplace as the advantages of a filterable, polymeric protecting group become more widely recognized. The paradigm shift has even extended to the search for metal-binding ligands, catalysts, and new materials.[31]

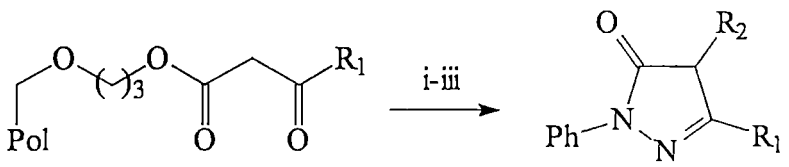
However, the solid-phase technique involves certain problems. The main disadvantages of solid-phase chemistry are the extra labour required to develop a solid-phase route, the limitations of the current range of commercially available supports and linkers as well as the means of monitoring reactions in real time. Solid-phase routes also necessitate additional steps to link and cleave to and from the support and are generally used to prepare <100mg final product. Another disadvantage with synthesis on a functionalized polymer is due to the difficulties caused by incomplete cleavage from the polymer backbone which results, sometimes, in the decomposition of the products. The choice of the solvent, which should swell the polymer, and the capacity of the functionalized polymer are other limitations of this technique for industrial synthesis.

IC.1.1 Applications of solid supported reactions

IC.1.1.1 Carbon-carbon bond forming reactions

IC.1.1.1.1 Reactions of enols, enolate equivalents and stabilized carbanions

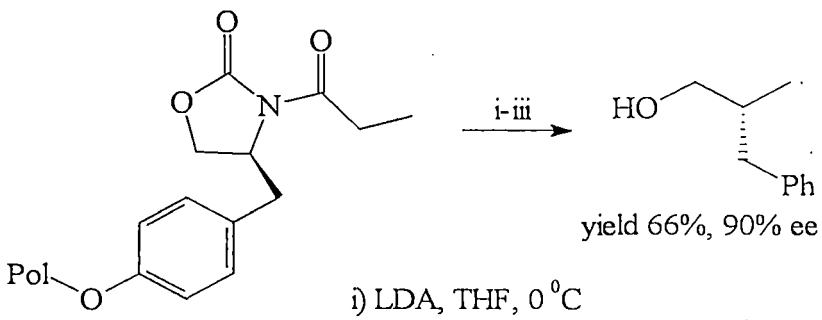
The development of efficient and reliable methods of forming carbon-carbon bonds remains an important goal in solid-phase synthesis. The reactions stabilized carbanions with carbon centered electrophiles are amongst the most fundamental process for construction of organic molecules, and consequently many of these reactions have been investigated on the solid-phase. Alkylation of β-ketoester was promoted by fluoride permitting the synthesis of 1-phenylpyrazolone derivative.[32]



i) R_2X, TBAF, THF, 52-66 ^{0}C
ii) $PhNHNH_2$, THF, $(MeO)_3CH$
iii) TFA, CH_3CN

52-95%

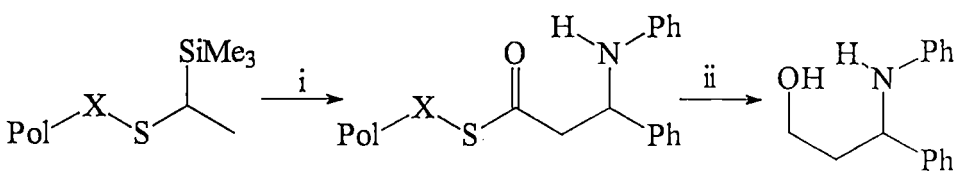
Chiral *N*-acyloxazolidinone function as chiral auxiliary as well as linker was reported in solid-phase variants of widely used Evans asymmetric alkylations of imide enolates.[33]



yield 66%, 90% ee

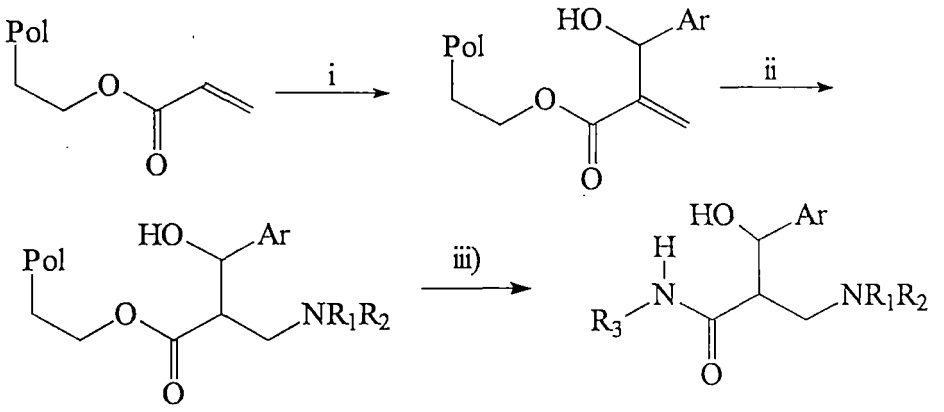
i) LDA, THF, 0 ^{0}C
ii) BnBr, iii) $LiBH_4$, r.t.

Supported silyl enol ethers readily participate in Mannich-type three-component condensation reactions, affording amino alcohol.[34]



i) PhCH=NPh, $Sc(OTf)_3$, CH_2Cl_2
ii) $LiBH_4$, THF, r.t.

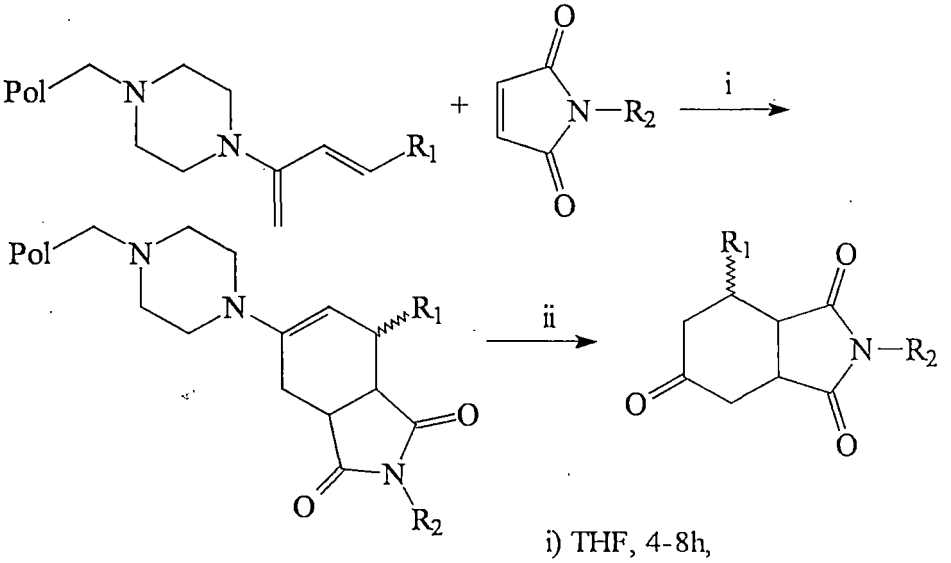
A Baylis-Hillman reaction conducted with an α,β-unsaturated ester component attached to the solid support, was used to the synthesis of 3-hydroxypropionamides.[35]



i) 3-Hydroxyquinuclidine, ArCHO, DMF
ii) R_1R_2NH, DMF iii) R_3NH_2, CH_2Cl_2, Me_3AL

IC.1.1.1.2 Pericyclic reactions

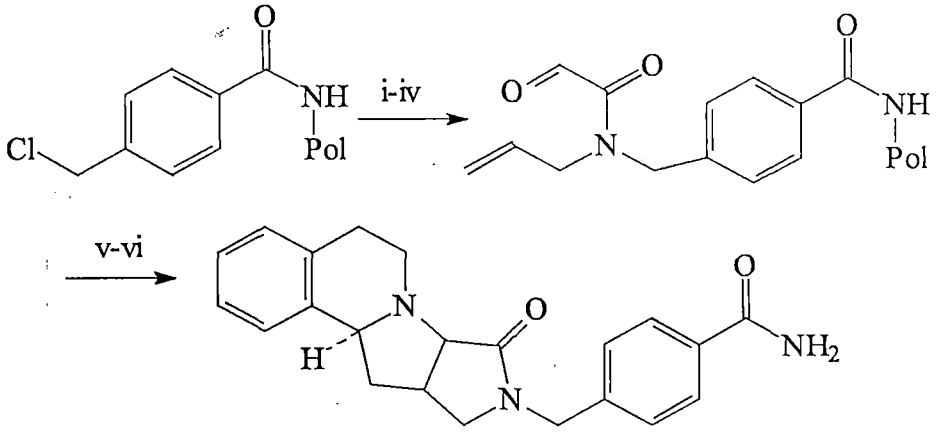
Crawshaw *et al.*[36] prepared a number of bicyclic adducts by Diels-Alder cycloaddition of an immobilized diene with an activated dienophile.



i) THF, 4-8h,
ii) 3% TFA, CH_2Cl_2

Solid-phase azomethine ylide [3+2] cycloadditions provide attractive entry to highly functionalized pyrrolidines, and several intramolecular examples have been

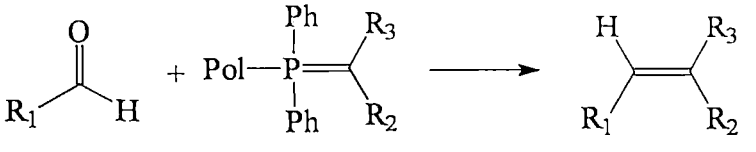
reported.[37] Marx *et al.*[38] reported the synthesis of polycyclic lactams using an intramolecular azomethine ylide cycloaddition strategy.



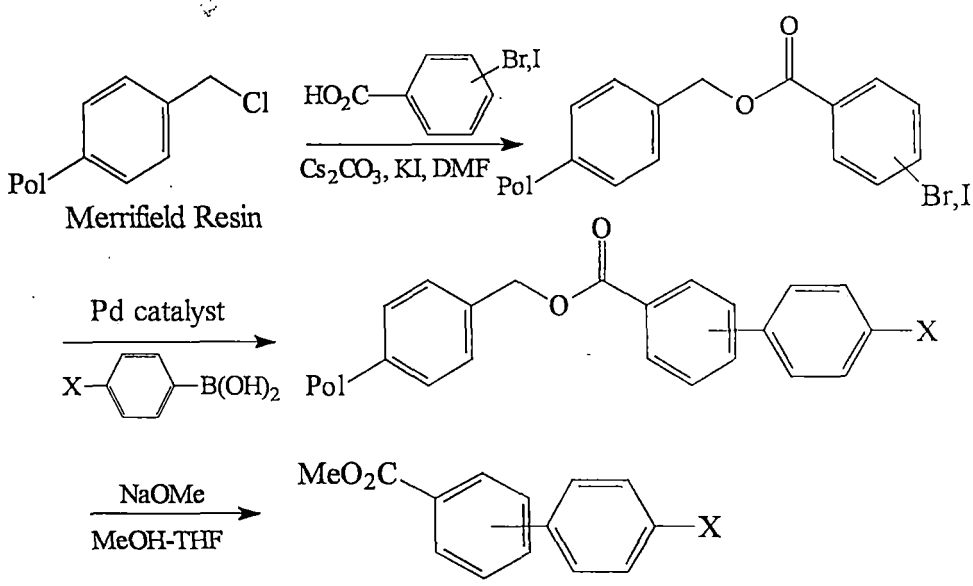
i) NaI, DMF, 80 ^{0}C, allylamine, ii) $AcOCH_2CO_2H$, DIC, DMAP, CH_2Cl_2,
iii) K_2CO_3, MeOH, DMF, iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2,
v) tetrahydroisoquinoline, toluene, heat, vi) TFA, H_2O.

IC.1.1.1.3 C–C Coupling reactions

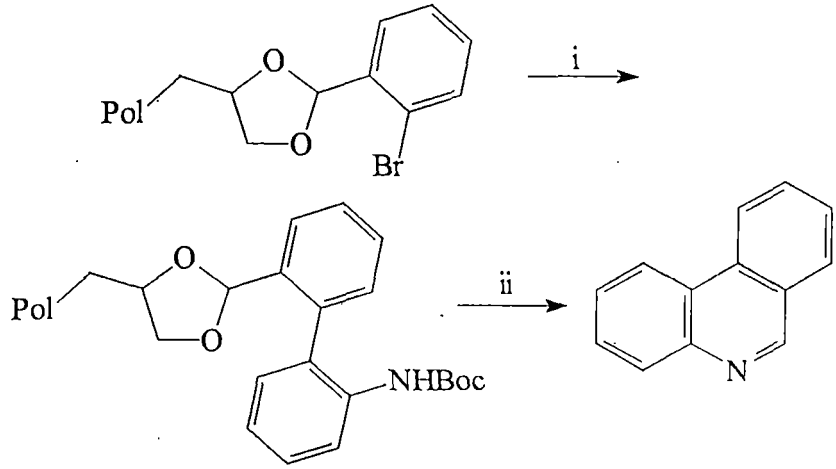
The Wittig reaction and the organophosphorous chemistry are the best studied examples of carbon-carbon coupling reactions promoted by functionalized polymers. Bolli and Ley[39] reported the preparation of alkenes by reacting aldehydes with polymer supported Wittig reagents.



Metal-catalyzed coupling reactions are very efficient and reliable methods for the introduction of new carbon-carbon bonds onto molecules attached to a solid support. Solid-phase Suzuki coupling was first utilized in the preparation of biaryls. Aryl boronic acids under a facile and efficient palladium catalyzed cross-coupling reaction with aryl bromides and iodides that are bound to a Merrifield Resin.[21b]



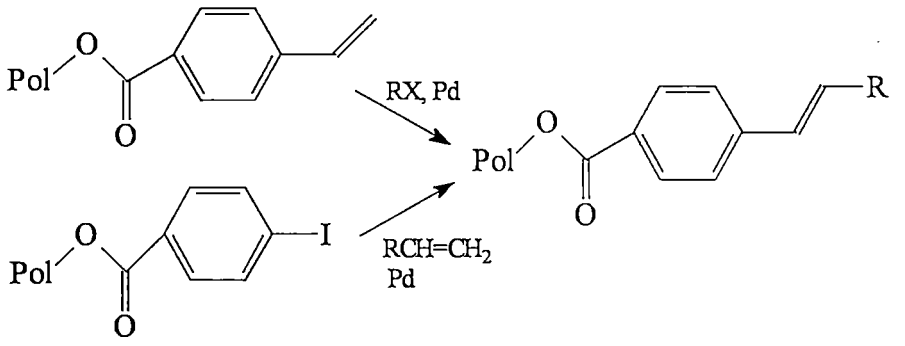
Chamoin *et al.*[40] used the Leznoff acetal linker[41] to tether *o*-bromo-benzaldehydes for Suzuki-Miyaura cross-coupling with aryl and heteroaryl boronic acids. Use of phenylboronic acid substituted in the *ortho* position with a protected amino group afforded, after TFA cleavage and spontaneous cyclization, the phenanthridine product.



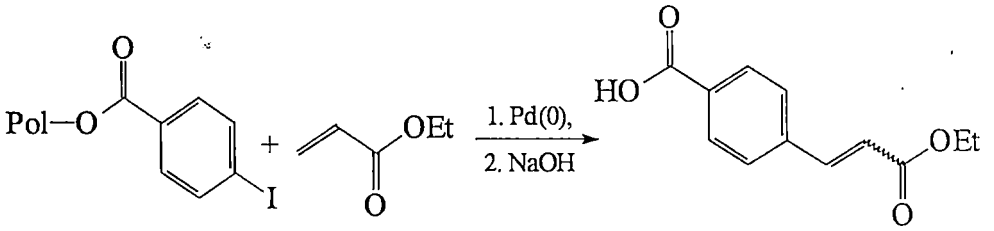
i) boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME; ii) TFA.

The intramolecular Heck reaction has been well-established as a powerful tool for the construction of complex polycyclic ring systems in the context of natural products. This process has been adapted in the solid-phase synthesis of several different types of molecules. Yu *et al.*[21c] used the reaction of polymer bound aryl

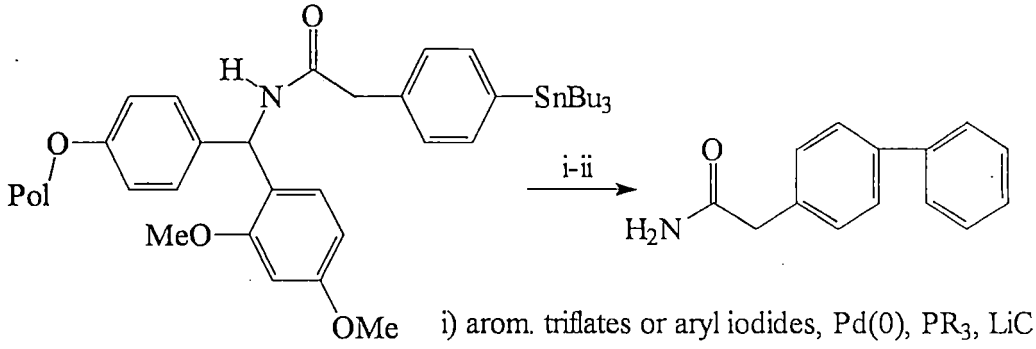
iodide or styrene with olefins or arylhalides in the generation of 1,2-disubstituted olefin libraries.



Hiroshige *et al.*[42] studied the formation of a C–C bond in the palladium-promoted vinylation of aryl iodide bound to a solid support.



Several applications of the Stille reaction for efficient carbon-carbon bond formation on solid-support have been reported.[21a] Forman and Sucholeiki[43] used the reaction for the preparation of biaryl derivatives and studied the reaction of polymer-bound aryl stannanes with aryl iodides or triflates.



i) arom. triflates or aryl iodides, Pd(0), PR_3, LiCl
ii) TFA/DCM

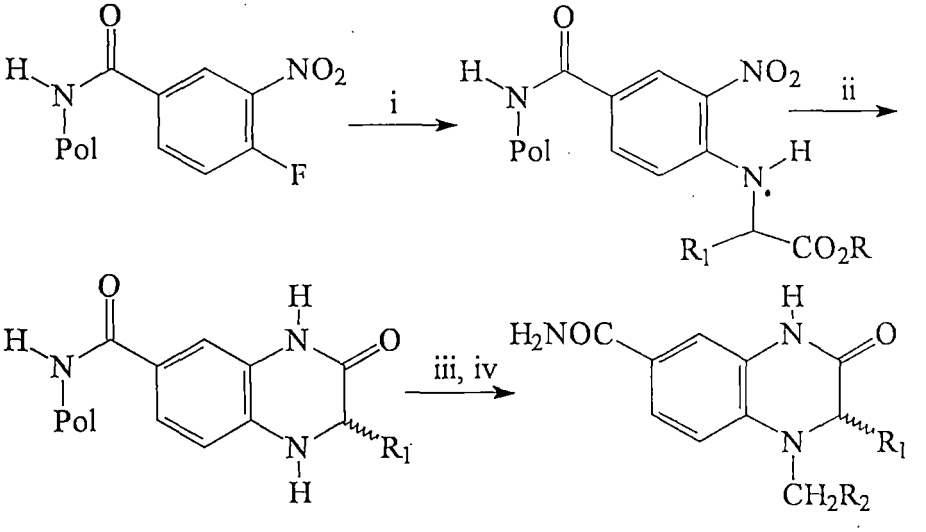
Not only polymer supported substrates used in synthesis, polymer supported catalysts were also used particularly in Heck and Suzuki reactions. Song *et al.*[21e] synthesized a polymer (fiber)-supported palladium catalyst to measure activity and

selectivity for Heck reactions and found that its activity remained unchanged after being recycled 20 times. Reusable resin plug-bound palladium catalyst was reported[21f] in the preparation of a Suzuki reaction based library and the removal of allyl ester protecting groups.

IC.1.1.2 Carbon-heteroatom bond forming reactions

IC.1.1.2.1 Nucleophilic aromatic substitution

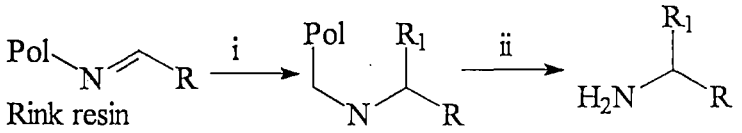
Nucleophilic aromatic substitution is an attractive approach to the functionalization of electron deficient aromatic rings, with the introduction of a wide range of readily accessible heteroaromatic nucleophile. A sequence of nucleophilic aromatic substitution of resin-bound 4-fluoro-3-nitrobenzoic acid derivative with amino acid esters followed by reductive cyclization led to the formation of tetrahydroquinoxalin-2-one.[44]



i) $H_2NCH(R)CO_2R$, ^iPrNEt, DMF, ii) $SnCl_2.H_2O$, DMF,
iii) R_2CH_2Br, K_2CO_3, Acetone, iv) TFA, H_2O

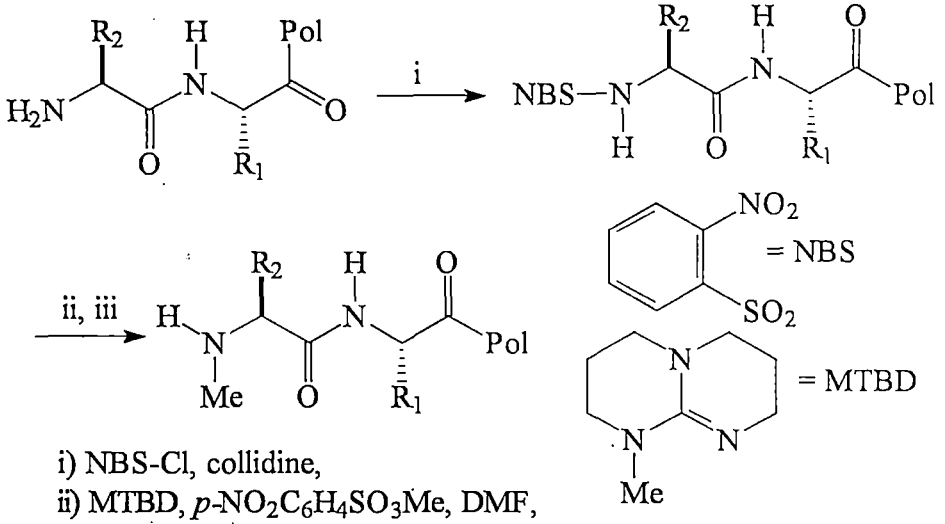
IC.1.1.2.2 Carbon-nitrogen bond formation

Direct *N*-alkylation of immobilized amines may not be particularly useful in many cases due to the potential for over alkylation; in fact this side reaction has been used to advantage in the design of REM Linker. The method of choice for the alkylation of primary amines is often reductive alkylation with a carbonyl compound, usually an aldehydes, in the presence of $Na(OAc)_3BH$,[45] $Na(CN)BH_3$,[46] or less commonly $NaBH_4$, $LiBH_4$[47] or $LiAlH_4$.[48]



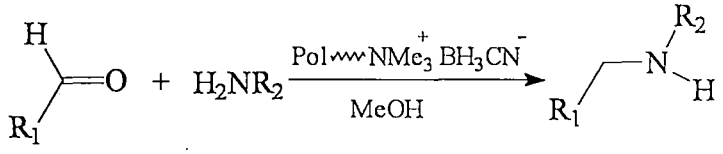
i) R_1MgX or R_1Li, Et_2O, toluene, or $LiBH_4$, THF
ii) TFA, H_2O, CH_2Cl_2

Miller and Scanlan have devised an operationally simple procedure for site-selective *N*-methylation of a growing peptide based on the Fukuyama amine synthesis.[49]



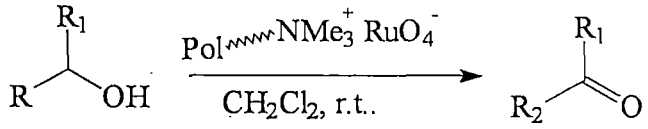
i) NBS-Cl, collidine,
ii) MTBD, *p*-$NO_2C_6H_4SO_3Me$, DMF,
iii) $HSCH_2CH_2OH$, DBU, DMF

Ley *et al.*[50] reported a reductive amination procedure on polymer supported cyanoborohydride (PSCBH).



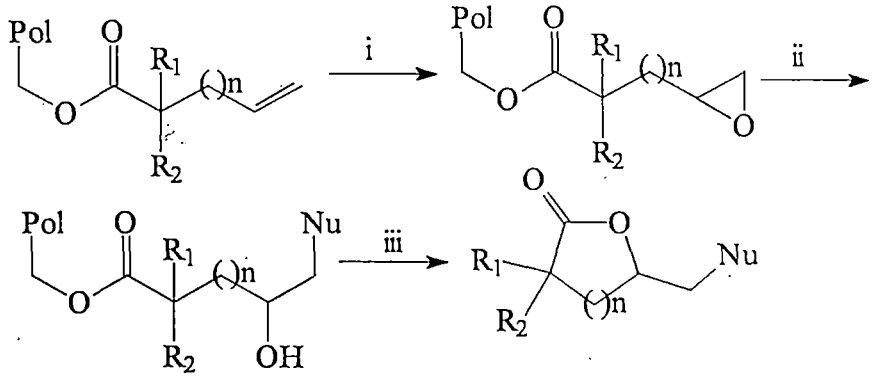
IC.1.1.3 Oxidation

Oxidation of alcohols to ketones and aldehydes can achieved on the solid-phase using standard reagents such as the SO_3.pyridine complex,[51] DMSO-oxalyl chloride-Et_3N, or the tetra-*n*-propylammonium perruthenate complex.[52] Recently, Hinzen and Ley reported a polymer supported perruthenat, a new oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones respectively.[53]



R = alkyl, aryl; R_1 = alkyl, H

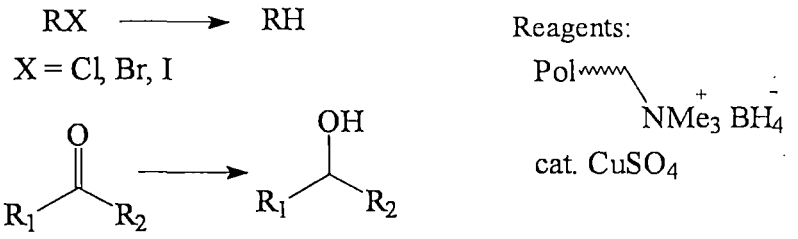
Epoxidation reactions of resin-bound olefins followed by nucleophilic ring opening afford secondary alcohols which underwent acid catalyzed lactonization leading to the release of five- or six-membered lactones from the resin.[54]



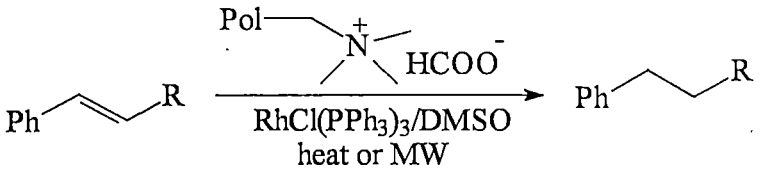
i) MCPBA, CH_2Cl_2, ii)NaN_3 or ArSNa, DMF, iii) TFA, CH_2Cl_2

IC.1.1.4 Reduction

Polymeric supports are not only suited for anchoring oxidants but have also been shown to be immobilize reducing agents very effectively.[55] The chemical modification of quaternary ammonium type resins, such as Amberlyst A-26, with $NaBH_4$,[56] $Na(CN)BH_3$ gives highly efficient and chemoselective reagents.[57] Recently, the polymeric backbones of these functionalized ion-exchange resins have been optimized.[57b] In fact, these functionalized resins have been used in many organic transformations including the reduction of aldehydes and ketones,[58] α,β-unsaturated carbonyl compounds,[59] benzyl and primary alkyl halides.[60] Aryl azides, arylsulfonyl azides could be transformed to the corresponding aromatic amines and aryl sulfonamides respectively, in up to 98% yield[61] and even the reductive amination of aldehydes and ketones in weakly acidic alcohol solvent has been achieved using the polymer-supported hydrides.[50,62] Borohydride attached with Amberlite IR 400 and catalytic amount of Cu_2SO_4 is powerful reducing agent and particularly useful for the reduction of alkyl halides including iodides, azides, aldehydes and ketones.[63]

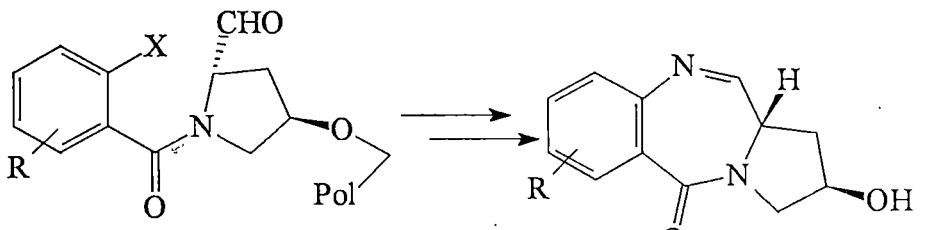


Recently, Desai and Danks reported the use of polymer supported formate for the reduction of alkenes under thermal or microwave conditions using Wilkinson's catalyst.[64] Initially they used Wilkinson's catalyst, polymer-supported formate derived from (aminomethyl)polystyrene as hydrogen source and subsequently they prepared formate supported on ion-exchange resin (Amberlite IRA 938 Cl^-) for reduction purpose.



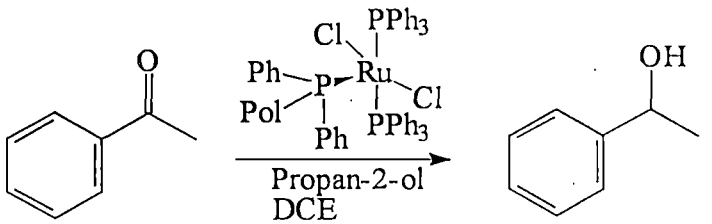
R = CO_2H, CO_2Me, CHO, $COCH_3$, CN, $CON(CH_3)_2$

Very recently, Kamal *et al.*[65] described an efficient and mild method for the reduction of aromatic nitro and azido groups on solid support using $Al/NiCl_2.H_2O$ and Al/NH_4Cl. This solid-phase reduction technique has been applied towards the synthesis of DNA binding pyrrolo[2,1-c]benzodiazepine antitumour antibiotics.



X = NO_2, N_3

Leadbeater[66] reported resin-bound ruthenium phosphine complex assessment of its use in transfer hydrogenation and hydrocarbon oxidation process.



IC.2.1 Present Work: Background, Objectives and strategy

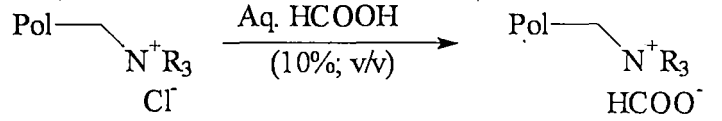
The success of using the combination of HCOOK and $Pd(OAc)_2$ (catalytic) in CTH of functionalized carbon-carbon and carbon-nitrogen double bonds prompted us to the development and use of this reagent supported on a solid matrix. In the recent years, the need for development of solid supported reagents has increased considerably. In view of this we set out to develop a polymer supported version of formate anion that is suitable for use as a transfer hydrogenation source. Recent environmental constraints also prompted to the development of clean and easily recycled reagents for use in synthetic chemistry.

The functionalized polymers have been emerged as versatile tools for solution-phase chemistry and automated parallel synthesis. The polymer supports have been used for anchoring several reducing agents such as, borohydrides, tin hydrides etc. These reducing agents immobilized on quaternary type ammonium resins such as Amberlyst-A-26, have been employed in many organic transformations including the reduction of aldehydes and ketones, α,β-unsaturated carbonyl compounds, α,β-unsaturated cyano acetates and conjugated nitroalkene.[6b] Although these immobilized hydrides have resulted in successful reduction of several conjugated systems, hydrides, in general, are either expensive, reactive or the residues pose a risk in its elimination. Therefore the design of ideal support with suitable reagent has been a subject of research for many synthetic chemists. A search in the literature revealed that Desai and Danks[64] in 2001, reported the reduction of cinnamic acid and its derivatives using polymer supported formate (PSF) in presence of Wilkinson's catalyst $[RhCl(PPh_3)_3]$. The formate anion was exchanged with Amberlite 938 resin (Cl^- form) and was used for reduction of cinnamic acid systems under both microwave and thermal conditions. They also compared the relative rates of reaction under microwave and thermal conditions. Since the literature suggests only one report on the reduction of cinnamic acid derivatives using polymer supported formate (PSF), we desired to undertake in detail the applications of PSF in metal catalyzed hydrogen transfer reduction of different electron-deficient alkenes and/or imines.

This section will describe our studies directed towards palladium-catalyzed transfer hydrogenation of alkenes, enamides, imines etc. using PSF as the source of hydrogen.

IC.2.2 Present Work: Results and Discussion

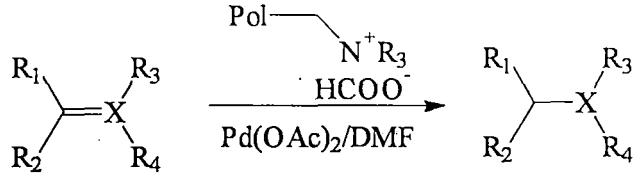
The PSF was prepared by washing Amberlite resin (IRA 420, Cl^- form) packed in a column with 10% formic acid solution repeatedly until the washings gave negative response to chloride ion (scheme VI). Finally the solid surface was washed several times with water and then dried under vacuum. The resulting resin formate was used directly for catalytic reduction. A mixture of unsaturated compound, palladium acetate (2 mol%) and resin formate in DMF was stirred at 70-75 ^{0}C for 10-16 h (Scheme VII). The progress of the reaction mixture was monitored on TLC. Usual work-up followed by purification afforded the anticipated products in good to excellent yields (Table 3).



Amberlite ® IRA-420
Chloride form taken in water

Amberlite ® IRA-420
Formate form

Scheme VI



$R_1 = R_2$ =Ph, Ar, H, X = C, N
R_3 and R_4 = CN, CO_2Et, CO_2Me, NHBoc, H, Ph

Scheme VII

The generality of this methodology has been investigated with different types of electron-deficient alkenes and imines (Table 3). We first examined reduction of alkylidene cyanoacetate (entries 1,2) using PSF and palladium acetate (2 mol%) in DMF. The PSF was employed in excess anticipating that not every functional site

needs to react. The reduction of the C-C double bond proceeded smoothly at 70-75 ^{0}C requiring only gentle agitation, work-up was then achieved by simple filtration, extraction with diethyl ether and evaporation. The reduced product was purified by column chromatography over silica gel. Both the cyano and ester groups remain unaffected under the reaction conditions. The reduction of dicyanoalkylidene derivative (entry 3) was found to occur with similar efficiency.

Based on this encouraging result, the scope and limitations of this transfer hydrogenation were further extended. As seen in Table 3, α,β-unsaturated ketones (entries 4-7) bearing potentially reducible groups were hydrogenated efficiently and as expected. The reaction, if continued for a longer period, resulted in partial reduction of the carbonyl functions as well (31%) (entry 4b).

Since dehydroamino acid derivatives are potential precursors to phenyl alanine or alanine based amino acids and their synthesis is one of the major interests of our laboratory, we examined reduction of enamides (entries 8, 9) using PSF and catalytic palladium acetate. Interestingly, while compound (entry 8) was not reducible under the present conditions, the *p*-acetyl compound (entry 9) underwent smooth reduction in good yield (70%). Although this selectivity is difficult to explain with evidence, the nucleophilicity at the β-carbon might be one of the possibilities. Further studies are under active pursuit in this direction.

In order to broaden the scope of our study, we carried out reduction of C–N double bond of the imines. The imine (entry 10) under similar conditions afforded the secondary amine in excellent yield (85%). Since the imines were derived from the corresponding carbonyl compounds, this overall one-pot protocol may be termed as direct reductive amination of carbonyl compounds using PSF and catalytic palladium acetate.

Surprisingly, our reaction condition was found unsuccessful for reduction of simple alkyl cinnamate (entry 11) and nitro olefin (entry 12). Desai and Danks carried

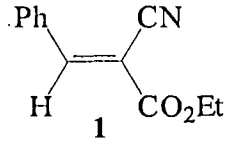
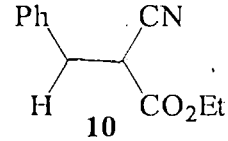
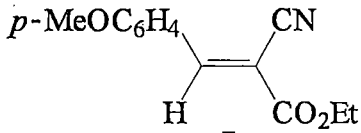
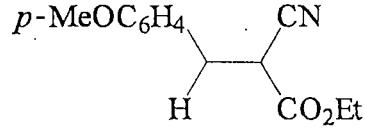
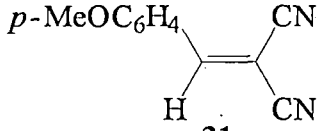
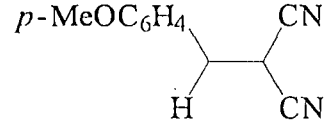
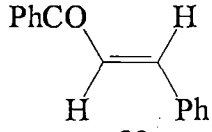
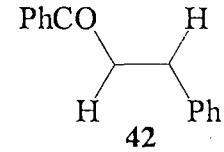
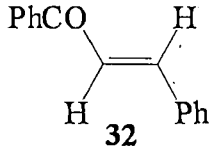
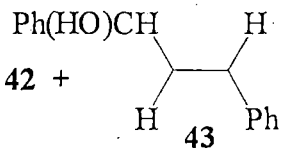
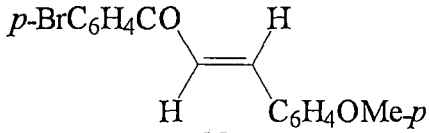
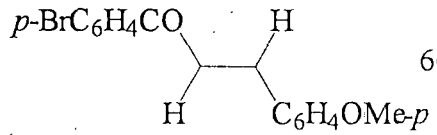
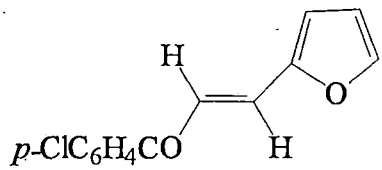
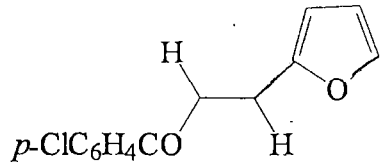
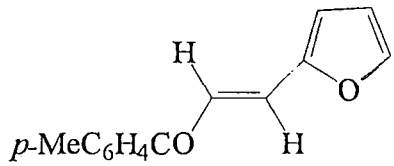
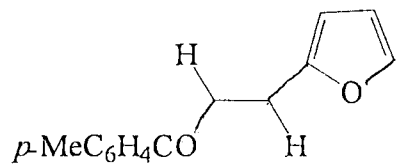
out reduction of alkyl cinnamate using PSF and $RhCl(PPh_3)_3$ (2.5 mol%) as the catalyst under microwave irradiation.[64] The nitro olefins are known to produce oximes under CTH using NH_4-formate.[67] We, however, obtained no change of the starting material while carrying out the reaction using PSF.

Dehalogenation of aromatic halides under CTH methods has been observed and the process is rapid while using microwaves.[68,69] The method described by Desai and Danks on the substrates was not employed to bearing reducible groups.[64]

From the overall observation, it appears that the rate of the reduction using PSF is slower than that using the HCOOK. The reason for this is not, however, clear at this point. Further mechanistic investigations will include in future work.

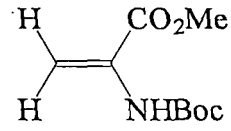
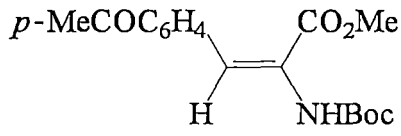
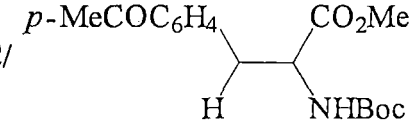
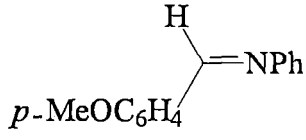
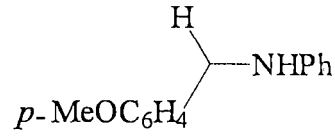
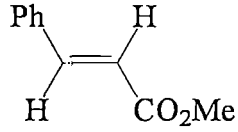
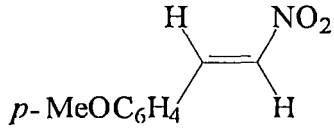
In conclusion we have shown that palladium-catalyzed transfer hydrogenation could be performed with a variety of electron-deficient alkenes as well as imines using the polymer supported formate (PSF) as the source of hydrogen. Some of the CTH methods employ formic acid and its salts, which have some drawbacks. As for example, ammonium formate often results in dehalogenation of aromatic halides[69] and formation of *N*-formanilide[70] from amine along with a practical problem due to its sublimable nature. Our method comprising potassium formate, although could eliminate the above problems, the present method involving PSF offers advantages over other formates in terms of environmental aspects. The method is operationally simple and applicable to a range of unsaturated organic compounds. The use of palladium catalyst showed some substrates selectivity. Other advantages are: clean work-up, high yields and environmentally benign. Future work will include studies directed towards mechanistic aspects as well as on the use of other transition metals complexes such as, rhodium and ruthenium metals with chelating phosphine complexes. The scale-up of the protocol and reuse of the resin-surface will also be studied as the extension work.

Table 3

Entry	Substrate	Temp./ Time	Product	% Yield
1.	 **1**	70 °C/ 10h	 **10**	85
2.	 **7**	70 °C/ 12h	 **16**	75
3.	 **31**	75 °C/ 10h	 **41**	81
4a.	 **32**	70 °C/ 10h	 **42**	82
4b.	 **32**	75 °C/ 16h	**42** +  **43**	56 +31
5.	 **33**	70 °C/ 12h	 **44**	60
6.	 **34**	70 °C/ 14h	 **45**	77
7.	 **35**	70 °C/ 14h	 **46**	70

Continued.....

Continued **Table 3**

Entry	Substrate	Temp./ Time	Product	% Yield
8.	 **36**	70 °C/ 14h	No reaction	
9.	 **37**	70 °C/ 10h	 **47**	70
10.	 **38**	70 °C/ 12h	 **48**	85
11.	 **39**	75 °C/ 14h	No reaction	
12.	 **40**	75 °C/ 14h	No reaction	

IC.3 Experimental

IC.3.1 Preparation of Polymer Supported Formate (PSF, Resin Formate)

Anion exchange resin (Amberlite' IRA-420 Cl^-, BDH, England) was packed on a column and then 10% HCOOH passed through the column in a drop by drop rate until a negative test for chloride ion ($AgNO_3$). After washing with water for several times, the resin was dried under vacuum. The resin thus obtained was ready for further application in hydrogenation reaction.

IC.3.2 4-Methoxybenzylidenemalononitrile (31)

A mixture of malononitrile (50 mmol), 4-methoxybenzaldehyde (55 mmol), ammonium acetate (10 mmol) and glacial acetic acid (40 mmol) in dry benzene (30 mL) was heated under reflux for 10 hours using Dean-Stark water separator. After usual work-up, the solvent was evaporated and the resultant solid was recrystallized from ether-light petroleum giving 4-methoxybenzylidenemalononitrile in 80% yield as yellow crystals, m.p. 113-114 ^{0}C [Lit.[71] 114-115 ^{0}C].

UV (MeOH): λ_{max} 348 nm.

IR (Nujol): ν_{max} 2310, 2222, 1512, 941, 833 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.93 (d, 2H, J = 8.4 Hz), 7.03 (d, 2H, J = 8.4 Hz), 6.67 (s, 1H), 3.99 (s, 3H).

IC.3.3 Preparation of α,β-unsaturated ketones

1,3-Diphenyl-2-propen-1-one (Chalcone) (32)

A solution of NaOH (0.8g) in water (8 mL) and rectified spirit (5 mL) was immersed in a bath of crushed ice and poured acetophenone (15 mmol). Then started the stirrer and add pure benzaldehyde (15 mmol). The temperature of the mixture was kept at about 25 ^{0}C and stirred vigorously for 3 hours. The reaction mixture kept in a refrigerator for overnight. Filter the product with suction on Buckner funnel, wash

with cold water until the washings are neutral to litmus. Recrystallized the solid from rectified spirit, m.p. 56-57 ^{0}C [Lit.[72] 56-57 ^{0}C].

UV (MeOH): λ_{max} 308.8 nm.

IR (Nujol): ν_{max} 3022, 2930, 1747, 1685, 1603, 1501, 1450, 1373, 1296 cm^{-1}.

Similarly the compounds (**33**), (**34**) and (**35**) were prepared from corresponding aldehydes and ketones.

1-(4-Bromophenyl)-3-(4-methoxyphenyl)-2-propen-1-one (33)

Yellow crystals, m.p. 143-144 ^{0}C.

UV (MeOH): λ_{max} 347.6 nm.

IR (Nujol): ν_{max} 3012, 2935, 1670, 1588, 1511, 1465, 1337, 1301 cm^{-1}.

1-(4-Chlorophenyl)-3-(furan-2-yl)-2-propen-1-one (34)

Yellow crystals, m.p. 83-84 ^{0}C.

UV (MeOH): λ_{max} 346.2 nm.

IR (Nujol): ν_{max} 3129, 3083, 1747, 1655, 1598, 1475, 1409, 1301, 1224 cm^{-1}.

3-(Furan-2-yl)-1-*p*-tolyl-2-propen-1-one (35)

Yellow crystals, m.p. 67-68 ^{0}C.

UV (MeOH): λ_{max} 347.0 nm.

IR (Nujol): ν_{max} 3155, 2919, 1757, 1655, 1603, 1552, 1481, 1332, 1286 cm^{-1}.

IC.3.4 Methyl 3-(4-acetophenyl)-2-(*tert*-butoxycarbonylamino)acrylate (37)

Step-1. L-Serine methyl ester hydrochloride

Acetyl chloride (2 mL, 28 mmol) was added dropwise over 10 minutes to dry methanol (13 mL) cooled to 0 ^{0}C and the resulting solution was stirred for 5 minutes. Solid L-serine (1 g, 10 mmol) was added in one portion and the solution heated to reflux for 2 hours. It was then allowed to come to room temperature and the excess

solvent was removed under reduced pressure. Trituration with dry ether gave the product as colourless solid.

Yield: 80.6% (1.25g), m.p. 115-116 ^{0}C.

Step-2. Methyl *N*-(*tert*-butoxycarbonyl)serinate

A heterogeneous mixture of L-serine methyl ester hydrochloride (5g, 32 mmol) in THF (100 mL) and Et_3N (7.0g, 69 mmol) was cooled to 0 ^{0}C and a solution of Boc_2O (7.15g, 31.8 mmol) in THF (50 mL) was added dropwise over a period of 30 minutes. The resulting mixture was allowed to warm to r.t. and stirred for 6 hours and then warmed to 50 ^{0}C and stirred at that temperature for 2 hours. The solvent was then removed *in vacuo* and the residue partitioned between ether (100 mL) and water (100 mL). The aqueous phase was extracted with ether (2×50 mL) and the combined ether extract was washed successively with 3% HCl (50 mL), 5% $NaHCO_3$ (50 mL) and brine (50 mL). It was then dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated to leave a pale yellow liquid which was purified by column chromatography over silica gel using EtOH-light petroleum (1:4) as eluent.

Yield: 94 % (6.65g).

IR (neat): ν_{max} 3400, 1715, 1514, 1368, 1165 cm^{-1}.

Step-3. Methyl 2-(*tert*-butoxycarbonylamino)acrylate (36)

A solution of methyl *N*-(*tert*-butoxycarbonyl)serinate (2.2g, 10 mmol) in CH_2Cl_2 (75 mL) was cooled to 0 ^{0}C and Et_3N (3g, 30 mmol) was added dropwise over 15 minutes to it. A solution of mesyl chloride (1.4 g, 12 mmol) in CH_2Cl_2 (25 mL) was then added dropwise over 30 minutes. The resulting solution was stirred for an hour at cold and then at r.t. for an additional hour. It was then washed successively with 0.5 % aq. $KHSO_4$ solution until neutral (25 mL), water and brine before being dried Na_2SO_4. Evaporation of solvent left a brown mass which was purified by column chromatography over silica gel using EtOH-light petroleum (1:15) as eluent. The product was obtained as a viscous liquid.

Yield: 82 % (1.61g).

IR (neat): ν_{max} 3423, 1718, 1634 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 7.1 (s, 1H, NH), 6.4; 5.8 (2H, vinyl), 4.0 (s, 3H, OMe), 1.7 (s, 9H).

Step-4. Methyl 3-(4-acetophenyl)-2-(*tert*-butoxycarbonylamino)acrylate (37)

A mixture of *p*-bromoacetophenone (0.597g, 3 mmol), methyl 2-(*tert*-butoxycarbonylamino)acrylate (**36**) (0.640g, 3.2 mmol), $Pd(OAc)_2$ (30mg, 0.13 mmol), Bu_4NBr (0.970g, 3 mmol) and $NaHCO_3$ (0.336g, 4 mmol) in DMF (8 mL) is stirred under a nitrogen atmosphere in a screw-cap sealed tube at 90 ^{0}C for 20 hours. After cooling, the reaction mixture is diluted with brine (30 mL) and extracted with ether (3×20 mL). The combined organic phase is washed with water (2×20 mL) and dried over Na_2SO_4. Evaporation of the solvent left a yellow residue which was purified by column chromatography over silica gel using EtOH-light petroleum (1:12) as eluent giving yellow crystals.

Yield: 77.31 % (0.740g), m.p. 94-95 ^{0}C.

UV (MeOH): λ_{max} 302 nm.

IR (Nujol): ν_{max} 3319, 2991, 1737, 1696, 1603, 1496, 1440 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.93 (d, 2H, J = 8.4 Hz), 7.60 (d, 2H, J = 8.4 Hz), 7.24 (s, 3H), 6.54 (br.s, 1H), 3.83 (s, 3H), 2.60 (s, 3H), 1.39 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 197.4, 165.6, 152.2, 139.0, 136.6, 129.5, 128.2, 127.4, 125.9, 81.2, 52.8, 28.0, 26.5.

Anal. Calcd. for $C_{17}H_{21}NO_5$ (319.36): C, 63.94; H, 6.63.

Found: C, 63.63; H, 6.89.

IC.3.5 *N*-(4-Methoxybenzylidene)aniline (38)

A solution of 4-methoxybenzaldehyde (1.36g, 10 mmol) and aniline (0.92g, 10 mmol) in rectified spirit (10 mL) was heated under reflux for 20 minutes. After cooling, the obtained solid filtered, washed with cold rectified spirit and recrystallized from aq. methanol to give white plates.

Yield 80 % (1.65g), m.p. 56-57 ^{0}C [Lit.[73] 57-58 ^{0}C].

UV (MeOH): λ_{max} 311.6 nm.

IC.3.6 Catalytic transfer reduction of alkenes, enamides and imine using Polymer Supported Formate (PSF, resin formate)

A representative procedure

Ethyl 2-cyano-3-phenylpropionate (10)

To a solution of ethyl 2-cyano-3-phenylacrylate (**1**) (0.203g, 1 mmol) in DMF (3 mL) was added $Pd(OAc)_2$ (5mg, 2 mol%). The reaction mixture was flashed with nitrogen and PSF (Resin Formate, 1 g) was added all at once. The reaction mixture was stirred in a screw-cap sealed tube at 70 ^{0}C for 10 hours. After cooling, the reaction mixture was diluted with water, filtered. The filtrate extracted with ether (3×15 mL). The combined ethereal layer was washed with brine, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by column chromatography over silica gel using EtOH-light petroleum (1:19) as eluent to furnish the desired product as colourless oil in 85 % (0.174g) yield. The TLC, ^{1}H- and ^{13}C-NMR spectra were identical as prepared previously by using HCOOK as hydrogen donor (page 35).

Using the same method the following compounds (**16**), (**41**)-(**48**) were prepared from their respective starting materials during the time and temperature as mentioned.

Ethyl 2-cyano-3-(4-methoxyphenyl)propionate (16)

Time: 12h; Temp: 70 ^{0}C.

Yield: 75 % (0.174g).

The TLC, ^{1}H- and ^{13}C-NMR spectra of this compound were identical with product as prepared previously by using HCOOK as hydrogen donor (page 37).

4-Methoxybenzylmalononitrile (41)

Time: 10h; Temp: 75 ^{0}C.

Yield: 81 % (0.150g), white crystal, m.p. 90-92 ^{0}C.

UV (MeOH): λ_{max} 226 nm.

IR (Nujol): ν_{max} 3022, 2259, 1614, 1511, 1260 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.17 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 3.79 (t, 1H, J = 6.8 Hz), 3.7 (s, 3H), 3.16 (d, 2H, J = 6.8 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 159.9, 130.3, 124.9, 115.0, 112.3, 55.3, 36.0, 25.2.

1,3-Diphenylpropan-1-one (42)

Time: 10h; Temp: 70 ^{0}C.

Yield: 82 % (0.172g), Light yellow crystals, m.p. 70-71 ^{0}C [Lit.[72] 73 ^{0}C].

UV (MeOH): λ_{max} 244.2 nm.

IR (Nujol): ν_{max} 3032, 2935, 1603, 1450, 1368, 1143 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.99 (dd, 2H, J = 6.0; 1.9 Hz), 7.55-7.52 (m, 1H), 7.47-7.42 (m, 2H), 7.30-7.20 (m, 5H), 3.30 (t, 2H, J = 7.1 Hz), 3.07 (t, 2H, J = 7.1 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 200.2, 142.3, 137.8, 134.0, 129.6, 127.1, 41.4, 31.1.

1,3-Diphenylpropan-1-ol (43)

Time: 16h; Temp: 75 ^{0}C.

Yield: 31 % (0.066g), Liquid.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.41-7.13 (m, 10H), 4.58 (t, 1H, J = 6.6 Hz), 2.73-2.54 (m, 2H), 2.38 (br. s, 1H, -OH, D_2O-exchangeable), 2.13-1.90 (m, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 144.5, 141.7, 128.4, 128.3, 128.2 127.5, 125.9, 125.7, 73.7, 40.3, 31.9.

1-(4-Bromophenyl)-3-(4-methoxyphenyl)propan-1-one (44)

Time: 12h; Temp: 70 ^{0}C.

Yield: 60 % (0.192g), yellow crystals, m.p. 67-68 ^{0}C.

UV (MeOH): λ_{max} 228.4 nm.

IR (Nujol): ν_{max} 2991, 2940, 1680, 1603, 1505, 1450, 1378, 1301, 1240 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.94 (d, 2H, J = 7.2 Hz), 7.43 (d, 2H, J = 7.2 Hz), 7.14 (d, 2H, J = 8.5 Hz), 6.83 (d, 2H, J = 8.5 Hz), 3.76 (s, 3H), 3.24 (t, 2H, J = 7.2 Hz), 3.00 (t, 2H, J = 7.2 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 201.1, 159.7, 138.6, 135.0, 134.7, 131.1, 130.3, 129.8, 115.7, 57.0, 42.4, 31.0.

1-(4-Chlorophenyl)-3-(furan-2-yl)propan-1-one (45)

Time: 14h; Temp: 70 ^{0}C.

Yield: 77 % (0.180g), viscous liquid.

UV (MeOH): λ_{max} 241.8 nm.

IR (neat): ν_{max} 1726, 1685, 1598, 1450, 1363, 1214 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.97 (d, 2H, J = 7.8 Hz), 7.47 (d, 2H, J = 7.8 Hz), 7.57 (m, 1H), 7.44 (m, 1H), 7.31 (m, 1H), 3.34 (t, 2H, J = 7.8 Hz), 3.09 (t, 2H, J = 7.8 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 198.6, 154.7, 141.1, 136.6, 133.1, 128.6, 128.0, 110.2, 105.3, 36.9, 22.4.

3-(Furan-2-yl)-1-*p*-tolylpropan-1-one (46)

Time: 14h; Temp: 70 ^{0}C.

Yield: 70 % (0.150g), white crystals, m.p. 77- 78 ^{0}C.

UV (MeOH): λ_{max} 252.4 nm.

IR (Nujol): ν_{max} 3124, 2930, 1680, 1603, 1516, 1414, 1306, 1178 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.80 (d, 2H, J = 8.0 Hz), 7.21 (dd, 1H, J = 3.1; 1.1 Hz), 7.18 (d, 2H, J = 8.0 Hz), 6.21 (dd, 1H, 3.1; 1.9 Hz), 5.97 (d, 1H, J = 2.4 Hz), 3.23 (t, 2H, J = 7.3 Hz), 3.00 (t, 2H, J = 7.3 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 198.3, 154.9, 143.9, 141.1, 134.3, 129.3, 128.1, 110.2, 105.3, 36.8, 22.6, 21.6.

Methy 3-(4-acetophenyl)-2-(*tert*-butoxycarbonylamino)propionate (47)

Time: 10h; Temp: 70 ^{0}C.

Yield: 70 % (0.224g), Colourless crystal, m.p. 72-73 ^{0}C.

UV (MeOH): λ_{max} 248 nm.

IR (Nujol): ν_{max} 3360, 2996, 1752, 1670, 1609, 1516, 1455, 1373 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.87 (d, 2H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.1 Hz), 5.05 (d, 2H, J = 7.7 Hz), 4.59 (t, 1H), 3.69 (s, 3H), 2.55 (s, 3H), 1.38 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 197.7, 171.9, 154.9, 141.7, 135.8, 129.5, 128.5, 54.1, 52.3, 38.3, 29.6, 28.2, 26.5.

Anal. Calcd. for $C_{17}H_{23}NO_5$ (321.38): C, 63.54; H, 7.21.

Found: C, 63.28; H, 7.62.

N-(4-Methoxylbenzyl)aniline (48)

Time: 10h; Temp: 70 ^{0}C.

Yield: 85 % (0.182g), pale yellow crystals, m.p. 44-45 ^{0}C [Lit[73] 46-47 ^{0}C].

UV (MeOH): λ_{max} 247.2 nm.

IR (neat): ν_{max} 2930, 1609, 1511, 1465, 1250 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.29 (d, 2H, J = 8.6 Hz), 7.18 (d, 2H, J = 8.6 Hz), 6.88-6.85 (m, 2H), 6.74 (t, 1H, J = 7.2 Hz), 6.66 (d, 2H, J = 8.5 Hz), 4.25 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 158.8, 147.5, 130.9, 129.8, 129.1, 118.0, 114.0, 113.3, 55.3, 48.1.

IC.4 References

1. (a) Sammelson, R.E.; Kurth, M. *Chem. Rev.* **2001**, *101*, 137. (b) Booth, R.J.; Hodges, J.C. *Acc. Chem. Res.* **1999**, *32*, 18.
2. Atherton, E.; Sheppard, R.C. In *Solid Phase Peptide Synthesis: A Practical Approach*; Oxford University Press, 1989.
3. Gait, J.M. In *Solid Phase Oligonucleotide Synthesis: A Practical Approach*; IRL, Oxford, 1989.
4. (a) Hermkens, P.H.H.; Otterheijm, H.C.J.; Rees, D.C. *Tetrahedron* **1996**, *52*, 4527. (b) Hermkens, P.H.H.; Otterheijm, H.C.J.; Rees, D.C.; *Tetrahedron* **1997**, *53*, 5643.
5. Merrifield, R.B.; *J. Am. Chem. Soc.* **1963**, *85*, 2149.
6. (a) Krchnak, V.; Holladay, M.W. *Chem. Rev.* **2002**, *102*, 61. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed. Eng.* **2001**, *40*, 650. (c) Brown, R.C.D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293. (d) Akelah, A. *Synthesis* **1981**, 413. (e) Akelah, A.; Sherrington, D.C. *Chem. Rev.* **1981**, *81*, 557.
7. (a) Leznoff, C.C. *Chem. Soc. Rev.* **1974**, *3*, 65. (b) Leznoff, C.C. *Acc. Chem. Res.* **1978**, *11*, 327.
8. Frechet, J.M.J. *Tetrahedron* **1981**, *37*, 663.
9. Crowly, J.J.; Rapoport, H. *Acc. Chem. Res.* **1976**, *9*, 135.
10. Merrifield, R.B. *Peptides* **1995**, *16*, 93.
11. Czarnik, A.W. *Biotechnol. Bioeng. (Combinat. Chem.)* **1998**, *61*, 77.
12. Li, W.; Yan, B. *J. Org. Chem.* **1998**, *63*, 4092.
13. Hutchins, S.M.; Chapman, K.T.; *Tetrahedron Lett.* **1994**, *35*, 4055.
14. Danishefsky, S.J.; McClure, K.F.; Randloph, J.T.; Ruggeri, R.B. *Science* **1993**, *260*, 1307.
15. Bunin, B.A.; Plunkett, M.J.; Ellman, J.A. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4708.
16. DeWitt, S.H.; Kiely, J.S.; Stankovic, C.J.; Schroeder, M.C.; Cody, D.M.R.; Pavia, M.R. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909.
17. Moon, H.; Schore, N.E.; Kurth, M.J. *J. Org. Chem.* **1992**, *57*, 6088.
18. Chen, C.; Randall, L.A.A.; Miller, R.B.; Jones, A.D.; Kurth, M.J. *J. Am. Chem. Soc.* **1994**, *116*, 2661.

19. Ojima, I.; Tsai, C.-Y.; Zhang, Z. *Tetrahedron Lett.* **1994**, *35*, 5785.

20. Pei, Y.; Moos, W.H. *Tetrahedron Lett.* **1994**, *35*, 5825.

21. (a) Franjen, R. *Can. J. Chem.* **2000**, *78*, 957. (b) Frenette, R.; Friesen, R.W. *Tetrahedron Lett.* **1994**, *35*, 9177. (c) Yu, K.-L.; Deshpande, M.S.; Vyas, D.M. *Tetrahedron Lett.* **1994**, *35*, 8919. (d) Deshpande, M.S. *Tetrahedron Lett.* **1994**, *35*, 5613. (e) Lin, K.; Song, M.; Cai, D.; Hao, X.; Wu, Y. *Tetrahedron Lett.* **2003**, *44*, 3955. (f) Atrash, B.; Reader, J.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 4779.

22. Geysen, H. M.; Rodda, S.J.; Mason, T.J. *Mol. Immunol.* **1986**, *23*, 709.

23. (a) Geysen, H. M.; Meloen, R.H.; Barteling, S.J. *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 3998. (b) Maeji, N.J.; Bray, A.M.; Geysen, H. M. *J. Immunol. Methods* **1990**, *134*, 23. (c) Valerio, R.M.; Bray, A.M.; Campbell, R.A.; Dipasquale, A.; Margellis, C.; Rodda, S.J.; Geysen, H. M.; Maeji, N.J. *Int. J. Pept. Protein Res.* **1993**, *39*, 1.

24. Houghten, R.A. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5131.

25. Lam, K.S.; Sroka, T.; Chen, M.L.; Zhao, Y.; Lou, Q.; Wu, J.; Zhao, Z.G. *Life Sci.* **1998**, *62*, 1577.

26. Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. *Int. J. Pept. Protein Res.* **1991**, *37*, 487.

27. (a) Ostresh, J.M.; Winkle, J.H.; Hamashin, V.T.; Houghten, R.A. *Biopolymers* **1994**, *53*, 1681. (b) Eichler, J.; Lucka, A.W.; Houghten, R.A. *Pept. Res.* **1994**, *7*, 300. (d) Houghten, R.A. *Annu. Rev. Pharmacol. Toxicol.* **2000**, *40*, 273. (e) Houghten, R.A.; Pinilla, C.; Appel, J.R.; Blodelle, S.E.; Dooley, C.T.; Eichler, J.; Nefzi, A.; Ostresh, J.M. *J. Med. Chem.* **1999**, *42*, 3743.

28. Bunin, B.A.; Ellman, J.A. *J. Am. Chem. Soc.* **1992**, *114*, 10997.

29. Blaney, P.; Grigg, R.; Shridharan, V. *Chem. Rev.* **2002**, *102*, 2607.

30. Nicolaou, K.C.; Pfefferkorn, J.A.; *Biopolymers* **2001**, *60*, 171.

31. a) Francis, M.B.; Jamison, T.F.; Jacobsen, E.N. *Curr. Opin. Chem. Biol.* **1998**, *2*, 422; b) Reetz, M.T. *Angew. Chem., Int. Ed. Eng.* **2001**, *40*, 284.

32. Tietze, L.F.; Hippe, T.; Steinmetz, A. *Synlett* **1996**, 1043.

33. Allin S.M.; Shuttleworth, S.J. *Tetrahedron Lett.* **1996**, *37*, 8023.

34. Kobayashi, S.; Moriwaki, M. *Tetrahedron Lett.* **1997**, *38*, 4251.

35. Prien, O.; Rolfing, K.; Thiel, M.; Kunzer, H. *Synlett* **1997**, 325.

36. Crawshaw, M.; Hird, N.W.; Irie, K.; Nagai, K. *Tetrahedron Lett.* **1997**, *38*, 7115.

37. (a) Hollinshead, S.P. *Tetrahedron Lett.* **1996**, *37*, 9157. (b) Bicknell, A.J.; Hird, N.W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2441.

38. Marx, M.A.; Grillot, A.-L.; Louer, C.T.; Beaver, K.A.; Bartlett, P.A. *J. Am. Chem. Soc.* **1997**, *119*, 6153.

39. Bolli, M.H.; Ley, S.V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2243.

40. Chamoin, S.; Houldsworth, S.; Kruse, C.G.; Bakker, W.I.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4179.

41. Leznoff, C.C. Wong, J.Y. *Can. J. Chem.* **1973**, *51*, 3756.

42. Hiroshige, M.; Hauske, J.R.; Zhou, P. *Tetrahedron Lett.* **1995**, *36*, 4567.

43. Forman, F.W.; Suchoeiki, I. *J. Org. Chem.* **1995**, *60*, 523.

44. Lee, J.; Murray, W.V.; Rivero, R.A. *J. Org. Chem.* **1997**, *62*, 3874.

45. (a) Krchnak, V.; Weichsel, A.S. *Tetrahedron Lett.* **1997**, *38*, 7299. (b) Gray, N.S.; Kwon, S.; Schultz, P.G. *Tetrahedron Lett.* **1997**, *38*, 1161.

46. (a) Mathews, J.; Rivero, R.A. *J. Org. Chem.* **1997**, *62*, 6090. (b) Rockwell, A.; Melden, M.; Copeland, R.A.; Hardman, K.; Decicco, C.P.; DeGrado, W.F. *J. Am. Chem. Soc.* **1996**, *118*, 10337.

47. Sarantakis, D.; Bicksler, J.J. *Tetrahedron Lett.* **1997**, *38*, 7325.

48. Altava, B.; Burguete, M.I.; Collado, M.; Luis, S.V.; Pozo, O.; Salvador, R.S. *Anal. Quim.* **1997**, *93*, 260.

49. Miller, S.C.; Scanlan, T.S. *J. Am. Chem. Soc.* **1997**, *119*, 2301.

50. Ley, S.V.; Bolli, M.H.; Hinzen, B.; Gerois, A.-G.; Hall, B.J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2239.

51. Furth, P.S.; Reitman, M.S.; Cook, A.F. *Tetrahedron Lett.* **1997**, *38*, 5403.

52. Yan, B.; Fell, J.B.; Kumaravel, G. *J. Org. Chem.* **1996**, *61*, 7467.

53. Hinzen, B.; Ley, S.V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1907.

54. LeHetet, C.; David, M.; Carreaux, F.; Carboni, B.; Sauleau, A. *Tetrahedron Lett.* **1997**, *38*, 5153.

55. Kirschning, A. *J. Prakt. Chem.* **2000**, *342*, 508.

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

57. (a) Hutchins, R.O.; Natale, N.R.; Taffer, I.M. *J. Chem. Soc.,Chem. Commun.* **1978**, 1088. (b) Yakabe, S.; Hirano, M.; Morimoto, T. *Synth. Commun.* **1999**, *29*, 295.

58. Yoon, N.M.; Park, K.B.; Gyoung, Y.S. *Tetrahedron Lett.* **1983**, *24*, 5367.

59. Sande, A.R.; Jagdale, M.H.; Mane, R.B.; Salunkhe, M.M. *Tetrahedron Lett.* **1984**, *25*, 3501.

60. Weber, J.V.; Faller, P.; Schneider, M. *C. R. Acad. Sci. Ser. 2* **299**, 1259, **1984**.

61. Kabalka, G.W.; Wadgaonkar, P.P.; Chatla, N. *Synth. Commun.* **1990**, *20*, 293.

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

63. Shim, T.B.; Yoon, N.M. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1101.

64. Desai, B.; Danks, T. N. *Tetrahedron Lett.* **2001**, *42*, 5963.

65. Kamal, A.; Reddy, K.L.; Devaiah, V.; Reddy, G.S.K. *Tetrahedron Lett.* **2003**, *44*, 4741.

66. Leadbeater, N.E. *J. Org. Chem.* **2001**, *66*, 2168.

67. Kabalka, G.W.; Pace, R.D.; Wadgaonkar, P.P. *Synth. Commun.* **1990**, *20*, 2453.

68. Banik, B.K.; Barakat, K.J.; Wagle, D.R.; Manhas, M.S.; Bose, A.K. *J. Org. Chem.* **1999**, *64*, 5746.

69. (a) Ram, S.; Ehrenkaufer, R.E. *Synthesis* **1988**, 91. (b) Ranu, B.C.; Sarkar, A.; Guchhait, S.K.; Ghosh, K. *J. Indian Chem. Soc.* **1998**, *75*, 690.

70. Reddy, P.G.; Kumar, G.D.K.; Baskaran, S. *Tetrahedron Lett.* **2000**, *41*, 9149.

71. Su, C.; Chen, Z.-C.; Zheng, Q.-G. *Synthesis* **2003**, 555.

72. Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. *Vogel's Text Book of Practical Organic Chemistry,* 5th edn.; Addison Wesley Longman Ltd. Harlow, 1989, 1034.

73. Ref. 72, p906.

Part II

Pd-Catalyzed C–N Hetero Cross Coupling Reactions: Synthesis of Amino Pyridines

II.1 Introduction: A Brief Review on Pd-Catalyzed C–N Hetero Cross Coupling Reactions

Aromatic amines are important substructures in natural products and are widely used in various organic materials.[1] Arylamines are attractive targets for chemical synthesis because of their prevalence and wide utility. One of their earliest applications was in the production of brightly coloured synthetic dyes, introduced in the late nineteenth century.[2] Arylamines have a large number of other applications and are thus attractive targets for chemical synthesis. They are found in biologically active compounds such as pharmaceuticals[3] and agrochemicals.[4] Several commonly occurring DNA lesions are arylamines, and they have been the target of recent synthetic efforts.[5] Arylamines have also been employed as ligands for transition metals,[6] and in the design of conductive polymers[1b] and other electronically interesting materials.[7]

Among hetero aromatic amines, aminopyridines are important compounds with a variety of applications. They are used as acyl transfer reagents in organic chemistry[8] and as ligands in inorganic and organometallic chemistry,[9] as fluorescent dyes[10] and are biologically important as central nervous system stimulant.[11]

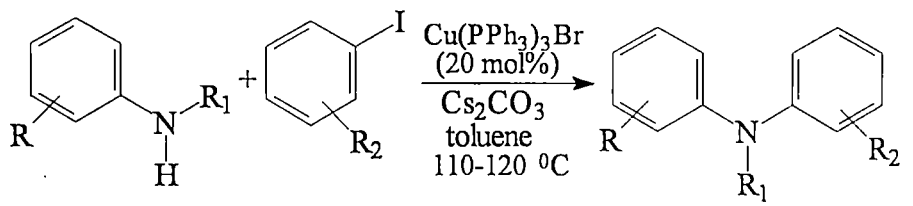
The historical importance of aromatic amines, which is also reflected in their industrial relevance, spurred interest in developing methods for their production. Over the years a number of cleverly designed and extremely useful methods of aryl C–N bond formation have been reported.[12] Most of the early preparative methods for aromatic amines involve electrophilic nitration and subsequent reduction, alkylation and dealkylation of amines, rearrangement, hydrogenolysis, aromatic nucleophilic substitution by S_NAr, benzyne or $S_{RN}1$ reactions.[13]

One of the most widely used methods for the synthesis of arylamines is the Ullmann coupling, in which an amine is coupled with an aryl halide in the presence of base and a copper catalyst.[12e]

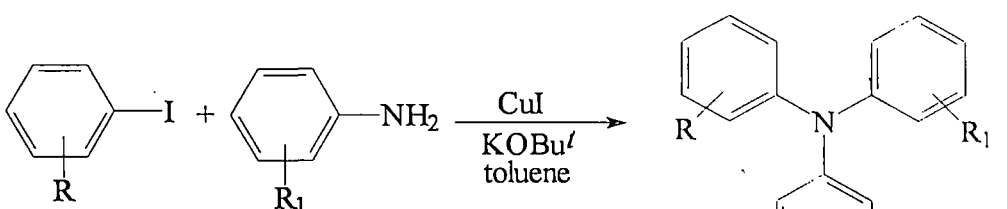
$$NuH + ArX \xrightarrow[\text{Base}]{\text{Cu metal or salts}} ArNu + HX$$

Nu = ArNH, Ar_2N; X = Br, Cl, I
Base = K_2CO_3, KOH, NaH

Traditionally, copper-catalyzed Ullmann coupling protocols necessitate the use of high temperature (>200 ^{0}C) providing low to moderate yield of amines and often require the use of stoichiometric amounts of copper reagents, which, on scale, leads to problems of waste disposal.[12b,14] Additionally, they have been plagued by poor substrate scope. However, there has been a resurgence of more economical copper-mediated systems that circumvent the limitations of classical Ullmann-Goldberg type couplings, which are known to require harsh reaction conditions.[15] Recently, milder Ullmann-type processes for C-N bond formation such as *N*-arylation of anilines,[16] amides,[17] imidazoles,[18] indoles,[17] and hydrazines[19] have been reported. Progress in the arylation of aliphatic amines, however, has been realized only in the context of chelating substrates,[15b] such as α- and β-amino acids[20] and β-amino alcohols[21] or in strategies utilizing less convenient or most costly arylating agents.[22] Gujadhur *et al.*[16b,c] have found that the copper complex $Cu(PPh_3)_3Br$, is active for amination of mono- and diarylamines to di- and triarylamines, respectively, using Cs_2CO_3 as a base at 120 ^{0}C.



Similarly Goodbrand and Hu[15a] have reported ligand-accelerated single-step catalytic synthesis of triarylamines with high selectivity using CuCl/1,10-phenanthroline catalyst system and KOH as a base at 125 ^{0}C. Chaudhari *et al.*[16a] described a simple and efficient methodology for the synthesis of triarylamines in a single step using a ligand-free CuI catalyst and potassium tertiary butoxide as the base.



R = H, *p*-OMe

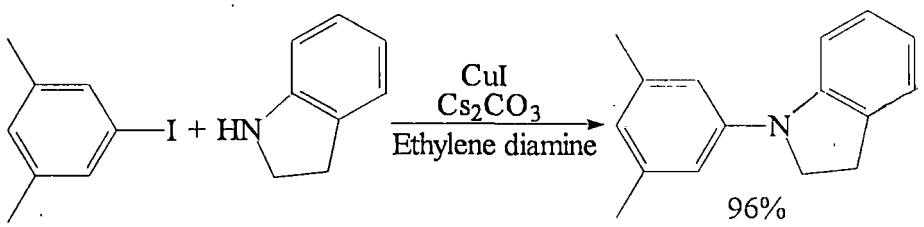
R_1 = H, *o*-Me, *p*-Me, *o*-OMe, *p*-OMe

90-99%

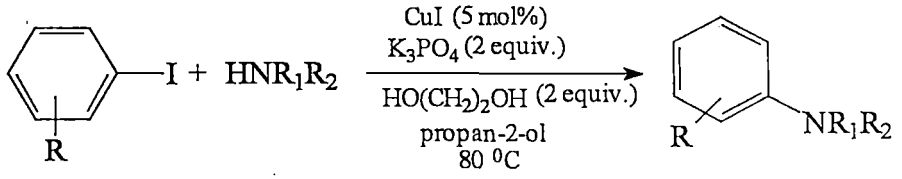
Kang *et al.*[22a] demonstrated the Cu-catalyzed *N*-arylation of amines with hypervalent iodonium compounds with secondary aliphatic amines, aromatic amines, azoles and amides accomplishing with catalytic CuI (10 mol%) or $Cu(acac)_2$ (5 mol%) in the presence of Na_2CO_3 or K_2CO_3 as a base in CH_2Cl_2 or toluene under mild conditions. The advantage of this method is that it can be carried out at room temperature and with weak base.

$$R_1R_2NH + ArIBF_4 \xrightarrow[Na_2CO_3 \text{ or } K_2CO_3]{CuI \text{ or } Cu(acac)_2 \text{ (cat)}} R_1R_2NAr$$

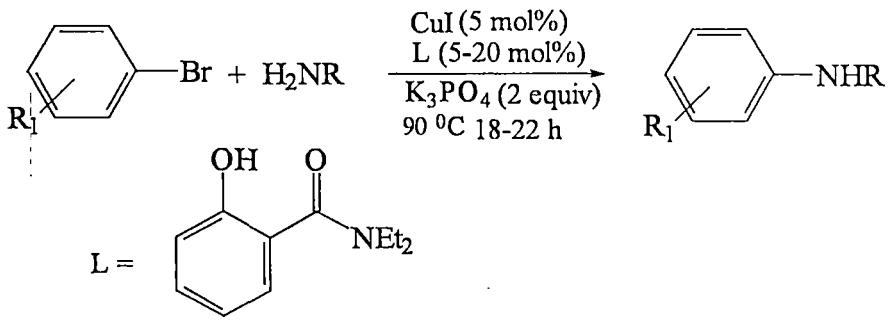
Kang *et al.*[17b] also described the Cu-catalyzed *N*-arylation of benzamides or nitrogen heterocycles with catalytic CuI (10 mol %) in the presence of ethylene diamine (10 mol %) as a ligand and K_3PO_4 or Cs_2CO_3 as a base under mild conditions.



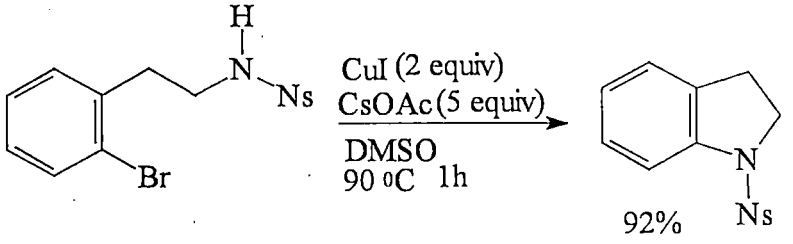
Recently, Buchwald *et al.*[17c] reported a mild, practical Cu-catalyzed amination of functionalized aryl iodides using air stable CuI as the catalyst, ethylene glycol as the ligand and unpurified propan-2-ol as the solvent. These reactions can be performed without protection from air or moisture.



Very recently, Kwong and Buchwald[23] reported a mild Cu-catalyzed coupling of primary amines to functionalized aryl bromides using air-stable CuI as the catalyst and structurally simple salicylamides as ligands.



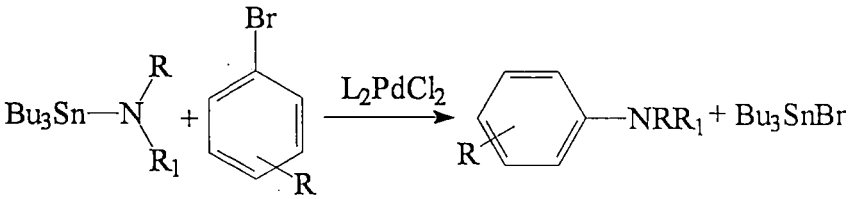
A unique combination of CuI and cesium acetate was found to mediate intramolecular amination of aryl halides under mild conditions.[24]



The catalytic amination of aryl halides represents a mild alternative to classical methods of aryl C–N bond formation and has many potential applications for the synthesis of aniline derivatives which are inaccessible through other routes.[25] Palladium-catalyzed amination reactions are fundamentally important organic transformations that have received tremendous attention over the past few years.[26] The transition metal-mediated coupling of amines with aryl halides is regeoselective, does not require activating groups, and occurs under relatively mild conditions. Recently, Buchwald *et al.*[27] and Hartwig *et al.*[28] have demonstrated a valuable method of palladium-catalyzed amination of various aryl halides and triflates with amines as a powerful tool for the synthesis of a variety of arylamines. The reactions can be carried out at a lower temperature under mild conditions than the copper-mediated classical Ullmann condensation. Elegant work by Buchwald,[27] Hartwig,[28] and others[29] has led to significant improvements in amination methodology since its discovery by Migita and co-workers in 1983.[30] Most of the reported methods employ electron-rich phosphine ligands,[31] possessing either a ferrocene[32] or a biphenyl backbone,[33] or bulky nucleophilic *N*-heterocyclic carbenes (sometimes referred to as "phosphine mimics").[29a,b,34] Chelating phosphines such as 1,1'-bis(diphenylphosphino)ferrocene (DPPF)[35] and 2,2'-bis(diphenylphosphino)1,1'-binaphthayl (BINAP)[36] have been demonstrated to exhibit improved catalytic activity in this type of transformation.

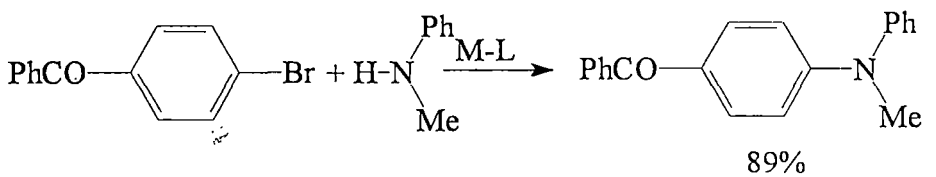
Commonly used base in palladium-catalyzed aminations are sodium *tert*-butoxide (*t*-BuONa),[27] Cs_2CO_3,[37] K_3PO_4,[28] MeONa and ^{i}PrONa.[39] The combination Pd/racemic BINAP is an excellent catalyst system for the coupling of primary amines with aryl bromides.[36] Additionally, the BINAP catalyst system functions well in the presence of the weak base Cs_2CO_3, allowing for a high level of functional group tolerance.[37] Although a general protocol had been developed for the palladium catalyzed cross coupling of primary and secondary amines with aryl bromides using sodium *tert*-butoxide (*t*-BuONa),[36a] this base presented problems with a number of common functional groups such as, esters, aldehydes, enolizable ketones, nitriles and nitro groups. The scope of this method was further expanded by the use of Cs_2CO_3,[36b,37] allowing the coupling of aryl bromides which were incompatible with *t*-BuONa.

Migita and co-workers[30] reported the first examples of the palladium catalyzed transformation of aryl bromides to arylamines *via* the uses of aminostannanes as activated amine.



$L_2PdCl_2 = [PdCl_2\{P(o\text{-tolyl})_3\}_2]$

Guram and Buchwald[40] subsequently developed methodology in which the Migita process was generalized and greatly simplified. The use of stoichiometric amounts of organotin compounds is the main disadvantage of this method both for ecological reasons and with regard to practicability. Independently, Buchwald *et al.*[41] and Hartwig *et al.*[42] reported the first catalytic amination of aryl bromides with free amines. Instead of isolation or generation of a tin amide *in situ*, the amination reactions were conducted by reaction of an aryl halide with the combination of amine and stoichiometric amounts of sterically hindered base such as, *t*-BuONa or silylamide base in toluene or THF at temperature 65-100 ^{0}C.

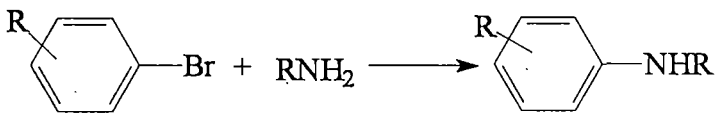


89%

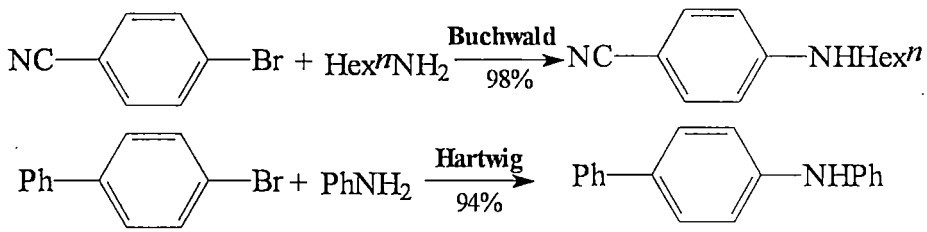
M-L = $Pd(dba)_2/2P(o\text{-tolyl})_3$ or $PdCl_2\{P(o\text{-tolyl})_3\}_2$

The research groups of Buchwald[36a] and Hartwig[35] reported amination reactions with palladium complexes of BINAP and DPPF as catalysts. These palladium complexes provided aminations of aryl bromides and iodides with primary alkyl amines, with cyclic secondary amines, and with anilines. It is ironic that the amination chemistry was first discovered upon use of a particular labile phosphane, but dramatically improved by the use of chelating ligands.

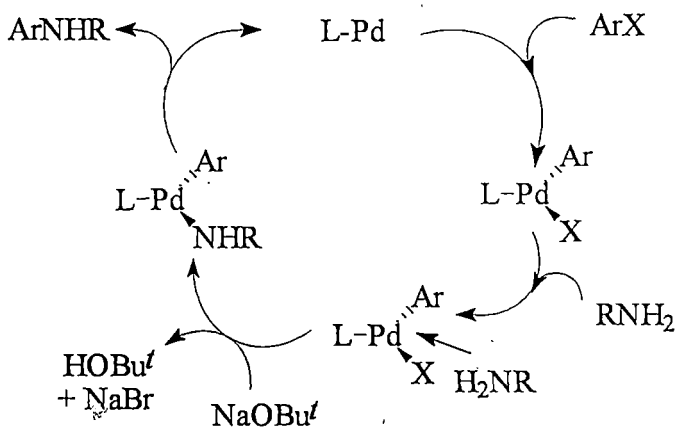
The Buchwald group found that a combination of $Pd_2(dba)_3$ and BINAP in the presence of *t*-BuONa performed as a superior catalyst for the cross coupling of amines with aryl bromides to afford aniline derivatives.[36a] The efficiency of BINAP as a ligand may be attributed to its ability to inhibit the formation of catalytically inactive palladium bis(amine) aryl halide complexes. This remarkable protocol is illustrated by the catalytic cross-coupling of 4-cyanobromobenzene with *n*-hexylamine to give the aminated product in 98% yield using only 0.05 mol% of catalyst.



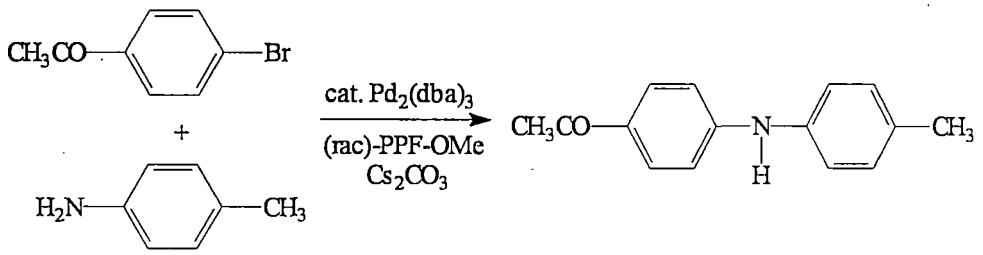
Buchwald	**Hartwig**
cat. $Pd_2(dba)_3$	cat. $(DPPF)PdCl_2$
BINAP	DPPF
$NaOBu^t$	$NaOBu^t$
toluene, 80 °C	THF, 100 °C



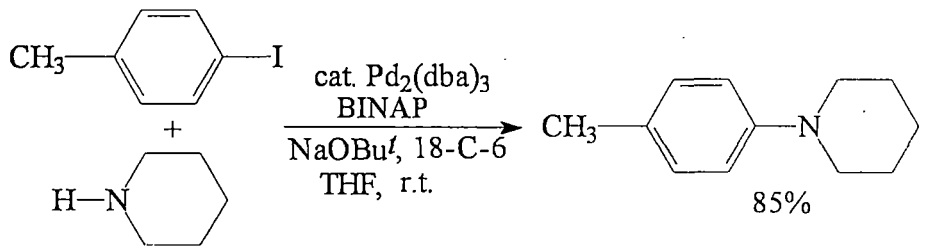
The Hartwig group discovered that $(DPPF)PdCl_2$ catalyst provide high yields of mixed, secondary arylamines from aryl halides and primary amines, notably in examples that gave low to moderate yields with the Pd(0)/P(*o*-tolyl)$_3$ catalyst system.[35] This study revealed several important concepts; firstly, the catalyst involves bis(phosphine) intermediates. Second, sterically encumbered phosphines are not necessary for the high-yielding, intermolecular amination of aryl halides. Finally, the observed favourable selectivity for reductive elimination over β-hydrogen elimination results from chelation and large bite angle, rather than from steric effects.



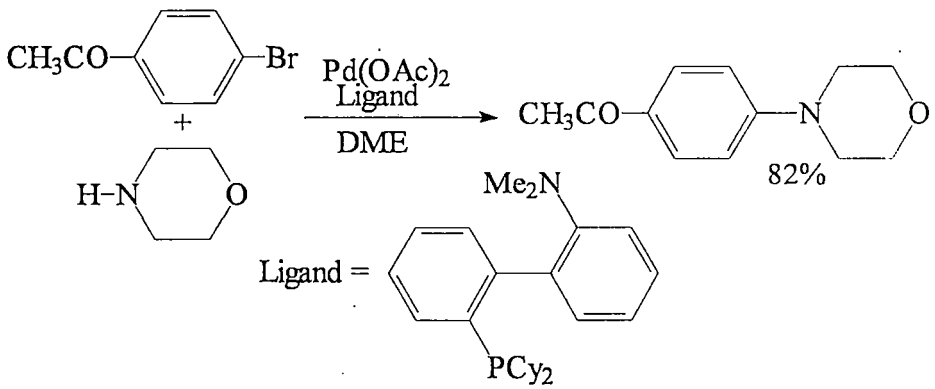
Buchwald *et al.*[32a] discovered that the ligand (*rac*)-PPF-OMe was superior for effecting aminations with acyclic secondary amines. It was noted that the combination of $Pd_2(dba)_3$ and (*rac*)-PPF-OMe allowed the reaction to proceed with the weaker base Cs_2CO_3. These new conditions are sufficiently mild to tolerate the presence of methyl and ethyl esters aldehydes, enolizable ketones and nitro groups, which are incompatible with reaction conditions which employ *t*-BuONa as the stoichiometric base.[37]



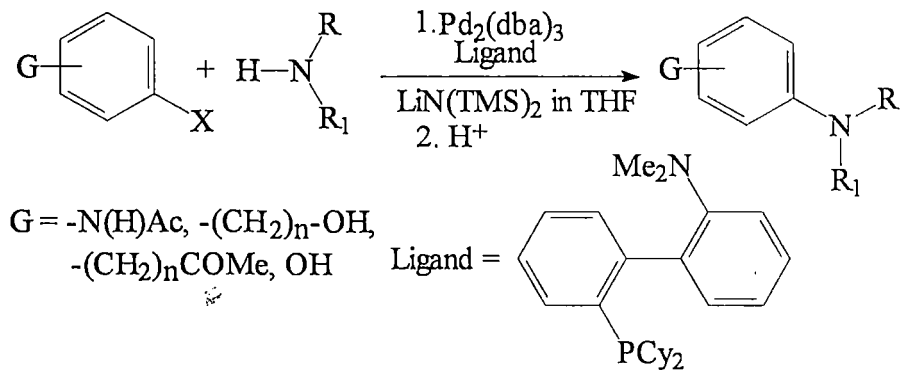
A further improvement in procedure has been reported by Wolfe and Buchwald,[43] which allows the catalytic amination of aryl iodides with piperidine in the presence of stoichiometric quantities of *t*-BuONa and 18-crown-6 and a catalytic amount of $Pd_2(dba)_3$/BINAP. This is a significant advancement for reactions involving thermally sensitive molecules or where it may be inconvenient to heat reaction mixture such as for large parallel syntheses or applications in combinatorial chemistry.



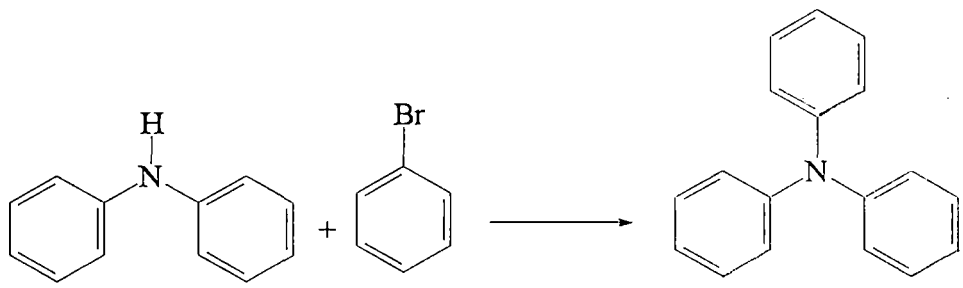
Buchwald *et al.*[33a,38] reported the palladium catalyzed amination of 4-bromoacetophenone with morpholine in the presence of $Pd(OAc)_2$, ligand, K_3PO_4 in DME.



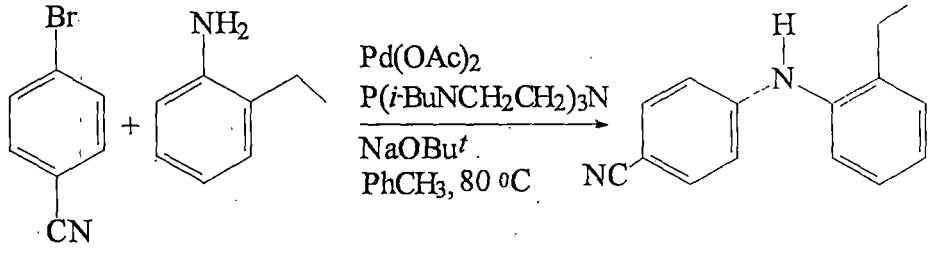
Recently, Buchwald *et al.*[44] described a method for the coupling reaction of amines with aryl halides containing alcohol, phenol, amide, or keto groups in the presence of $LiN(TMS)_2$.



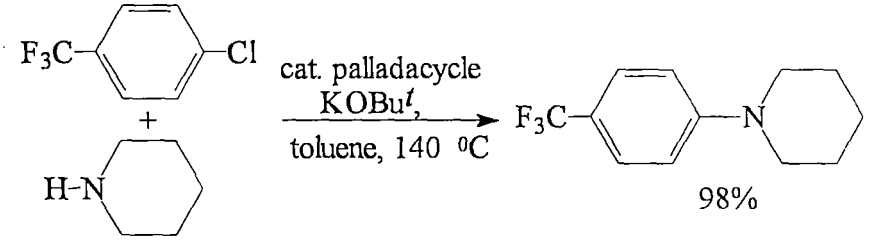
Very recently, Prashad *et al.*[45] reported an efficient palladium catalyzed amination of aromatic bromides with hidered *N*-alkyl substituted anilines either using the combination of $Pd(OAc)_2$ and P(*t*-Bu)$_3$ or a palladium(I) tri-*tert*-butylphosphine bromide dimmer, $[Pd(\mu\text{-}Br)(t\text{-}Bu_3P)]_2$, a new, commercially available, and easily handled catalyst.



Verkade *et al.*[46] showed the bicyclic triaminophosphine P(*i*-BuNCH$_2$CH$_2$)$_3$N serves as an effective ligand for the palladium catalyzed amination of a wide array of aryl bromides and iodides.



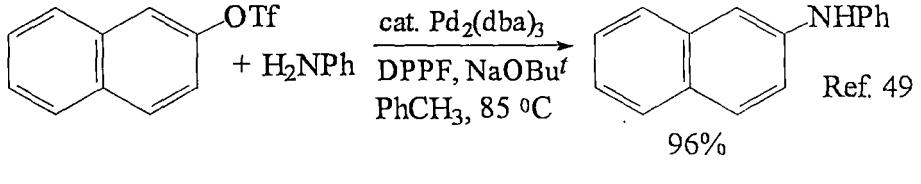
The first palladium-catalyzed coupling reaction of aryl chlorides with amines was reported by Beller *et al.*[47]

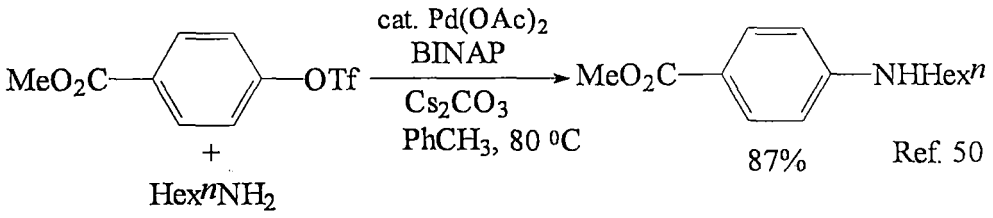


Subsequently Reddy and Tanaka[48] described Pd(PCy$_3$)Cl$_2$ catalyzed reaction of aryl chlorides and secondary amines in the presence of *t*-BuONa to give the corresponding amines in good to excellent yields.

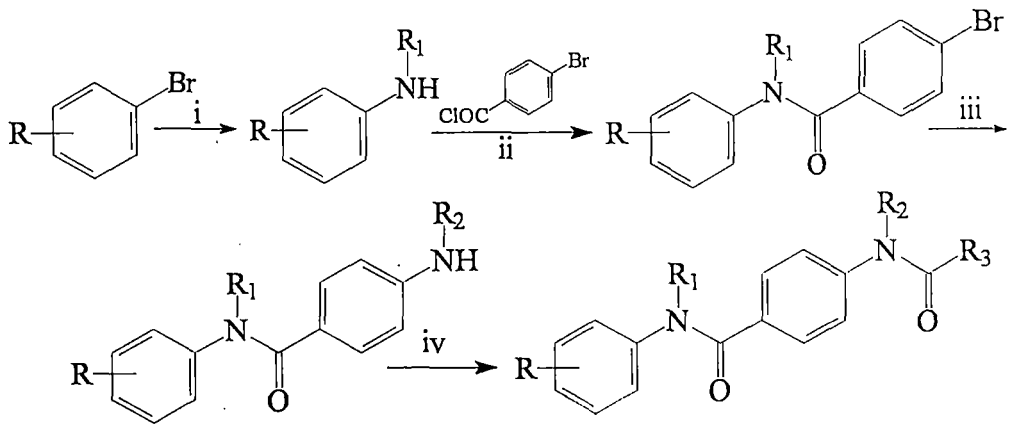
$$ArCl + RNHR_1 \xrightarrow[NaOBu^t, PhCH_3,\ 120\ ^oC,\ 6\text{-}12h]{Pd(PCy_3)_2Cl_2} ArNRR_1$$

The conversion of phenols to arylamines clearly has considerable synthetic value. Given the simple conversion of phenols to aryl triflates, and the application of aryl triflates in Stille and Suzuki couplings, it was no surprise that Hartwig[49] and Buchwald[50] independently extended their amination chemistry to include aryl triflates as coupling partners.



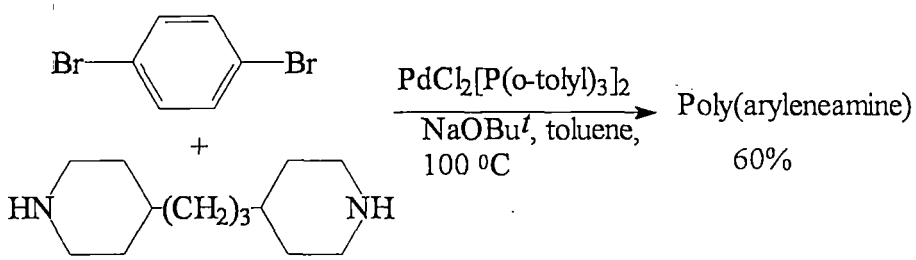


Frost and Mendonca have reported the successful implementation of an iterative palladium catalyzed amination strategy to prepare an array of peptide analogues by parallel synthesis.[51] The combination of $Pd_2(dba)_3$/DPPF proved to be an active catalyst for the efficient introduction of different nitrogen functionality.

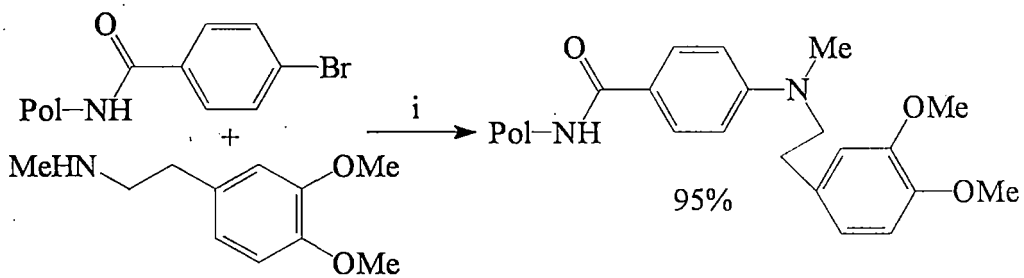


i) R_1NH_2, cat. [$PdCl_2$(dppf)], DPPF, $NaOBu^t$, THF, 100 °C
ii) Et_3N, DMAP, CH_2Cl_2,
iii) R_2NH_2, cat. [$PdCl_2$(dppf)], DPPF, $NaOBu^t$, THF, 100 °C
iv) R_3COCl, Et_3N, DMAP, CH_2Cl_2,

The amination methodology has recently found application in polymer synthesis. The reaction of aryl dibromide with secondary amine proceeds smoothly in the presence of stoichiometric $NaOBu^t$ and catalytic $PdCl_2[P(o\text{-tolyl})_3]_2$ to give new poly(aryleneamine).[52]

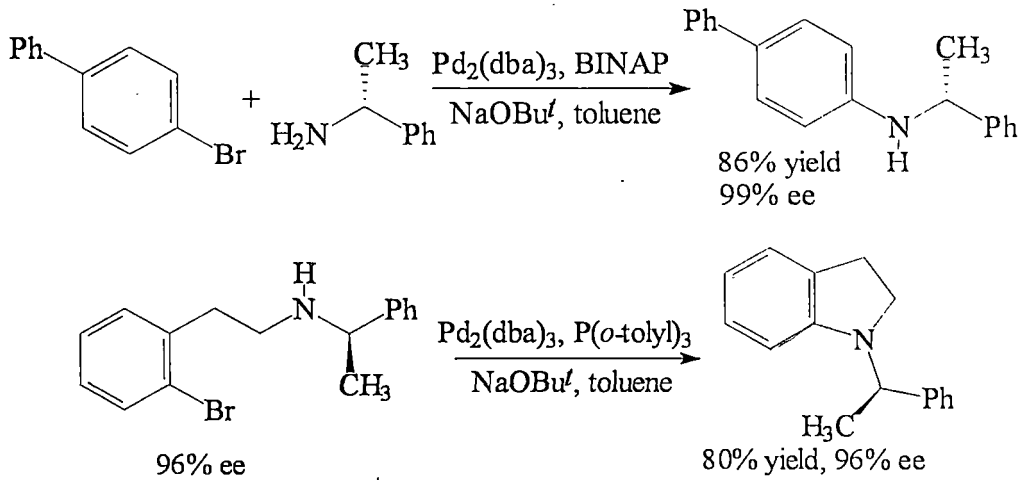


Two groups have reported methods for the solid phase synthesis of aryl amines employing the palladium catalyzed amination protocol. Willoughby and Chapman reported that the Pd(0)/P(*o*-tolyl)$_3$ catalyst system is effective in the coupling of secondary amines with polymer bound aryl bromide to afford high yields of the products.[53] The use of BINAP as a ligand allowed the coupling of primary amines in high yields and with excellent purities. Ward and Farina independently reported similar findings.[54] This methodology will no doubt prove useful for constructing combinatorial libraries of aniline derivatives for biological screening.

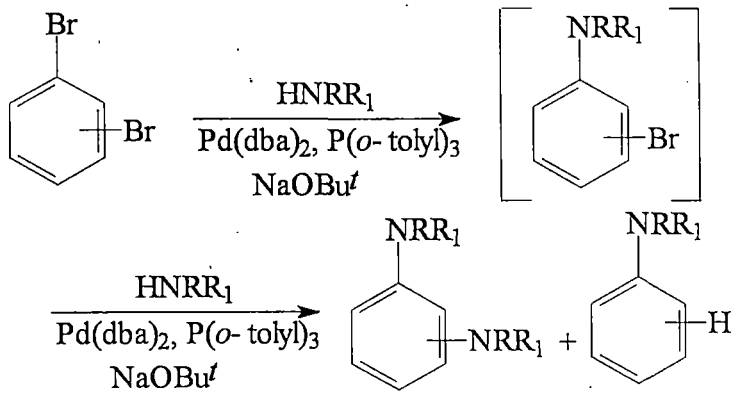


i) cat. $Pd_2(dba)_3P(o\text{-tolyl})_3$, $NaOBu^t$, dioxane,

In principle, palladium-catalyzed amination of enantiomerically pure amines could lead to racemization, although Buchwald and co-workers have shown that, under appropriate conditions, the coupling can take place without any erosion of enantiomeric excess.[55]

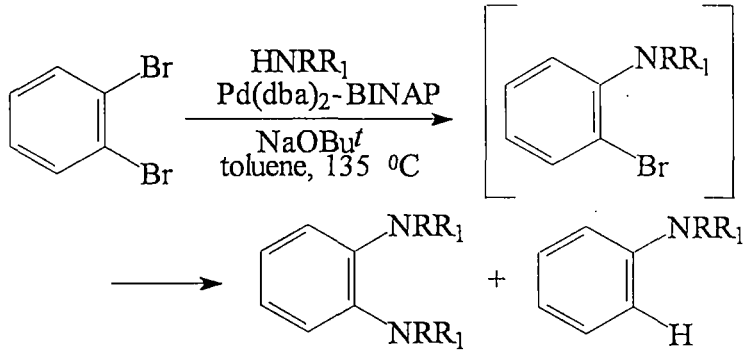


Beletskaya *et al.*[29e] performed double amination of dibromobenzenes with secondary amines in the presence of $Pd(dba)_2/P(o\text{-tolyl})_3$ and sodium *tert*-butoxide in moderate to good yields. Reductive dehalogenation of aryl dibromides is a major side reaction under these conditions.



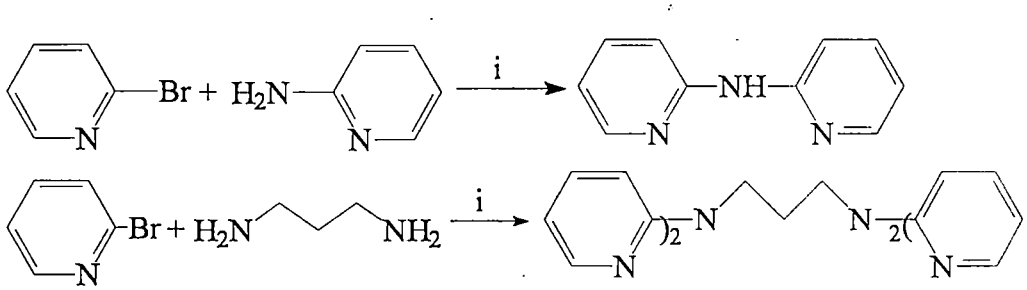
$HNRR_1$ = morpholine, piperidine, $HNEt_2$

Bisamination[29f] of 1,2-dibromobenzene was achieved in one-pot using $Pd_2(dba)_3$-BINAP catalytic conditions. A combination of elevated reaction temperature and excess base accelerated the reaction sufficiently for one-pot bisamination. Chiral, unsymmetrical dianilines were efficiently prepared by a sequential application of the amination. The couplings were successful for a range of aliphatic amines. The incorporation of an α-chiral primary amine can likewise be accomplished using this protocol without racemization.



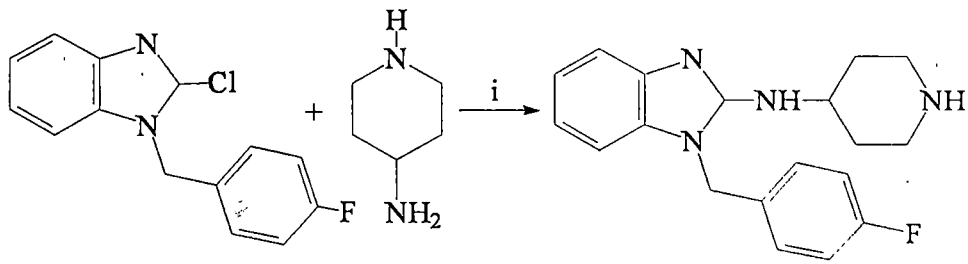
$HNRR_1$ = morpholine, pyrrolidine, 2-phenyl ethylamine

The Buchwald groups have revealed that the palladium-catalyzed amination strategy can be effectively applied to the synthesis of aminopyridines and this protocol represents a significant improvement relative to existing procedures which often require activated substrates and harsh reaction conditions.[56] The reaction of 2-bromopyridine with 2-aminopyridine produced the interesting product in 87% yield. This was also an effective strategy for preparing diarylated diamines.



i) cat. $Pd_2(dba)_3$, BINAP, $NaOBu^t$, toluene, 70 °C

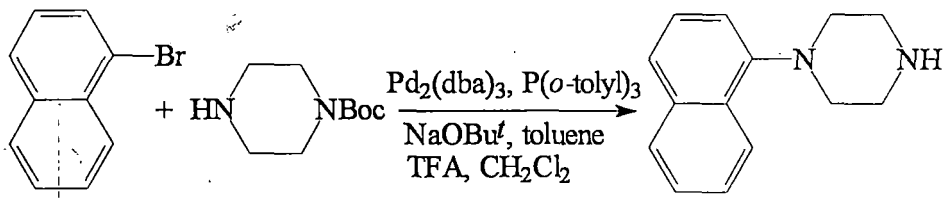
The group of Senanayake has reported the application of a unique palladium-catalyzed amination reaction in a concise synthesis of the potent H_1-antihistaminic norastemizole.[57] This is a remarkably efficient process considering a primary amine is being selectively coupled in the presence of a secondary amine.



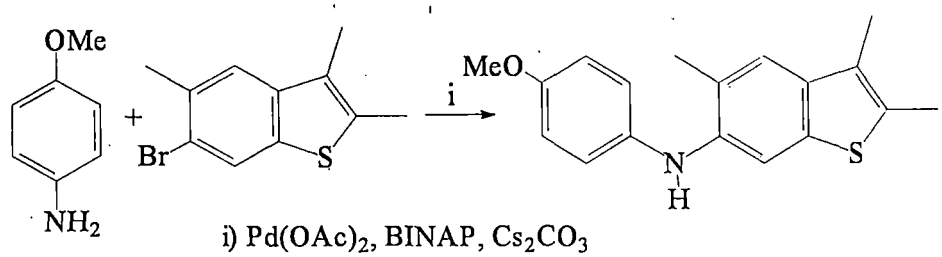
i) cat. $Pd_2(dba)_3$, BINAP, $NaOBu^t$, toluene

Thomas *et al.*[58] reported a convenient procedure for the synthesis of bicyclic arylpiperazines which involves the reaction of *N-tert*-butoxycarbonylpiperazine (*N*-Boc-piperazine) with bicyclic bromoarenes under conditions developed by

Buchwald,[40,41] followed by standard deprotection of the Boc-protected arylpiperazines with trifluoroacetic acid.



Very recently, Queiroz *et al.*[59] described the synthesis of diarylamines in the benzo[b]thiophene series bearing electron donating or withdrawing groups, by palladium-catalyzed amination of aryl halides using $Pd(OAc)_2$, racemic BINAP as ligand and Cs_2CO_3 as base.

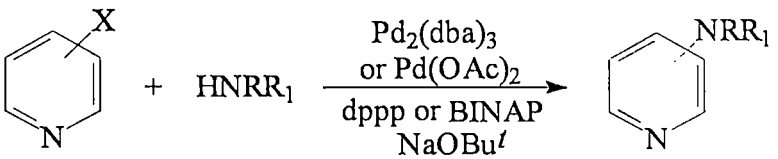


i) $Pd(OAc)_2$, BINAP, Cs_2CO_3

II.2.1 Present Work: Background, Objectives and Strategy

Heteroaromatic amines constitute an important pharmacophoric moiety present in many drugs acting on various pharmacological targets. For example, aminopyridines are important biologically active compounds and are known to act as central nervous system stimulant.[11] Besides, their derivatives are often used as ligand in coordination and organometallic chemistry,[9] and have found industrial applications as fluorescent dyes.[10] Aminothiophenes are useful precursors for natural products,[60] pharmaceuticals,[61] conjugated polymers,[62] and other related materials.[63] The aminopyridazine nucleus can be found in dopaminergic, serotoninergic, cholinergic and GABA-ergic ligands as well as in monoamine oxidase and acetylcholine esterase inhibitors.[64]

Most of the early preparative methods for aminopyridines involve aromatic nucleophilic substitution by S_NAr, benzyne or $S_{RN}1$ reactions.[13] These methods either suffer from a nucleophilic regiocontrol problem, the need for very high temperature or the presence of specific functionality on the heterocyclic ring. None of these shows a combination of good yields and high selectivity. Buchwald and others[25,35,41,58] have recently developed chelating bis-phosphine palladium-catalyzed cross-coupling reactions that allow the preparation of aminopyridines from their corresponding halopyridines[36b,56] (Scheme VIII).

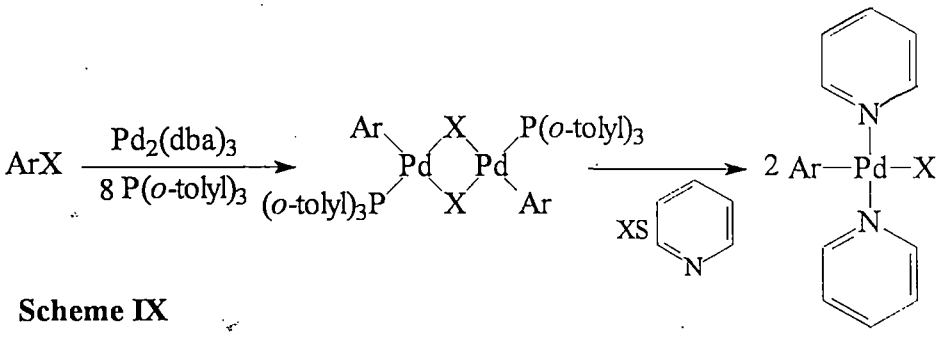


Scheme VIII

The method involves Pd(0)/bis-phosphine complexes as the effective catalyst for oxidative addition to the carbon-halogen bond, followed by coupling with the amine. The amination is catalyst-specific (Pd-ligand complexes) and very sensitive to

the nature of the base.[25,41] Although this reaction efficiently produces aminopyridines in the presence of chelating bis-phosphine/Pd(0) complexes, the use of strong bases such as sodium *tert*-butoxide is not desirable and remains associated with problems as in the case of direct amination using NaNHR or $NaNR_2$.[13,65] Furthermore, the use of strong bases greatly limits the functional group tolerance of the process.[36b] The weaker base (Cs_2CO_3) has been employed for haloaromatics[36b] and halothiophenes,[61b] but not in the case of halopyridines and its use is limited due to high solubility in organic solvents and its hygroscopic nature.

Many nitrogen heterocycles are strongly binding ligands for late-transition metals.[28b] As a result, heteroaromatic halides with basic nitrogen atoms will displaces weakly binding ligands such as, P(*o*-tolyl)$_3$, so that the original catalyst system containing P(*o*-tolyl)$_3$ as ligand was ineffective for amination with heteroaromatic substrates that could bind to palladium. It has been shown in stoichiometric studies that pyridine displaces P(*o*-tolyl)$_3$ to form palladium-pyridine complexes[66] (Scheme IX).

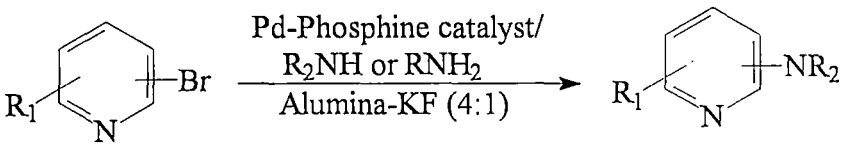


Scheme IX

However, chelating phosphanes are not displaced by pyridine. Thus, the advent of amination reaction with chelating ligand would favour the amination of pyridyl halides.[56]

The use of base is one of the keys to the success of this coupling reaction, we investigated palladium-catalyzed cross coupling of bromopyridines and amines on a KF-alumina (basic) surface. KF-alumina has been successfully employed in many other cases so as to exploit its basicity on the surface[67] and very recently palladium-

catalyzed C–C couplings (Suzuki, Heck, Stille, Trost-Tsuji) have been reported using KF-alumina under mono-mode microwave irradiation.[68] The role of mono- or bis-phosphine ligands in palladium catalyzed C–N hetero cross-coupling of halopyridines on a solid surface could be an interesting study. This present work describes our results, which constitute a convenient and efficient heterogeneous method for C–N coupling by Pd-catalyzed amination of halopyridines on KF-alumina (basic) surface (Scheme X).



P(*o*-tolyl)$_3$, DPPF, BINAP; Pd sources: $PdCl_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(acac)_2$, $Pd[PPh_3]_4$

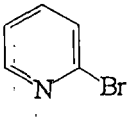
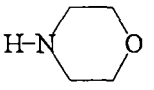
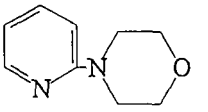
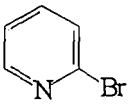
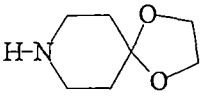
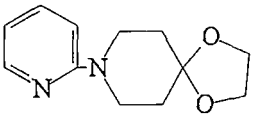
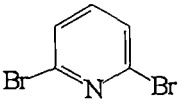
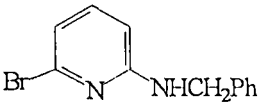
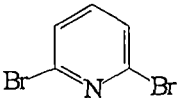
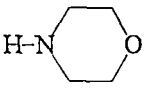
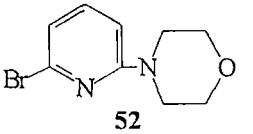
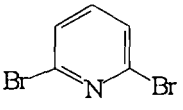
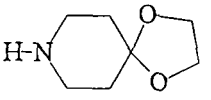
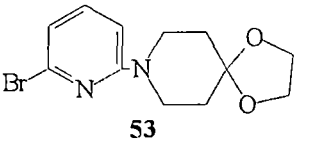
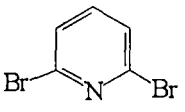
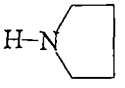
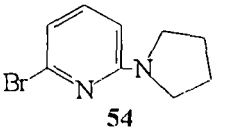
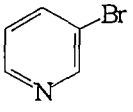
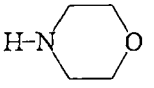
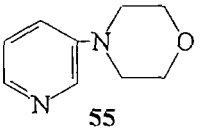
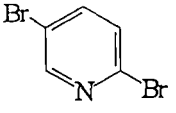
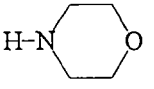
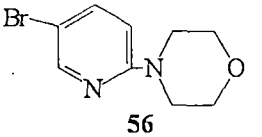
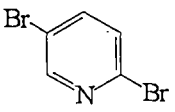
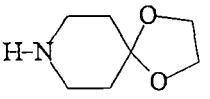
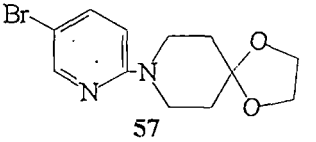
Scheme X

II.2.2 Present Work: Results and Discussion

As we can see from the results presented in Table 4, the amination on KF-alumina surface works with different bromopyridines. While 2-bromopyridine (entries 1 and 2) reacts with different amines smoothly, 3-bromopyridine (entry 7) undergoes amination in relatively poor yield. Amination of dibromopyridines affords only monoamine derivatives in good to excellent yields. In the case of 2,5-dibromopyridine (entries 8 and 9), amination occurs selectively at the 2-position. Buchwald observed complete bis-amination of 2,6-dibromopyridine using $Pd_2(dba)_3$-dppp catalyst in the presence of excess amine.[56] Our conditions, however, yielded monoamines as the major products even after prolonged reaction times and in the presence of excess amine (entries 3-6). This selectivity offers an advantage for further reaction with the other halogen substituents. In the bicyclic systems, 4-bromoisoquinoline (entries 10 and 11) and 3-bromoquinoline (entries 12 and 13) undergo amination efficiently.

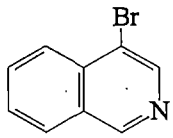
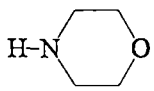
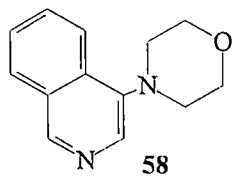
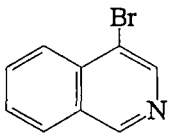
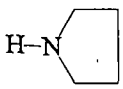
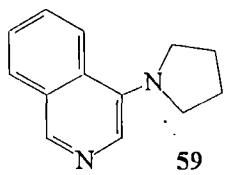
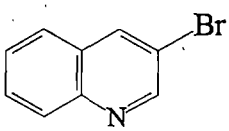
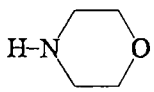
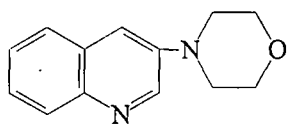
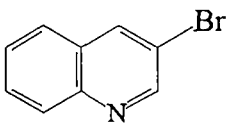
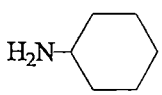
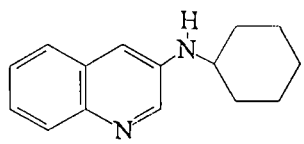
A great deal of experimentation on the cross coupling of bromopyridines with primary and secondary amines was carried out in order to optimize the reaction conditions. Palladium sources, ligand, solvent and the support ($KF\text{-}Al_2O_3$) were optimized and several details are worthy of comment. Firstly, different palladium sources like $PdCl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(acac)_2$ and $Pd[PPh_3]_4$ complexing with either mono-phosphine [P(*o*-tolyl)$_3$] or bis-phosphines (BINAP and DPPF) were employed as the catalytic systems. The $PdCl_2[P(o\text{-tolyl})_3]_2$ and $Pd_2(dba)_3$/BINAP complexes were found to be most effective in this amination process (Table 4). The formation of bis-(pyridyl) complexes using monophosphine ligands, as proposed by Buchwald,[56] might possibly be avoided under these conditions. The reactions were carried out with or without a solvent. Clean reactions and better yields of the aminopyridines were obtained when the reactions were carried out on $KF\text{-}Al_2O_3$ surface with a slight excess of amine and without solvent. Toluene and xylene have been used as solvents with almost similar effects, whilst the presence of DMF as a co-solvent induces faster debromination (entry 10). 2-Bromopyridine (entries 1 and 2) also yields 10-15% of 2,2'-bipyridyls by intermolecular coupling and such coupling is further increased in the presence of a solvent. The major limitations of this protocol are that 3-bromopyridine fails to cross-couple with primary amines and partial dehalogenation (5%) was observed in the case of 3-bromopyridine, 3-bromoquinoline and 4-bromoisoquinoline.

Table 4

Entry	Bromoarene	Amine	Catalyst[a]	Conditions[b] time (h)	Product	%Yield[c]
1.			[A]	2 / 8	 **49**	70
2.			[A]	2 / 8	 **50**	58
3.		H_2NCH_2Ph	[H]	2 / 8	 **51**	90
4.			[A]	1,2 / 5	 **52**	78
5.			[A]	2 / 5	 **53**	62
6.			[A]	2 / 5	 **54**	91
7.			[F]	1,2 / 9	 **55**	48
8.			[A]	1,2 / 5	 **56**	92
9.			[A]	2 / 5	 **57**	73

continued.....

Continued **Table 4**

Entry	Bromoarene	Amine	Catalyst[a]	Conditions[b]/ time (h)	Product	%Yield[c]
10.			[E],[F]	1,2 / 6	 **58**	86
11.			[F]	2 / 6	 **59**	90
12.			[F]	2 / 6	 **60**	78
13.			[F]	2 / 8	 **61**	68

[a] [A] Pd[(*o*-tolyl)$_3$P]$_2$Cl$_2$; [B] Pd$_2$(dba)$_3$-P(*o*-tolyl)$_3$; [C] Pd[PPh$_3$]$_4$; [D] Pd$_2$(dba)$_3$-dppf; [E] Pd(OAc)$_2$-dppf; [F] Pd$_2$(dba)$_3$-BINAP; [G] Pd(acac)$_2$-dppf; [H] Pd(OAc)$_2$-BINAP.

[b] 1. Alumina-KF in toluene/90-100 ^{0}C; 2. Alumina-KF without solvent at 90-100 ^{0}C.

[c] Yields are reported on the basis of pure isolated products (2-3 runs) and calculated on the basis of recovered starting material (for entries **6**, **7**, **9**).

In conclusion, we have shown that Pd(0) catalyzed amination of bromopyridines can be performed smoothly on the surface of basic alumina admixed with KF. The simplicity of the experiment conditions, good to excellent yields and favourable safety aspects represent a significant improvement and useful extension relative to Buchwald's procedure using the strong base, sodium *tert*-butoxide. Future work will include studies with more base-sensitive functionalities on the heterocyclic nucleus as well as with chiral amines.

II.3 Experimental

General procedure

Preparation of activated Al_2O_3/KF

A mixture of basic alumina (Brockmann, Activity I) and KF (4:1) (5g) was taken in THF (5 mL) and after stirring for 30 min. at room temperature it was evaporated to dryness. The solid residue was heated at 250 ^{0}C under vacuum (0.5 mm of Hg) for 4 h, cooled under N_2 and used for reaction.

2-Benzylamino-6-bromopyridine (**51**)

To a mixture of 2,6'-dibromopyridine (0.437g, 2 mmol), benzylamine (0.856g, 8 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol) and (±) BINAP (0.050g, 0.08 mmol) was added activated Al_2O_3-KF (2g). The mixture was intimately stirred at 90-100 ^{0}C for 8 h under nitrogen. After cooling to room temperature the semi-solid mass was washed repeatedly with ether (4×15 mL), combined and concentrated. The residue was purified by silica gel column chromatography (petroleum-ether:EtOAc = 20:1) to give amine **51** (0.475g, 90%); m.p. 85 ^{0}C.

IR (Nujol): ν_{max} 3293, 1603, 1562, 1536, 1434, 1367 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 7.27-7.36 (m, 5H), 7.20 (dd, 1H, *J* = 8.2; 7.5 Hz), 6.73 (d, 1H, *J* = 7.5 Hz), 6.24 (d, 1H, *J* = 8.2 Hz), 5.18 (br.s, 1H), 4.46 (d, 2H, *J* = 5.9 Hz).

^{13}C-NMR ($CDCl_3$): δ 158.7, 140.2, 139.5, 138.3, 128.7, 127.4, 127.3, 116.1, 104.5, 46.3.

Compounds (**49**), (**50**), (**52**) – (**61**) were prepared using similar conditions as mentioned in Table 4.

4-Pyridin-2-yl-morpholine (**49**)

Yield: 70%, Liquid.

IR (neat): ν_{max} 2966, 1603, 1486, 1440, 1378, 1312, 1240 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 8.20 (d, 1H, *J* = 4.5 Hz), 7.49 (m, 1H), 6.64 (m, 2H), 3.82 (t, 4H, *J* = 4.8 Hz), 3.48 (t, 4H, *J* = 4.8 Hz).

^{13}C-NMR ($CDCl_3$): δ 159.4, 147.7, 137.3, 113.6, 106.7, 66.5, 45.4.

8-Pyridin-2-yl-1,4-dioxa-8-aza-spiro[4,5]decane (**50**)

Yield: 58%, Liquid.

IR (neat): ν_{max} 2960, 1598, 1562, 1486, 1440, 1363, 1235 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 8.16 (d, 1H, *J* = 4.4 Hz), 7. 48 (m, 1H), 6.66 (d, 1H, *J* = 8.5 Hz), 6.56 (m, 1H), 3.96 (s, 4H), 3.68 (t, 4H, *J* = 5.4 Hz), 1.75 (t, 4H, *J* = 5.4 Hz).

^{13}C-NMR ($CDCl_3$): δ 158.7, 147.7, 137.3, 112.5, 106.9, 64.1, 43.2, 34.1.

Anal. Calcd. for $C_{12}H_{16}N_2O_2$ (220.27): C, 65.43; H, 7.32.

Found: C, 65.12; H, 7.44.

4-(6-Bromopyridin-2-yl)morpholine (**52**)

Yield: 78%, m.p. 55-56 ^{0}C.

^{1}H-NMR ($CDCl_3$): δ 7.30 (dd, 1H, *J* = 8.1; 7.5 Hz), 6.78 (d, 1H, *J* = 7.5 Hz), 6.50 (d, 1H, *J* = 8.1 Hz), 3.79 (t, 4H, *J* = 4.9 Hz), 3.49 (t, 4H, *J* = 4.9 Hz).

^{13}C-NMR ($CDCl_3$): δ 158.8, 140.6, 139.9, 116.9, 105.1, 66.9, 45.6.

8-(6-Bromopyridin-2-yl)-1,4-dioxa-8-aza-spiro[4,5]decane (**53**)

Yield: 62%, m.p. 99-100 ^{0}C.

IR (Nujol): ν_{max} 2966, 1588, 1552, 1491, 1440, 1342, 1245 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 7.24 (dd, 1H, *J* = 8.3 Hz), 6.68 (d, 1H, *J* = 7.4 Hz), 6.53 (d, 1H, *J* = 8.3 Hz), 3.97 (s, 4H), 3.65 (t, 4H, *J* = 5.5 Hz), 1.73 (t, 4H, *J* = 5.5 Hz).

^{13}C-NMR ($CDCl_3$): δ 158.39, 139.9, 139.3, 115.2, 104.6, 64.1, 42.9, 34.1.

Anal. Calcd. for $C_{12}H_{15}BrN_2O_2$ (299.17): C, 48.18; H, 5.05.

Found: C, 48.02; H, 5.38.

2-Bromo-6-pyrrolidin-1-yl-pyridine (**54**)

Yield: 91%, m.p. 88-89 ^{0}C.

IR (Nujol): ν_{max} 2976, 1603, 1537, 1496, 1388 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 7.19 (dd, 1H, *J* = 8.1; 7.5 Hz), 6.61 (d, 1H, *J* = 7.5 Hz), 6.20 (d, 1H, *J* = 8.1 Hz), 3.40 (t, 4H, *J* = 6.6 Hz), 1.99 (t, 4H, *J* = 6.6 Hz).

^{13}C-NMR ($CDCl_3$): δ 157.1, 140.3, 138.7, 113.7, 104.4, 46.7, 25.3.

4-Pyridin-3-yl-morpholine (**55**)

Yield: 48%, Liquid.

IR (neat): ν_{max} 2966, 1665, 1583, 1496, 1455, 1352, 1255 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 8.22 (s, 1H), 8.04 (m, 1H), 7.19 (m, 2H), 3.80 (t, 4H, J = 4.5 Hz), 3.11 (t, 4H, J = 4.5 Hz).

4-(5-Bromopyridin-2-yl)morpholine (**56**)

Yield: 92%, m.p. 84-85 ^{0}C.

IR (Nujol): ν_{max} 2966, 1588, 1547, 1475, 1388, 1312, 1235 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 8.20 (s, 1H), 7.55 (dd, 1H, J = 6; 3 Hz), 6.52 (d, 1H, J = 8 Hz), 3.81 (t, 4H, J = 6 Hz), 3.46 (t, 4H, J = 6 Hz).

^{13}C-NMR ($CDCl_3$): δ 157.4, 148.5, 139.8, 108.2, 66.5, 45.5.

Anal. Calcd. for $C_9H_{11}BrN_2O$ (243.10): C, 44.47; H, 4.56.

Found: C, 44.42; H, 4.72.

8-(5-Bromopyridin-2-yl)-1,4-dioxa-8-aza-spiro[4,5]decane (**57**)

Yield: 73%, m.p. 83-84 ^{0}C.

IR (Nujol): ν_{max} 2960, 1588, 1486, 1404, 1363, 1245 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 8.16 (d, 1H, J = 2.4 Hz), 7.50 (dd, 1H, J = 8.9; 2.4 Hz), 6.57 (d, 1H, J = 8.9 Hz), 3.99 (s, 4H), 3.65 (t, 4H, J = 5.5 Hz), 1.74 (t, 4H, J = 5.5 Hz).

^{13}C-NMR ($CDCl_3$): δ 157, 148.4, 139.6, 108.4, 107.3, 64.3, 43.5, 34.2.

4-Morpholin-4-yl-isoquinoline (**58**)

Yield: 86%, m.p134-136 ^{0}C.

^{1}H-NMR ($CDCl_3$): δ 8.98 (s, 1H), 8.19 (s, 1H), 8.11 (d, 1H, J = 8.3 Hz), 7.95 (d, 1H, J = 8.1 Hz), 7.59 (m, 1H), 3.97 (t, 4H, J = 4.4 Hz), 3.17 (t, 4H, J = 4.4 Hz).

^{13}C-NMR ($CDCl_3$): δ 148.1, 143.1, 132.6, 131.3, 129.8, 129.2, 128.0, 127.2, 122.4, 67.2, 53.1.

4-Pyrrolidin-1-yl-isoquinoline (**59**)

Yield: 90%, Liquid.

IR (neat): ν_{max} 2960, 1629, 1578, 1501, 1409, 1342, 1255 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 8.76 (s, 1H), 8.14 (d, 1H, J = 8.7 Hz), 8.02 (s, 1H), 7.86 (d, 1H, J = 7.6 Hz), 7.49-7.60 (m, 2H), 3.45 (t, 4H, J = 6.5 Hz), 1.99 (t, 4H, J = 6.5 Hz).

^{13}C-NMR ($CDCl_3$): δ 144.1, 141.3, 129.5, 129.2, 128.4, 128.0, 127.5, 126.5, 123.8, 52.0, 25.1.

3-Morpholin-4-yl-quinoline (**60**)

Yield: 78%, m.p. 91-92 ^{0}C.

IR (Nujol): ν_{max} 2960, 1603, 1496, 1455, 1388, 1271, 1224 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 8.79 (d, 1H, J = 2.5 Hz), 8.00 (d, 1H, J = 8 Hz), 7.69 (d, 1H, J = 8 Hz), 7.53 (m, 2H), 7.34 (d, 1H, J = 2.5 Hz), 3.93 (t, 4H, J = 4.8 Hz), 3.28 (t, 4H, J = 4.8 Hz).

^{13}C-NMR ($CDCl_3$): δ 144.4, 144.2, 142.8, 128.7, 128.5, 127.1, 126.4, 126.3, 116.2, 66.4, 48.9.

Cyclohexyl-quinolin-3-yl-amine (**61**)

Yield: 68%, m.p. 118-119 ^{0}C.

IR (Nujol): ν_{max} 3232, 3053, 2930, 1609, 1542, 1486, 1393, 1363, 1240 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 8.37 (d, 1H, J = 2.7 Hz), 7.90-7.93 (m, 1H), 7.55-7.60 (m, 1H), 7.30-7.44 (m, 2H), 6.96 (d, 1H, J = 2.7 Hz), 3.97 (br.s, 1H), 3.33 (m, 1H), 2.06-2.11 (m, 2H), 1.64-1.81 (m, 2H), 1.18-1.43 (m, 6H).

^{13}C-NMR ($CDCl_3$): δ 143.5, 141.7, 140.6, 129.5, 128.8, 126.7, 125.6, 124.4, 109.9, 51.4, 32.8, 25.7, 24.8.

II.5 References

1. (a) Buckingham, J. *Dictionary of Natural Products*, University Press: Cambridge, MA, 1994. (b) D'Aproano, G.; Schiavon, G.; Zotti, G.; Leclerck, M. *Chem. Mater.* **1995**, *7*, 33.
2. Waring, D.R.; Hallas, G. *The Chemistry and Application of Dyes*, Plenum: New York, 1990.
3. (a) Kleeman, A.; Enjel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 3rd edn.; Thieme: Stuttgart, 1999. (b) Negwer, M. *Organic-Chemical Drugs and Their Synonyms: (An International Survey)*, 7th edn.; Akademie Verlag: Berlin, 1994.
4. Montgomery, J.H. *Agrochemical Desk Reference: Environmental Data*, Lewis Publishers: Chelsea, MI, 1993.
5. (a) Lakshman, M.K.; Keeler, J.C.; Hilmer, J.H.; Martin, J. *J. Am. Chem. Soc.* **1999**, *121*, 6090. (b) De Riccardis, F.; Johnson, F. *Org. Lett.* **2000**, *2*, 293.
6. Greco, G.E.; Popa, A.I.; Schrock, R.R. *Organometallics* **1998**, *17*, 5591.
7. Ito. A.; Taniguchi, A.; Yamabe, T.; Tanaka, K. *Org. Lett.* **1999**, *1*, 741.
8. Hofle, G.; Steglich, W. *Synthesis* **1972**, 619.
9. (a) Kempe, R.; Arndt, P. *Inorg. Chem.* **1996**, *35*, 2644. (b) Alvila, L.; Pakkanen, T.A. *J. Mol. Catal.* **1993**, *84*, 145.
10. (a) Sathyamoorthi, G.; Soong, M.L.; Ross, T.W.; Boyer, J.H. *Heteroatom Chem.* **1993**, *4*, 603. (b) Araki, K.; Mutai, T.; Shingemitsu, Y.; Yamade, M.; Nakajima, T. Kurada, S.; Shimao, I. *J. Chem. Soc.; Perkin Trans, 2* **1996**, 613.
11. Lechet, P.; Tesheff, S.; Bownan, W.C. *Aminopyridines and Similarly Acting Drugs*, Pergamon Press: Oxford, New York, 1982.
12. (a) Hattori, T.; Sakamoto, J.; Hayashizaka, N.; Miyano. S. *Synthesis* **1994**, 199. (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (c) Semmelhack, M.F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1395. (d) Mitchell, H.; Leblanc, Y. *J. Org. Chem.* **1994**, *59*, 682. (e) Paine, A.J. *J. Am. Chem. Soc.* **1987**, *109*, 1496.
13. Smith, B.M.; March, J. *March's Advanced Organic Chemistry*, 5th edn.; John Wiley and Sons, Inc. New York. 2001.
14. Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

15. (a) Goodbrand, H.B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670. (b) Arterburn, J.B.; Pannala, M.; Gonzalez, A.M. *Tetrahedron Lett.* **2001**, *42*, 1475.

16. (a) Kelkar, A.A.; Patil, N.M.; Chaudhari, R.V.L. *Tetrahedron Lett.* **2002**, *43*, 7143. (b) Gujadhur, R.; Venkataraman, D.; Kintigh, J.T. *Tetrahedron Lett.* **2001**, *42*, 4791. (c) Gujadhur, R.K.; Bated, C.G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4135.

17. (a) Antilla, J.C.; Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (b) Kang, S.-K.; Kim, D.-H.; Park, J.-N. *Synlett* **2002**, 427. (c) Kwong, F.Y.; Klapars, A.; Buchwald, S.L. *Org. Lett.* **2002**, *4*, 581.

18. Kiyomori, A.; Marcoux, J.-F.; Buchwald, S.L. *Tetrahedron Lett.* **1999**, *40*, 2637.

19. Wolter, M.; Klapars, A.; Buchwald, S.L. *Org. Lett.* **2001**, *3*, 3803.

20. Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583.

21. Job, G.E.; Buchwald, S.L. *Org. Lett.* **2002**, *4*, 3703.

22. (a) Kang, S.-K.; Lee, S.-H.; Lee, D. *Synlett* **2000**, 1022. (b) Lam, P.Y.S.; Vincent, G.; Bonne, D.; Clark, C.G. *Tetrahedron Lett.* **2002**, *43*, 3091. (c) Sorensen, R.J. *J. Org. Chem.* **2000**, *65*, 7747.

23. Kwong, F.Y.; Buchwald, S.L. *Org. Lett.* **2003**, *5*, 793.

24. Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231.

25. Yang, B.H.; Buchwald, S.L. *J. Organomet. Chem.* **1999**, *576*, 125.

26. Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Sythesis*, John Wiley and Sons: Chichester, England, 1995.

27. Wolfe, J.P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S.L. *Acc. Chem. Res.* **1998**, *31*, 805.

28. (a) Hartwig, J.F. *Acc. Chem. Res.* **1998**, *31*, 852. (b) Hartwig, J.F. *Angew. Chem.; Int. Ed. Eng.* **1998**, *37*, 2046.

29. (a) Huang, J.; Grassa, G.A.; Nolan, S.P. *Org. Lett.* **1999**, *1*, 1307. (b) Grassa, G.A.; Viciu, M.S.; Huang, J.; Nolan, S.P. *J. Org. Chem.* **2001**, *66*, 7729. (c) Bolm, C.; Hilderbrand, J.P. *J. Org. Chem.* **2000**, *65*, 169. (d) Li, R.; He, M.Y.; DeShang, P.; Clark, C.G. *J. Am. Chem. Soc.* **2000**, *122*, 7600. (e) Beletskaya, I.P.; Bessmertnykh, A.G.; Guilard, R. *Tetrahedron Lett.* **1999**, *40*, 6393. (f) Rivas, F.M.; Riaz, U.; Diver, S.T. *Tetrahedron: Asymmetry* **2000**, *11*, 1703.

30. Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

31. (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617. (b) Hartwig, J.F.; Kawatsura, M; Hauck, S.I.; Shaughnessy, K.H.; Alcazar-Roman, L.M. *J. Org. Chem.* **1999**, *64*, 5575.

32. (a) Marcoux, J.-F. Wagaw, S.; Buchwald, S.L. *J. Org. Chem.* **1997**, *62*, 1568. (b) Hamann, B.C.; Hartwig, J.F. *J. Am. Chem. Soc.* **1998**, *120*, 7369.

33. (a) Wolfe, J.P.; Tomori, H.; Sadighi, J.P.; Yin, J.; Buchwald, S.L. *J. Org. Chem.* **2000**, *65*, 1158. (b) Bei, X.; Uno, T.; Norris, J.; Turner, H.W.; Weinberg, W.H.; Guram, A.S. *Organometallics* **1999**, *18*, 1840.

34. Stauffer, S.R.; Lee, S.; Stambuli, J.P.; Hauck, S.I.; Hartwig, J.F. *Org. Lett.* **2000**, *2*, 1423.

35. Driver, M.S.; Hartwig, J.F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

36. (a) Wolfe, J.P.; Wagaw, S.; Buchwald, S.L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (b) Wolfe, J.P.; Buchwald, S.L. *J. Org. Chem.* **2000**, *65*, 1144.

37. Wolfe, J.P.; Buchwald, S.L. *Tetrahedron Lett.* **1997**, *38*, 6359.

38. Old, D.W.; Wolfe, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

39. Prashad, M.; Hu, B.; Lu, Y.; Draper, R.; Har, D.; Repic, O.; Blacklock, T.J. *J. Org. Chem.* **2000**, *65*, 2612.

40. Guram, A.S.; Buchwald, S.L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.

41. Guram, A.S.; Rennels, R.A.; Buchwald, S.L. *Angew. Chem.; Int. Ed. Eng.* **1995**, *34*, 1348.

42. Loui, J.; Hartwig, J.F.; *Tetrahedron Lett.* **1995**, *36*, 3609.

43. Wolfe, J.P.; Buchwald, S.L. *J. Org. Chem.* **1997**, *62*, 6066.

44. Harris, M.C.; Huang, X,; Buchwald, S.L. *Org. Lett.* **2002**, *4*, 2885.

45. Prashad, M.; Mak. X.Y.; Liu, Y.; Repic, O. *J. Org. Chem.* **2003**, *68*, 1163.

46. Urgaonkar, S.; Nagarajan, M.; Verkade, G.J. *J. Org. Chem.* **2003**, *68*, 452.

47. Beller, M.; Riermeier, T.H.; Reisinger, C.-P.; Herrmann, W.A. *Tetrahedron Lett.* **1997**, *38*, 2073.

48. Reddy, N.P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807.

49. Loui, J.; Driver, M.S.; Hamann, B.C.; Hartwig, J.F.; *J. Org. Chem.* **1997**, *62*, 1268.

50. Wolfe, J.P.; Buchwald, S.L. *J. Org. Chem.* **1997**, *62*, 1264.

51. Frost, C.G.; Mendonca, P. *Chem. Lett.* **1997**, 1159.

52. Kanbara, T.; Honma, A.; Hasegawa, K. *Chem. Lett.* **1996**, 1135.

53. Willoughby, C.A.; Chapman, K.T. *Tetrahedron Lett.* **1996**, *37*, 7181.

54. Ward, Y.D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993.

55. Wagaw, S.; Rennels, R.A.; Buchwald, S.L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.

56. Wagaw, S.; Buchwald, S.L. *J. Org. Chem.* **1996**, *61*, 7240.

57. Hong, Y.; Tanoury, G.J.; Scott Wilkinson, H.; Bakale, R.P.; Wald, S.A.; Senanayake, C.H. *Tetrahedron Lett.* **1997**, *38*, 5607.

58. Kerrigan, F.; Martin, C.; Thomas, G.H. *Tetrahedron Lett.* **1998**, *39*, 2219.

59. Ferreira, I.C.F.R.; Queiroz, M.-J.R.P; Kirsch, G. *Tetrahedron* **2003**, *59*, 975.

60. Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. *Org. Lett.* **1999**, *1*, 197.

61. (a) Pinto, I.L.; Jarvest, R.L.; Serafinowska, H.T.; *Tetrahedron Lett.* **2000**, *41*, 1597. (b) Luker, T.J.; Beaton, H.G.; Whiting, M.; Mete, A.; Cheshire, D.R. *Tetrahedron Lett.* **2000**, *41*, 7731.

62. (a) Roncali, J. *Chem. Rev.* **1992**, *92*, 711. (b) Schopf, G.; Kossmehl, G. *Adv. Pol. Sci.* **1997**, *129*, 1.

63. Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Chem. Commun.* **2000**, 133.

64. (a) Contreras, J.M.; Parrot, I.; Sippl, W.; Rival, Y.; Wermuth, C.G. *J. Med. Chem.* **2001**, *44*, 2707. (b) Wermuth, C.G. *J. Heterocycl. Chem.* **1998**, *35*, 1091.

65. (a) Joule, J.A.; Mills, K. *Heterocyclic Chemistry*, 4th edn.; Blackwell Science: Oxford, 2000, 71. (b) Jamart-Gregoire, B.; Leger, C.; Caubere, P. *Tetrahedron Lett.* **1990**, *31*, 7599. (c) Walters, M.A.; Shay, J.J. *Synth. Commun.* **1997**, *27*, 3537.

66. Paul, F.; Patt, J.; Hartwig, J.F. *Organometallics* **1995**, *14*, 3030.

67. (a) Blass, B.E.; Harris, C.L.; Portlock, D.E.; *Tetrahedron Lett.* **2001**, *42*, 1611. (b) Kabashima, H.; Tsuji, H.; Nakata, S.; Tanaka, Y.; Hattori, H. *Appl. Cat. A* **2000**, *194-195*, 227.

68. Villemin, D.; Caillot, F. *Tetrahedron Lett.* **2001**, *42*, 639.

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 2, pp. 291–296, 2003

Palladium Mediated Chemoselective Reduction of α,β-Unsaturated Cyano Esters with Potassium Formate

Basudeb Basu,* Md. Mosharef Hossain Bhuiyan, and Satadru Jha

Department of Chemistry, University of North Bengal, P.O. North Bengal University, Darjeeling, India

ABSTRACT

A number of α,β-unsaturated cyano esters have been chemoselectively reduced with potassium formate as hydrogen donor, and palladium(II) acetate as homogeneous catalyst, in DMF without any concomitant reduction of cyano or carboxylate or halogen groups.

Key Words: Hydrogen transfer reduction; α,β-Unsaturated cyano esters; α,β-Unsaturated tin carboxylate; Palladium acetate; Potassium formate.

*Correspondence: Basudeb Basu, Department of Chemistry, University of North Bengal, P.O. North Bengal University, Darjeeling 734430, India. Fax: +91 353 2581546; E-mail: basu_nbu@hotmail.com.

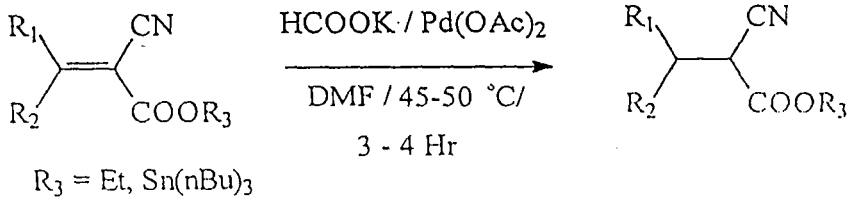
DOI: 10.1081/SCC-120015714 0039-7911 (Print); 1532-2432 (Online)
 www.dekker.com

Chemoselective reduction of carbon–carbon multiple bond in conjugated systems is an important process in organic synthesis.[1] Despite the bewildering variety of reducing agents available to synthetic chemists, new and selective reductants are in constant demand. Transition metal-catalyzed hydrogen transfer reaction with the aid of a hydrogen donor, such as trialkyl ammonium formate,[2] and other hydrides like *n*-Bu_3SnH,[3] NaH_2PO_3/H_2O,[4] $Ph_2SiH_2/ZnCl_2 \cdot H_2O$,[5] triethoxysilane–water,[6] are some of the examples employed for selective conjugate reduction. In most cases, direct source of hydride is used for conjugate addition to the more nucleophilic β-carbon, whereas formic acid and its salts are believed to be a source of hydride in situ,[7] which eventually adds to the β-carbon. Cacchi et al.[8] has recently reported a combination of $Pd(OAc)_2$/HCOOK as a convenient alternative reductant for conjugate reduction of α,β-unsaturated carbonyl compounds. On the other hand, reduction of conjugated nitriles and cyano esters using molecular hydrogen or Pd-catalyzed hydride-transfer afforded with reduction of the cyano group as well.[9] For example, reduction of α,β-unsaturated cyano esters in presence of Pd/C and *p*-menthene (as hydrogen donor) led to reduction of not only the C=C double bond, but also the nitrile function to a methyl group.[10] Moreover, reduction of nitrile using a combination of Pd/C and formic acid seemed to be very variable in many other examples.[11] Early studies on reduction of alkylidenecyanoacetic esters using sodium borohydride at room temperature led to reduction of C=C double bond as well as reduction of the ester to alcohol.[12] Sodium borohydride has however been successfully used for reduction of **1a**[13] and sodium cyanoborohydride has selectively reduced α,β-unsaturated esters, nitriles, and nitro compounds.[14] However, metal hydrides are generally highly reactive and expensive reagents and cyanoborohydride generates toxic byproducts upon workup. Very recently, Hantzsch 1,4-dihydropyridines (HEH) has been employed for selective reduction of α,β-unsaturated cyano esters.[15] This procedure, however, involves specific reagent (Hantzsch 1,4-dihydropyridines) and after the reaction the redox products require separation. Consequently, it appeared to us of interest to check the efficacy of $Pd(OAc)_2$/HCOOK combination in reduction of more functionalized α,β-unsaturated cyano esters. The study could be of further importance, as the soluble chiral Pd-catalyzed hydrogen transfer reactions are known to induce asymmetry in the product.[16] The chiral Pd-complex catalyzed conjugate reduction without any concomitant reduction of other functional groups might produce asymmetric compounds for further elaboration to useful synthetic intermediates. We wish to report that α,β-unsaturated

cyanoesters possessing other sensitive functional groups can be smoothly converted into the corresponding saturated cyanoacetates according to Sch. 1. The reduction appeared to be mild and efficient as the nitrile, ester (alkyl and tri-*n*-butyl stannyl), and halogen functions remain unaffected.

A series of α,β-unsaturated cyano esters (**1a–i**) have been prepared from their carbonyl substrates condensed with ethyl cyanoacetate under Knoevenagel condition.[17] The unsaturated cyano ester was dissolved in DMF and added $Pd(OAc)_2$ (2 mol%), HCOOK (2 equivalent) and stirred at 45–50°C for 3–4 h in a screw-cap sealed tube under N_2. After usual workup, the product was purified by column chromatography over silica gel to afford the reduced product in good to excellent yield (Table 1). Although dehalogenation of halo-aromatics is known under transfer reduction using heterogeneous catalyst,[18] the present method did not proceed with cleavage of carbon–halogen bond (Entry **1b**). The stannyl ester (Entry **1h**), prepared from its ethyl ester by transesterification with *bis*-tri-*n*-butyltin oxide,[19] also survived demetallation under the reaction condition.[20] To observe any effect of ligand participation in the catalytic process, the reaction was carried out in presence of various ligands, such as PPh_3, P(*o*-tolyl)$_3$ and TMEDA with the alkylidenecyanoacetic ester (**1i**). In all the experiments, a smooth conversion to the reduced product with excellent yield was obtained. Choice of solvent is an important factor governing the activity of soluble catalyst in transfer reduction.[11] As most soluble catalysts are often coordinated to solvent, DMF was found to be superior in comparison to non-polar solvents like toluene or carbon tetrachloride.

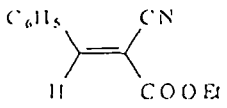
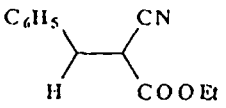
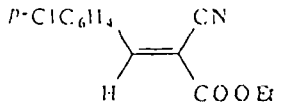
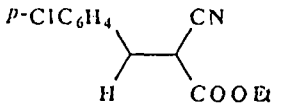
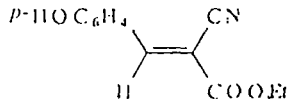
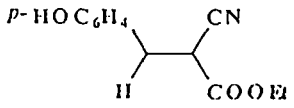
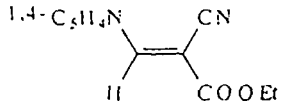
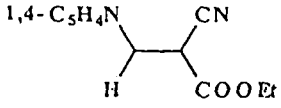
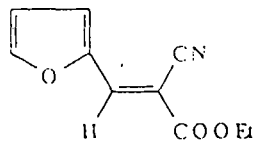
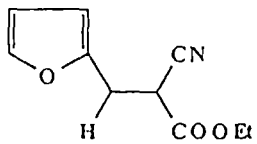
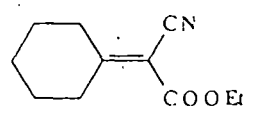
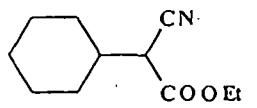
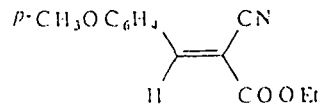
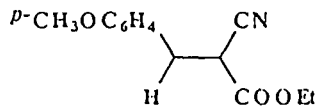
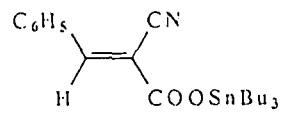
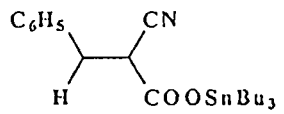
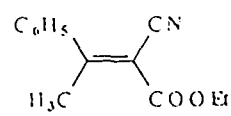
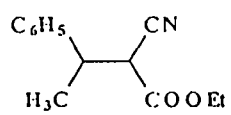
Thus the present study constitutes a useful condition for selective reduction of C=C double bond of α,β-unsaturated cyano esters using $HCOOK/Pd(OAc)_2$ as simple and inexpensive reductant. The reaction possibly involves hydride transfer in situ at the β-carbon and proceeds without any concomitant reduction of cyano, ester, or halogen groups. The ability of this reductant to perform conjugate reduction on functionalized



R_3 = Et, Sn(nBu)$_3$

Scheme 1.

Table 1. Reduction of α,β-unsaturated cyano esters by using HCOOK and catalytic $Pd(OAc)_2$.

No.	Olefin	Temp./time	Product	Yield (%)[a]
1a		45°C/3 h		92
1b		45°C/4 h		96
1c		50°C/4 h		95
1d		50°C/3 h		87
1e		45°C/4 h		79
1f		50°C/4 h		76
1g		45°C/4 h		95
1h		50°C/3 h		75
1i[b]		50°C/3 h		88

[a]Yields refer to single runs and are for pure, isolated products; all compounds were fully characterized by IR, UV, and ^{1}H- and ^{13}C-NMR spectra.
[b]The reaction was also carried out in presence of PPh_3, P(*o*-tolyl)$_3$, and TMEDA.

alkylidenecyanoacetate in a controlled fashion is noteworthy. The homogeneous catalytic condition offers further use of chiral ligands to promote asymmetric induction. Future studies will be attempted in this direction.

EXPERIMENTAL

A representative procedure (Table 1, Entry **1c**) is as follows: To a solution of the unsaturated cyano ester (0.50 g, 2.62 mmol) in DMF (5 mL) was added $Pd(OAc)_2$ (12 mg, 2 mol%), HCOOK (0.44 g, 5.24 mmol) and stirred the reaction mixture in a sealed tube (screw-cap) under N_2 at 45°C for 4 h. The mixture was cooled, diluted with water and extracted with ether (3 × 15 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel and elution with ethyl acetate–light petroleum (1:9) afforded the desired product as colorless oil in 79% yield. IR (neat): ν_{max} 2244, 1747 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, 3H, $J = 7.1$ Hz), 3.28 (m, 2H), 3.79 (m, 1H), 4.26 (q, 2H, $J = 7.1$ Hz), 6.23 (s, 1H), 6.30 (s, 1H), 7.34 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.3, 36.1, 37.3, 63.3, 108.7, 110.9, 115.9, 142.8, 149.3, 165.4.

ACKNOWLEDGMENTS

We are grateful to the Department of Science and Technology, Govt. of India, for financial support (No. SP/S1/G-13/97). SJ is a JRF under the above project.

REFERENCES

1. March, J. *Advanced Organic Chemistry*, 4th Ed.; John Wiley & Sons. Inc.: New York, 1992; 774–775.
2. Cortese, N.A.; Heck, R.F. J. Org. Chem. **1978**, *43* (20), 3985–3987.
3. (a) Keinan, E.; Gleize, P.A. Tetrahedron Lett. **1982**, *23* (4), 477–480; (b) Four, P.; Guibe, F. Tetrahedron Lett. **1982**, *23* (17), 1825–1828.
4. (a) Sala, R.; Doria, G.; Passarotti, C. Tetrahedron Lett. **1984**, *25* (40), 4565–4568; (b) Spyriounis, D.M.; Ikonomidis, G.; Demopoulos, V.J. Org. Prep. Proced. Int. **1989**, *21*, 515.
5. Keinan, E.; Greenspoon, N. J. Am. Chem. Soc. **1986**, *108* (23), 7314–7325.
6. Tour, J.M.; Cooper, J.P.; Pendalwar, S.L. J. Org. Chem. **1990**, *55* (11), 3452–3453.
7. Oshima, M.; Yamazaki, H.; Shimiju, I.; Nisar, M.; Tsuji, T. J. Am. Chem. Soc. **1989**, *111* (16), 6280–6287.

8. Arcadi, A.; Bernocchi, E.; Cacchi, S.; Marinelli, F. Synlett. **1991**, 27–28.
9. Brieger, G.; Nestrick, T. J. Chem. Rev. **1974**, *74* (5), 567–580.
10. Kindler, K.; Luhrs, K. Justus Liebigs Ann. Chem. **1967**, *28*, 707.
11. (a) Johnstone, R.A.W.; Wilby, A.H.; Entwistle, I.D. Chem. Rev. **1985**, *85* (2), 129–170; (b) Hussey, B.J.; Johnstone, R.A.W.; Entwistle, I.D. Tetrahedron **1982**, *38* (24), 3775–3781.
12. (a) Marshall, J.A.; Carroll, R.D. J. Org. Chem. **1965**, *30* (8), 2748–2754; (b) Meschino, J.A.; Bond, C.H. J. Org. Chem. **1963**, *28*, 3129.
13. Shia, K.-S.; Chang, N.-Y.; Yip, J.; Liu, H.-J. Tetrahedron Lett. **1997**, *38* (44), 7713–7716.
14. Hutchins, R.O.; Rotstein, D.; Natale, N.; Fanelli, J. J. Org. Chem. **1976**, *41* (20), 3328–3329.
15. Zhu, X.-Q.; Zou, H.-L.; Yuan, P.-W.; Liu, Y.; Cao, L.; Cheng, J.-P. J. Chem. Soc., Perkin Trans 2 **2000**, 1857–1861.
16. Zassinovich, G.; Mestroni, G.; Gladiali, S. Chem. Rev. **1992**, *92* (5), 1051–1069.
17. Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. *Vogel's Textbook of Practical Organic Chemistry*, 5th Ed.; Addison Wesley Longman Limited: Harlow, 1989; 686.
18. (a) Entwistle, I.D.; Jackson, A.E.; Johnstone, R.A.W.; Telford, R.P. J. Chem. Soc., Perkin Trans. I **1977**, (4), 443–444; (b) Sasson, Y.; Blum, J. J. Org. Chem. **1975**, *40* (13), 1887–1896.
19. Deb, C.; Basu, B. Ind. J. Chem. **1992**, *31B* (3), 131–132.
20. Deb, C.; Basu, B. J. Organomet. Chem. **1993**, *443*, C24–C25.

Received in the UK October 10, 2001

SYNLETT

Accounts and
Rapid Communications in
Synthetic Organic Chemistry

REPRINT

With Compliments of the Author

Thieme

A Simple Protocol for Direct Reductive Amination of Aldehydes and Ketones Using Potassium Formate and Catalytic Palladium Acetate

Basudeb Basu,* Satadru Jha, Md. Mosharef H. Bhuiyan, Pralay Das

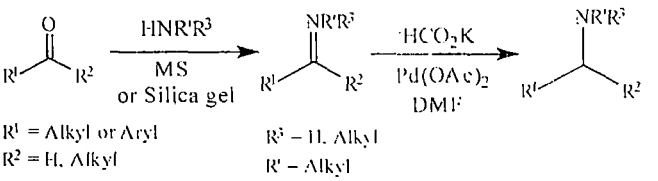
Department of Chemistry, North Bengal University, Darjeeling 734 430, India
Fax +91(353)581546; E-mail: basu_nbu@indiatimes.com

Received 29 October 2002

Abstract: A method for direct reductive amination of aldehydes and ketones, including α,β-unsaturated carbonyl compounds, has been developed, which requires potassium formate as reductant and palladium acetate as catalyst. Suitable amines include both primary and secondary aliphatic and aromatic amines.

Key words: reductive amination, potassium formate, palladium acetate, one-pot reaction

The direct reductive amination of carbonyl compounds[1] is a useful organic transformation for preparing primary, secondary and tertiary amines. The carbonyl compound initially reacts with ammonia or amine to form an imine, which then undergoes reduction in presence of hydrogen or hydride ion (Scheme 1). The term 'direct reductive amination' is used to describe a reaction in which a mixture of the carbonyl compound and the amine is treated with suitable reducing agent in a one-pot operation.[1b] Several reductive systems are known to effect the reduction of the C–N double bond of the imine. The Borch reduction,[2] one of the early methods, involves sodium cyanoborohydride, [$NaBH_3CN$], as the reductant. However, use of excess reagent (up to 5-fold) along with toxic cyanide as the by-product limits its wide applications. The alternative sodium triacetoxyborohydride, [$NaBH(OAc)_3$],[3] has not been successful for aromatic and unsaturated ketones. Other reagents include $ZnCl_2$–$Zn(BH_4)_2$;[4] $NiCl_2$–$NaBH_4$;[5] Ti(*i*-PrO)$_4$–polymethylhydrosiloxane;[6] Ti(*i*-PrO)$_4$–$NaBH_4$;[7] Bu_3SnH;[8] Bu_2SnClH and Bu_2SnIH;[9] decaborane;[10] silica gel–$Zn(BH_4)_2$;[11] Et_3SiH–trifluoroacetic acid;[12] pyridine–BH_3;[13] phenylsilane–dibutyltin dichloride.[14] 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 is not recommended for large-scale preparation as the residual insoluble tin compounds pose a great risk in its elimination. 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 Leuckart reaction, often yields the N-formyl derivative of the amine instead of the free amine.[15] Recently, we[16a] and other groups[16b] have shown that potassium formate promoted by palladium acetate can reduce 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. We report herein our observation, which 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 1

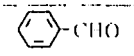
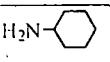
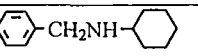
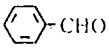
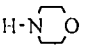
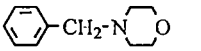
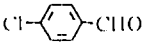
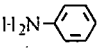
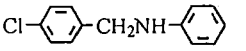
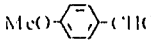
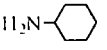
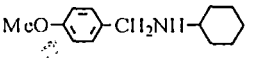
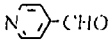
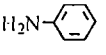
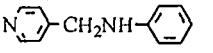
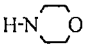
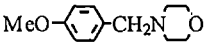
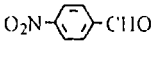
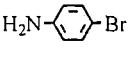
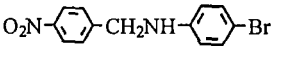
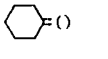
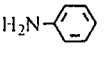
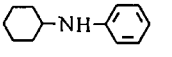
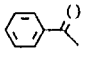
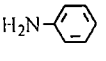
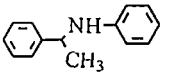
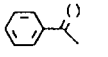
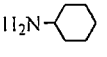
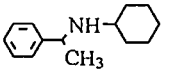
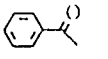
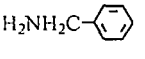
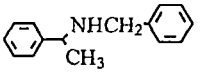
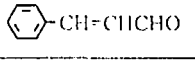
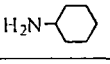
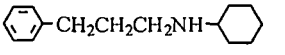
To examine the scope of this reaction, a variety of aldehydes and ketones were reductively aminated with aliphatic and aromatic amines (Table 1). Both primary and secondary amines, such as morpholine (entries 2 and 6) have been used. Reactions with substrates bearing potentially reducible functional groups including chloro (entry 3), bromo and nitro (entry 7) yielded anticipated products without detectable reductive side products. 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). 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 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.[11] 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

Synlett 2003, No. 4, Print: 12 03 2003.
Art Id.1437-2096,E;2003,0,04,0555,0557,ftx,en;D24402ST.pdf.

ISSN 0936-5214

Table 1 Direct Reductive Amination of Aldehydes and Ketones with HCO_2K and Catalytic $Pd(OAc)_2$

Entry	Substrate 1	Amine 2	Condition[a]/Temp./ Time (h)	Product3	Yield (%)[b]
1			A/40 °C/3		68
2			A/40 °C/4		62
3			A/50 °C/5		67
4			A/40 °C/3		75
5			A/40 °C/3		86
6			A/50 °C/5		67
7			A/50 °C/5		56
8			B/50 °C/5		70
9			B/60 °C/6		76
10			B/60 °C/6		83
11			B/60 °C/6		80
12			B/50 °C/5		69

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

[b] Yield are reported after chromatographic purification (2–3 runs). Satisfactory spectral data were obtained for all the amines (products).

(2–3 equiv) and heated at 40–60 °C for 3–6 hours.[17] 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 catalysed 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.

Acknowledgement

Financial support from the Department of Science & Technology, New Delhi (Grant No. SP/S1/G13/97) is gratefully acknowledged. We are thankful to Professor B. C. Ranu, Department of Oragnic Chemistry, Indian Association for the Cultivation of Science, Calcutta 700 032, India for his help in doing some of the experiments.

References

(1) For a recent review, see: (a) Tarasevich, V. A.; Kozlov, N. G. *Russ. Chem. Rev.* **1999**, *68*, 55. (b) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(2) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(3) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595.

(4) Bhattacharyya, S.; Chatterjee, A.; Duttachowdhury, S. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1.

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

(6) Chandrasekhar, S.; Reddy, C. R.; Ahmed, M. *Synlett* **2000**, 1655.

(7) Bhattacharyya, S.; Neidigh, K. A.; Avery, M. A.; Williamson, J. S. *Synlett* **1999**, 1781.

(8) Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synlett* **2000**, 556.

(9) Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synthesis* **2000**, 789; and references cited therein.

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

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

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

(13) Bomann, M. D.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995.
(14) Apodaca, R.; Xiao, W. *Org. Lett.* **2001**, *3*, 1745.
(15) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley and Sons: New York, **2001**, Chap. 16, 1187.
(16) (a) Basu, B.; Bhuiyan, M. M. H.; Jha, S. *Synth. Commun.* **2003**, *33*, 289. (b) Arcadi, A.; Bernocchi, E.; Cacchi, S.; Marinelli, F. *Synlett* **1991**, 27.
(17) **General Procedure for Aldehydes.** For the aldehydes (listed in Table 1) except cinnamaldehyde:
A solution of *p*-anisaldehyde (680 mg, 5 mmol) and cyclohexylamine (500 mg, 5 mmol) in dry DMF (5 mL) was magnetically stirred at r.t. for 4 h, in presence of molecular sieves (4 Å). To the resulting reaction mixture were added HCOOK (840 mg, 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 ether (3 × 20 mL). The combined extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the crude product, which was purified by column chromatography over silica gel. Elution with ethyl acetate–hexanes (1:19; R_f 0.26) furnished *N*-cyclohexyl *p*-methoxybenzyl amine **4** (815 mg, 75%) as an oil: IR(neat): 1246, 1300, 1510, 1610, 2851, 2925 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.31 (m, 6 H), 1.61 (br, 1 H), 1.70–1.92 (m, 4 H), 2.43–2.50 (m, 1 H), 3.73 (s, 2 H), 3.78 (s, 3 H), 6.84 (d, 2 H, *J* = 8.3 Hz), 7.22 (d, 2 H, *J* = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 26.2, 33.4, 50.3, 55.2, 56.0, 113.7, 129.2, 132.9, 158.4.

Pergamon

Tetrahedron Letters 43 (2002) 7967–7969

TETRAHEDRON LETTERS

Palladium-catalysed amination of halopyridines on a KF-alumina surface

Basudeb Basu,* Satadru Jha, Niranjan K. Mridha and Md. Mosharef H. Bhuiyan

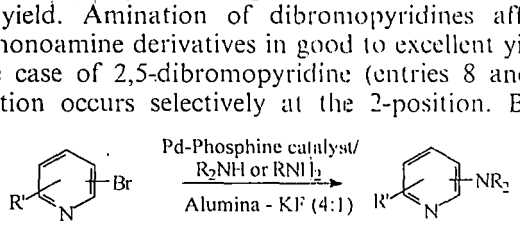
Department of Chemistry, University of North Bengal, Darjeeling 734 430, India

Received 19 February 2002; revised 22 August 2002; accepted 30 August 2002

Abstract—Palladium-catalysed C–N hetero cross-coupling reactions between bromopyridines and amines (both primary and secondary) can be efficiently performed on a KF-alumina (basic) surface, thus negating the use of strong bases such as sodium *tert*-butoxide. The reaction conditions are optimised with reference to catalytic systems, solvents and the surface.

Aminopyridines are versatile intermediates for synthetic transformations to biologically active compounds[1] and are known to act as central nervous system stimulants.[2] Their derivatives are often used as ligands in coordination and organometallic chemistry,[3] and have found industrial applications as fluorescent dyes.[4] Most of the early preparative methods for aminopyridines involve aromatic nucleophilic substitution by S_NAr, benzyne or $S_{RN}1$ reactions.[5] These methods either suffer from a nucleophilic regiocontrol problem, the need for very high temperature or the presence of specific functionality on the heterocyclic ring. None of these methods show a combination of good yields and high selectivity. Buchwald and others[6] have recently developed chelating bis-phosphine-palladium catalysed cross-coupling reactions that allow the preparation of aminopyridines from their corresponding halopyridines.[7] The method involves Pd(0)/bis-phosphine complexes as the effective catalyst for oxidative addition to the carbon–halogen bond, followed by coupling with the amine. The amination is catalyst-specific (Pd–ligand complexes) and very sensitive to the nature of the base.[6a,d] Although this reaction efficiently produces aminopyridines in the presence of chelating bis-phosphine/Pd(0) complexes, the use of strong bases such as sodium *tert*-butoxide is not desirable and remains associated with problems such as in the case of direct amination using NaNHR or $NaNR_2$.[5,8] Furthermore, the use of strong bases greatly limits the functional group tolerance of the process.[9] The weaker base (Cs_2CO_3) has been employed for haloaromatics[9] and halothiophenes,[10] but not in the case of halopyridines and its use is limited due to high solubility in organic solvents and its hygroscopic nature. Since the use of a base is one of the keys to the success of this coupling reaction, we investigated palladium-catalysed cross coupling of bromopyridines and amines on a KF-alumina (basic) surface. KF-alumina has been successfully employed in many other cases so as to exploit its basicity on the surface[11] and very recently Pd-catalysed C–C couplings (Suzuki, Heck, Stille, Trost-Tsuji) have been reported using KF-alumina under mono-mode microwave irradiation.[12] This report describes our results, which constitute a convenient and efficient heterogeneous method for C–N coupling by Pd-catalysed amination of halopyridines on KF-alumina (basic) surface (Scheme 1).

As can be seen from the results presented in Table 1, the amination on KF-alumina surface works with different bromopyridines. While 2-bromopyridine (entries 1 and 2) reacts with different amines smoothly, 3-bromopyridine (entry 7) undergoes amination in relatively poor yield. Amination of dibromopyridines affords only monoamine derivatives in good to excellent yields. In the case of 2,5-dibromopyridine (entries 8 and 9), amination occurs selectively at the 2-position. Buch-



(*o*-Tolyl)$_3$P, DPPF, BINAP; Pd-sources: $PdCl_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(acac)_2$, $Pd[PPh_3]_4$

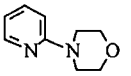
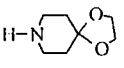
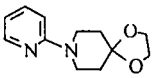
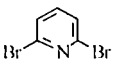
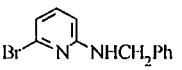
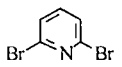
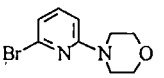
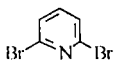
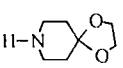
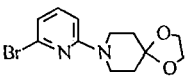
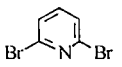
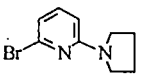
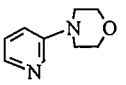
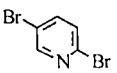
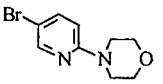
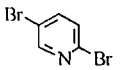
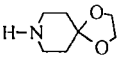
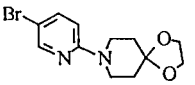
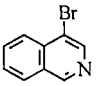
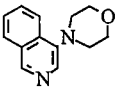
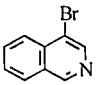
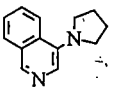
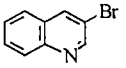
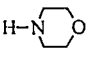
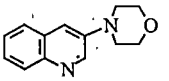
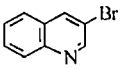
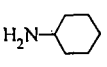
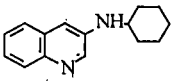
Scheme 1.

Keywords: aminopyridines; palladium catalyst; carbon–nitrogen cross coupling; KF-alumina.

* Corresponding author. Tel.: +91-353-581425; fax: +91-353-581546; e-mail: basu_nbu@hotmail.com

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01852-X

Table 1.

Entry	Bromoarene	Amine	Catalyst	Conditions[b]/ time (h)	Product	Yield(%)[c]
1			[A]	2 / 8		70
2			[A]	2 / 8		58
3		H_2NCH_2Ph	[H]	2 / 8		90
4			[A]	1 , 2 / 5		78
5			[A]	2 / 5		62
6			[A]	2 / 5		91
7			[F]	1 , 2 / 9		48
8			[A]	1 , 2 / 5		92
9			[A]	2 / 5		73
10			[E], [F]	1 , 2 / 6		86
11			[F]	2 / 6		90
12			[F]	2 / 6		78
13			[F]	2 / 8		68

[a] [A] Pd[(*o*-tolyl)$_3$P]$_2$Cl$_2$; [B] Pd$_2$(dba)$_3$ - P(*o*-tolyl)$_3$; [C] Pd [PPh$_3$]$_4$; [D] Pd$_2$(dba)$_3$ - dppf; [E] Pd(OAc)$_2$ - dppf ; [F] Pd$_2$(dba)$_3$ - BINAP ; [G] Pd(acac)$_2$ - dppf ; [H] Pd(OAc)$_2$ - BINAP

[b] 1. Alumina - KF in Toluene / 90 - 100 °C; 2. Alumina - KF without solvent at 90-100 °C.

[c] Yields are reported on the basis of pure isolated products (2-3 runs) and calculated on the basis of recovered starting material (for entries **6, 7, 9**).

wald observed complete bis-amination of 2,6-dibromopyridine using Pd$_2$(dba)$_3$-dppe catalyst in the presence of excess amine.[7a] Our conditions, however, yielded monoamines as the major products even after prolonged reaction times and in the presence of excess amine (entries 3–6). This selectivity offers an advantage for further reaction with the other halogen substituents. In the bicyclic systems, 4-bromoisoquinoline (entries 10 and 11) and 3-bromoquinoline (entries 12 and 13) undergo amination efficiently.

A great deal of experimentation on the cross coupling of bromopyridines with primary and secondary amines was carried out in order to optimise the reaction conditions. Palladium sources, ligand, solvent and the support (KF-Al_2O_3) were optimised and several details are worthy of comment. Firstly, different palladium sources like $PdCl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(acac)_2$ and $Pd[PPh_3]_4$ complexing with either mono-phosphine [(*o*-tolyl)$_3$P] or bis-phosphines (BINAP and DPPF) were employed as the catalytic systems. The Pd[(*o*-

tolyl)$_3$P]$_2$Cl$_2$ and Pd$_2$(dba)$_3$/BINAP complexes were found to be most effective in this amination process (Table 1). The formation of bis-(pyridyl) complexes using monophosphine ligands, as proposed by Buchwald,[7a] might possibly be avoided under these conditions. The reactions were carried out with or without a solvent. Clean reactions and better yields of the aminopyridines were obtained when the reactions were carried out on KF-Al_2O_3 surface with a slight excess of amine and without solvent. Toluene and xylene have been used as solvents with almost similar effects, whilst the presence of DMF as a co-solvent induces faster debromination (entry 10). 2-Bromopyridine (entries 1 and 2) also yields 10–15% of 2,2′-bipyridyls by intermolecular coupling and such coupling is further increased in the presence of a solvent. The major limitations of this protocol are that 3-bromopyridine fails to cross-couple with primary amines and partial dehalogenation (<5%) was observed in the case of 3-bromopyridine, 3-bromoquinoline and 4-bromoisoquinoline.

In conclusion, we have shown that Pd(0) catalysed amination of bromopyridines can be performed smoothly on the surface of basic alumina admixed with KF. The simplicity of the experimental conditions, good to excellent yields and favourable safety aspects represent a significant improvement and useful extension relative to Buchwald's procedure using the strong base, sodium *tert*-butoxide. Future work will include studies with more base-sensitive functionalities on the heterocyclic nucleus as well as with chiral amines.

Experimental

General procedure

Preparation of activated Al_2O_3/KF: A mixture of basic alumina (Activity I according to Brockmann) and KF (4:1) (5 g) was taken in THF (5 mL) and after stirring for 30 min at room temperature it was evaporated to dryness. The solid residue was heated at 250°C under vacuum (0.5 mm of Hg) for 4 h, cooled under N_2 and used for reaction.

To a mixture of 2,6-dibromopyridine (473 mg, 2 mmol), benzylamine (856 mg, 8 mmol), Pd(OAc)$_2$ (10 mg, 0.04 mmol) and (±) BINAP (50 mg, 0.08 mmol) was added activated Al_2O_3/KF (2 g). The mixture was intimately stirred at 90–100°C for 8 h under nitrogen. After cooling to room temperature the semi-solid mass was washed repeatedly with ether (4×15 ml), combined and concentrated. The residue was purified by silica gel column chromatography (petroleum-ether:EtOAc= 20:1) to give 2-benzylamino-6-bromopyridine (475 mg, 90%); mp 85°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.46 (d, 2H, J=5.9 Hz), 5.18 (br.s, 1H), 6.24 (d, 1H, J=8.2 Hz), 6.73 (d, 1H, J=7.5 Hz), 7.20 (dd, 1H, J=8.2; 7.5 Hz), 7.27–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.3, 104.5, 116.1, 127.3, 127.4, 128.7, 138.3, 139.5, 140.2, 158.7.

Acknowledgements

We thank the Department of Science and Technology, New Delhi for financial support (Grant No. SP/S1/G13/97). S.J. is a Junior Research Fellow under this project.

References

1. (a) Montgomary, J. A.; Secrist, J. A. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R.; Rees, C. W.; Potts, K. T., Eds.; Pergamon: Oxford, 1984; Vol. 5, p. 607; (b) Katrizky, A. R.; Qiu, G.; Long, Q.-H.; He, H.-Y.; Steel, P. J. *J. Org. Chem.* **2000**, *65*, 9201–9205; (c) Benigni, R.; Giuliani, A.; Franke, R.; Gruska, A. *Chem. Rev.* **2000**, *100*, 3697–3714.
2. (a) Lechat, P.; Tesleff, S.; Bowman, W. C. *Aminopyridines and Similarly Acting Drugs*; Pergamon: Oxford, 1982; (b) Broekkamp, C. L. E.; Leysen, D. B.; Peeters, W. M. M.; Pinder, R. M. *J. Med. Chem.* **1995**, *38*, 4615–4633.
3. (a) Kempe, R.; Arndt, P. *Inorg. Chem.* **1996**, *35*, 2644–2649; (b) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497–526.
4. (a) Sathyamoorthy, G.; Soong, M. L.; Ross, T. W.; Boyer, J. H. *Heteroatom. Chem.* **1993**, *4*, 603–608; (b) Araki, K.; Mutai, T.; Shigemitsu, Y.; Yamada, M.; Nakajima, T.; Kuroda, S.; Shimao, I. *J. Chem. Soc., Perkin Trans. 2* **1996**, 613–617.
5. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; John Wiley and Sons: New York, 2001; pp. 850–893.
6. (a) Guram, A.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348–1350; (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218; (c) Kerrigan, F.; Martin, C.; Thomas, G. H. *Tetrahedron Lett.* **1998**, *39*, 2219–2222; (d) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146.
7. (a) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240–7241; (b) Wolfe, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.
8. (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, 2000; pp. 71–120; (b) Jamart-Gregoire, B.; Leger, C.; Caubere, P. *Tetrahedron Lett.* **1990**, *31*, 7599–7602; (c) Walters, M. A.; Shay, J. J. *Synth. Commun.* **1997**, *27*, 3573–3577.
9. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.
10. Luker, T. J.; Beaton, H. G.; Whiting, M.; Mete, A.; Cheshire, D. R. *Tetrahedron Lett.* **2000**, *41*, 7731–7735.
11. (a) Blass, B. E.; Harris, C. L.; Portlock, D. E. *Tetrahedron Lett.* **2001**, *42*, 1611–1613; (b) Kabashima, H.; Tsuji, H.; Nakata, S.; Tanaka, Y.; Hattori, H. *Appl. Cat. A* **2000**, *194–195*, 227–240.
12. Villemin, D.; Caillot, F. *Tetrahedron Lett.* **2001**, *42*, 639–642.

Catalytic Transfer Reduction of Alkenes and Imines Using Polymer Supported Formates

Md. Mosharef H. Bhuiyan and Basudeb Basu*

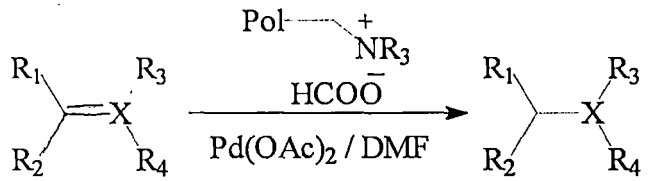
Department of Chemistry, University of North Bengal, Darjeeling 734 430, India
E-mail: basu_nbu@indiatimes.com

Abstract: A method for catalytic transfer hydrogenation of C–C and C–N double bonds with the aid of polymer supported formate (PSF) as the hydrogen donor and palladium acetate as the catalyst is described.

Catalytic transfer hydrogenation (CTH) with the aid of hydrogen donor is a useful alternative method to catalytic hydrogenation by molecular hydrogen.[1] In transfer hydrogenation, several organic molecules such as hydrocarbons,[2] primary and secondary alcohols,[3] formic acid and its salts[4] have been employed as the hydrogen source. The use of inorganic reagents like hydrazine is less frequent.[1b] The use of hydrogen donor has some advantages over the use of molecular hydrogen since it avoids the risks and the constraints associated with hydrogen gas as well as the necessity of pressure vessels and other equipment. During last decades, asymmetric transfer hydrogenation has been accomplished by using chiral metal complexes.[5]

The functionalized polymers have been emerged as versatile tools for solution-phase chemistry and automated parallel synthesis.[6] The polymeric supports have been used for anchoring several reducing agents such as, borohydrides,[7] tin hydrides[8] etc. These hydrides are either expensive, reactive or the residue poses a risk in its elimination. Therefore, the design of ideal support with suitable reagents has been a subject of research for many synthetic chemists. In connection with our interests in catalytic transfer reduction of alkenes and imines using a combination of potassium formate and catalytic palladium acetate,[9] we envisioned that whether the source of hydrogen donor i.e. the formate anion could be supported on a solid surface. The ionic exchange of formate anion with a resin exchanger might be used as hydrogen donor in CTH. This might give some advantages about its reusability, ease separation of the reduced product, clean and green reaction. While searching in the literature, to our knowledge, only a single report from Desai and Danks has been reported where formic is anchored with Amberlite (IRA 938) or impregnated on alumina surface and employed in rhodium(I)-catalyzed reduction of some cinnamic acid systems using microwaves.[10] We therefore desired to investigate in details the application of PSF in

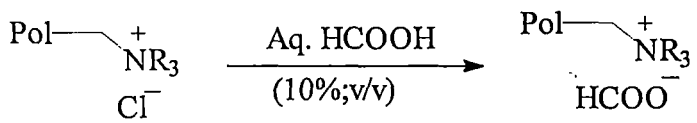
metal-catalyzed hydrogen transfer reduction of different electron deficient alkenes and/or imines. Herein we disclose our results illustrating the synthetic utility of PSF in transition metal-catalyzed transfer hydrogenation of a variety of electron deficient alkenes and imines (Scheme I).



$R_1 = R_2 =$ Ph, Ar, H, X = C, N
R_3 and R_4 = CN, COOEt, COOMe, NHBoc, H, Ph

Scheme I

The PSF was prepared by washing Amberlite resin (IRA 420, Cl^-) packed in a column with 10% formic acid solution repeatedly until the washings gave negative response to chloride ion (Scheme II). Finally the solid surface was washed with water several times and then dried under vacuum. The resulting resin formate was used directly for catalytic reduction. A mixture of unsaturated compound, palladium acetate (2 mol%) and resin formate in DMF was stirred at 70-75 ^{0}C for 10-16h (Table 1). After cooling and diluted with water, the mixture was extracted with ether, which on evaporation afforded the desired product, purified by column chromatography on silica.



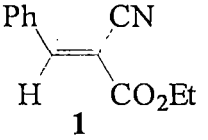
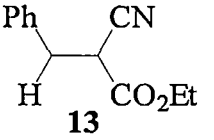
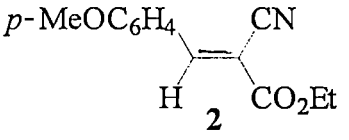
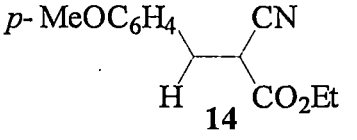
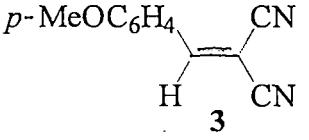
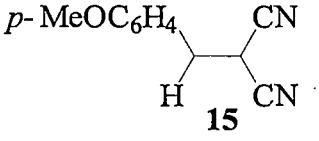
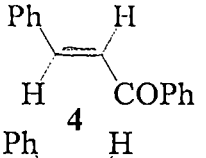
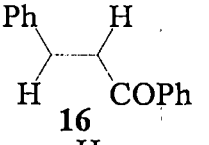
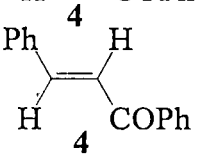
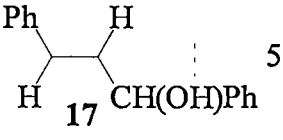
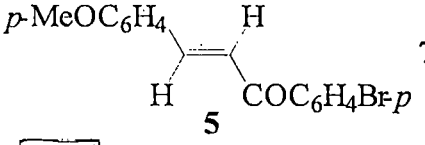
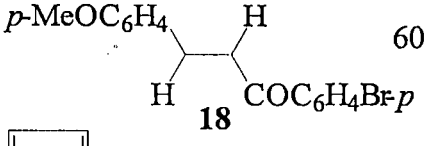
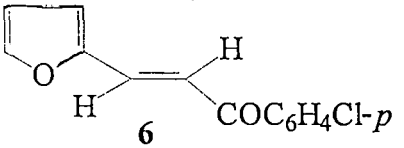
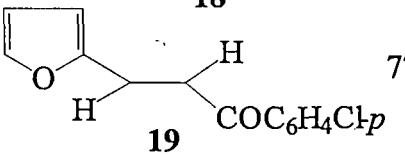
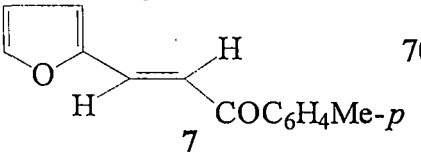
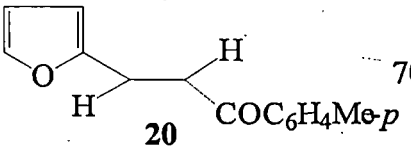
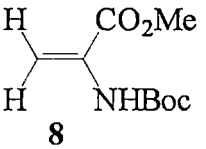
Amberlite® IRA-420 Chloride form taken in water

Amberlite® IRA-420 Format form

Scheme II

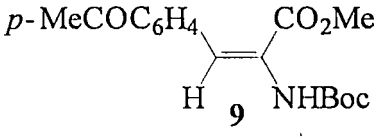
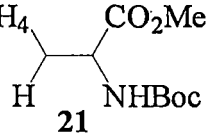
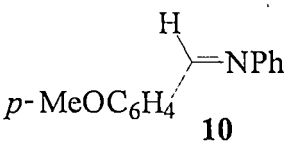
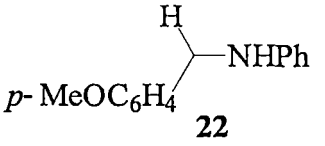
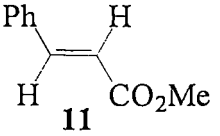
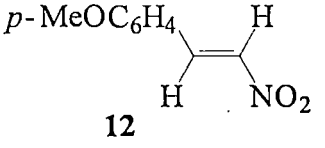
The generality of this methodology has been investigated with different types of electron-deficient alkenes and imines (Table 1). We first examined reduction of alkylidene cyanoacetate (entries 1,2) using PSF and palladium acetate (2 mol%) in DMF. The PSF was employed in excess anticipating that not every functional site needs to react. The reduction of the C-C double bond proceeded smoothly at 70-75 ^{0}C requiring only gentle agitation, work-up was then achieved by simple filtration, extraction with diethyl ether and evaporation. The reduced product was purified by column chromatography over silica gel. Both the cyano and ester groups remain unaffected under the reaction conditions. The reduction of dicyanoalkylidene derivative (entry 3) was found to occur with similar efficiency.

Table 1

Entry	Substrate	Temp./ Time	Product	%Yield
1.	 **1**	70 °C/ 10h	 **13**	85
2.	 **2**	70 °C/ 12h	 **14**	75
3.	 **3**	75 °C/ 10h	 **15**	81
4a.	 **4**	70 °C/ 10h	 **16**	82
4b.	 **4**	75 °C/ 16h	**16** +  **17**	56 + 31
5.	 **5**	70 °C/ 12h	 **18**	60
6.	 **6**	70 °C/ 14h	 **19**	77
7.	 **7**	70 °C/ 14h	 **20**	70
8.	 **8**	70 °C/ 14h	No reaction	

Continued.....

Continued..... Table 1

Entry	Substrate	Temp./ Time	Product	%Yield
9.	 **9**	70 °C/ 10h	 **21**	70
10.	 **10**	70 °C/ 12h	 **22**	85
11.	 **11**	75 °C/ 14h	No reaction	
12.	 **12**	75 °C/ 14h	No reaction	

Based on this encouraging result, the scope and limitations of this transfer hydrogenation were further extended. As seen in Table 1, α,β-unsaturated ketones (entries 4-7) bearing potentially reducible groups were hydrogenated efficiently and as expected. The reaction, if continued for a longer period, resulted in partial reduction of the carbonyl functions as well (31%) (entry 4b).

Since dehydroamino acid derivatives are potential precursors to phenyl alanine or alanine based amino acids[11] and their synthesis is one of our major interests, we examined reduction of enamides (entries 8, 9) using PSF and catalytic palladium acetate. Interestingly, while compound (entry 8) was not reducible under the present conditions, the *p*-acetyl compound (entry 9) underwent smooth reduction in good yield (70%). Although this selectivity is difficult to explain with evidence, the nucleophilicity at the β-carbon might be one of the possibilities.

In order to broaden the scope of our study, we carried out reduction of C–N double bond of the imines. The imine (entry 10) under similar conditions afforded the secondary amine in excellent yield (85%). Since the imines were derived from the corresponding carbonyl compounds, this overall one-pot protocol may be termed as direct reductive amination of carbonyl compounds using PSF and catalytic palladium acetate.

Surprisingly, our reaction condition was found unsuccessful for reduction of simple alkyl cinnamate (entry 11) and nitro olefin (entry 12). Desai and Danks carried out

reduction of alkyl cinnamate using PSF and $RhCl(PPh_3)_3$ (2.5 mol%) as the catalyst under microwave irradiation. The nitro olefins are known to produce oximes under CTH using NH_4-formate.[12] We, however, obtained no change of the starting material while carrying out the reaction using PSF.

Dehalogenation of aromatic halides under CTH methods has been observed[13] and the process is rapid while using microwaves.[14] The method described by Desai and Danks on the substrates was not employed to bearing reducible groups.
From the overall observation, it appears that the rate of the reduction using PSF is slower than that using the HCOOK. The reason for this is not, however, clear at this point. Further mechanistic investigations will include in future work.

In conclusion we have shown that palladium-catalyzed transfer hydrogenation could be performed with a variety of electron-deficient alkenes as well as imines using the polymer supported formate (PSF) as the source of hydrogen. The method is operationally simple and applicable to a range of unsaturated organic compounds. The use of palladium catalyst showed some substrates selectivity. Other advantages are: clean work-up, high yields and environmentally benign. Future work will include studies directed towards mechanistic aspects as well as on the use of other transition metals complexes such as, rhodium and ruthenium metals with chelating phosphine complexes. The scale-up of the protocol and reuse of the resin-surface will also be studied as the extension work.

Experimental

A representative procedure

Methy 3-(4-acetophenyl)-2-(*tert*-butoxycarbonylamino)propionate (**21**): To a solution of methyl 3-(4-acetophenyl)-2-(*tert*-butoxycarbonylamino)-acrylate (**9**) (0.321g, 1 mmol) in DMF (3 mL) was added $Pd(OAc)_2$ (5mg, 2 mol%). The reaction mixture was flashed with nitrogen and PSF (Resin Formate, 1 g) was added all at once. The reaction mixture was stirred in a screw-cap sealed tube at 70 ^{0}C for 10 hours. After cooling, the reaction mixture was diluted with water, filtered. The filtrate extracted with ether (3×15 mL). The combined ethereal layer was washed with brine, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by column chromatography over silica gel using EtOH-light petroleum (1:4) as eluent to furnish the desired product **21** as colourless crystals in 70 % (0.224g) yield, m.p. 72-73 ^{0}C. UV (MeOH): λ_{max} 248 nm. IR (neat): ν_{max} 3360, 2996, 1752, 1670, 1609, 1516, 1455, 1373 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.87 (d, 2H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.1 Hz), 5.05 (d, 2H, J = 7.7 Hz), 4.59 (t, 1H), 3.69 (s, 3H), 2.55 (s, 3H), 1.38 (s, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 197.7, 171.9, 154.9, 141.7, 135.8, 129.5, 128.5, 54.1, 52.3, 38.3, 29.6, 28.2, 26.5. Anal. Calcd. for $C_{17}H_{23}NO_5$ (321.38): C, 63.54; H, 7.21. Found: C, 63.28; H, 7.62.

References

1. (a) Brieger, G.; Nestrick, T.J. *Chem. Rev.* **1974**, *74*, 657. (b) Johnstone, R.A.W.; Wilby, A.H.; Entwistle, I.D. *Chem. Rev.* **1985**, *85*, 129.
2. Braude, E.A.; Linstead, R.P. *J. Chem. Soc.* **1954**, 3544.
3. Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931 and references cited therein.
4. (a) Fache, F.; Schilz, E.; Tommasino, M.L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159. (b) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (c) Ram, S.; Ehrenkaufer, R.E. *Synthesis* **1988**, 91.
5. Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051.
6. Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed. Eng.* **2001**, *40*, 650.
7. (a) Gibson, H.W.; Baily, F.C. *J. Chem. Soc.,Chem. Commun.* **1977**, 815. (b) Yakabe, S.; Hirano, M.; Morimoto, T. *Synth. Commun.* **1999**, *29*, 295.
8. Delmond, B.; Dumartin, G. In *Solid State Organometallic Chemistry: Methods and Applications,* Gielen, M.; Willem, R.; Wrackmeyer, B. Eds.; Wiley, Chichester, 1999, 445.
9. (a) Basu, B.; Bhuiyan, M.M.H.; Jha, S. *Synth. Commun.* **2003**, *33*(2), 291. (b) Basu, B.; Jha, S.; Bhuiyan, M.M.H.; Das, P. *Synlett* **2003**, (4), 555.
10. Desai, B.; Danks, T.N. *Tetrahedron Lett.* **2001**, *42*, 5963.
11. (a) Basu, B.; Frejd, T. *Acta Chem. Scand.* **1996**, *50*, 316. (b) Basu, B.; Chattopadhyay, S.K.; Ritzen, A.; Frejd, T. *Tetrahedron: Asymmetry* **1997**, *8*, 1841. (c) Ritzen, A.; Basu, B.; Chattopadhyay, S.K.; Dossa, F.; Frejd, T. *Tetrahedron: Asymmetry* **1998**, *9*, 503.
12. Entwistle, I.D.; Jackson, A.E.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 443.
13. Sasson, Y.; Blum, J. *J. Am. Chem. Soc.* **1975**, *40*, 1887.
14. Banik, B.K.; Barakat, K.J.; Wagle, D.R.; Manhas, M.S.; Bose, A.K. *J. Org. Chem.* **1999**, *64*, 5746.

P303

PALLADIUM MEDIATED CHEMOSELECTIVE REDUCTION OF ENAMIDES ON A SOLID SUPPORTED REDUCING AGENT

Bhuiyan M.M.H. and Basu B.*

Department of Chemistry, North Bengal University, Darjeeling 734 430, Indian Overseas Bank. Phone 0353)582425; Fax 0353) 581546; Email: basu_nbu@indiatimes.com

Chemoselective reduction of carbon-carbon multiple bond in conjugated systems is an important process in organic synthesis. Despite the bewildering variety of reducing agents available to synthetic chemists, new and selective reductants are in constant demand. Transition metal-catalyzed hydrogen transfer reaction with the aid of a hydrogen donor, such as trialkyl ammonium formate, and other hydrides like n-Bu_3SnH, NaH_2PO_3/H_2O, $Ph_2SiH_2/ZnCl_2.H_2$), triethoxysilane-water are some of the examples employed for selective conjugate reduction. In most cases, direct source of hydride is used for conjugate addition to the more nucleophilic β-carbon, whereas formic acid and its salts are believed to be a source of hydride *in situ*, which eventually adds to the β-carbon. Recently we and other groups have shown that a combination of $Pd(OAc)_2$/HCOOK as a convenient alternative reductant for conjugate addition of α,β-unsaturated nitriles, esters, and ketones.

As a further development to this procedure, we studied similar reduction on a solid surface and extended our reaction conditions to enamides. The enamides or α acylaminoacrylic acids are normally reduced by molecular hydrogen in presence of homogeneous transition metal catalysts (including asymmetric hydrogenation) and under high pressure. The present method might be an alternative for reduction of enamides and related substrates including asymmetric reduction.

The present poster will describe some of our observations on reduction of enamides and related substrates using a combination of $Pd(OAc)_2$/HCOOK as the reductant.