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]

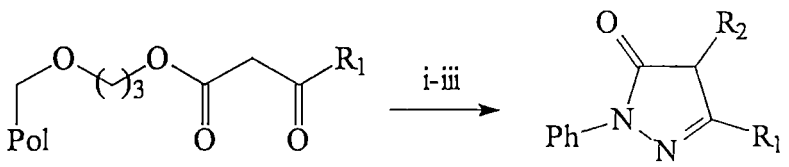
However, the solid-phase technique involves certain problems. The main disadvantages of solid-phase chemistry are the extra labour required to develop a solid-phase route, the limitations of the current range of commercially available supports and linkers as well as the means of monitoring reactions 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

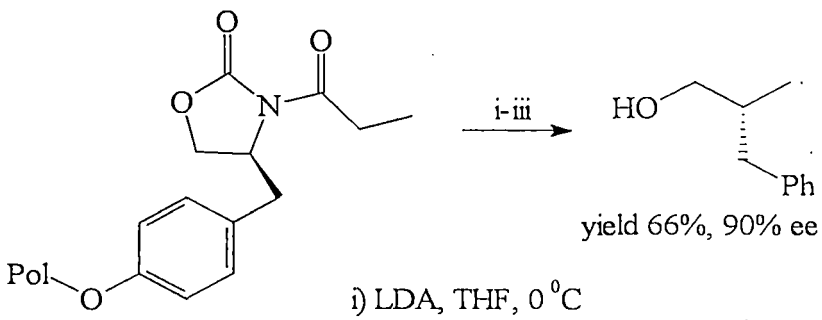
The development of efficient and reliable methods of forming carbon-carbon bonds remains an important goal in solid-phase synthesis. The reactions stabilized carbanions with carbon centered electrophiles are amongst the most fundamental process for construction of organic molecules, and consequently 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%

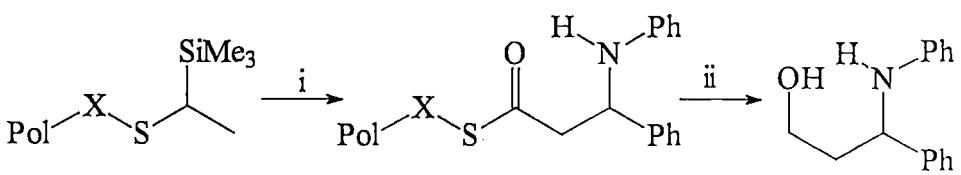
Chiral *N*-acyloxazolidinone function as chiral auxiliary as well as linker was reported in solid-phase variants of widely used Evans asymmetric alkylations of imide enolates.[33]



yield 66%, 90% ee

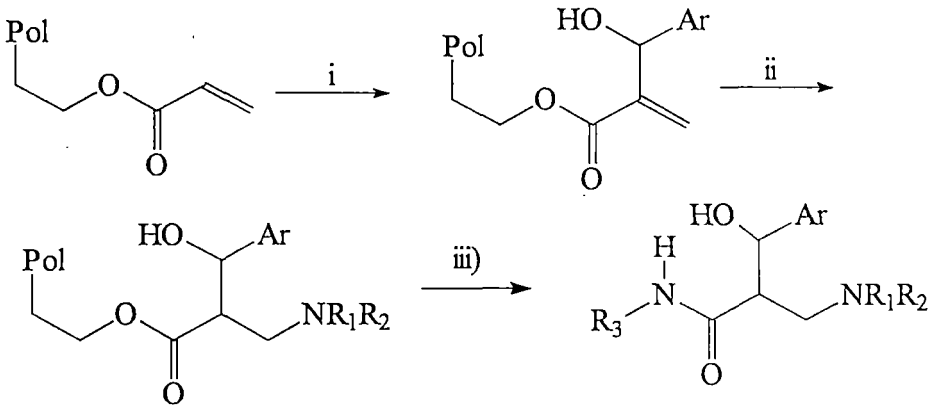
i) LDA, THF, 0 ^{0}C
ii) BnBr, iii) $LiBH_4$, r.t.

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.

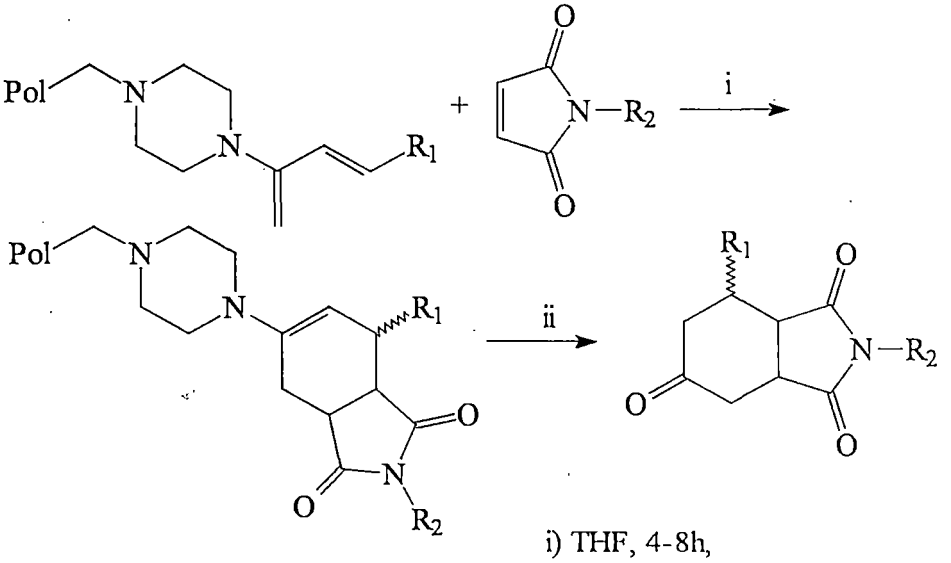
A Baylis-Hillman reaction conducted with an α,β-unsaturated ester component attached to the solid support, was used to the synthesis of 3-hydroxypropionamides.[35]



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

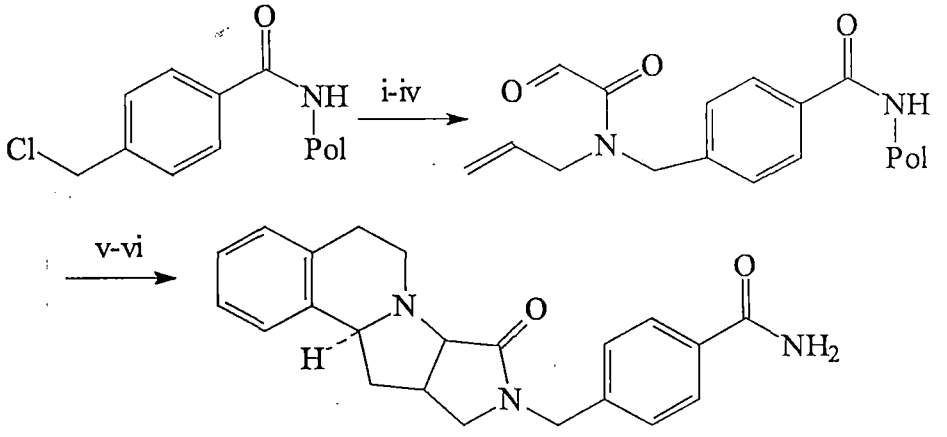
Crawshaw *et al.*[36] prepared a number of bicyclic adducts by Diels-Alder cycloaddition of an immobilized diene with an activated dienophile.



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

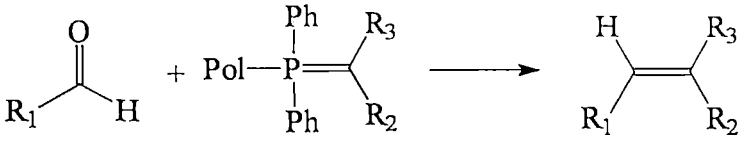
reported.[37] Marx *et al.*[38] reported the synthesis of polycyclic lactams using an intramolecular azomethine ylide cycloaddition strategy.



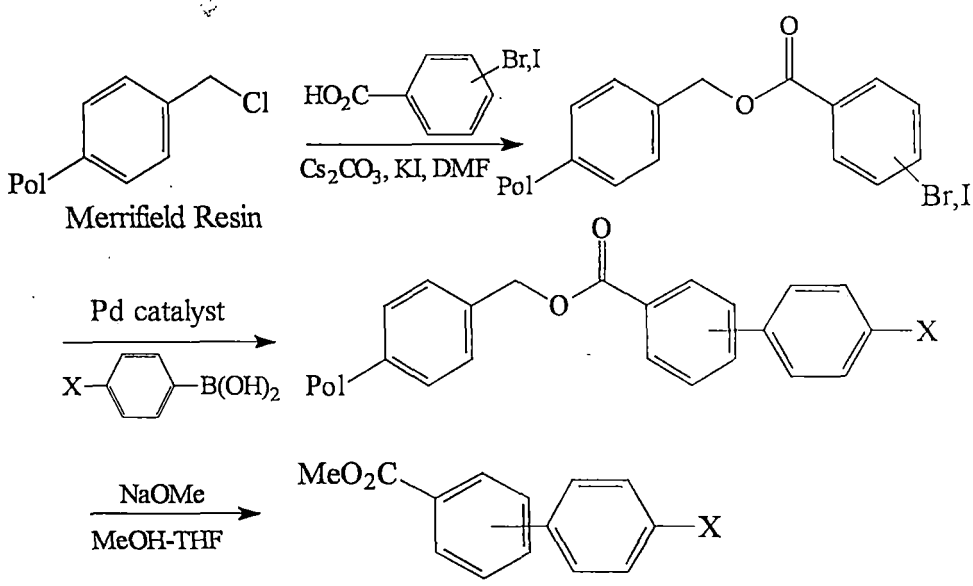
i) NaI, DMF, 80 ^{0}C, allylamine, ii) $AcOCH_2CO_2H$, DIC, DMAP, CH_2Cl_2,
iii) K_2CO_3, MeOH, DMF, iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2,
v) tetrahydroisoquinoline, toluene, heat, vi) TFA, H_2O.

IC.1.1.1.3 C–C Coupling reactions

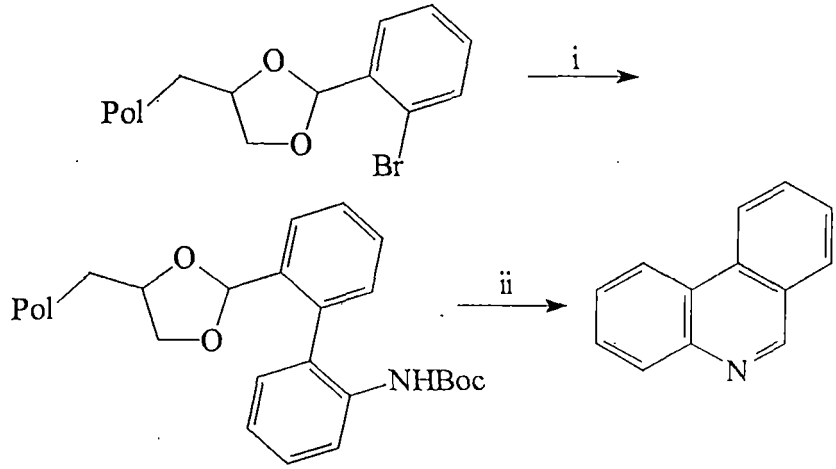
The Wittig reaction and the organophosphorous chemistry are the best studied examples of carbon-carbon coupling reactions promoted by functionalized polymers. Bolli and Ley[39] reported the preparation of alkenes by reacting aldehydes with polymer supported Wittig reagents.



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]



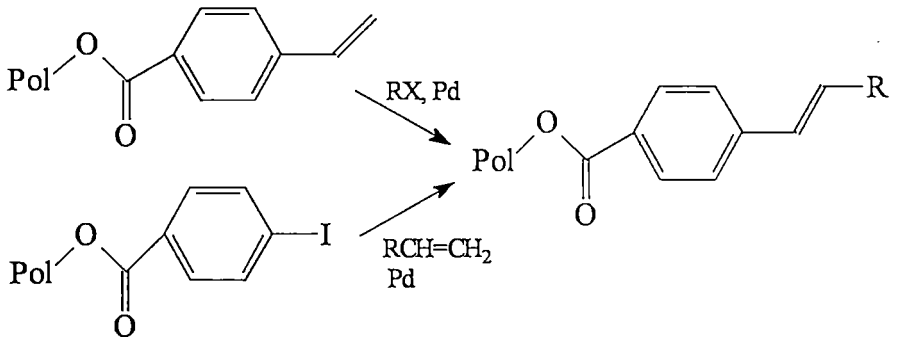
Chamoin *et al.*[40] used the Leznoff acetal linker[41] to tether *o*-bromo-benzaldehydes for Suzuki-Miyaura cross-coupling with aryl and heteroaryl boronic acids. Use of phenylboronic acid substituted in the *ortho* position with a protected amino group afforded, after TFA cleavage and spontaneous cyclization,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



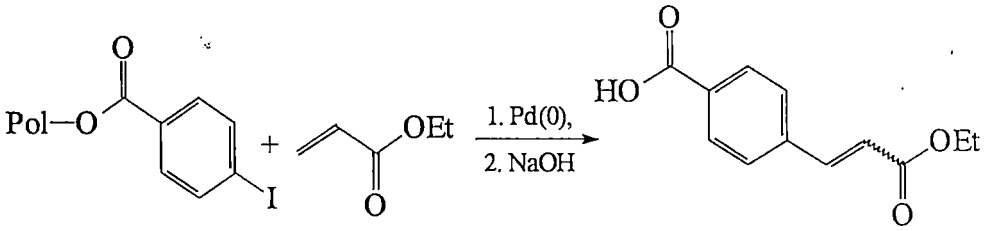
i) boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME; ii) TFA.

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

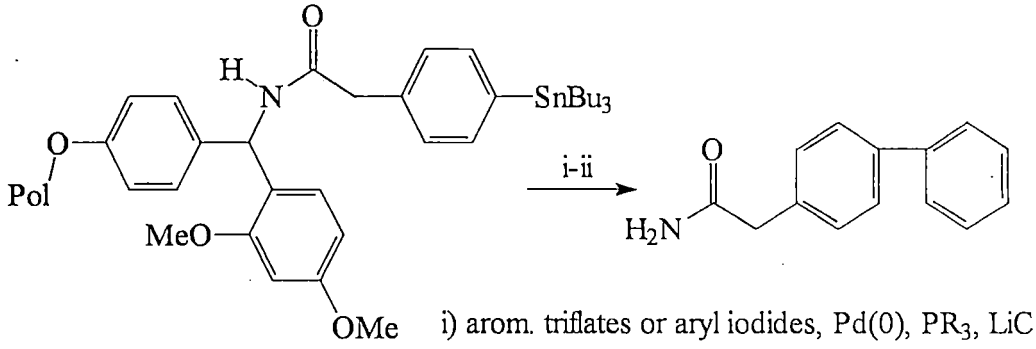
iodide or styrene with olefins or arylhalides in the generation of 1,2-disubstituted olefin libraries.



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

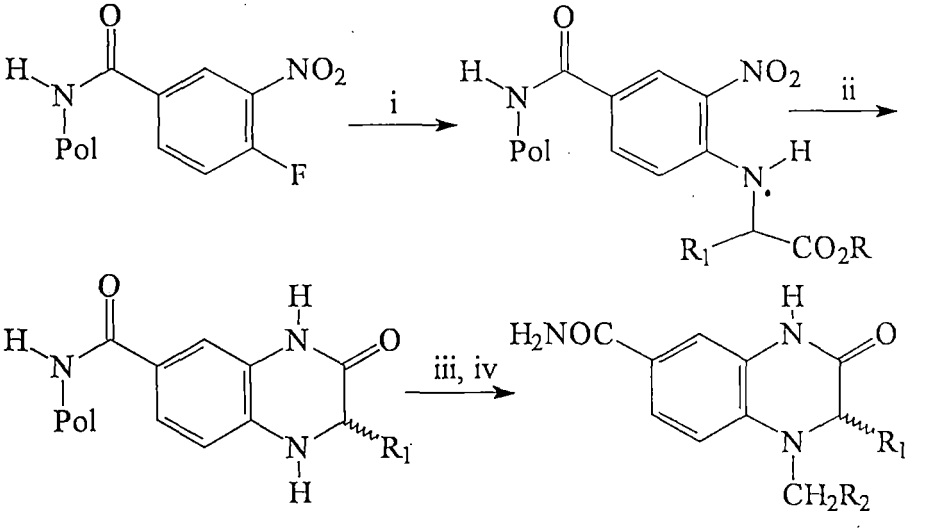
Not only polymer supported substrates used in synthesis, polymer supported catalysts were also used particularly in Heck and Suzuki reactions. Song *et al.*[21e] synthesized a polymer (fiber)-supported palladium catalyst to measure activity and

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

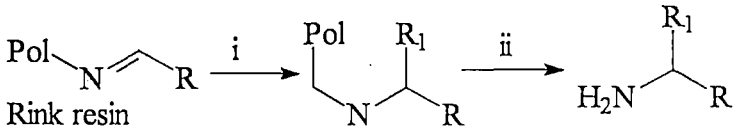
Nucleophilic aromatic substitution is an attractive approach to the functionalization of electron deficient aromatic rings, with the introduction of a wide range of readily accessible heteroaromatic nucleophile. A sequence of nucleophilic aromatic substitution of resin-bound 4-fluoro-3-nitrobenzoic acid 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

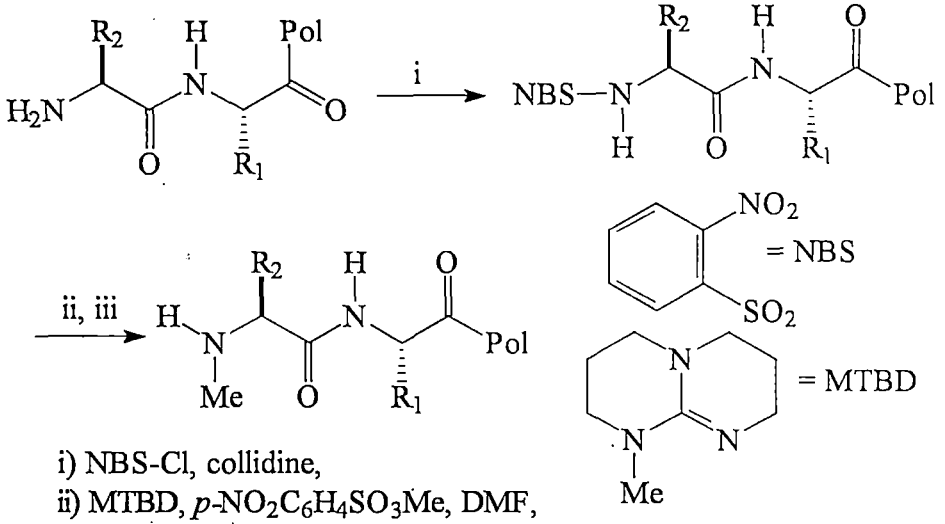
IC.1.1.2.2 Carbon-nitrogen bond formation

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]



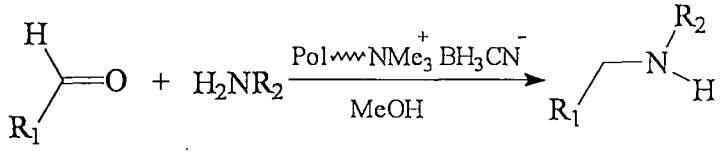
i) R_1MgX or R_1Li, Et_2O, toluene, or $LiBH_4$, THF
ii) TFA, H_2O, CH_2Cl_2

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]



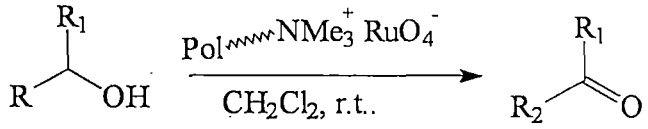
i) NBS-Cl, collidine,
ii) MTBD, *p*-$NO_2C_6H_4SO_3Me$, DMF,
iii) $HSCH_2CH_2OH$, DBU, DMF

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



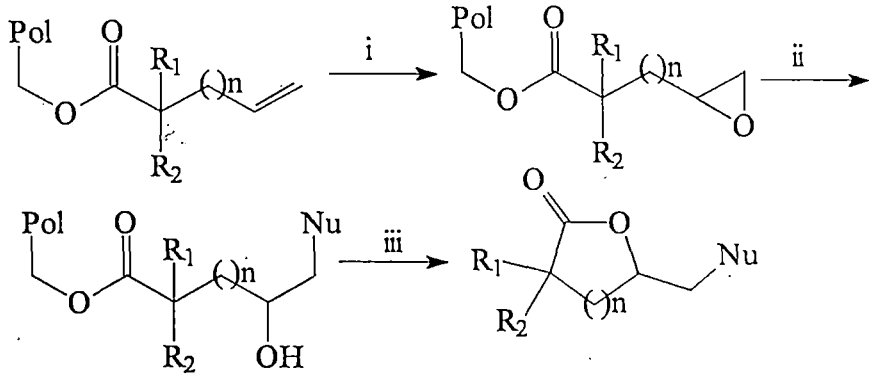
IC.1.1.3 Oxidation

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

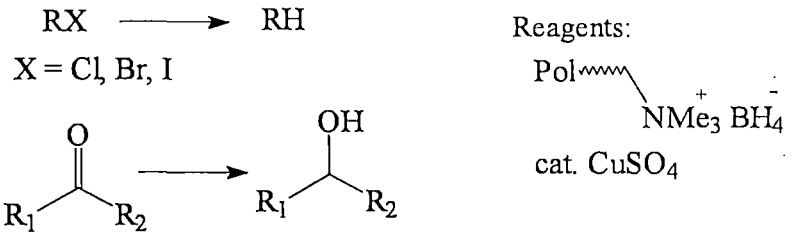
Epoxidation reactions of resin-bound olefins followed by nucleophilic ring opening afford secondary alcohols which underwent acid catalyzed lactonization leading to the release of five- or six-membered lactones from the resin.[54]



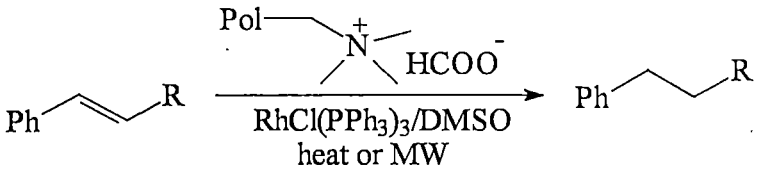
i) MCPBA, CH_2Cl_2, ii)NaN_3 or ArSNa, DMF, iii) TFA, CH_2Cl_2

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]

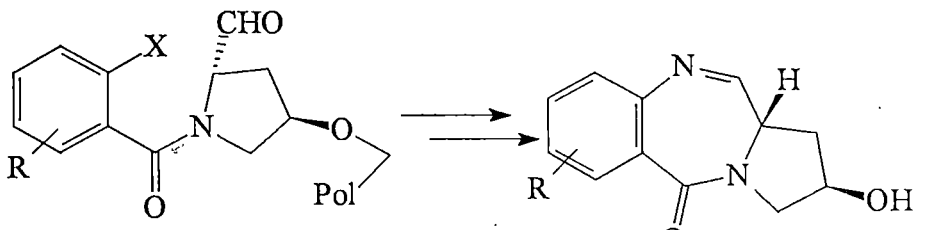


Recently, Desai and Danks reported the use of polymer supported formate for the reduction of alkenes under thermal or microwave conditions using Wilkinson's catalyst.[64] Initially they used Wilkinson's catalyst, polymer-supported formate derived from (aminomethyl)polystyrene as hydrogen source and subsequently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



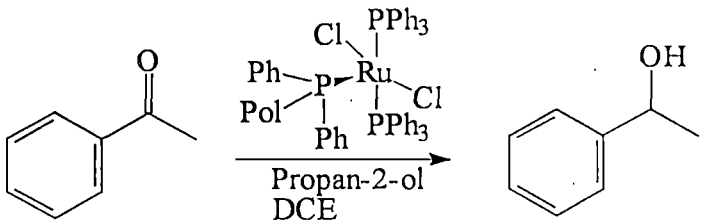
R = CO_2H, CO_2Me, CHO, $COCH_3$, CN, $CON(CH_3)_2$

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

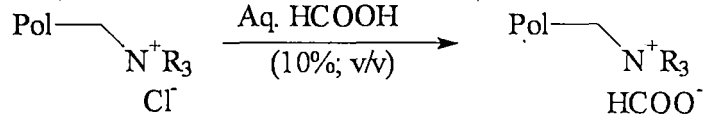
The success of using the combination of HCOOK and $Pd(OAc)_2$ (catalytic) in CTH of functionalized carbon-carbon and carbon-nitrogen double bonds prompted us to the development and use of this reagent supported on a solid matrix. In the recent years, the need for development of solid supported reagents 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

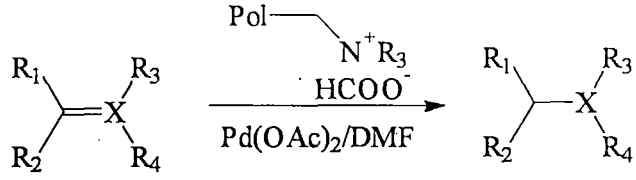
The PSF was prepared by washing Amberlite resin (IRA 420, Cl^- form) packed in a column with 10% formic acid solution repeatedly until the washings gave negative response to chloride ion (scheme VI). Finally the solid surface was washed several times with water and then dried under vacuum. The resulting 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

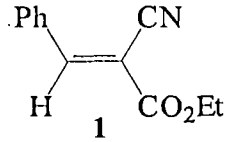
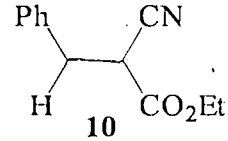
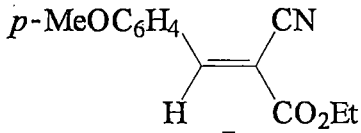
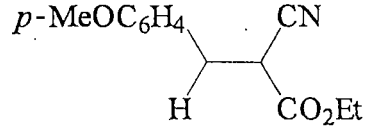
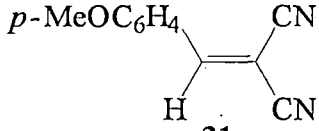
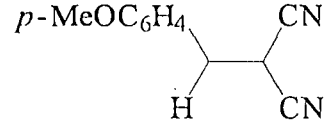
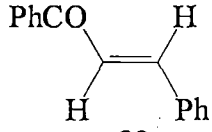
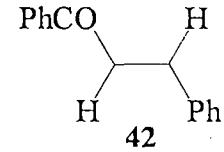
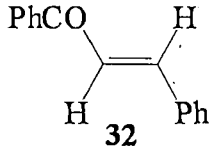
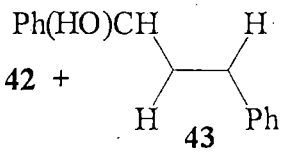
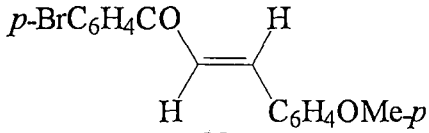
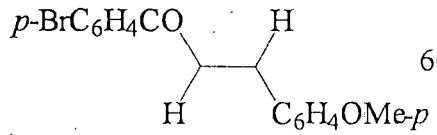
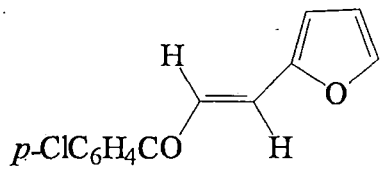
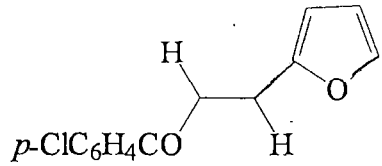
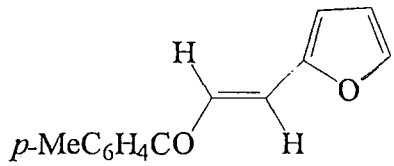
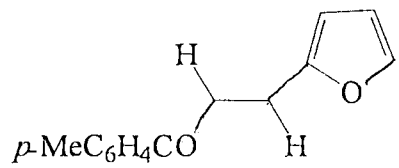
out reduction of alkyl cinnamate using PSF and $RhCl(PPh_3)_3$ (2.5 mol%) as the catalyst under microwave irradiation.[64] The nitro olefins are known to produce oximes under CTH using NH_4-formate.[67] We, however, obtained no change of the starting material while carrying out the reaction using PSF.

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.

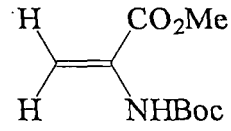
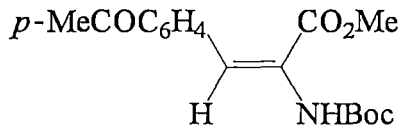
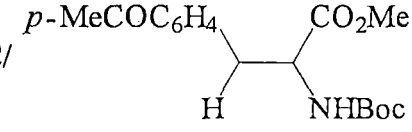
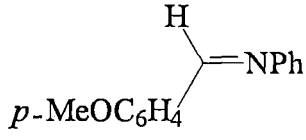
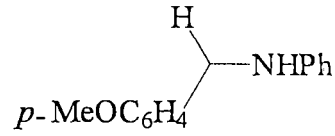
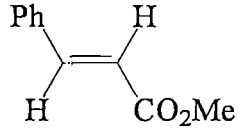
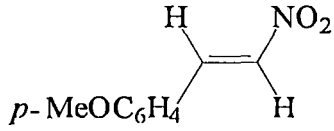
In conclusion we have shown that palladium-catalyzed transfer hydrogenation could be performed with a variety of electron-deficient alkenes as well as imines using the polymer supported formate (PSF) as the source of hydrogen. Some of the CTH methods employ formic acid and its salts, which have some 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.

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