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

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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.

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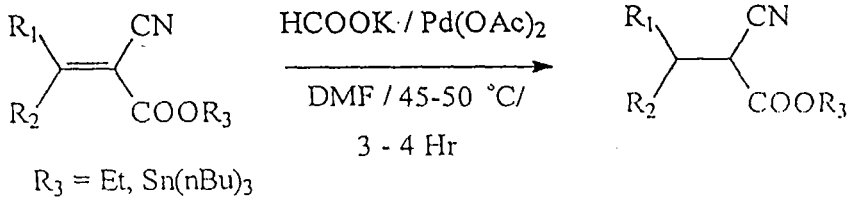
Chemoselective reduction of carbon–carbon multiple bond in conjugated systems is an important process in organic synthesis.[1] Despite the bewildering variety of reducing agents available to synthetic chemists, new and selective reductants are in constant demand. Transition metal-catalyzed hydrogen transfer 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.

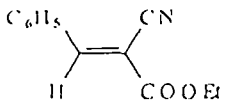
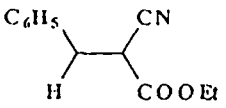
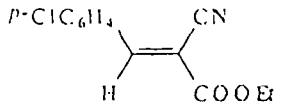
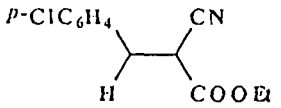
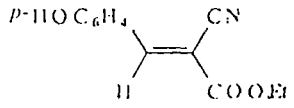
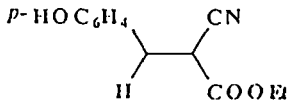
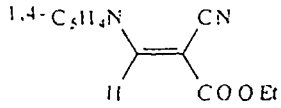
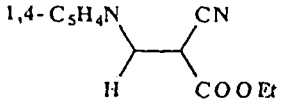
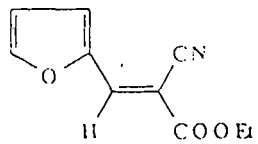
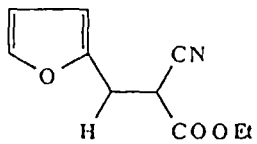
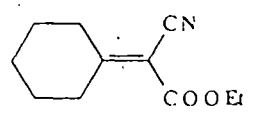
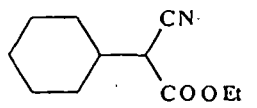
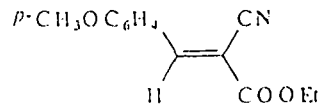
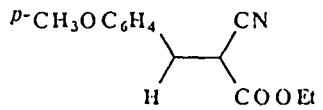
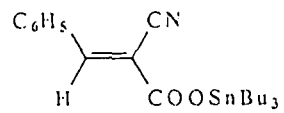
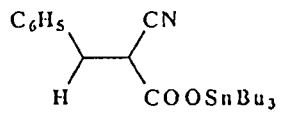
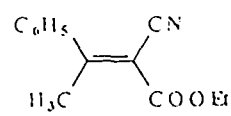
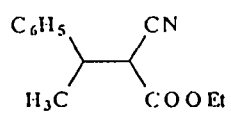
Thus the present study constitutes a useful condition for selective reduction of C=C double bond of α,β-unsaturated cyano esters using $HCOOK/Pd(OAc)_2$ as simple and inexpensive reductant. The reaction possibly involves hydride transfer in situ at the β-carbon and proceeds without any concomitant reduction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

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

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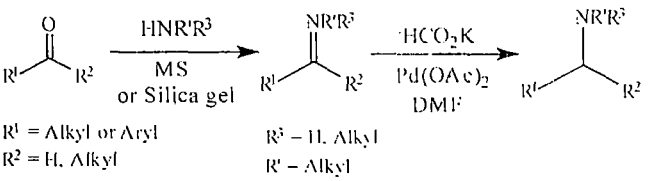
Abstract: A method for direct reductive amination of aldehydes and ketones, including α,β-unsaturated carbonyl compounds, has been developed, which requires potassium formate as reductant and palladium acetate as catalyst. Suitable amines include both primary and secondary aliphatic and aromatic amines.

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

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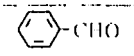
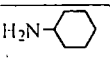
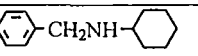
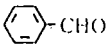
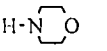
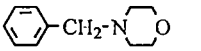
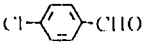
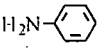
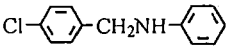
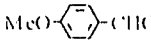
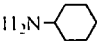
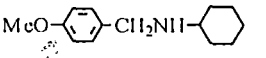
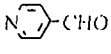
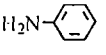
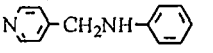
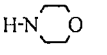
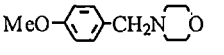
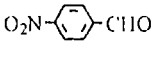
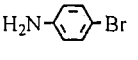
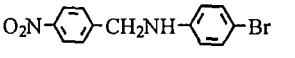
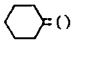
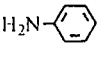
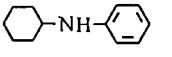
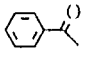
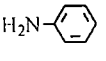
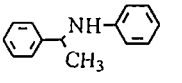
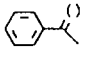
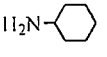
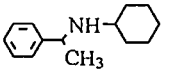
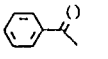
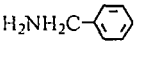
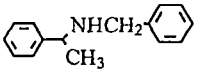
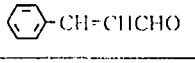
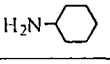
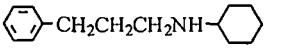
Table 1 Direct Reductive Amination of Aldehydes and Ketones with HCO_2K and Catalytic $Pd(OAc)_2$

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

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(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.

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

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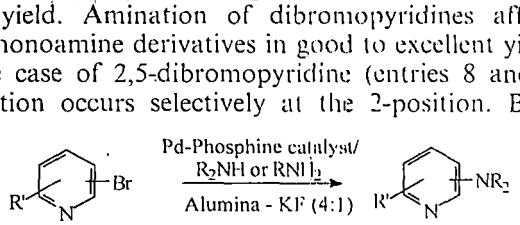
Abstract—Palladium-catalysed C–N hetero cross-coupling reactions between bromopyridines and amines (both primary and secondary) can be efficiently performed on a KF-alumina (basic) surface, thus negating the use of strong bases such as sodium *tert*-butoxide. The reaction conditions are optimised with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

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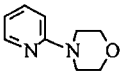
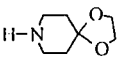
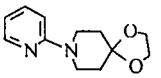
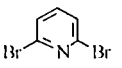
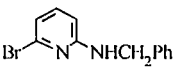
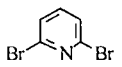
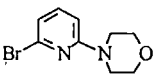
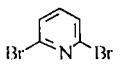
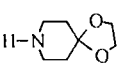
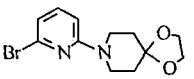
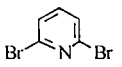
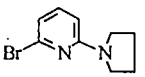
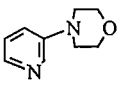
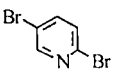
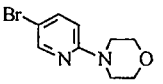
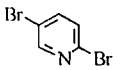
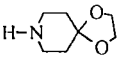
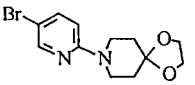
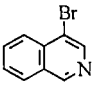
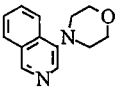
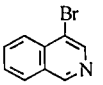
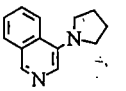
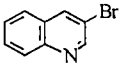
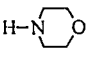
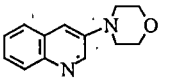
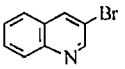
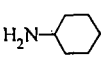
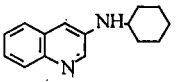
PII: S0040-4039(02)01852-X

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

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Catalytic Transfer Reduction of Alkenes and Imines Using Polymer Supported Formates

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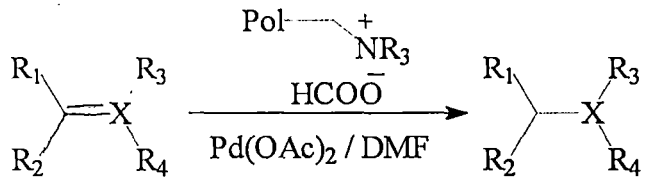
Abstract: A method for catalytic transfer hydrogenation of C–C and C–N double bonds with the aid of polymer supported formate (PSF) as the hydrogen donor and palladium acetate as the catalyst is described.

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

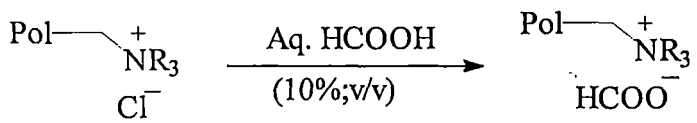
metal-catalyzed hydrogen transfer reduction of different electron deficient alkenes and/or imines. Herein we disclose our results illustrating the synthetic utility of PSF in transition metal-catalyzed transfer hydrogenation of a variety of electron deficient alkenes and imines (Scheme I).



$R_1 = R_2 =$ 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.



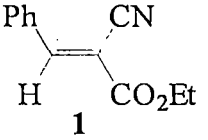
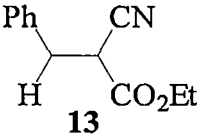
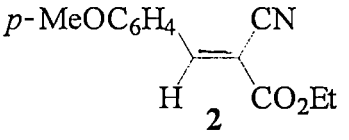
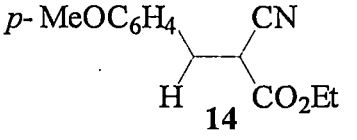
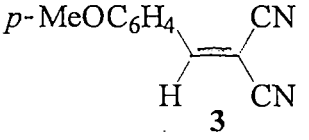
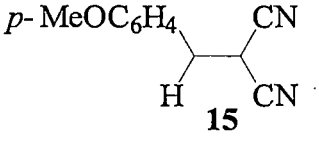
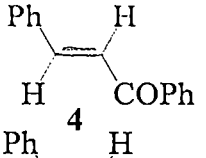
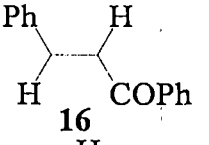
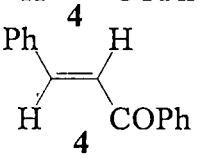
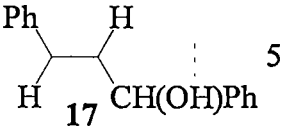
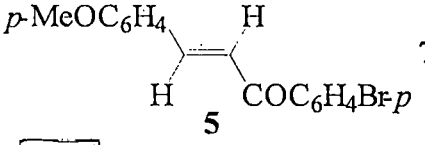
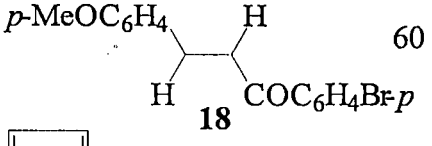
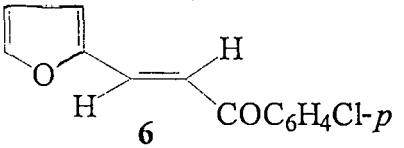
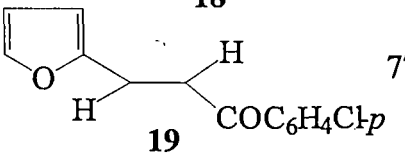
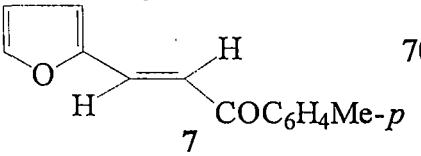
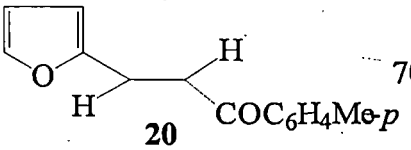
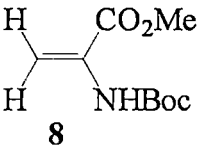
Amberlite® IRA-420 Chloride form taken in water

Amberlite® IRA-420 Format form

Scheme II

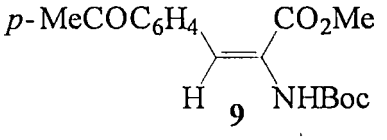
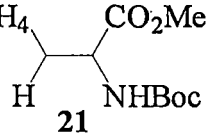
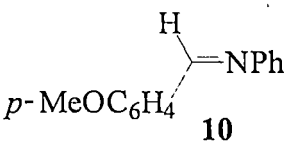
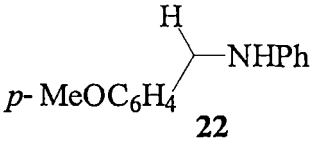
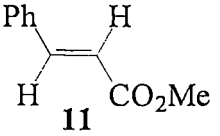
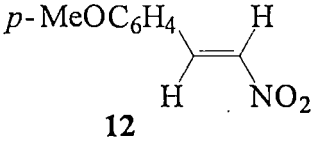
The generality of this methodology has been investigated with different types of electron-deficient alkenes and imines (Table 1). We first examined reduction of alkylidene cyanoacetate (entries 1,2) using PSF and palladium acetate (2 mol%) in DMF. The PSF was employed in excess anticipating that not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

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P303

PALLADIUM MEDIATED CHEMOSELECTIVE REDUCTION OF ENAMIDES ON A SOLID SUPPORTED REDUCING AGENT

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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.