Investigations on Synthetic Organic Transformations: Application to C–C and C–N Bond Forming Processes

Thesis submitted for the degree of doctor of philosophy in science, University of North Bengal

by

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To whom it may Concern

This is to certify that Mr. Sajal Das has carried out his research works under my supervision and guidance. His thesis "***Investigations on Synthetic Organic Transformations: Application to C–C and C–N Bond Forming Processes***" is based on the original works and is being submitted for the award of Doctor of Philosophy (Science) Degree in Chemistry in accordance with the Rules and regulations of the University of North Bengal.

23.11.2007

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Dedicated to my
Parents

DECLARATION

The research work embodied in this thesis entitled "***Investigations on Synthetic Organic Transformations: Application to C–C and C–N Bond Forming Processes***" has been carried out at Department of Chemistry, North Bengal University, Darjeeling, under the supervision of Prof. Basudeb Basu, Department of Chemistry, North Bengal University, Darjeeling. To my belief this thesis or any part of it has not been submitted before at any University or Institution for Ph.D. or any other degree or diploma.

Date: 23-11-2007

Place: North Bengal University

Sajal Das

(SAJAL DAS)

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I take the opportunity to thank all the faculties and staffs of this department from whom, I have always received complete cooperation.

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Finally, I would like to thank my parents, brothers and my friend Sonali. Without their constant selflessness, love, and support, I would not be half the person that I am today.

I am thankful to CSIR, New Delhi, for awarding Junior and Senior research Fellowships and to University of North Bengal for providing infrastructural facilities.

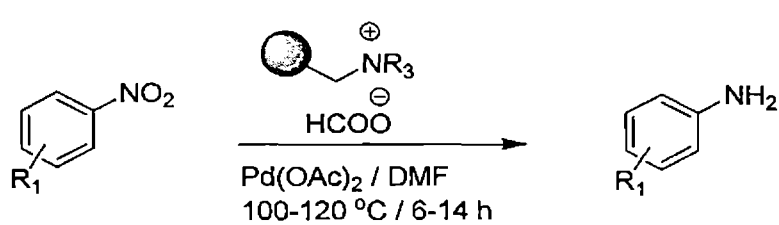
SUMMARY

Research works embodied in this thesis entitled "***Investigations on Synthetic Organic Transformations: Application to C–C and C–N Bond Forming Processes***" were initiated in April 2004, in the Department of Chemistry, North Bengal University, Darjeeling 734 013 under the guidance of Professor B. Basu, Department of Chemistry, North Bengal University.

Investigations described in this thesis are primarily concerned with studies directed towards development of immobilized reagents and catalysts and their applications in carbon–carbon and carbon–nitrogen bond–forming reactions. The thesis has been divided into two parts: Part–I & Part–II. Part–I comprises three sections.

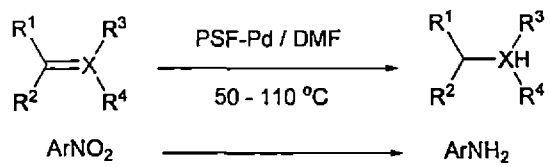
Part–I: As a prelude, a brief and relevant review on the present status of solid phase organic reactions has been presented since it was first demonstrated by Merrifield & Letsinger. The use of various polymeric supports to immobilize reagents/catalysts and their applications have been presented in a concise manner highlighting nature of immobilization, applications, recovery and lifetime of the polymer–bound species.

Section–A describes a new methodology entitled "***Pd–Cataiyzed transfer hydrogenation (CTH) using recyclable polymer–supported formate (PSF): Efficient and chemoselective reduction of nitroarenes***". Since the catalytic transfer hydrogenation (CTH) with the aid of a stable hydrogen donor is useful alternative method to catalytic hydrogenation by molecular hydrogen, a brief discussion on the use of various H–donors and its applications have also been included. In the present work, Amberlite resin (formate as the counter anion), have been employed in combination with catalytic palladium acetate for the selective reduction of nitroarenes to corresponding anilines. The procedure is chemo-selective for nitroarenes, while other potentially reducible functional groups such as carbonyl, ester, halide *etc.* remain unaffected. Other advantages include: clean work–up, high yields and reusability of the supported reagent.



The work has been published in *Molecular Diversity*, **2005**, *9*, 259–262.

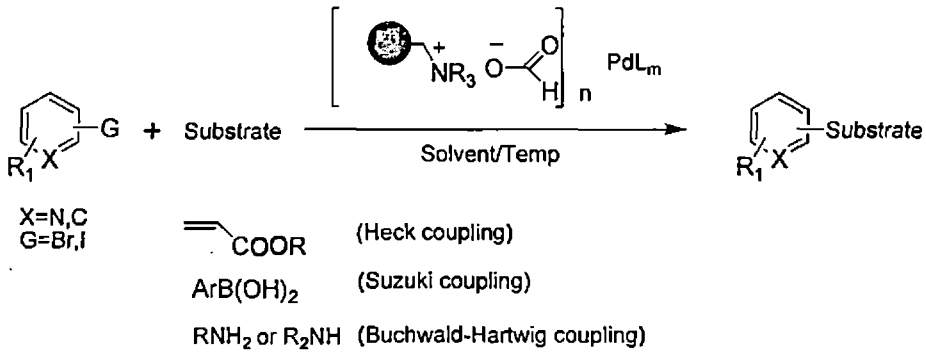
Part–I: section–B deals with "***Co–immobilized formate anion and palladium on a polymer surface: a novel heterogeneous combination for transfer hydrogenation***". Catalyst recovery after reaction is a major challenge in catalytic organic transformations. It becomes more advantageous when both reagent and catalyst are anchored to the same polymeric backbone. The formate anion and the Pd catalyst have been co–immobilized effectively on an inexpensive Amberlite ion–exchange resin. The resulting Pd–soaked resins (PSF–Pd) proved to be a versatile and heterogeneous reductant for transfer hydrogenation of functionalized alkenes, imines, nitroarenes and 1,2–diketones. This technique also demonstrates high chemoselectivity in reduction of aikenes, imines, nitro groups, thus establishing an efficient, environmentally benign, economically friendly and sustainable process.



A brief account of this work has been published on *Tetrahedron Lett.* **2005**, 46, 8591–8593.

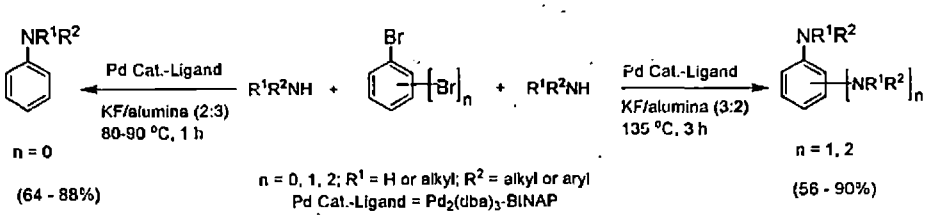
Part–I: section–B of this dissertation represents development of resin–bound palladium catalyst, and its applications to C–C and C–N coupling reactions. The title of this part is: ***"Palladium Supported on Poly–ionic Resins as Efficient, Ligand–free & Recyclable Catalyst for Heck, Suzuki–Miyaura and Buchwald–Hartwig Reactions"***. The present work has shown that poly–ionic Amberlite Resin formate (designated herein as ARF), derived from commercially available Amberlite® resin chloride by simple rinsing with aqueous formic acid, could be soaked with $Pd^{(0)}$ from palladium salts – the formate counter anion being the reducing source. The resulting resin–supported Pd(0), ARF–Pd, showed high catalytic activity in Suzuki–Miyaura, Heck (C–C) and Buchwald–Hartwig (C–N) couplings with a range of substrates. The catalyst may be recovered easily and quantitatively without leaching and recycled for five runs tested without any significant loss of activity. The nature of deposition of

palladium on the surface has been studied with the help of various techniques, such as FT–IR spectroscopy, ^{13}C MAS NMR spectroscopy, Scanning Electron Micrographs, XPS studies etc.



This work has been submitted for publication.

Part–II of this dissertation describes about an efficient and selective methodology for palladium–catalyzed amination of aromatic halides (Br or I) mediated on KF/Alumina surface. A brief introduction on Pd–catalyzed Buchwald–Hartwig type of C–N coupling has been presented. The present work constitutes solvent free one–pot protocol for one–pot selective mono– or poly–aminations based on the proportions of KF and alumina employed. The base sensitive functional groups remain unaffected under the conditions and no reductive debromination leading to other byproducts has been observed in this procedure ***"Palladium–Catalyzed Selective Amination of Haloaromatics on KF–Alumina Surface"***.



A brief account of this work has been published in *Synlett.* **2005**, 1275–1278.

List of Publications & Poster Presentations

List of Publications

1. Transfer hydrogenation using recyclable polymer–supported formate (PSF): Efficient and chemoselective reduction of nitroarenes, B. Basu,* P. Das, **S. Das**, *Mol. Diversity*, **2005**, *9*, 259–262.
2. Co–immobilized formate anion and palladium on a polymer surface: a novel heterogeneous combination for transfer hydrogenation, B. Basu,* **S. Das**, P. Das and A. K. Nanda, *Tetrahedron Lett.* **2005**, *46*, 8591–8593.
3. Palladium–catalyzed selective amination of haloaromatics on KF–alumina surface, B. Basu,* P. Das, A. K. Nanda, **S. Das**, S. Sarkar, *Synlett*, **2005**, 1275.
4. Recent Advances in KF/Alumina Promoted Organic Reactions, B. Basu,* P. Das, **S. Das**, *Curr. Org. Chem. In press* (**2007**).
5. Poly–ionic Heterogeneous Phenylating Agent for Base–free Suzuki–Miyaura Coupling Reaction, B. Basu,* **S. Das**, S. Kundu, B. Mandal, Synlett. *In press* (**2007**).
6. Palladium Supported on Poly–ionic Resins as Efficient, Ligand–free & Recyclable Catalyst for Heck, Suzuki–Miyaura and Buchwald–Hartwig Reactions, B. Basu,* **S. Das**, P. Das, B. Mandal, D. Banerjee, F. Alamqvist* (*Communicated*).
7. Role of copper in catalyzing aryl (& heteroaryl) -Nitrogen (or -Oxygen) bond formation under ligand-free and solvent-free conditions, B. Basu,* **S. Das**, B. Mandal, *Indian. J. Chem B. In press* (**2007**).

Paper Presented in Symposia/ Conferences

8. **Sajal Das** and Basudeb Basu,* "Transfer Hydrogenation Using Recyclable Polymer Supported Formate (PSF): Efficient and Chemoselective Reduction of Nitroarenes" *7th National Symposium in Chemistry (NSC–7)*, CRSI, held at Indian Association for the Cultivation of Science, Kolkata, Feb. 4–6, 2005.
9. **Sajal Das**, Bablee Mandal, Basudeb Basu,* "Co–immobilization of Reagent and Catalyst on a Polymeric Surface: A Novel Heterogeneous system for

Transfer Hydrogenation"; *8th National Symposium in Chemistry (NSC–8)*, CRSI, held at Indian Institute of Technology, Mumbai, Feb.3–5, 2006.

10. Bablee Mandal, **Sajal Das** and Basudeb Basu,* "Ruthenium (III) Catalyzed Chemoselective Transfer Hydrogenation of Aldehydes/Ketones Using Polymer Supported Formate as Stable H–Donor" *International Symposium on Current Perspectives in Organic Chemistry*, held at Indian Association for the Cultivation of Science, Kolkata, December 7–9, 2006.
11. **Sajal Das**, Sekhar Kundu, Basudeb Basu,* "Poly–Ionic Heterogeneous Arylating Agent for Suzuki–Miyaura Coupling Reaction: Synthesis of Biphenyls" *9th National Symposium in Chemistry (NSC–9)*, CRSI, 2007 held at Delhi University, New Delhi–110 007, February 1–3, 2007.
12. Susmita Pal, Bablee Mandal, **Sajal Das**, Sekhar Kundu, Sangita Mustafy, Basudeb Basu,* "Highly Efficient, Recyclable Rhodium Catalyst Immobilized on Poly-Ionic Resins: Application in the Heck-type Coupling reactions" *10th National Symposium in Chemistry (NSC–9)*, CRSI, 2008 will be held at IISc. Bangalore, February 1–3, 2008.

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Section C **"Palladium Supported on Poly-ionic Resins as Efficient, Ligand-free & Recyclable Catalyst for Heck, Suzuki-Miyaura and Buchwald-Hartwig Reactions"**

Part II

"Palladium-Catalyzed Selective Amination of Haloaromatics on KF-Alumina Surface"

List of Abbreviations

AD	Asymmetric dihydroxylation
ARF	Amberlite resin formate
ARF–Pd	Palladium soaked on ARF
AIBN	Azo bis isobutyronitrile
BER	Borohydride exchange resin
BINAP	2,2'–*bis*(diphenylphosphino)1,1'–binaphthayl
CD	Cyclodextrin
COD	1,4-cyclooctadiene
CTH	Catalytic transfer hydrogenation
dba	dibenzylideneacetone
DCDMH	1,3–dichloro–5,5–dimethylhydantoin
DCM	Dichloromethane
DENs	Dendrimers
DMAP	N,N-Dimethylpyridine-4-amine
DMF	N,N-Dimethyl formamide
DMSO	Dimethyl sulfoxide
DPPF	1,1'–*bis*(diphenylphosphino)ferrocene
DVB	Divinylbenzene
HT	Hydrotalcite
IBX	Iodoxybenzoic acid
LDH	Layered Double Hydroxides
MC	Microencapsulated
MCPBA	*m*-Chloro per benzoic acid
NMO	N–methylmorpholine N–oxide
NMP	N-methyl pyrolidone
PEG	Poly(ethylene glycol)
PS	Polystyrene
PSF	Polymer Supported Formate
PSF–Pd	Palladium Supported on PSF
ROMP	Ring-opening metathesis polymerization
Sep	Sepiolite
TCSM	Tetrahedral complex and supported metal
TEAF	Triethylammonium formate
TFA	Trifluro acetic acid
thd	2,2,6,6–tetramethyl–3,5–heptanedionato
THF	Tetra hydro furan
TON	Turnover number
TPPTS	Triphenylphosphinesulfonate
TsDPEN	(*R,R*)–N–(p–tolylsulfonyl)–1,2–diphenylethylene diamine

Part I

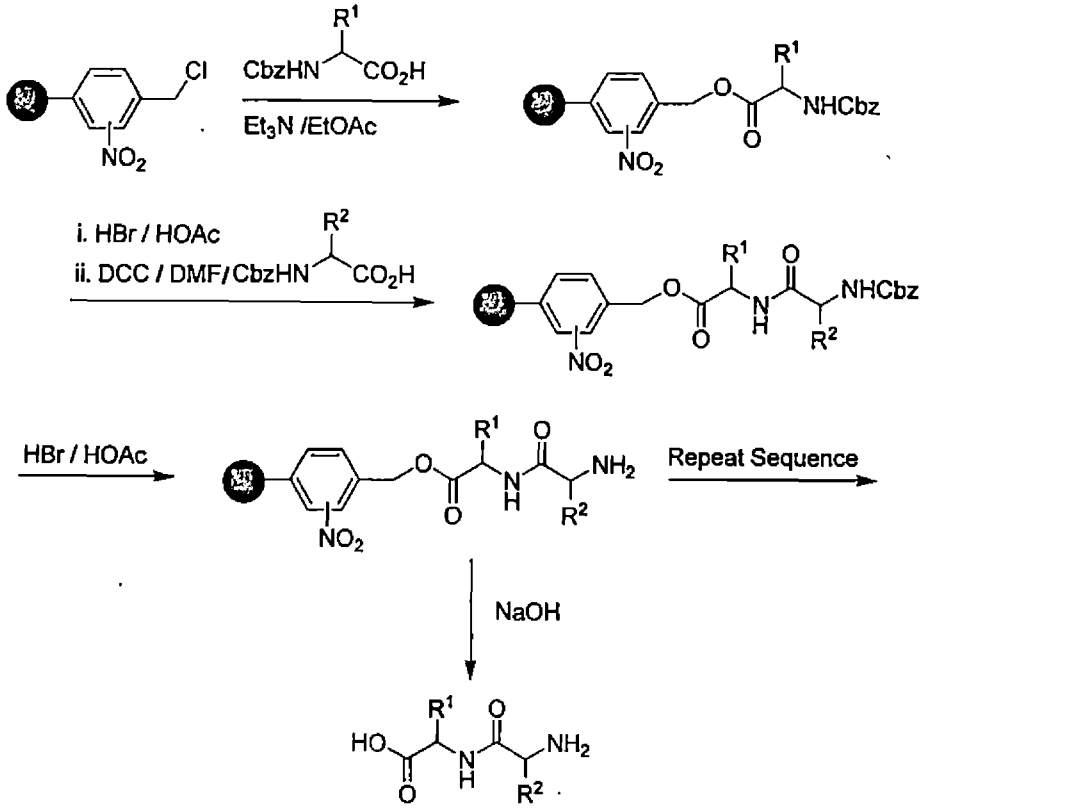
Solid Phase Organic Synthesis (SPOS)

I.1: Solid Phase Organic Synthesis (SPOS): A Brief Introduction

The creativity and art of organic synthesis has reached an interesting stage in its development. Although we now have some excellent methods to effect the construction of target molecules, with an ever increasing level of complexity, there is a need to find new, strategically important processes which are environmentally cleaner, more efficient and which lead to greater structural variation in a shorter period of time. The demand of modern society for new, functional chemical entities has driven the development of novel technologies which have begun to produce compounds at greater rate than ever before thought possible. These methods are revolutionizing the way we think, plan and optimize chemical processes and have far reaching consequences, particularly in the pharmaceutical and agrochemical sectors. In the future the impact will be even greater influencing both materials and catalyst design.

Merrifield[1] & Letsinger[2] introduced the solid phase technique for the preparation of large number of compounds in a multi parallel fashion. Merrifield first synthesized L–leucyl–L–lanylglycyl–L–valine via attachment of the intermediates to a polymeric backbone (Scheme 1). He used chloromethylated polystyrene resin as supporting materials. This was soon to revolutionize in organic synthesis due to the speed and simplicity of the technique. Actually this involves using a polymeric resin or other solid materials to support a substrate, which can then be elaborated using an excess of reagents and coupling components to drive reactions to completions. The desired molecule is then detached from the solid support and isolated following simple filtration. The interesting point of such solid phase synthesis is designing the covalent linker group, some time referred to as a 'handle' to attach the reagents/catalysts or substrates on to the polymeric backbone. The suitable linkers[3] can be synthesized from conventional linkers by simple coupling or substitution reactions (Merrifield, Wang, and Rink resins[4]).

Scheme 1



This general process has become the backbone of modern combinatorial chemistry and is now a widely used technique.[5] Medicinal chemists are increasingly challenged with the demand for large amounts of high purity compounds and ever–growing structural complexity of target molecules. Producing a variety of complex organic compounds in high purity and with restricted time requirements remains the major challenge. Each synthesized compound requires purification from all other components present in the reaction mixture, such as excess reagents, catalysts, by–products and solvents. In many cases the isolation and purification steps account for the majority of the time and cost of the organic synthesis. Polymer–assisted solution phase synthesis that comprises mainly polymer–supported reagents, catalyst and scavengers, offers significant advantages compare to the conventional fine chemicals synthesis.

Despite the impressive success and advantages of this type of solid phase organic synthesis, there are also severe limitations to this approach, which are worth noting. Firstly, the reactions can be slow relative to their solution phase counterparts and it can be difficult to monitor the progress of the reaction. Although several new techniques have been developed in recent years to monitor the progress of the solid

phase reactions[6] (*e. g.* use of FT–IR, MALDI–MS, Gel phase and MAS NMR etc.), these techniques still do not provide same quality of analyses as compared to conventional solution phase techniques (*e. g.* TLC, GC–MS, LC–MS, SFC–MS, NMR *etc.*) A second fundamental feature of this approach is that additional steps are required to attach the substrate and detach the product from the resins: often a vestigial part of the linker unit is found in the final product and linker compatibility with reagents used can be a source of problems or limitations.

Solid supported reagents[7] and scavengers[8] have been used in organic synthesis programs since 1946.[9] In recent years however, many new and several improved solid–supported reagents/catalyst have been developed, an ever increasing number which are commercially available. The increased level of interest has largely been due to the need to generate large numbers of new compounds in a cleaner, faster and more efficient manner, and the potentials of these reagents to achieve this.

Solid–supported reagents/catalysts are attractive because one of the key advantages is that it is possible to use excess reagent to drive reactions to completion and as work–up is made by simple filtration to separate products, the chemistry is clean. Filtration also results in isolation of the solid–supported species, which is a crucial feature in cases either where the reagent acts as a catalyst, or where the spent material can be regenerated and recycled.[10] Another attractive aspect is that toxic, noxious or hazardous reagents and their by–products can be immobilized and therefore not released into solution and thereby improving their acceptability, utility and safety profile. More than one reagent can be used simultaneously and due to site isolation reagents, even species that are incompatible in solution may be used together to achieve one–pot transformation that are not possible in homogeneous solution. Furthermore, if the reaction proceeds poorly or generates by–products and impurities, scavengers or catch and release techniques can lead to isolation of pure products in a simple fashion without need for conventional work–up and purification procedures. The fact that only simple work–up operations are necessary, involving filtration and solvent removal or exchange, is a crucial feature in the libraries generation as the chemistry should then be viable for automation using robotic devices.

I.2: Reagents/Catalyst Supported onto Polymers and Applications

Designing and synthesis (or exploring the availability) of the polymeric frameworks with suitable linkers remains the primary task of SPOS, and various techniques have been adopted for attachment of the reagents and/or catalysts. A brief status of the literature reports is therefore pertinent to delineate here.

Generally, reagents and catalysts are immobilized onto polymer surface involving (a) covalent binding (b) entrapment, where a pre–formed catalyst is enveloped within a polymer network, and (c) ion–pairing, where cations or anions are bound to complementary resin sites. By far methods (a) and (c) are most commonly used for their broad applicability, the fact that stable, active catalysts and reagents are formed and insignificant leaching. Binding is usually effected in two ways: (i) grafting the catalyst or reagent onto the pre–derivatized supports or (ii) copolymerization of the active species with styrene and divinylbenzene (DVB). In micro–encapsulation the polymers are physically enveloped by thin films of reagents or catalysts, and perhaps stabilized by the interaction between π electrons of benzene rings of the polystyrene used as a polymer backbone and vacant orbital of reagents or catalysts. The size of microcapsule achievable has been reduced from a few micrometers to nanometers only to gain the sufficient activity.[11] Since the literature is quite vast, a concise account of various kinds of attachment of few relevant reagents and catalysts followed by specific applications in different organic transformations has been presented here.

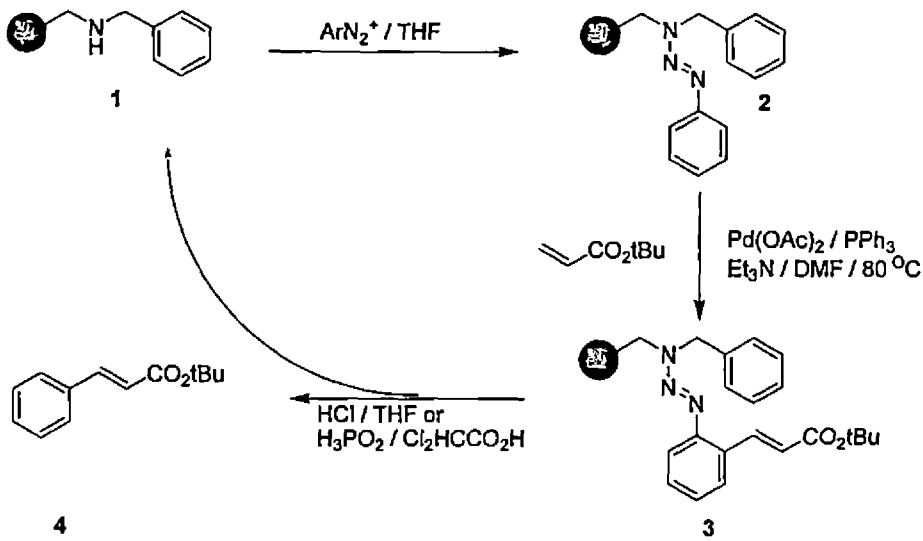
I.2.1. Covalent Binding of Reagents

I.2.1.A.1: Nitrogen as a linker: Heck Coupling

The benzylamine resin **1** was synthesized in one step from Merrifield resin. Diazonium salts were coupled to the resin to give the triazine **2**, which was used in a Heck coupling reaction[12] to give **3**. The cleavage was facilitated with either HCl in THF or reductive deamination using H_3PO_2 in dichloroacetic acid to give the Heck coupling product **4** in 81% yields (Scheme 2). Other reactions were performed after the Heck reaction on different substrates, including Sharpless dihydroxylation and Diels–Alder, in good yields. After the reaction the benzylamine resin can be reused

with only slight loss of activity. Gordon *et al.*[13] recently reported that polystyrene supported amine act as base for Heck coupling reaction in $scCO_2$.

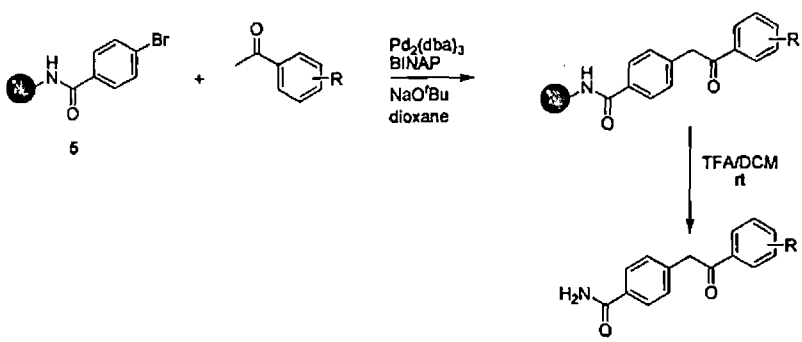
Scheme 2



I.2.1.A.2: α–Arylation of Ketones

Griebenow *et al.*[14] recently reported the α–arylation of ketones with the aid of solid phase synthesis by adapting the standard protocol of α–arylation reported by Buchwald & Hartwig.[15] In this case they initially prepared immobilized 4–bromobenzamide **5** by the reaction between polystyrene Rink amide resin and 4–bromobenzoic acid chloride. The supported 4–bromobenzamide **5** was reacted with ketone in presence of $Pd_2(dba)_3$ and finally treatment with trifluro acetic acid (TFA) yielded the desired product (Scheme 3). Both aromatic and aliphatic methyl ketone undergoes this reaction with similar efficiency.

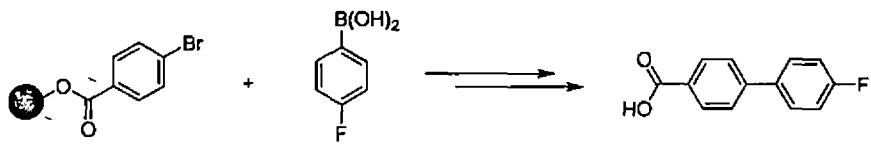
Scheme 3



I.2.1.B: Suzuki-Miyaura Coupling Reaction

Recently Suzuki–Miyaura (SM) coupling is one of the most important tools for C–C bond forming reaction. The solid phase SM cross coupling[16] strategy has been largely developed by reacting the resinbound aryl halides **6** with solution–phase boronic acids followed by the consecutive treatment with 1 N sodium hydroxide and 12 N hydrochloric acid (Scheme 4).[16k] Recently, methods have been developed for attaching boronic acids to macroporous polymer supports and these supported boronic acids[16f] have been successfully used in the SM cross–coupling reaction.

Scheme 4



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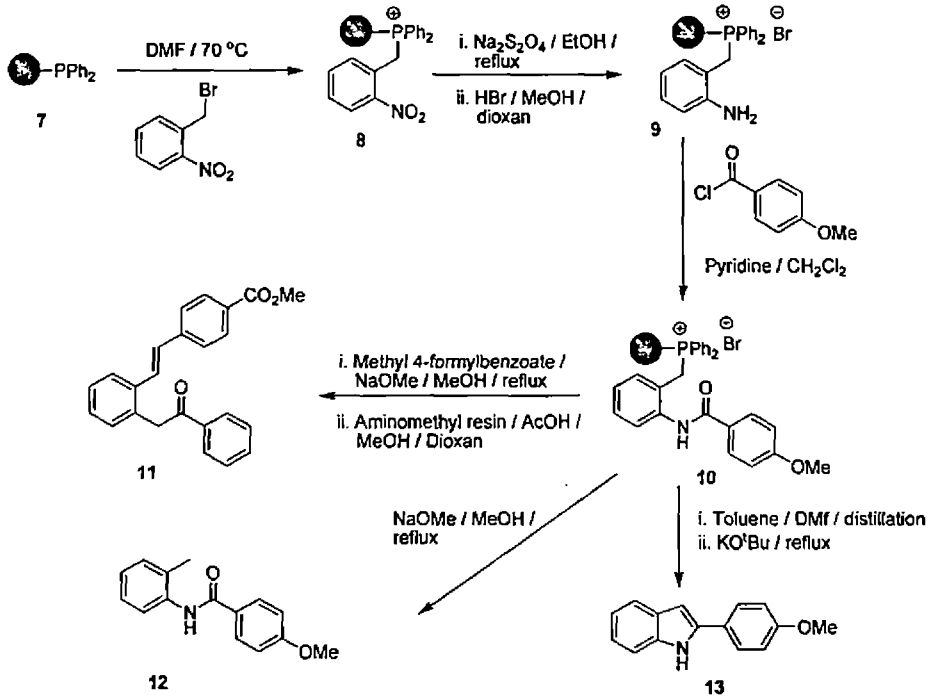
I.2.1.C: Polymer–Supported Triphenylphosphine Linker

Functionalized polymer–bound phosphonium salt has also been utilized to synthesize three different types of molecules, depending on the reaction conditions. Commercially available polystyrene–bound phosphine **7** was loaded with 2–nitrobenzylbromide to give the resin–bound phosphonium salt **8**, which was converted to aniline **9**, then acylated giving the phosphonium resin **10**. Cleavage could then be facilitated by intramolecular Wittig reaction giving a 3:1 (*E/Z*) mixture of **11**, in 82% overall yield (Scheme 5). The aminomethyl resin was used as a solid–phase scavenger reagent for the excess aldehyde used. Hydrolysis of carbon–phosphonium bond generated the 2–methylanilide **12** in 81% overall yield. Intramolecular Wittig reaction occurred upon distillation prior to adding base, giving indole **13** in 78% yields. DMF was a necessary co–solvent in the intramolecular Witting reaction.[17]

Scheme 5

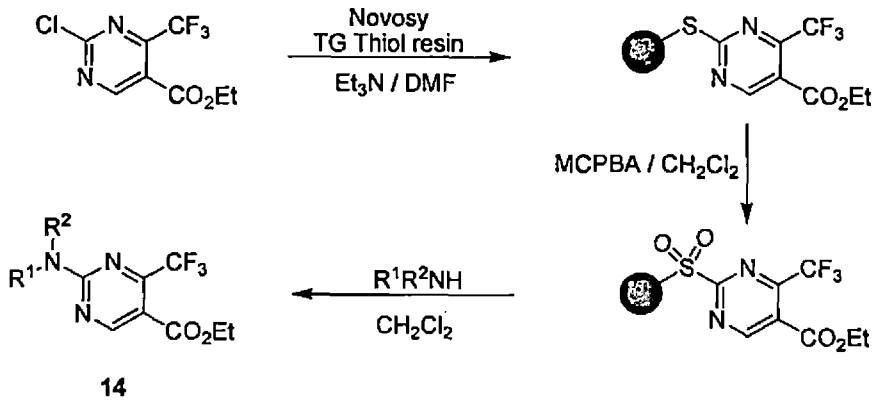


Similar to triphenylphosphine, triphenylarsine[18] is also a versatile reagent for organic synthesis, but the reports regarding supported triphenylarsine are few.[19] Supported triphenyl arsine used as a ligand for metal catalyzed coupling reactions.[20]

I.2.1.D: Polymer–Supported Sulfur Linker

Suto *et al.*[21] first introduced the sulfur–based linker for solid–phase synthesis. Oxidative activation of a sulfide to a suifone allowed nucleophilic displacement of the sulfone, incorporating further diversity into the final compound. They used this technique to synthesize functionalized pyrimidines **14**, as outlined in scheme 6.

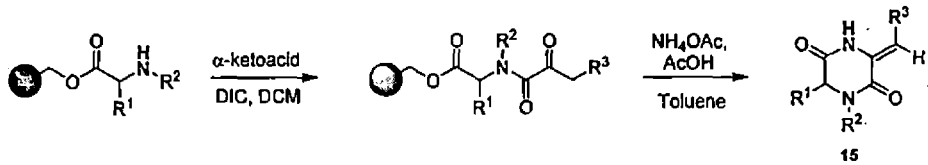
Scheme 6



I.2.1.E: *Synthesis of Heterocycles*

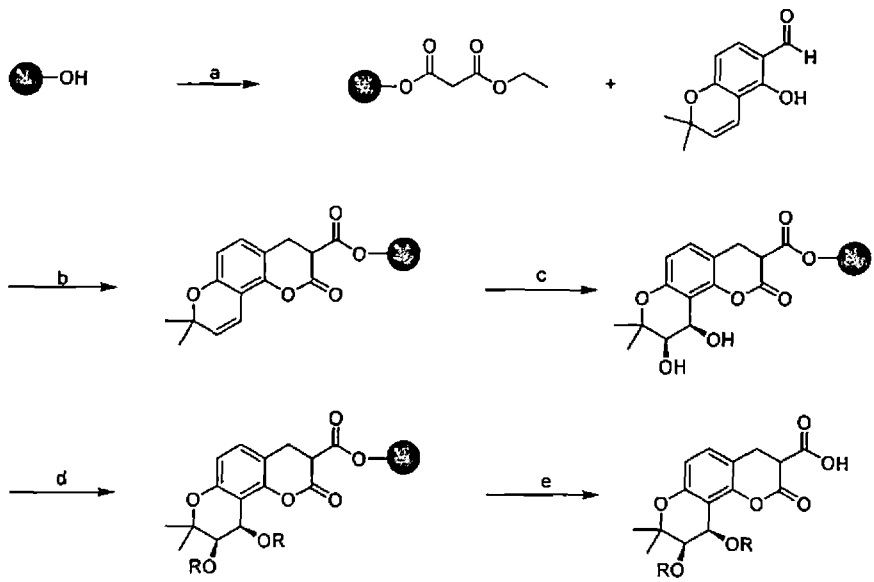
Smith *et al.*[22] developed a solid phase synthesis of piperazine–2,5–diones on Kaiser oxime resin.[23] Diazepinediones were prepared the same way. For the preparation of histidine containing piperazine–2,5–diones, Sabatino *et al.*[24] linked the histidine via the side chain to the trityl resin. When a polymer supported N–alkylated amino acid was acylated by a α–keto acid, cyclative cleavage in the presence of ammonium acetate yielded 3–alkylidene–piperazine–2,5–dione **15**, predominantly as the *Z* isomer, as outlined in scheme 7.[25]

Scheme 7



(3′*R*, 4′*R*)–di–*O*–(–)–camphanoyl–(+)–*cis*–khellactone (DCK) displayed extremely potent inhibitory activity against HIV–1 replication.[26] Therefore, (3′*R*, 4′*R*)–di–*O*–*cis*–substituted khellactones have proven to be crucial drug leads and have elicited considerable pharmaceutical interest. Thus, a general method of rapidly preparing analogues of khellactones would be advantageous and merits investigation for drug discovery. Xia *et* al.[27] developed a novel, straightforward, easily automated solid–phase procedure for the synthesis of (3′*R*,4′*R*)–di–*O*–*cis*–acyl–3–carboxyl khellactone **16**. The procedure is particularly useful because of its efficiency and ease of operation (Scheme 8).

Scheme 8



16

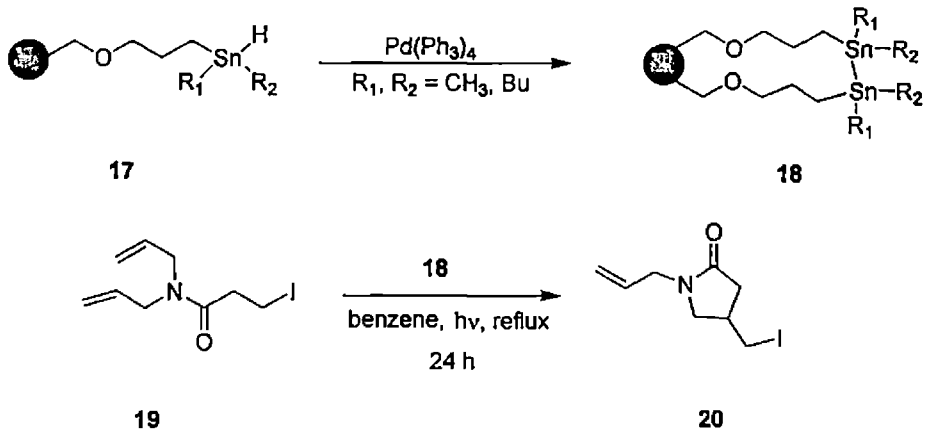
a) ethyl potassium malonate, rt;
b) pyridine, piperidine, rt;
c) $K_3[Fe(CN)_6]$, OsO_4, K_2CO_3, $(DHQ)_2$-PHAL, t-BuOH/H_2O, rt;
d) (1) R2COOH, 1 equiv DIC; (2) DIEA, DMAP;
e) 50% TFA/CH_2Cl_2

The strategy they used is to attach a polystyrene resin to the khellactone ring skeleton through a C–3 carboxylate group. The linker group of the Wang resin could serve as a carboxyl protecting group, because a free carboxyl is not compatible with the asymmetric dihydroxylation (AD) or acylation reaction conditions.

I.2.1.F: Free Radical Cyclization Reactions

Hernán and Kilburn described the synthesis of a polymer–supported distannane reagent **18** comprising cross–linking a polystyrene–bound tin hydride[28] **17**. Reagent **18** was successfully applied in free radical cyclization reactions involving the transfer of iodine atom. For example, the diallyl amide **19** underwent efficient cyclization to compound **20** using the distannane reagent **18** (Scheme 9).

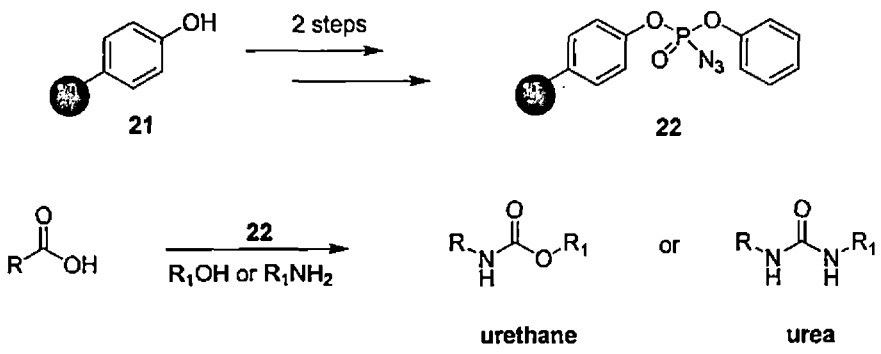
Scheme 9



I.2.1.G: Polymer-Supported Phosphoryl Azide

The preparation of a polymer–bound diphenylphosphoryl azide **22** in two steps from a phenol resin **21** (Scheme 10) was reported by Lu and Taylor.[29] The synthetic utility of reagent **22** was demonstrated in the conversion of various carboxylic acids to urethanes and urea derivatives via Curtius rearrangement. Reagent **22** was moisture–tolerant and the toxic phosphoryl azide group remains resin bound.

Scheme 10

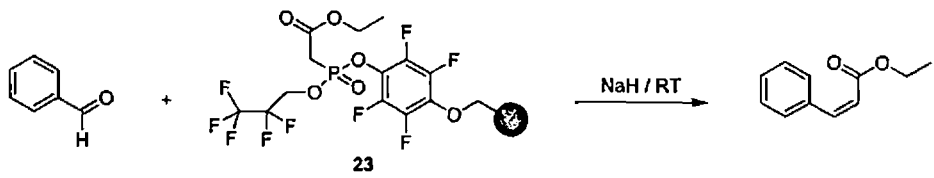


I.2.1.H: Polymer-Supported Phosphonate Reagents

Martina and Talyor described the synthesis of phosphonate resins and evaluated their potential for the selective preparation of Z–isomer of α, β–unsaturated esters from aldehydes.[30] The polymer supported fluorinated phosphonate **23** was the

most effective reagent in the synthesis (Scheme 11). The products were isolated by filtration of the resin without the need for chromatographic separation.

Scheme 11



23

I.2.2: Ionic Binding of Reagents: Ion Exchange Resins

An ion exchange resin is a polymer with electrically charged sites at which one ion may replace another. Natural soils contain solids with charged sites that exchange ions, and certain minerals called zeolites are quite good exchangers. Ion exchange also takes place in living materials because cell walls, cell membranes, and other structures have charges. In natural waters and in waste waters, there are often undesirable ions and some of them may be worth recovering. For example, cadmium ion is dangerous to health but is not present usually at concentrations that would justify recovery.

Most synthetic resins are based on styrene co–polymerized with DVB. Conventional ion–exchange resins include a range of anion (chloromethylated, aminated etc.) and cation resins (sulfonated). Styrene/DVB structures are the preferred matrices for ion–exchange resins because they offer significant capacity and stability over other resin structures.

The amount of cross–linking depends on the proportions of different monomers used in the polymerization step. Practical ranges are 4–16%. Resins with very low cross–linking tend to be watery and change dimensions markedly depending on which ions are bound. Properties that are interrelated with cross–linking are: moisture content, capacity, equilibration rate etc.

Copolymers of styrene containing low amounts of divinylbenzene (1–4%) possess following characteristics:

- High degree of permeability.
- Large moisture content

- Lower capacities on wet volume basis.
- High equilibrium rates.
- Reduced physical stability.
- Selectivity of various ions is decreased, but ability to accommodate larger ions is increased.

Copolymers of styrene containing high amounts of divinylbenzene (12–16%) exhibit characteristic in the opposite direction.

Synthetic ion–exchange resins are usually cast as porous beads with considerable external and pore surface where ions can attach. If a substance is adsorbed to an ion exchange resin, no ion is liberated. Testing for ions in the effluent will distinguish between removal by adsorption and removal by ion exchange. Of course, both mechanisms may be significant in certain cases, and mass balances comparing moles removed with moles of ions liberated will quantify the amounts of adsorption and ion exchange.

The total capacity of an ion–exchange resin is defined as the total number of chemical equivalents available for exchange per some unit weight or unit volume of resin. The capacity may be expressed in terms of milli–equivalents per gram of dry resin or in terms of milli–equivalents per gram of resin or in terms of milli–equivalents per milliliter of wet resin.[31]

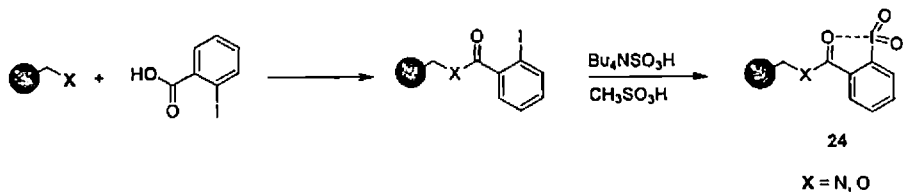
The more highly cross–linked a resin, the more difficult it becomes to introduce additional functional groups. Sulfonation is carried out after the cross–linking has been completed and the sulfonic acid groups are introduced inside the resin particle as well as over its surface. Likewise, the quaternary ammonium groups are introduced after the polymerization has been completed and they too are introduced both inside the particle as well as on its surface. Fewer functional groups can be introduced inside the particles when they are highly cross–linked and hence the total capacity on a dry basis drops slightly.

Recent examples of use of ionic resin especially for oxidation, reduction and related reactions are mentioned below highlighting the scope for using ionic resin as commercially cheap, stable and environmentally benign solid polymeric framework.

I.2.2.A: Oxidation Reactions

The selective oxidation of primary and secondary alcohols to the corresponding carbonyl compounds has found wide application in organic synthesis. This process provides the synthesis of structurally diverse carbonyl compounds, which are useful for subsequent reactions. Lee *et al.* designed polymer–supported 2–iodoxybenzoic acid (IBX) esters and amides **24** (Scheme 12) which can be employed for high–yielding oxidation of a range of primary and secondary benzylic alcohols to the corresponding carbonyl compounds. The spent polymeric reagents can easily be removed by filtration.

Scheme 12

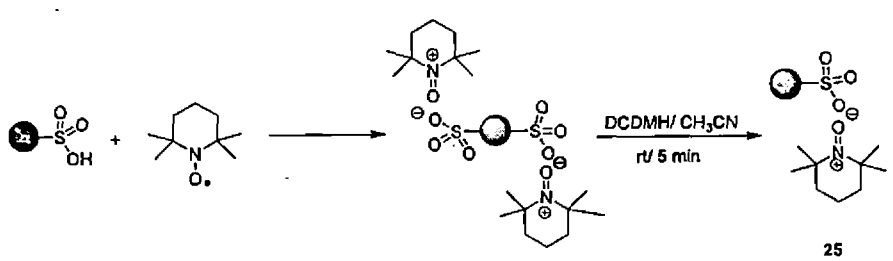


24

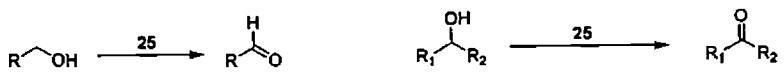
X = N, O

Bhattarcharyya et al. reported the synthesis and application of a novel polymer–supported oxidizing agent MP–TsO–TEMPO **25**, based on an oxo–ammonium salt of TEMPO (Scheme 13).[32]

Scheme 13



25



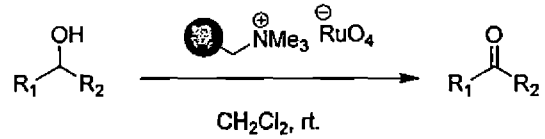
R = Ar, CH=CH2

R1 = Ar
R2 = alkyl, Ar or CR1R2 = (CH2)n

The reagent **25** was prepared from MP–TsOH, a commercially available polymer–supported sulfonic acid, and can be activated to its full capacity using 1,3–

dichloro–5,5–dimethylhydantoin (DCDMH). The reagent MP–TsO–TEMPO has primary applications in selective oxidation of activated primary and secondary alcohol such as benzylic, allylic, acetylenic andalicyclic alcohols. The resulting aldehydes or ketones could be isolated in high yields by filtration of the resin and evaporation of solvents. Oxidation of alcohols to ketones and aldehydes can be achieved on the solid phase using standard reagents such as the SO_3.pyridine complex,[33] DMSO–oxalyl chloride–Et_3N, or tetra–*n*–propylammonium perruthenate complex.[34] Recently, Hinzen and Ley reported a polymer–supported perruthenate, a new oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones respectively (Scheme 14).[35]

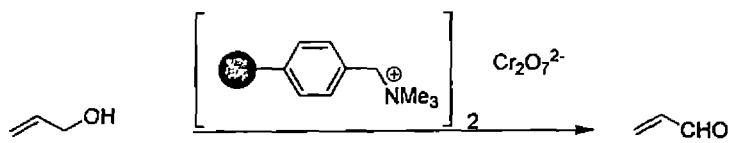
Scheme 14



R_1 = alkyl, aryl; R_2 = alkyl, H.

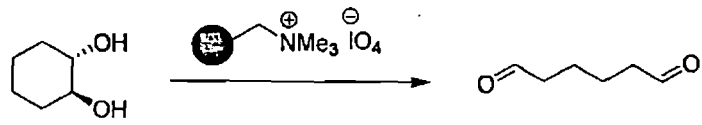
Polymer–supported quaternary ammonium perchromate (counter anion) converts allylic alcohols to α,β–unsaturated aldehydes, whereas saturated alcohols remain unaffected under the similar conditions (Scheme 15).[36]

Scheme 15



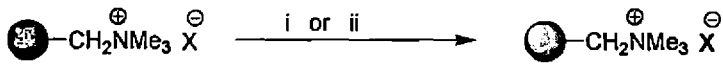
Periodates oxidize various functional groups, but due to solubility limitations, these salts are typically only utilized in hydroxylic media. Polymer–supported periodate, however, can be used in a variety of solvents, and in many cases, filtering off the resin and evaporating the solvent gives clean oxidized product. Quinols are converted to quinones, 1,2–diols are cleaved to the corresponding carbonyl compounds, sulfides are oxidized to sulfoxides, and triphenylphosphine is converted to triphenylphosphine oxide (Scheme 16).[37]

Scheme 16



The preparations of the periodate forms **28** of the macroporous ion–exchange resins Amberlyst 26 and Amberlite IRA 904 from their corresponding chloride forms **26** and of the iodate analogues **29** from the hydroxide version of those matrices **27**, as shown in scheme 17, were first described by Harrison and Hodge.[37]

Scheme 17



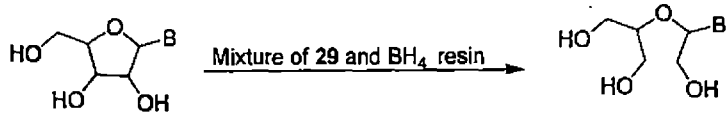
26 X = Cl
27 X = OH

28 X = IO_4
29 X = IO_3

Reagents and conditions: i $NaIO_4$ (aq); ii HIO_3 (aq)

The reagents **28** & **29** have been used for the oxidation of dihydroxybenzene to corresponding quinone. The cleavage of 1,2–diols, to corresponding carbonyl species, could easily be achieved with the reagent **28**. An interesting application of periodate resin **28**, in conjunction with resin–bound borohydride, was the conversion of nucleosides **30** to the corresponding trihydroxynucleosides **31**, as described by Bessodes and Antonakis.[38] Simply filtering a solution of the nucleoside through a column containing a well–mixed bed of a 1+1 mixture of the two resins facilitated the reaction (Scheme 18).

Scheme 18



30 **31**

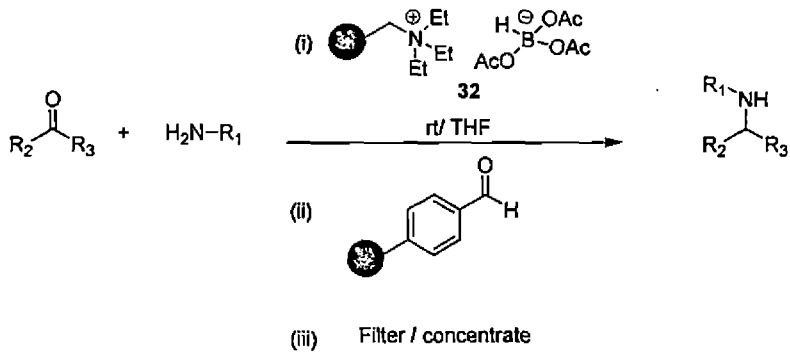
B = Adenine, Cytosine, Guanine, uracil

The process described was therefore extremely clean, and has the advantage that due to the fact that no reaction takes place between the resin bound materials, the intermediate dialdehyde need not be isolated. Periodate–containing resins have also been successfully employed in the high–yielding and remarkably clean oxidations of α–haloketones[39] into carboxylic acids, and in the rapid conversion of a range of sulfides to sulfoxides.[40]

I.2.2.B: Reduction and Reductive Amination

Amines and their derivatives are the most abundant structural moieties present in the CMC (comprehensive medicinal chemistry) database.[41] The reductive amination of carbonyl compounds provides expedient access to structurally diverse amines and has wide application in organic and medicinal chemistry. Bhattarcharyya *et. al.* have reported a novel polymer–supported triacetoxyborohydride reagent **32** (Scheme 19) for the reductive amination of aldehydes and ketones.[42] The bound triacetoxy–borohydride reagent **32** is stable and provides a broad scope and reactivity in reductive amination reactions, using primary amines, secondary amines and their salts under mild conditions. These reactions can be conveniently carried out in solvents, such as THF, DMF or NMP.

Scheme 19

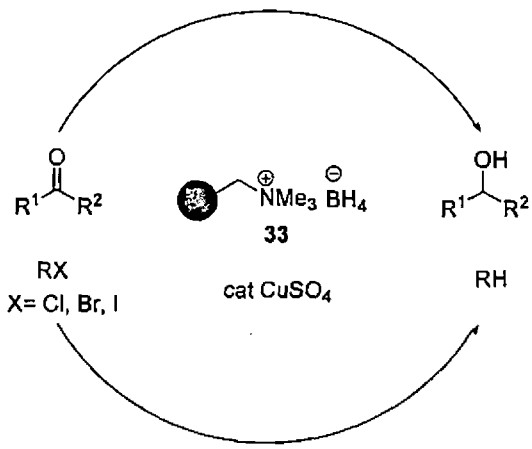


Immobilized reducing agents have been used as the source of hydrogen or hydrides in reduction of different functional groups in organic molecules.[43] The chemical modification of quaternary ammonium type resins, such as Amberlyst® A–26, with $NaBH_4$[44] and $NaCNBH_3$ gives highly efficient and chemoselective reducing agents.[45] The cross–linked polymer–supported $Zn(BH_4)_2$ [46] has been employed in reduction of aldehyde in presence of ketones and that of $Zr(BH_4)_4$ [47] could reduce ketones also, while conjugated double bonds remained unreacted. Formic acid anchored with Amberlite Resins (anion exchange) has been used as hydrogen donor in catalytic transfer hydrogenation (CTH).[48]

When borohydride is attached to Amberlite® IRA 400 and treated with a catalytic amount of $CuSO_4$, a functionalized polymer **33** is obtained, which can act as an efficient reductant towards different functional groups like aryl halide, azides,

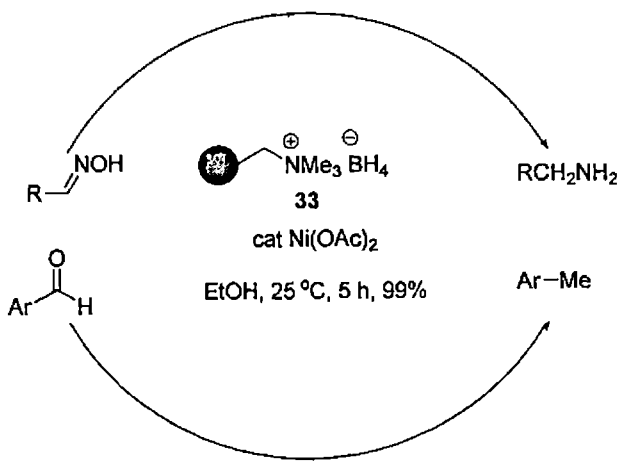
aldehydes, and ketones.[49] (Scheme 20) Borohydride exchange resin (BER) is useful for conversion of thioacetates to thiols by palladium–catalyzed methanolysis,[50] and selenium to dialkyl selenides.[51]

Scheme 20



The addition of a catalytic amount of nickel (II) acetate affords a very powerful and highly chemoselective[52] functionalized polymer **33**, which allows reduction of nitro[53] and azido[54] groups as well as of aryloximes[55] to the corresponding primary amines. Alkyl and aryl halides[56] tosylates,[56a] and benzaldehydes[57] are remarkably converted into alkanes in moderate to excellent yields (Scheme 21).

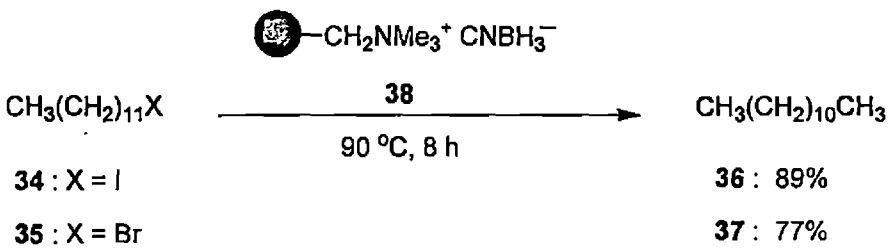
Scheme 21



These results compare favourably with those obtained by Hutchins *et al.* when using supported cyanoborohydride (**38**).[45a] The material, which was prepared

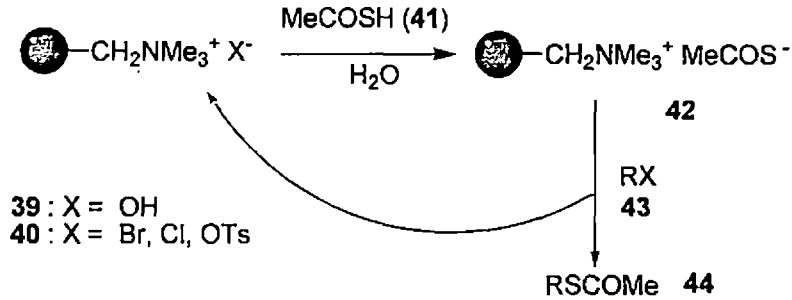
on Amberlyst A–26, was also employed to effect the conversion of pyridinium bromides into tetrahydropyridine derivatives, dimethylation of amines, reduction of ketones, and dehalogenations of **34** and **35** to alkane **36** & **37** in good yields (Scheme 22). The time taken to achieve the desired conversions was reported to be greater than that required with standard solution phase cyanoborohydride, presumably due to less efficient substrate/polymer contact, but the reactions were extremely clean. The toxic cyanide residues associated with free sodium cyanoborohydride are retained on the Amberlyst resin, and not extracted into either aqueous or organic media. The resin can be regenerated by a simple washing procedure, as in the case of borohydride resin **33**.

Scheme 22



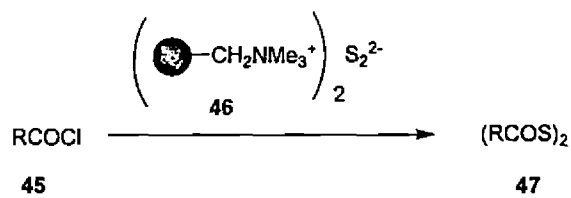
The immobilization of thioacetic acid **41** on Amberlyst A26 (hydroxy form) **39** has proved useful for the clean conversion of alkyl halides **43** into thioacetates **44** (Scheme 23).[58] The reactions were performed under a variety of conditions dependent upon the nature of the substrate, but always with a slight excess of resin **42**. The reaction conditions are relatively mild; with alkyl bromides reacting readily at room temperature, whilst chlorides and tosylates require slightly more vigorous treatment. Secondary alkyl bromides require the application of elevated temperatures, but the reaction is clean, with no elimination products being observed. The spent resin **42**, containing halide or tosylate groups, can be efficiently recycled simply by washing with dilute sodium hydroxide solution and treatment with thioacetic acid.

Scheme 23



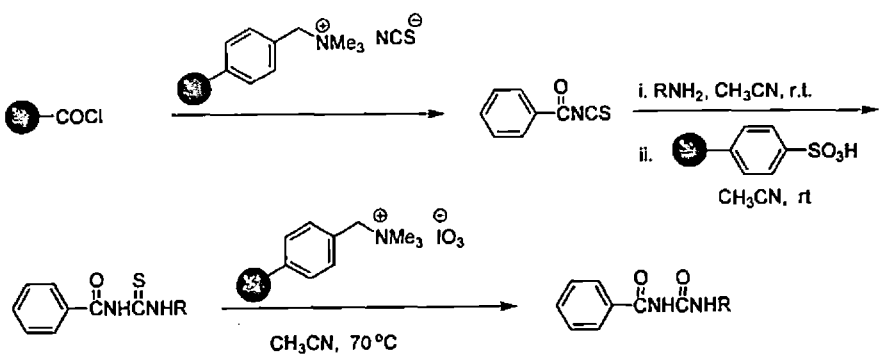
Tamami and Kiasat reported the synthesis of acyl disulfides **47**, using sulfur supported on Amberlyst A26.[59] Reagent **46** was readily prepared from elemental sulfur and the ion–exchanger, and are postulated to contain sulfur as S_2^{2-} units. This material rapidly, and cleanly, converts acid chlorides **45** to the corresponding diacyl disulfides, with no trace of the acyl sulfides being found, shown in scheme 24.

Scheme 24



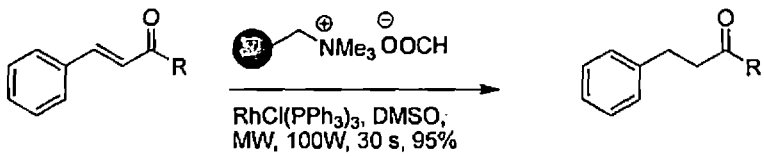
The substituted ureas have drawn considerable attention in a number of investigations due to their biological activity and wide variety of applications.[60] Most syntheses of ureas have been reported using conventional solution methods and solid–phase synthesis.[61] Recently Yang *et al.*[62] reported a simple, fast and flexible method for synthesis of ureas using polymer–supported reagents as shown in scheme 25. They carried out the synthesis of thioureas by reaction of poly(ethyl glycol) bound benzoyl chloride with amines.[63]

Scheme 25



Danks *et al.* reported a facile reduction of cinnamic acid and its alkyl esters using a mixture of Amberlite® IRA 938 resin–supported formate and Wilkinson's catalyst in a minimum quantity of DMSO under microwave irradiations (Scheme 26).[64]

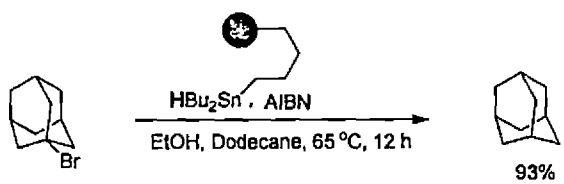
Scheme 26



R = OH, OCH_3, OCH_2CH_3

Other important groups of functionalized polymers with reductive properties include polymer–supported organotin reagents, especially tin hydrides.[65] These types of polymer–supported tin hydrides have been employed for the reduction of sulfonic esters, xanthates, or alkyl halides[66] including tertiary bromides like adamantyl bromide.[67]

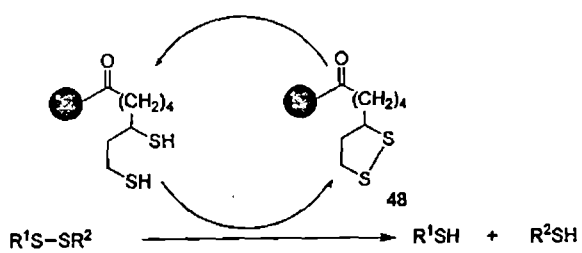
Scheme 27



Polymeric backbone is Amberlite XE 305

Polymer bound dithiol, a biomimetic tool for the reduction of disulfides, was developed by Gorecki and Potchornik.[66] The polymer bound dithiol was prepared by the treatment of disulfide **48** with $NaBH_4$ (Scheme 28).

Scheme 28



I.3: Solid Supported Catalysts

I.3.1: Introduction

In an era, when the world has been increasingly aware of the limits of its natural resources and the problems relating to environmental impact of disposing of waste materials, the chemical industries are under considerable pressure to discover, develop and to utilize more efficient, cleaner and "green" manufacturing protocols. The areas, which have seen the most change in recent years, have been the pharmaceutical and agrochemical sectors. These communities are constantly seeking new ways to meet the demands for new, diverse and structurally interesting molecules. Homogeneous catalysis has a number of drawbacks, in particular, the lack of reuse of the catalyst or at least the problem of recycling of the catalyst. This leads to a loss of expensive metal and ligands and to impurities in the products and need to remove the residual metals.[69] The heavy metal contamination with the product is undesirable and must be limited to ppm or even lower levels in large–scale pharmaceutical processes.[70]

The heterogeneous catalysis is a most promising option to over come those problems. Solid–supported catalysts are complex assemblies. Their preparation is a challenging task. Minor changes of their preparation conditions can significantly influence the delicate balance of conflicting demands: high activity, high selectivity, and long lifetime. Depending on the matrix used, the immobilized complexes can be isolated from reaction mixture via either filtration or judicious selection of a second solvent for the selective precipitation of matrices out of the reaction mixtures or extraction of the scaffolds into an orthogonal liquid phase. Thereby, immobilization of a soluble catalyst on a support allows the facile recovery and reuse of expensive and toxic catalytic heavy metal species, which cut costs and provide environmental protection benefits in industrials processes. Several approaches have been explored utilizing various immobilization techniques on solid or colloidal supports, and aiming towards efficient recovery and reuse of the active catalysts. The major thrust to achieve success in designing and developing polymer–supported metal catalysts broadly include: improved stability within the polymer matrix, increased selectivity for reactions, enhanced regio–selectivity, reusability for several runs and superior asymmetric induction due to site–specific chiral catalysts. In this brief literature review the various types of immobilized palladium catalyst onto the different

heterogeneous surface and their application in various coupling reactions have been highlighted.

Among the various catalytic processes, transition metal–catalyzed organic reactions constitute the central part of contemporary organic synthesis. Transition metal catalyzed carbon–carbon and carbon–heteroatom bond forming reactions are of the most important fundamental transformations in synthetic chemistry.[71] Homogeneous palladium catalysis has gained enormous relevance in various coupling reactions such as Heck, Stille, Suzuki, Sonogashira, and Buchwald–Hartwig reactions.[72] This type of catalysis provides high reaction rate and high TON (turnover number) and often affords high selectivities and yields. The properties of such palladium catalysts can be tuned by ligands, such as phosphines, amines, carbenes, dibenzylideneacetone (dba), etc. Proper ligand design has led to catalysts, that tolerate weak leaving groups such as chloride, exhibit higher TON and reaction rates, have improved lifetimes, and are suitably stable to run the reactions without the exclusion of water or air and at lower temperatures. The structure of the catalytic species is often known, and structure–activity relations could be established. Recent developments of ligand–free palladium catalysts have provided interesting and practically important alternatives to ligand assisted methodologies.

Generally palladium is fixed to a solid support,[73] such as activated carbon,[74] zeolites and molecular sieves,[73a,75] metal oxides[73a,76] (mainly silica or alumina but also MgO, ZnO, TiO_2, ZrO_2), clays,[77] alkali and alkaline earth salts ($CaCO_3$, $BaSO_4$, $BaCO_3$, $SrCO_3$), porous glass,[78] organic polymers,[73a] or polymers embedded in porous glass.[79] On the other hand, palladium can also be fixed to a solid support as a complex; that is, the ligands are covalently bound to the support. Both techniques allow one to separate the heterogeneous catalyst after the reaction or to reuse it as long as it is not too deactivated.[80] Alternatively such catalysts can also be used in continuous–flow systems[79a] or in flow injection microreactors.[81] Normally, supported palladium catalysts require more drastic reaction conditions than homogeneous catalysts, but this does not cause problems as far as the stability of the catalysts is concerned, because they often are relatively stable. In this way, somewhat lower activities can be compensated to some extent by using higher temperatures and catalyst loadings. Djakovitch *et al.* reported a comparative study of homogeneous versus heterogeneous catalysis of palladium catalyst in Heck reactions.[82] Palladium immobilized onto zeolites showed higher activity than free $Pd(OAc)_2$ or $[Pd(C_3H_5)Cl]_2$,

probably because of the stabilization of the active palladium species by the zeolite framework.[75d] The comparatively high stability of palladium on solid supports sometimes allows running the reaction even under normal ambient conditions, that is, without the exclusion of air.[83] Solid supported palladium catalysts often show higher activities than homogeneous catalysts, probably because of their higher stability.[84] The application of supported palladium was introduced into palladium–catalyzed coupling reactions relatively late (early 1970s) but has been increasingly used up to now.[85] Palladium can be deposited on a solid support in different ways.[78b,86] The preferred mode of deposition however depends also on the type of support.

An excellent review article[87] covering various types of heterogeneous palladium catalysts and their applications in different carbon–carbon coupling reactions has been published in 2007. A short account of pertinent approaches is therefore discussed here.

I.3.2: *Covalent Binding of Catalyst*

I.3.2.A: *Silica as a Support*

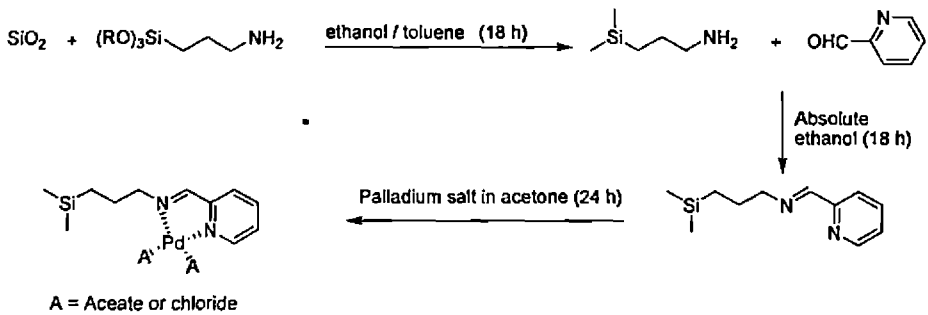
Silica, a neutral oxide, is totally hydroxylated and the hydroxyl layer covered with physically absorbed water.[88] Removal of water[89] at higher temperature results an amorphous porous[90] silica gel having the surface area up to 1000 m^2 /g.

Two methods are usually followed for the preparation of silica–supported catalyst. One is impregnation and other is grafting. Pd/SiO_2, Ru/SiO_2, Pt/SiO_2 etc. catalysts were prepared by impregnation. In these cases a calculated amount of $Pd(thd)_2$, $Ru(thd)_2$ or $(CH_3)_3(CH_3C_5H_4)Pt$ [thd is 2,2,6,6–tetramethyl–3,5–heptanedionato] was introduced to silica in the presence of toluene, distilled water or ammonia solution (25%) as a solvent.

In case of grafting[91] the catalyst is prepared by building up a suitable ligand on the surface of a commercial mesoporous silica gel followed by the complexation of the metal [palladium (II)] (Scheme 29). Thorough conditioning of the catalyst including prolonged treatment with hot solvents helps to ensure catalyst stability in subsequent reactions. This supported palladium catalyst has been successfully used for Heck reaction and the catalyst can be reused in these reactions without noticeable loss of activity. Aminopropyltriethoxysilane modified silica were loaded with Pd nanoparticles by treating with $Pd(OAc)_2$ (Scheme 29). These catalysts worked well in Suzuki reaction of aryl bromides with arylboronic acids (K_3PO_4,

toluene, 100 °C) when chelating diamines and triamines were used as organic modifiers.[91d] An optimal catalyst could be reused four times without a significant loss of activity, but the activity decreased in further runs. Suzuki coupling of less reactive aryl chlorides and bromides could be achieved with a Pd catalyst on mercaptopropyl-modified mesoporous silica (SBA-15-SH-Pd).[76g] It could be reused four times without any loss of catalytic activity.

Scheme 29



Transition metal complex catalysis can be activated for the hydrogenation by tethering them to a silica-supported metal heterogeneous catalyst.[92] The combined homogeneous-heterogeneous catalyst consisting of tethered complex on a supported metal, TCSM (tetrahedral complex and supported metal), not only has the advantages of a conventional SiO_2-tethered complex catalyst but also functions by synergetic action of the two catalyst components (TCSM) in the catalytic reactions. For example rhodium isocyanide complex $RhCl[CN(CH_2)_3Si(OC_2H_5)_3]_3$ (Rh-CNR_3), when tethered on silica-supported palladium (Pd-SiO_2), gives the TCSM catalyst Rh-CNR_3/Pd-SiO_2, which is much more active for hydrogenation of arenes than the separate homogeneous Rh-CR_3 complex catalyst, the separate heterogeneous supported palladium catalyst, or the Rh-CNR_3 complex catalyst tethered on just SiO_2.[92a-b] A possible explanation for the high activities of the TCSM catalysts involves considering Pd-SiO_2 as the site where H_2 is dissociated and spills over onto the SiO_2. Silica is also the site of tethered complex which may bind and activate the arene substrate for reaction with the "spillover" hydrogen. It should be emphasized, however, that the mechanism for arene hydrogenation is not known and the other mechanisms[92c] must also be considered. Yang *et al.* [93] designed a TCSM catalyst, with the choice of two catalyst components, and employed it in reduction reaction. The rhodium complexes BF_4 (Rh(N-P)) and BF_4 (Rh(N-N)) were tethered on silica-supported palladium (Pd-SiO_2) to give the TCSM catalysts Rh(N-P)/Pd-SiO_2 and

Rh(N-N)/Pd-SiO_2. They used bipyridyl and pyridylphosphine chelating ligands that bind strongly to the metal ion, which significantly reduce leaching of metal.

I.3.2.B: Dendrimer as a Support

The word 'dendrimer' derive from the Greek word dendra, which refers to a tree. To put it in simpler terms, a dendrimer is polymer that branches. It is an artificially manufactured or synthesized molecule built up from branched units called monomers. Dendrimers are a novel class of three–dimensional nanoscale, core–shell structures having a variety of repeated units such as amides, amines, carbosilanes, siloxanes, esters, ethers, phenyl–acetylenes, various organometallics, amino acids that can be precisely synthesized for a wide range of applications. Several unique properties of DENs[94] make them attractive for catalytic applications.

- Solubility can be controlled principally by the chemical composition of the dendrimer periphery.[94b] This provides a means for carrying out reactions in green solvents such as water and supercritical CO_2.[94a–b]
- Particles are encapsulated within the dendrimer,[94] no additional ligands are required for stabilization.
- Small size of dendrimer means that they have a high surface–area–to–volume ratio, which is important for high efficiency.
- Catalytic groups placed at the core of a dendrimer allow controlling the microenvironment.

In addition, catalytic groups can be incorporated at the surface of a dendrimer. Catalytic groups at the surface are readily available for reaction, especially in larger dendrimers, which adopt a globular conformation with most terminal groups located at the surface. The loading on these systems is extremely high due to the inherent nature of dendrimer structures. The monometallic palladium DENs can be used as catalysts for hydrogenations,[95] Heck coupling,[96] Suzuki coupling[97] and Stille reaction.[65] These reactions are characterized by the coupling of an organostannane[98] derivative with a carbon electrophile in the presence of palladium(0).

There are many examples[99] of the use of peripherally fictionalized dendrimers in catalysis of reactions including the Kharash addition, hydrolysis, decarboxylation, Heck couplings, polyurethane formation, oxidation, (bromides and thiophenes), allylic

alkylation, Stille couplings, Knoevenagel condensations, Michael–addition, nucleophilic addition, asymmetric hydrogenation, and so on.

I.3.2.C: Cyclodextrine as a Support

The catalysis of metal nanoparticles with diameters smaller than 5 nm is very attractive because of the large fraction of metal atoms that reside on their surfaces, thus affording very efficient use of the metal. However, to exhibit catalytic activity, metal surface sites must remain accessible to the substrate molecules. The surface modification of gold,[100] platinum,[101] and palladium[101] nanoparticles with cyclodextrin (CD) receptors,[102] (fig 1) which remain capable of binding appropriate solution guests. CD–capped platinum and palladium nanoparticles (diameter: 13–16 nm) were water soluble and exhibited catalytic activity for the hydrogenation of allylamine.[101] The water soluble palladium nanoparticles that covalently attach with CD behave as an active catalysts for the hydrogenation of alkenes in aqueous media.

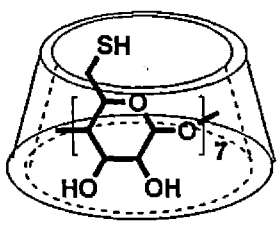
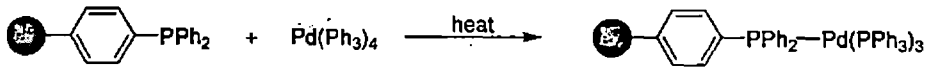


Figure 1: HS–β–CD

I.3.2.D: Polymer (Triphenylphosphine) as a Support

Triphenylphosphine, a common organophosphorus compound, is widely used in organic synthesis. Triphenylphosphine is a good coordinating ligand,[103] it binds well to most transition metals, especially those in the middle and late transition metal group 7 to 10. Polymer–supported triphenylphosphine **49** (PS–PPh_2; PS is polystyrene) has attracted much attention as a ligand for immobilization of metal complexes[7a,104] as it is the supported analogue of the ubiquitous simple tertiary phosphine ligand PPh_3. In 1976 Pittman *et al.*[105] first reported the preparation (Scheme 30) and use of the supported analogue **50** of the well–known palladium complex $Pd(PPh_3)_4$.

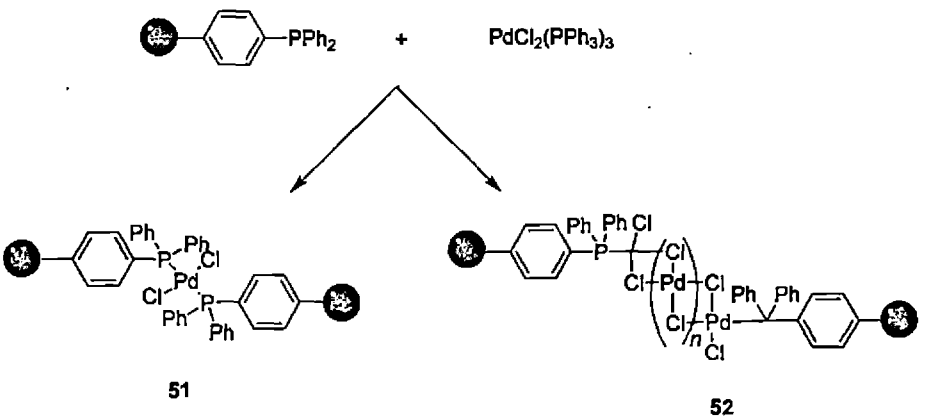
Scheme 30



49 50

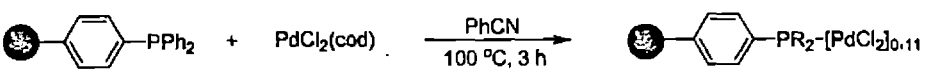
Hallberg and co–workers[106] have prepared supported analogues of $PdCl_2(PPh_3)_2$ from PS–PPh_2 and $PdCl_2$–$(PhCN)_2$ again by simple mixing of the two components (Scheme 31). They prepared supported complexes with Pd:P ratios of 1:1, 1:2, 1:3, and 1:4 and found that the bonding of the metal to the support changes with metal loading, complex **51** being formed at low metal loading and **52** at higher metal loading. Similar methodology was used by Miyaura and Inada[107] for the preparation of **53** (Scheme 32), this complex being shown to be highly active in cross–coupling reactions involving chloropyridines and activated aryl chlorides.

Scheme 31



51 52

Scheme 32

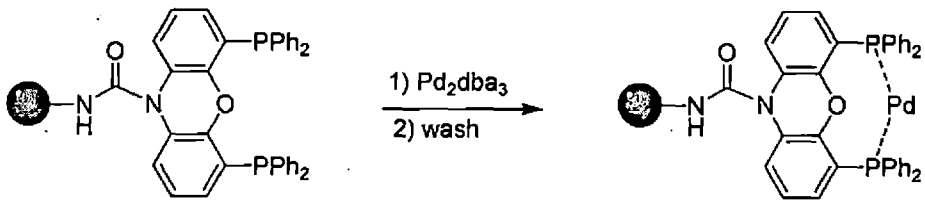


53

Depréle *et al.*[108] designed a reusable polymer supported palladium catalyst for the preparation of H–phosphinic acids. The active catalyst, obtained by treating polymer supported nixantphos with Pd_2dba_3 and washing, (Scheme 33) was air–stable and did not require particular handling precautions. Water has a great role in hydrophosphinylation reaction because high amount of water suppress the reaction rate. As expected the P–C bond–forming reaction does not take place in the absence of ligand, and transfer hydrogenation occurs instead. But the supported catalyst **54**

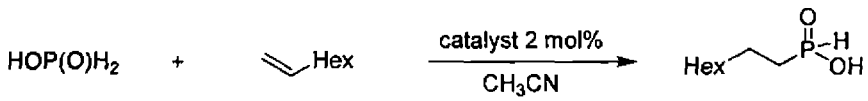
uniformly furnishes good yield and appears significantly more water–tolerant than its homogeneous counterpart (Scheme 34).

Scheme 33



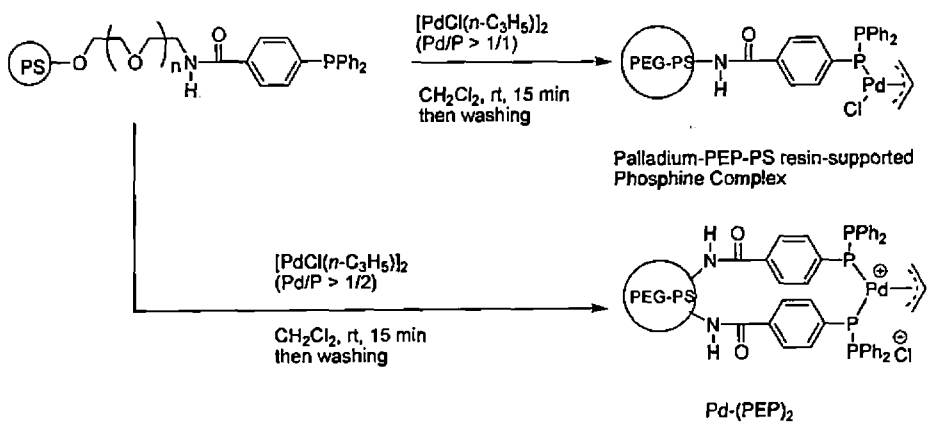
54

Scheme 34



Uozumi *et al.*[109] reported preparation of amphiphillic resin–supported triarylphosphine–palladium complexes bound to a poly(ethylene glycol)–polystyrene (PEG–PS) graft copolymers, which exhibit the high catalytic activity in allylic substitution reactions of allyl acetates with various neucleophiles in aqueous media under mild reaction conditions.[110] The PEG–PS resin–supported palladium–monophosphine complex Pd–PEP can be prepared by treatment of resin–supported phosphine[110a] with an excess amount of di(*μ*–chloro)*bis*(η^3–allyl)dipalladium(II) ([PdCl(η^3–C_3H_5)]$_2$) (Pd/P > 1/1) followed by the removal of unimmobilized ([PdCl(η^3–C_3H_5)]$_2$) by washing with chloroform (Scheme 35).

Scheme 35

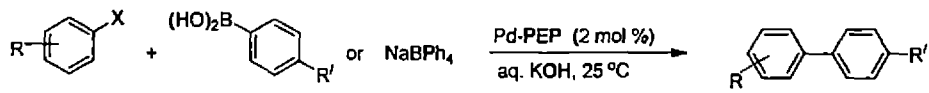


Pd-(PEP)$_2$

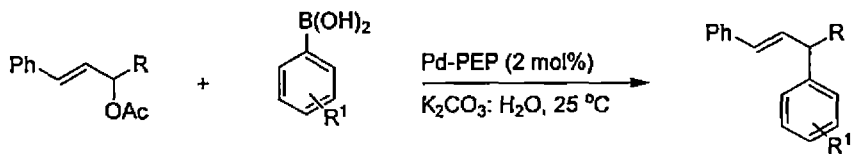
Resin–supported palladium–*bis*(triarylphosphine) complex[110a] [Pd–(PEP)$_2$] catalyzed the Suzuki coupling reaction with high yield of corresponding biphenyl

product in water (Scheme 36). The cross coupling using water–soluble phosphine ligand, triphenylphosphinesulfonate sodium salt (TPPTS) showed lower catalytic activity.[111] Palladium–triphenylphosphine complex did not catalyze the reactions in water owing to its insolubility. The catalyst Pd–PEP is also active for the allylic arylation of cinnamyl acetate with phenyl boronic acid in aqueous medium (Scheme 37). The supported catalyst Pd–PEP showed much lower catalytic activity in organic solvent than in water.[109]

Scheme 36

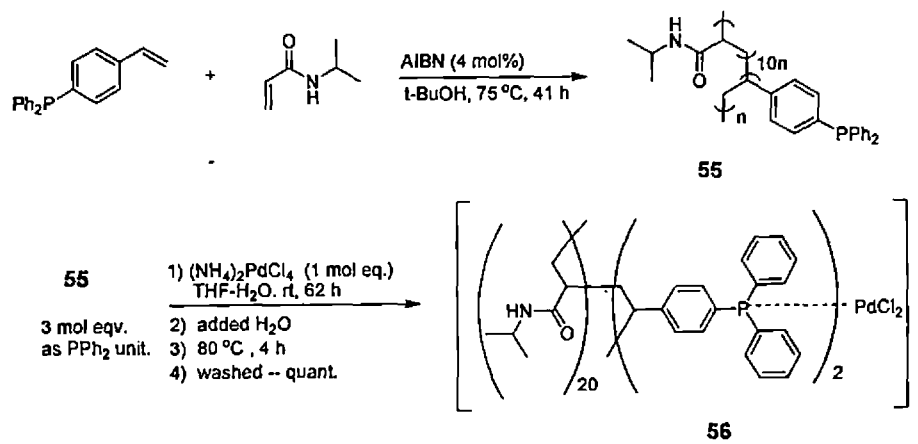


Scheme 37



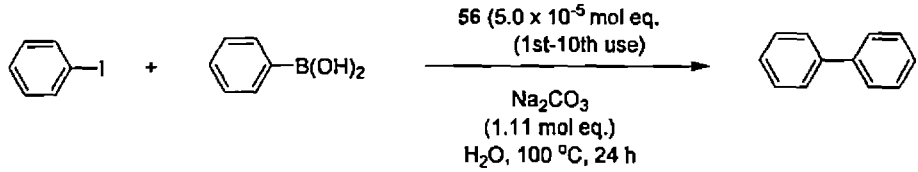
Yamada *et al.*[112] introduced the self assembled process between non–cross–linked amphiphilic copolymer ligands and an inorganic species for the preparation of highly active, insoluble catalyst.[113] For example, a tungsten catalyst was formed from phosphotungstic acid and poly (N–isopropylacrylamide) with an ammonium salt.[113a] This catalyst used in ppm molar equivalent, brought about an efficient epoxidation of allylic alcohols. Since this self–assembled catalyst exhibits great potential Yamada *et al.* applied similar technique for the preparation of self–assembled palladium catalyst (Scheme 38).[112b]

Scheme 38



The complex **56** was so active that only (5×10^{-5}) mol equiv was sufficient to catalyze the Suzuki–Miyaura coupling between iodobenzene and phenylboronic acid under the organic solvent free conditions (Scheme 39). The reaction proceeded efficiently to give biphenyl up to 95%. The catalyst was recovered after reaction and reused up to 10 times without loss of its activity.

Scheme 39

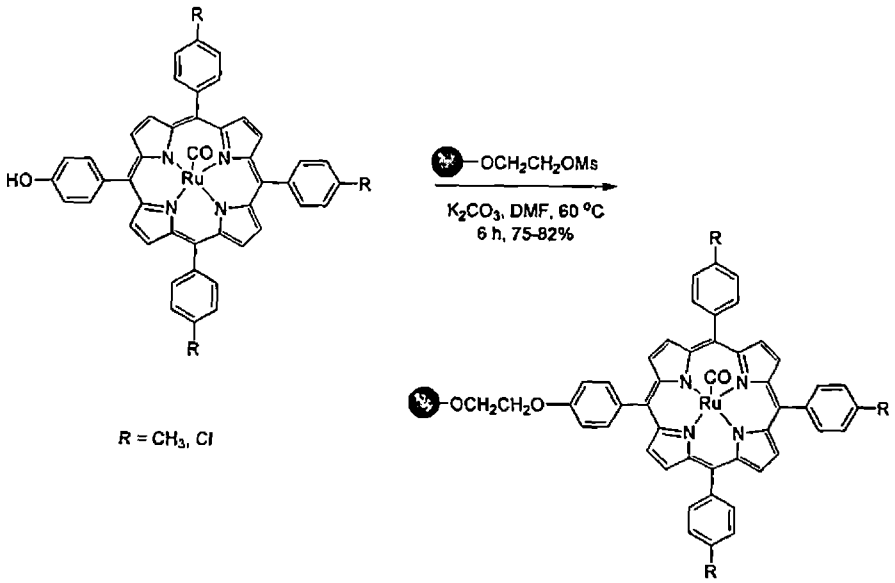


Entry	catalyst	yield
1	1st use	95%
2	10 th use	93%
3	1st-10th consecutive use	av: 95%

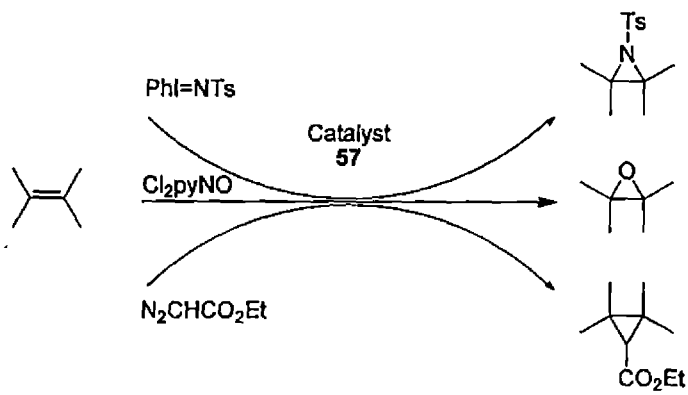
I.3.2.E: Supported Ruthenium Catalyst

There is a growing interest in developing ruthenium porphyrin catalysts for carbon–oxygen,[114] carbon–nitrogen,[115] and carbon–carbon[116] bond–forming reactions. Extensive studies have demonstrated that ruthenium porphyrins exhibit high stability and remarkable selectivity in catalyzing organic oxidations by 2,6–dichloropyridine N–oxide and cyclopropanation of alkenes by diazo compounds. However, the catalytic reactions proceed in homogeneous media, rendering recycling of the ruthenium catalyst. Ruthenium complexes anchored with insoluble polymer supports[117] results heterogeneous catalyst that suffers from limited mobility. Zhang *et al.*[118] prepared soluble polymer–supported ruthenium porphyrin catalysts by treatment of ruthenium porphyrins with methoxypoly(ethylene glycol) (Scheme 40). Catalyst **57** exhibits high reactivity, selectivity, and stability in epoxidation and cyclopropanation of alkenes (Scheme 41).

Scheme 40



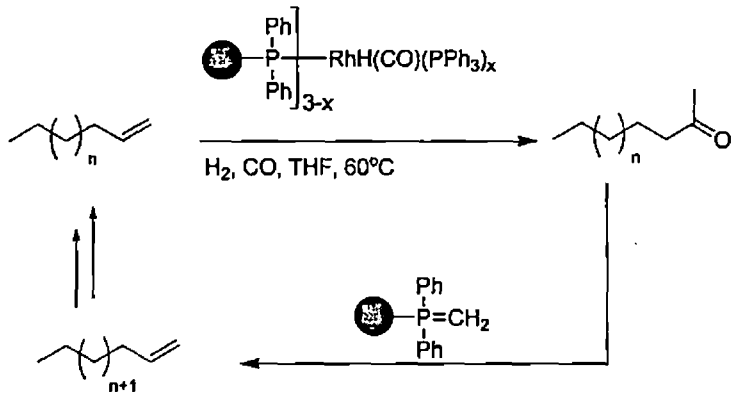
Scheme 41



I.3.2.F.1: Supported Rhodium Catalyst: Homologation of Alkenes

Regen *et al.*[119] reported a chain homologation of alkenes with polymer–supported rhodium catalyst (Scheme 42). In this strategy, a polystyrene supported rhodium catalyst effects a hydroformylation of the alkene with synthesis gas to generate aliphatic aldehydes. These then react with a polystyrene–supported Witting reagent to produce two carbon homologated alkenes which can then re–enter the reaction cycle. Advantages of this strategy include milder reaction conditions and less complex mixture than traditional alkene homologation methods.

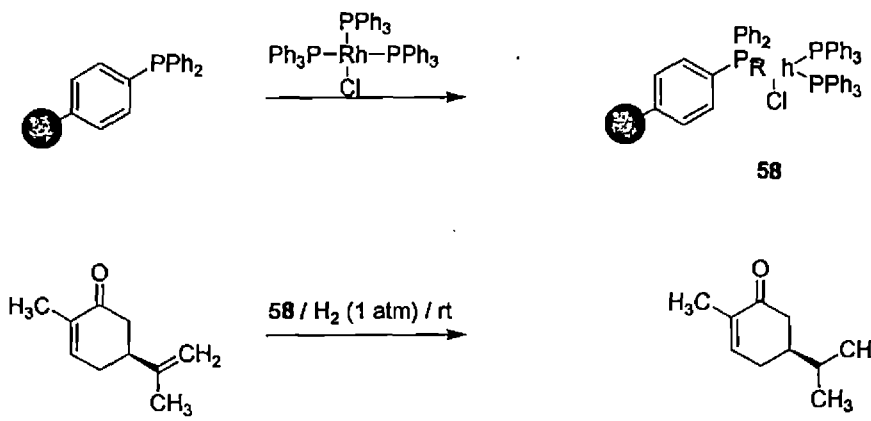
Scheme 42



I.3.2.F.2: Hydrogenation of Terminal Alkenes or Alkynes

Polymer–supported rhodium catalyst[120] on ROMPgel was developed by Barrett *et al.*[121] The ROMPgel–supported triphenylphosphine rhodium(I) chloride catalyst **58** was prepared from a triphenylphosphine ligand supported on ROMPgel (Scheme 43). The immobilized catalyst **58** has been successfully employed for selective hydrogenation of a range of terminal alkenes and alkynes in the presence of more hindered alkenes (Scheme 43). The hydrogenated products were isolated in their pure forms by filtration of the supported catalyst.

Scheme 43



I.3.3: Microencapsulation of Catalyst

Microencapsulation is a process for entrapping materials within a shell or coating, which is typically polymeric in nature. Microcapsules of polymer-coated

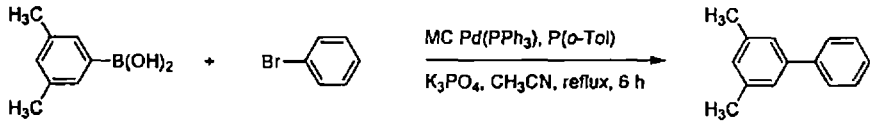
catalyst are formed upon cooling a homogeneous solution of the catalyst and a polymer or copolymer. This technique was exploited in the preparation of polystyrene-coacervated OsO_4,[122] $Pd(Ph_3)_4$,[123] and $Sc(OTf)_3$.[124] More recently, Kobayashi and co-workers have further developed this technique by building reactive oxirane functionality into the copolymer.[125] In this case, following coacervation of the homogeneous catalyst, the copolymer can be cross-linked thermally to form more chemically resistant cross-linked microcapsules. This technique has been exploited to form so-called "polymer-incarcerated" homogeneous $Pd(Ph_3)_4$ catalysts.[125] Various other methods and materials have been described in the literature for entrapping homogeneous metal complexes and metal nanoclusters including sol-gel materials,[126] dendrimers,[96a] and polyoxyalkylene resins.[127] The permeability and size of the microcapsules, and the coordinating properties of the matrix can be tuned by selecting the type of wall-forming oligomer or monomer, type and quantity of porogenic (i.e., organic) solvent, agitation conditions, chain extenders, and other additives. The polyurea matrix was selected, because of its ability to ligate transition-metal salts, which was considered important for both efficient microencapsulation and subsequent retainment of the metal within the matrix when used as a catalyst.[11b] It was also considered that the polyurea matrix would be relatively inert to chemical modification and give a physically robust material. Microencapsulation is widely practiced industrially and has found use in such diverse applications as drug delivery systems,[128] radiation therapies,[129] cell entrapment,[130] and the controlled release of pesticides.[131]

I.3.3.A: Microencapsulated Palladium

I.3.3.A.1: Suzuki Coupling

Kobayashi *et al.*[123] have reported the use of microencapsulated (MC) $Pd(PPh_3)_4$ for catalysis of both Suzuki coupling reaction (Scheme 44). The catalyst was prepared by the addition of $Pd(PPh_3)_4$ to a cyclohexane solution of linear PS (Mw ca. 280 000) at 40 °C followed by cooling to 0 °C. After addition of hexane to harden the polymer capsule the MC catalyst was collected by filtration. Best results were achieved using 20 mol% of catalyst and 20 mol% of PPh_3 as an external ligand.

Scheme 44

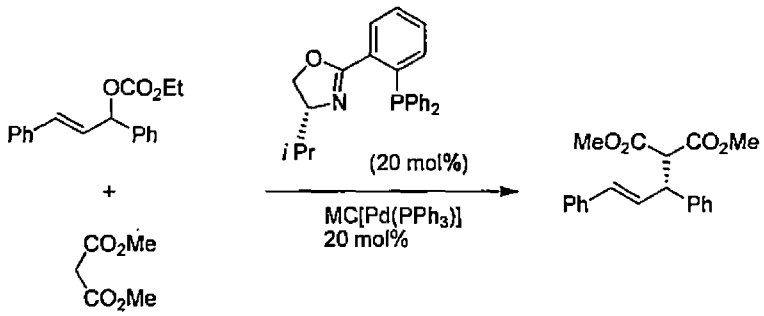


83 %

I.3.3.A.2: Asymmetric Allylation Reaction

Asymmetric allylation was also carried out using MC Pd (prepared from $Pd(PPh_3)_4$) and a soluble chiral ligand (Scheme 45).[123] The reaction was found to proceed in good yield with an *ee* (83%).

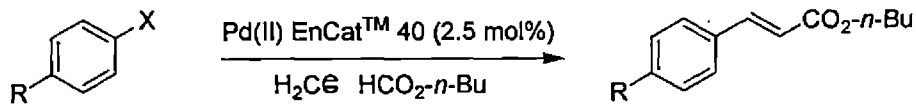
Scheme 45



I.3.3.A.3: The Heck Coupling

Pd(II) EnCat™ [132] has been effectively utilized in a series of Heck couplings in conventional organic solvents and in $scCO_2$ (Scheme 46).[133] With $(n\text{-Bu})_4NOAc$, a series of unsaturated esters were produced in high yields (with the exception of the reaction with 4-bromoanisole) without the addition of phosphine ligands. It was noted that the yields were generally higher in $scCO_2$ even at a lower catalyst loading.

Scheme 46



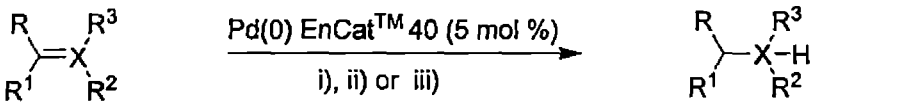
X = Br, Cl
R = NO_2, OMe, F, H

I.3.3.A.4: Hydrogenation

The reduction of Pd(II) EnCat™ 40 with hydrogen produces Pd(0) EnCat™ 40, which is an effective catalyst for the selective hydrogenation of unsaturated bonds in alkenes, alkynes, imines, and nitro groups (Scheme 47).[132] Recovery of the catalyst is simple compared to that of palladium-on-carbon, levels of metal contamination in the crude products are extremely low, and the catalyst can be

readily recycled. All of the initial hydrogenations reported were carried out with Pd(0) EnCat™ 40 pre-reduced under hydrogen (50 bar) for two days. It was found that this prereduction of Pd(II) EnCat™ 40 was necessary for high activity and reduced reaction times. The hydrogenations were carried out under a hydrogen atmosphere either in an autoclave or maintained by a hydrogen-filled balloon.

Scheme 47



conversion ~ 100%

R, R^1, R^2, R^3 = H, alkyl, aryl,
X = C, N

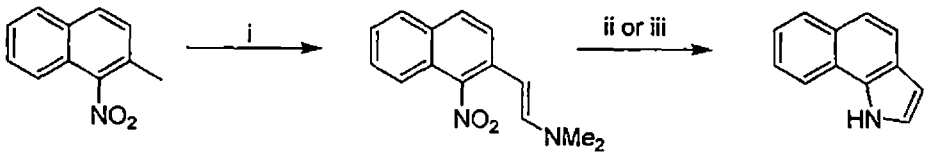
i) H_2 (balloon), EtOH, rt, 2-60 h
ii) H_2 (balloon), EtOH-MeCN (1:1), 60 °C, 3-5 h
iii) H_2 (50 bar), EtOH, rt, 18 h

I.3.3.A.5: Catalytic Transfer Hydrogenation (CTH)

I.3.3.A.5.1: Reduction of the Aryl Nitro Group

Pd(0) EnCat™ 40NP has been employed in the reductive cyclization of various Leimgruber–Batcho-derived enamines to form the corresponding indoles (Scheme 48).[134] Hydrogenation of the aryl nitro group was carried out under transfer-hydrogenation conditions to give the indole in high yield. The catalyst was recycled without noticeable loss in activity, and the reaction was accelerated by microwave irradiation at 120 °C. Thus, the combination of microwave-accelerated enamine formation and the use of a recyclable, easily removed catalyst for the reductive cyclization in the Leimgruber–Batcho reaction provide an industrially attractive route to indoles.

Scheme 48



85 %

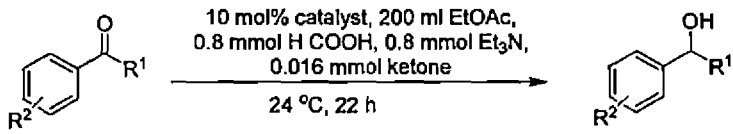
ii) 78%
iii) 68%

i) CuI or $Yb(OTf)_3$, DMF, μw, 180 °C, 4.5 h
ii) Pd(0) EnCat™ 40NP (6 mol%), EtOAc, HCO_2H, Et_3N, 24 °C, 24 h
iii) Pd(0) EnCat™ 40NP (6 mol%), EtOAc, HCO_2H, Et_3N, μw, 120 °C, 2 h

I.3.3.A.5.2: Reduction of Aryl Ketones

Palladium (II) acetate, microencapsulated in polyurea [PdEn–Cat™], acts as an efficient recyclable catalyst for a number of key transformations.[11b,135] Polyurea–encapsulated Pd(0) [Pd^0EnCat] in combination with formic acid is highly active for CTH of aryl ketones and nitro groups.[136] The [Pd^0EnCat] not only exhibits high reactivity but also resists leaching of palladium. At the same time, the catalyst has been proven to be highly chemoselective in the reduction of carbonyl and nitro groups. The catalyst can be recyclable up to five times without loss of its activity.

Scheme 49

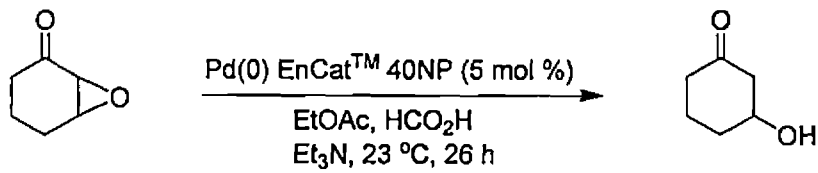


I.3.3.A.5.3: Reductive Ring Opening of Epoxides

The reductive ring opening of epoxides by hydrogenolysis in the presence of Pd(0) EnCat™ 40NP has been investigated.[137] For example, the hydrogenolysis of *trans*-stilbene oxide gave the alcohol in 99% isolated yield after 5 h. Over-reduction of the alcoholic C–O bond was not observed at a detectable level even after prolonged reaction times. This illustrates the clear advantage of Pd(0) EnCat™ 40NP over Pd/C in terms of chemoselectivity. Under identical conditions, 10% Pd/C gave the desired secondary alcohol in 80% yield from *trans*-stilbene oxide and in only 48% yield from methylstyrene oxide.[138] In these Pd(0) EnCat™ 40NP reductions, the catalyst was recovered by simple filtration and reused without loss of activity. In the case of *trans*-stilbene oxide, the catalyst was recycled through 10 successive

hydrogenolysis reactions and, in each case, gave high isolated yields (96–99%) of the corresponding benzylic alcohol. Moreover, the level of palladium in the reaction medium following filtration of the catalyst was below the detection limit (5 ppm) of ICP analysis.[137]

Scheme 50

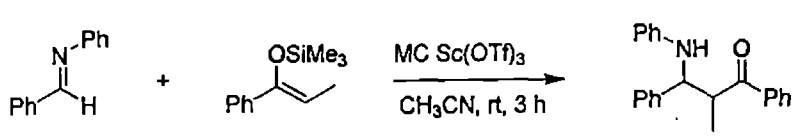


I.3.3.B: Microencapsulated $Sc(OTf)_3$

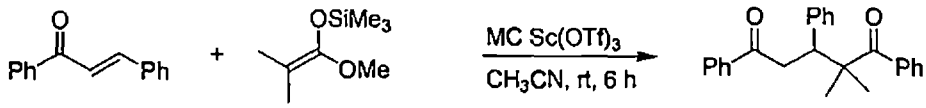
Lewis acid catalyzed reactions are of great current interest because of the unique reactivities and selectivities that can be achieved as well as for the mild conditions used.[139] Kobayashi developed polymer–supported scandium Lewis acids based on Nafion[140] and a polyacryronitrile derivative;[141] however, their reactivity was lower than for the monomeric Lewis acids. To overcome that problem they planned to utilize the polymer–supported Lewis acid, (microencapsulated Lewis acid), which is readily prepared, having higher activity than the monomeric Lewis acid, is recoverable and reusable, for many synthetic reactions. They have used MC $Sc(OTf)_3$ in several fundamental and important Lewis acid–catalyzed carbon–carbon bond–forming reactions. It was found that MC $Sc(OTf)_3$ effectively activated aldimines. Imino aldol[142] (Scheme 46) aza Diels–Alder,[142,143] cyanation,[144] and allylation[145] reactions of aldimines proceeded smoothly using MC $Sc(OTf)_3$ to afford respectively the synthetically useful β–amino ester, tetrahydro–quinoline, α–aminonitrile, and homoallylic amine derivatives in high yields. At the same time MC $Sc(OTf)_3$ also effectively catalyzed the Aldol and Friedel-Crafts acylation reaction (Scheme 51).[142b]

Scheme 51

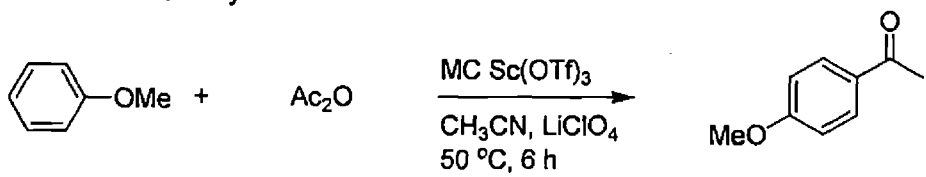
Imino Aldol Reaction



Aldol Reaction



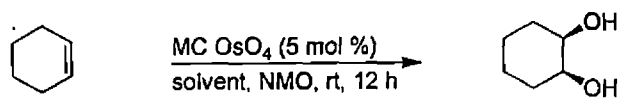
Friedel-Crafts Acylation



I.3.3.C: Microencapsulated Osmium Tetraoxide

Osmium tetraoxide (OsO_4) is the most reliable reagent for the dihydroxylation of olefins to give the corresponding diols.[146] The reaction proceeds in the presence of catalytic amount of OsO_4 using a co–oxidant such as hydrogen peroxide, *tert*–butylhydroperoxide, N–methylmorpholine N–oxide (NMO). Although a number of processes have gained wide acceptance in this dihydroxylation, few fruitful industrial applications have been accomplished, probably because OsO_4 is highly toxic, expensive, and volatile and can not be recovered. Kobayashi *et al.*[147] reported microencapsulated osmium tetraoxide, on polystyrene resin, that can be recovered and reused and that is effective in dihydroxylation of olefins (Scheme 52). The osmium tetraoxide immobilized onto a polymer on the basis of physical envelopment by the polymer and on electron interactions between the π electrons of the benzene rings of the polystyrene–based polymer and a vacant orbital of the Lewis acid.

Scheme 52



I.3.4: Ionic Binding of Catalyst

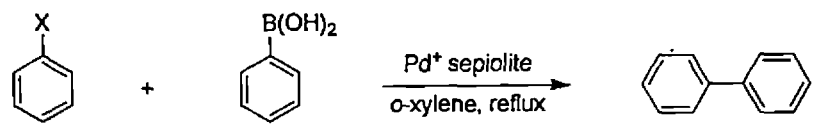
Various ways are known for ionic binding between a solid phase and a metal (either as metal or in its cationic form), a brief account of which is delineated below.

I.3.4.A: Sepiolite as a Support

Sepiolite is an abundant fibrous talc–like mineral of $Si_{12}Mg_8(OH)_4O_{30}.8H_2O$ formula whose structure is formed by an array of parallel channels, consisting of a double layer of SiO_4 tetrahedra sandwiching an internal octahedral sheet of MgO_6 layer.[148] Sepiolites have typically a surface area around 200 m^2/g that together with the availability of this mineral at robustness of its structure makes them suitable materials as supports in heterogeneous catalysis.[149] The Mg^{2+} ion, located at the edges, can easily be replaced with Na^+ ion on treatment with sodium hydroxide. To the neutral or alkali–exchanged sepiolites, $PdCl_2$ was added following the incipient wetness procedure. This Pd^{2+} exchanged sepiolites are highly efficient and reusable catalyst for Suzuki reaction[150] upon addition of external base. The alkali metal exchange sepiolites behave as solid bases having similar strength as acetate or carbonate. Corma *et al.*[151] designed a bi–functional catalyst where the sepiolite not only plays a passive role as support, but also an active role providing the basic sites necessary in the catalysis of both Suzuki and Heck reaction (Scheme 53 & 54). The activity of alkali sepiolite decreases significantly going from $PdCl_2$–NaSep to $PdCl_2$–Ksep or $PdCl_2$–CsSep. The activity of this sepiolite decreases on recycling due to the deactivation of the novel metal or due to the consumption of the basic sites. The most likely rationalization of the loss of activity would be a depletion of the sepiolite basic framework by the HX acid formed during reaction. The sepiolite can reactivate in part by flowing water steam to assist desroption of halogen acid. $PdCl_2$ supported on neutral sepiolites exhibit excellent balance for the Heck and Suzuki reaction but it cannot be reactivated.

Scheme53

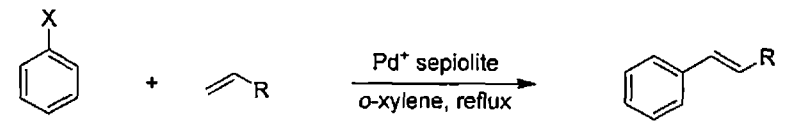
Suzuki Coupling



X = I, Br

Scheme 54

Heck Coupling



X = I, Br

I.3.4.B: Zeolites as a Support

Zeolites are microporous crystalline solids with well–defined structures. Generally, they contain silicon, aluminium and oxygen in their framework, cations, water and/or other molecules within their pores. Zeolites have the ability to act as catalysts for chemical reactions that take place within the internal cavities. Zeolites are often known as a shape–selective catalyst due to their unique micro porous nature, where the shape and size of a particular pore system exerts a steric influence on the reaction, controlling the access of reactants and products.

As zeolites have ion–exchange properties, different metal ion can easily be introduced into it. The heterogeneous palladium catalyst can be prepared by introducing palladium into zeloites. Djakovitch *et al.*[75d] have prepared several "palladium" exchanged zeolites by immobilization of different palladium species: palladium particles [Pd(0)], ionic species ([Pd(II)] and $[Pd(NH_3)_4]^{2+}$) and the neutral complexes $[(Pd(OAc)_2]$ and $[Pd(C_3H_5)Cl]_2$). The catalysts loaded with [Pd(0)], [Pd(II)],and $[Pd(NH_3)_4]^{2+}$ were prepared by ion exchange of Na–Y zeolites. Michalik *et al.*[152] used Na–Y zeolites for loading the palladium. Firstly they exchanged with $CaCl_2$ and prepared Ca–Y zeolites. After that palladium was introduced into the zeolites as $[Pd(NH_3)_4]^{2+}$ by ion exchange with two different amounts of 0.01 M palladium tetra amine chloride solution at room temperature. After a period of 24 h, $[Pd(NH_3)_4]^{2+}$–NaY was obtained. These immobilized palladium catalyst was successfully used for Heck coupling reaction in the presence of extrinsic base and after reaction the catalyst was recovered and reused for several run without significant loss of activity. Leaching of palladium catalyst depends on the nature of solvent. No palladium leaching[153] is observed when toluene is used as a solvent. However the use of extrinsic base could be avoided, by introducing basicity in the zeolite framework through alkali metal ion exchange.[154] Corma *et al.*[155] have prepared three different basic zeolites containing palladium. This bi–functional catalyst, containing noble

metal and basic sites, are active for Heck coupling[156] and Suzuki coupling[157] reaction. The solid catalyst reused after washing with water and a minor decrease in the catalytic activity was observed. Pd(II)–NaY zeolite or Pd(0)–NaY zeolite performed very well in Suzuki reactions of aryl bromides without the addition of a ligand.[158] The catalysts exhibited excellent activity with K_2CO_3 or Na_2CO_3 as base at room temperature allowing high yields to be achieved after short reaction times. As a further way to solid–supported palladium catalysts, the complexes $PdCl_2[Ph_2P(CH_2)_4SO_3Na]$ or K were directly loaded to alkylsulfonated mesoporous supports. The resulting heterogeneous catalyst, was applied to the Suzuki coupling of 4–iodoanisole with phenylboronic acid, also showed an enhanced activity on recycling.[159]

I.3.4.C: Hydrotalcite as a Support

Hydrotalcite (HT) is a synthetic aluminium–magnesium–hydroxycarbonate. It just likes anionic clays[160] having the general formula $[M^{(II)}\ (1-x),\ M^{(III)}\ x(OH)_2]^{x+}\ [(A^{n-})x/n\ yH_2O]^{x-}$ where x = 0.1–0.33, $M^{(II)}$ = Mg, Cu, Ni, Co and Mn; $M^{(III)}$ = Al, Fe, Cr, and Ga; A^{n-} is an interlayer anion such as CO_3^{2-}, NO_3^- and SO_4^{2-}. Hydrotalcite can also be used for the preparation of supported catalyst.[160a,161] Palladium(II) supported hydrotalcite[160c] and related Ni–Al hydrotalcite[160d] have been used in the oxidation of alcohols using molecular oxygen. Bennur *et al.*[162] synthesized palladium containing Mg–Al hydrotalcites[163] from soluble salts of the metals (palladium acetate) in the required atomic ratios by co–precipitation in a solution containing a slight excess of Na_2CO_3 along with NaOH at pH 10.[164] After precipitation the precipitate was washed repeatedly with water till the filtrate was neutral to litmus then dried and directly used for Heck coupling reaction.

I.3.4.D: Metal hydroxide

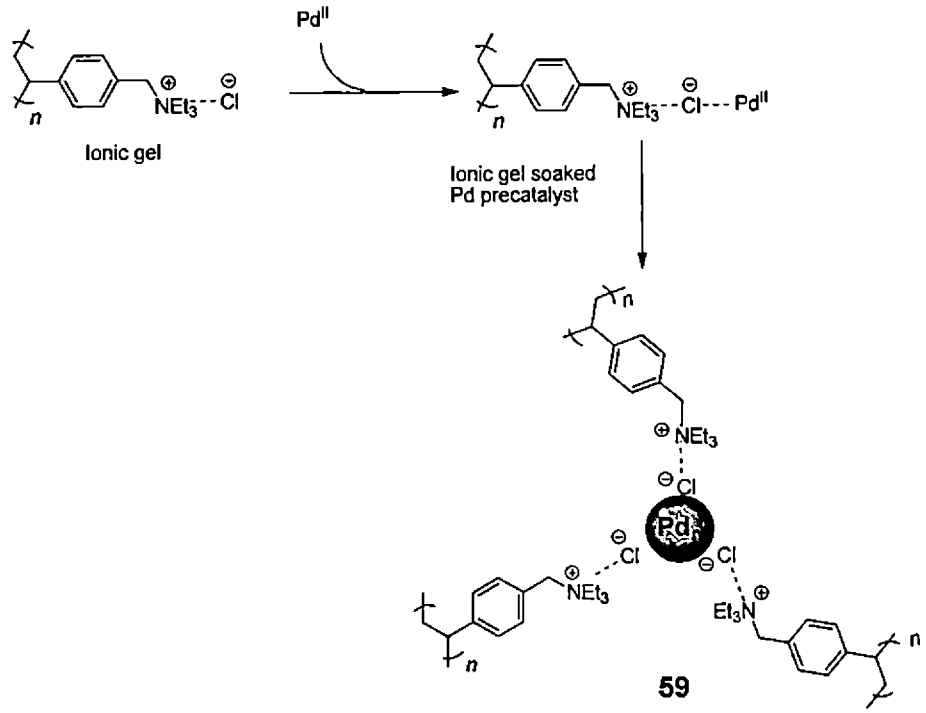
The development of phosphine free new recyclable heterogeneous catalyst is highly desirable catalytic system to dispense the use of expensive and air–sensitive basic phosphines for palladium catalyzed coupling reactions. Choudary *et al.*[165] reported, Mg–Al layered double hydroxides (LDH) and the Merrifiled resin as a surface to anchor the nano palladium(0) catalyst. It not only stabilized the nano palladium particles but also provided the adequate electron density to the anchored palladium(0) species to facilitate the oxidative addition.

LDHs have recently received much attention in view of their potential usefulness as materials,[166] anion exchangers, and more importantly as catalyst. [160d-e,167] The LDHs consist of alternating cationic $M(II)_{1-x}$ $M(III)_x(OH)_2^{x+}$and anionic A^{n-} zH_2O layers.[168] The positively charged layers contain edge–shared metal (II) and metal (III) hydroxide octahedral, with charges neutralized by anions located in the interlayer spacing or at the edges of the lamellae. Tetrachloropalladate $(PdCl_4)^{2-}$ was exchanged onto chloride saturated LDH [composition $Mg(1-x)Alx(OH)_2$ $(Cl)_x.zH_2O$] to obtain a dark brown colored LDH–Pd(II). The supported palladium salts were then reduced with hydrazine hydrate, giving an air stable black powder of nano palladium catalyst which catalyzed various coupling reactions such as Heck, Suzuki, Sonogashira and Stille affording excellent yields.

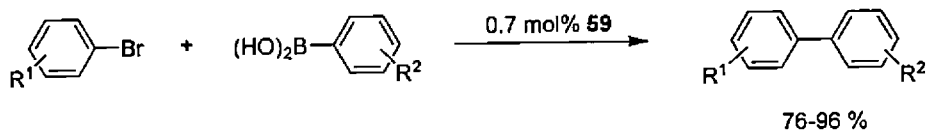
I.3.4.E: Polyionic Gel as a Support

Ionic liquids attracted great attention as alternative reaction media in organic synthesis because it is highly polar which often increase the reaction rate and the product selectivity.[169] To benefit such reactivity advantages offered by the polar ionic environments without suffering from the drawbacks, Thiot *et al.*[86d] investigated the insoluble polyionic gel beads, which constitute a highly polar microenvironment, suitable for both efficient metal scavenging and active heterogeneous catalyst preparation. Palladium and rhodium metals are efficiently soaked onto the polar microenvironment of polyionic gel beads due to strong non–covalent interactions between metal and ions within the polyionic gel (Scheme 55).[86d] The resulting palladium soaked polyionic gel **59** act as an efficient heterogeneous recyclable catalyst for Suzuki coupling (Scheme 56).[86d]

Scheme 55



Scheme 56



Section A

"Pd-Catalyzed transfer hydrogenation (CTH) using recyclable polymer-supported formate (PSF): Efficient and chemoselective reduction of nitroarenes"

I.A.1: Present Work: Background, Objectives and Strategy

Reduction of organic compounds is important synthetically both in the laboratory and in industry. Reduction generally means that the addition of hydrogen to an unsaturated bond or substitution of a group by hydride ion. Reduction of multiple bonds using molecular hydrogen (H_2) in presence of metal catalyst (generally heterogeneous Pd on charcoal or any other homogeneous metal catalysts) has long been known to be a robust procedure. The catalytic transfer hydrogenation reaction can be generalized as follows:

$$DHx + nA \xrightarrow[\text{solvent}]{\text{catalyst}} nAHx + D \qquad (1)$$

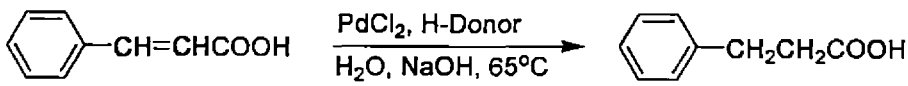
The donor compound DHx can be, in principle, be any organic compound whose oxidation potential is sufficiently low so that the hydrogen transfer can occur under mild conditions. At higher temperatures, especially in the presence of catalysts, almost any organic compound can donate hydrogen (catalytic cracking), but this has little potential for controlled synthesis.

Of all the methods available for addition of hydrogen to organic compounds, heterogeneous catalytic transfer reactions have been relatively underutilized. This lack of popularity can be traced to the relatively meager success of much of the earlier research which suggested that the technique was of only limited scope and could provide only modest yields of products. The earlier pioneering work by Braude[170] was largely ignored because of poor yields and long reactions times, but the situation has changed considerably following the appearance[171] of stimulating review and the introduction of greater catalyst loadings and different hydrogen donors.[172] Another reason for the underutilization of transfer reduction has been very successful exploitation of molecular hydrogen and hydrides for reduction of organic compounds.

The most popular H–donors are alcohols, including chiral ones, and formic acid.[173] More recently, formic acid and its salts such as ammonium formates, potassium formate, alkyl–ammonium formates, in particular triethylammonium formate (TEAF), have proven to be useful sources of hydrogen, due to their solubility in organic solvents.[174] Since dehydrogenation of formic acid derivatives is an irreversible and exothermic process,[175] this usually overwhelms the energetic

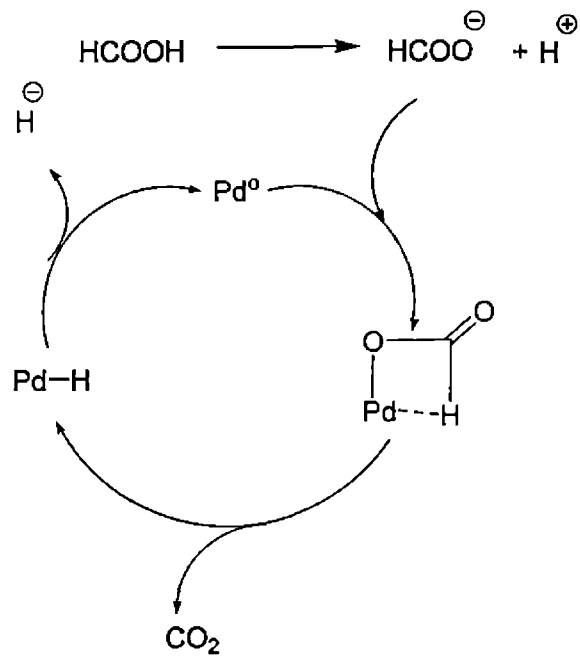
requirement of the reduction process. The use of such H–donors is recommended in reactions where unfavorable energetic balances are expected. Arterburn *et al.*[176] reported a convenient, effective method for the reduction of unsaturated carboxylic acids using non–pyrophoric catalyst $PdCl_2$, HCOOH and NaOH base in water (Scheme 57).

Scheme 57



A plausible mechanism of metal (palladium) catalyzed decomposition of formic acid or its salt is given below (Scheme 58). Formic acid gets ionized into H^+ and $HCOO^-$ in reaction medium. Then the formate anion ($HCOO^-$) is adsorbed on the active site of palladium catalyst and liberates CO_2 together with Pd–H, which supplies H^- (hydride) that is actually responsible for transfer hydrogenation reaction.

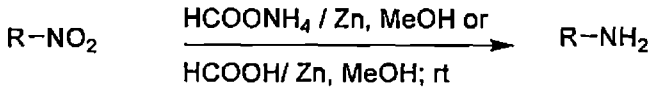
Scheme 58



With the aid of CTH aliphatic and aromatic nitro compounds are selectively reduced to corresponding amine in good yields. Cyclohexene, α–phellandrene, formic acid and its salt are used extensively as H–donor for the reduction of nitro

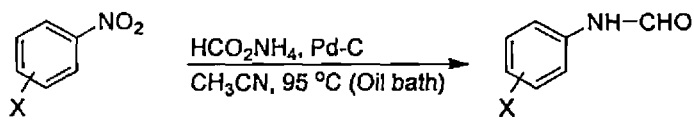
group. Gowda *et al.*[177] have developed the selective reduction of nitro group to corresponding amine as follows (Scheme 59).

Scheme 59



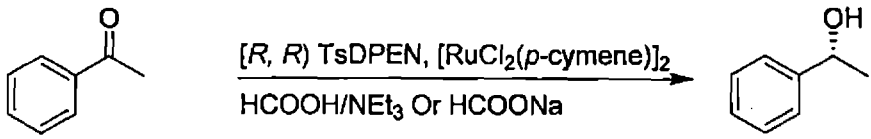
Formanilides have been widely used in the synthesis of biologically active compounds[178] such as N,N–diaryl ureas,[61a] cancer chemotherapeutic agents[178] and quinolone antibacterial.[179] N–Formyl compounds are lewis bases, which are known to catalyze allylation[181] and hydrosilylation.[182] Pratap and Baskaran[183] made an interesting observation that ammonium formate in an aprotic solvent like acetonitrile can function as a formylating agent[184] apart from being a source of hydrogen. Based on this observation, they have developed a novel and highly selective procedure (Scheme 60) for the direct conversion of aryl nitro compounds to formanilides in acetonitrile under CTH conditions.

Scheme 60



Asymmetric transfer hydrogenation, which affords chiral compounds, is one of the most important enantioselective catalytic transformations because of its high enantioselectivity, high product yield and operation simplicity. During the last decades thousands of chiral catalysts have been developed for a great variety of enantioselective transformations, and many of them are known to be highly effective.[185] Asymmetric transfer hydrogenation with ruthenium complexes has recently emerged as an effective approach to asymmetric carbonyl reduction,[186] although metal complexes of samarium,[187] rhodium,[188] iridium[186d,189] have been used successfully. Recently, Lui *et al.*[190] reported ruthenium catalyzed asymmetric transfer hydrogenation of ketones (Scheme 61) in HCOOH/NEt_3, as well in water with HCO_2Na as a hydrogen source, in later combination they used sodium dodecyl sulfate as the phase transfer catalyst. They used (*R,R*)–N–(p–tolylsulfonyl)–1,2–diphenylethylene diamine as a chiral ligand [TsDPEN].

Scheme 61



99% Conversion
97% ee

The selective reduction of functional groups is a common need in organic synthesis. Catalytic transfer hydrogenation (CTH) with the aid of a stable hydrogen donor is a useful alternative method to catalytic hydrogenation by molecular hydrogen.[171a,175,191] The use of a H–donor has some advantages over molecular hydrogen since it avoids the risks and the constraints associated with hydrogen gas as well as the necessity for pressure vessels and other equipment. Formic acids and its salts are frequently employed as hydrogen donor in CTH reactions. Formate anion supported on a polymer backbone acts as a stable hydrogen donor.[192] Ammonium formate that acts as a H–donor in CTH reaction often leads the N–formyl derivatives[184] when nitro group is treated with ammonium formate in presence of Pd catalyst.

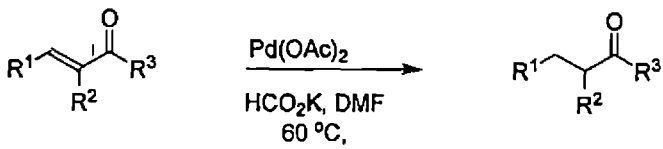
I.A.2: Present Work: Results and Discussion

From the above discussion on catalytic transfer hydrogenation (CTH), it is established that hydrogenation using molecular hydrogenation, which requires special apparatus, the H_2 gas of high purity, might be avoided by using this alternative technique. Although several organic and inorganic compounds have been shown to be useful as H–donors in CTH, formic acid and its salts have occupied a major part of transfer hydrogenations.

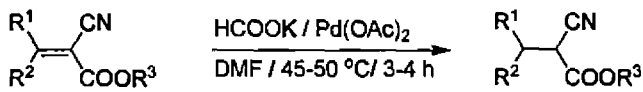
Although ammonium formate ($HCOONH_4$) has been employed as H–donor for the reduction of different functionality, researches from Cacchi's group[192] and from our laboratory[193] have shown that potassium formate (HCOOK) is a better choice than ammonium formate. Cacchi *et al.* reported that a combination of palladium acetate and potassium formate [$Pd(OAc)_2$/HCOOK] is a convenient alternative reductant for selective reduction of α,β–unsaturated carbonyl compounds to corresponding saturated carbonyl compounds (Scheme 62). On the other hand, reduction of conjugated nitriles and cyano ester using molecular hydrogen or

palladium catalyzed hydride–transfer afforded reduction of cyano group as well.[171a] To overcome such problems we used the combination of potassium formate and palladium acetate in DMF for the selective reduction of α, β–unsaturated cyano ester, possessing other sensitive functional groups, into corresponding saturated cyano ester scheme 63.

Scheme 62



Scheme 63



R^3 = Et, Sn(nBu)$_3$

Problems associated with using $HCOONH_4$, such as byproducts originated from reaction with ammonia, sublime–able nature etc., which might cause further reactions with the products,[183] (page 46) could be avoided by replacing with HCOOK. With the advent of immobilized techniques employed successfully in various organic transformations, we were looking for a simple and efficient polymer–supported H–donor to be used in CTH. We reasoned that such supported reagent could be used in excess to drive the reaction to completion and thereafter be separated from the reaction mixture by simple filtration. Various functionalized polymers have emerged as potential solid supports as tools for immobilization of reagents/catalysts. Literature reports reveal that while polymeric supports have been used for anchoring several reducing agents such as borohydrides,[49,50,51] tin hydrides[194] etc., solid supported H–donors have rarely been employed in CTH. To be more specific, ion–exchange resins have rarely been used to immobilize any suitable H–donor, except one report by Desai and Danks.[64] They reported that polymer (ion–exchange resins) supported formate can be used in Rh(I) catalyzed reduction of cinnamic acids (described in page no. 20). But their method lacks general applications and optimization with substrates bearing other reducible groups and other multiple bonds.[64]

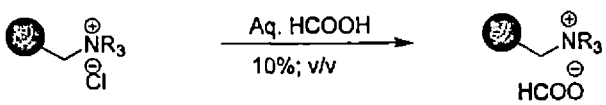
While exploring this area of research, we chose to use commercially available inexpensive Amberlite resins in its chloride form. Amberlite IRA® 900 (or IRA® 420) Cl ion–exchange resin is a cross–linked polymeric resin of styrene and divinylbenzene (1–2%). Functionally, it is aminomethyl polystyrene and its mechanical robustness, chemical inertness and facile functionalization are some of the attractive features of choice. The PSF (Polymer Supported Formate) was prepared by rinsing Amberlite resin (IRA® 420, Chloride form) packed in a column with 10% formic acid solution repeatedly until the washing gave negative response to chloride ion (Scheme 64). Finally the solid surface was washed several times with water and then dried under vacuum. The Amberlite resin formate was initially characterized by FT–IR spectral data, and compared with the corresponding absorption data of other salts (Table 1).

Table 1

Entry	Symmetric Stretching (ν_{max}) cm^{-1}	Anti–symmetric Stretching (ν_{max}) cm^{-1}
$HCOONH_4$	1354	1595
HCOOK	1348	1593
PSF	1344	1593

The resulting resin formate when treated with catalytic amount of palladium acetate (2 mol% with respect to substrate) in DMF, an efficient reductant is generated that can be used for the reduction of nitroarenes (Scheme 65).

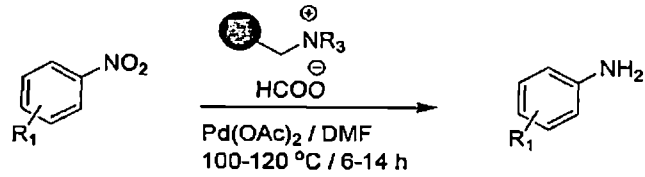
Scheme 64



Amberlite® IRA 420
Chloride form taken in water

Amberlite IRA 420
Formate form

Scheme 65

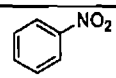
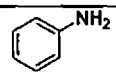
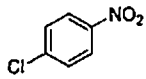
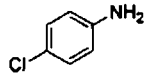
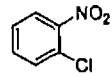
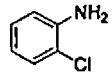
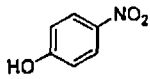
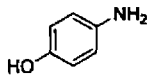
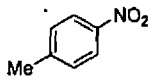
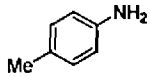
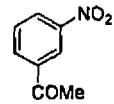
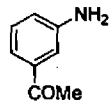
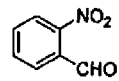
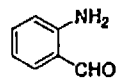
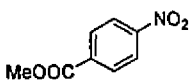
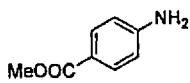
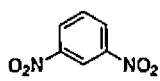
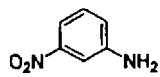
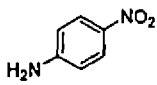
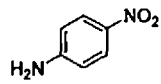
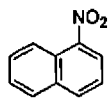
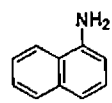
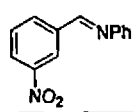
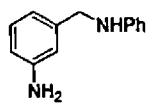


Reduction of nitroarenes to anilines is a synthetically important transformation, both in the laboratory and in industry.[195] A large number of methods have therefore been developed for the reduction of nitro groups. The reagents that are generally employed for the reduction include catalytic hydrogenation[196] with Pd/C, Raney Ni and PtO_2 or dissolving metal reduction, for example, with Sn/HCl,[197] Fe/HCl[198] and Fe/AcOH.[199] Reduction of aromatic nitro compounds with indium powder in ethanolic ammonium chloride[200] or SmI_2[201] results in selective reduction. Most of these methods require high pressure, specific hydrogenation apparatus, harsh reaction conditions or use of expensive metals and therefore lack the desired generality for true synthetic utility. Moreover, poor selectivity was reported in the reduction of aromatic nitro compounds bearing other potentially reducible groups such as carbonyl and halogen substituents.

The reduction of nitro group was carried out using 2 mol% $Pd(OAc)_2$ and formylated (aminomethyl)polystyrene (PSF) in a minimum quantity of DMF at 100–120 °C for 6–14 hours (Table 2). After filtration, extraction with ether followed by chromatographic purification afforded the desired anilines in good yields. The anilines in most cases were identified by comparison of spectroscopic data and/or melting points with literature values. Initially, reduction of nitrobenzene leading to aniline was performed in 82% yield. Concomitant reductive elimination of halogen on aromatic nucleus is often associated with transfer hydrogenation[202] and therefore poor selectivity was observed in the reduction of aromatic nitro compounds bearing halogen substituent. In our conditions, however, *o*– and *p*–chloronitrobenzene underwent reduction of the nitro group chemoselectively leading to corresponding chloroanilines in 71% and 77% yield respectively. *p*–Nitrophenol and *p*–nitrotoluene also underwent smooth reduction of the nitro group leading to the desired anilines. The selective and rapid reduction of nitro groups in the presence of carbonyl functionalities is also a highly valuable transformation in organic synthesis. The development of an efficient solid phase–bound reagent to achieve this goal has attracted considerable effort recently. We therefore investigated reduction of *m*–

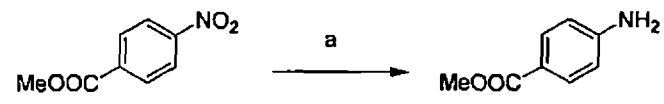
nitroacetophenone, *o*–nitrobenzaldehyde and methyl *p*–nitrobenzoate. The results showed that the formylated (aminomethyl)polystyrene (PSF) can effect highly efficient reduction of nitro groups in the presence of carbonyl functionalities. In transfer reduction of polynitrobenzenes, it was reported that use of much greater proportions of catalyst to substrates afforded only aminonitroarenes.[191C] In a typical case, dinitroarenes (*o*–, *m*–, *p*–) are reported to yield corresponding nitroanilines in 90% yields. At our hand, reduction of *p*–dinitrobenzene gave *p*–nitroaniline in 92% yield and further reduction to *p*–diaminobenzene was not possible. Previously, we[48] observed reduction of the C=N bond of imine using PSF and catalytic $Pd(OAc)_2$. The imine bearing a nitro group was examined under this condition and we obtained reduction of nitro group in addition to the imino group.

Table 2

Entry	Nitroarene	Temp (°C)/ Time (h)	Anilines	Yield[b], (%)
1		100 / 8		82
2		110 / 8		77
3		120 / 12		71
4		100 / 10		78
5		100 / 8		70
6		110 / 8		85
7		120 / 14		66
8		100 / 6		90
9		110 / 10		92
10		120 / 12		No reaction
11		110 / 10		77
12		100 / 12		66

In order to explore the efficiency and stability of the H–donor (PSF), recycling was examined with methyl *p*–nitrobenzoate as a substrate. Reduction proceeds to completion giving excellent yields through three successive recycle runs (Table 3). It should be noted that after separation of the Amberlite resin at the end of the three successive runs, the PSF can be easily generated and could be reused in further reductions.

Table 3



Run	1	2	3
Yield (%)	90	90	84
Time/ h	6	7	8

[a] Reagents and conditions: 2 mol% $Pd(OAc)_2$/ PSF (0.5 g/1 mmol nitro compound)/ DMF (1 ml)/ 100 °C.

I.A.3: Conclusion

In summary, we have demonstrated that polymer–supported formate (PSF) can efficiently perform reduction of nitroarenes leading to anilines under palladium–catalyzed transfer hydrogenation conditions in small–scale reactions. The procedure is chemoselective for nitro group; and several other potentially reducible functionalities such as ketone, aldehyde, ester, and halide substituents on aromatic ring remain unaffected. Other advantages are clean work–up, high yields, and reusability of the PSF for at least three times and regeneration of PSF by reusing the recovered resin.

I.A.4.A: Experimental Section: General

All reactions were performed in screw cap sealed tubes flashed with nitrogen. The minimal reaction times were determined by monitoring TLC of the reaction mixture. Silica gel (60–120 mesh) was used for chromatographic purifications. DMF was dried by distillation over P_2O_5. ^{1}H–NMR and ^{13}C–NMR were recorded at 300 MHz and 75 MHz respectively using Bruker AV–300 spectrometer. TMS was used as an internal standard and NMR spectral values are reported in ppm unit. Amberlite® IRA–420 Cl^- standard grade (14–52 mesh) and palladium acetate were purchased from commercial suppliers and were used directly.

I.A.4.A: Preparation of Polymer Supported Formate (PSF)

Anion exchange resin (Amberlite® IRA–420 Cl^-) was packed on a column and washed with water for two to three times. 10% aq. solution of formic acid was passed through it at slow rate of flow until washing gave the negative response to chloride ion ($AgNO_3$). The resin beads were washed with water for several times and dried

under vacuum. The resin thus obtained was then used for transfer hydrogenation reaction.

I.A.4.B: General Procedure for Reduction of Nitroarene to Aniline

To a mixture of nitroarene (2 mmol) and palladium acetate (0.04 mmol, 2 mol%) in freshly distilled DMF (2 ml) was added PSF (1 g) and the reaction mixture was purged with N_2 for 2–3 min. The screw–cap tube was tightened and placed in a pre–heated oil bath for several hours (Table 2). After completion of the starting material as analyzed by TLC, the reaction mixture was taken in water, filtered through a cotton–bed and washed with ether. The ethereal layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified either by column chromatography over silica gel or by crystallization to afford the desired aniline.

I.A.4.C: Spectral Analysis of Compounds

Entry 1: Aniline

Reaction temp: 100 °C; Time: 8 h,

Yield: 82%, (obtained as liquid); IR (neat): ν_{max} 3379, 2924, 2854, 1605, 1496, 1280 cm^{-1}.

Entry 2: 4–Chloroaniline:

Reaction temp: 110 °C; Time: 8 h,

Yield: 77%; (solid) mp 69–70 °C, (lit[203] mp 70-71 °C); IR (nujol): ν_{max} 3379, 2920, 2862, 1612, 1490, 1458, 1373, 1281 cm^{-1}.

Entry 3: 2-Chloroaniline

Reaction temp: 120 °C, Time: 12 h;

Yield: 71% (obtained as liquid); IR (neat): ν_{max} 3368, 2914, 2862, 1510, 1458 cm^{-1}.

Entry 4: 4–Aminophenol:

Reaction temp: 100 °C, Time: 10 h;

Yield: 78%; (solid) mp 184-185 °C, (lit[203] mp 186 °C); IR (nujol): ν_{max} 3340, 3294, 2910, 2854, 1612, 1512, 1466, 1380 cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ = 6.28 (d, J = 8.24 Hz, 2H), 6.19 (d, J = 8.24 Hz, 2H), 3.00 (bs, 2H); ^{13}C NMR (75 MHz, CDCl3): δ = 148.85, 138.41, 115.58, 115.22.

Entry 5: 4–Toluidine:

Reaction temp: 100 °C, Time: 8 h,

Yield: 70%; (solid) mp 45–46 °C,(lit[203] mp 45 °C); IR (nujol): ν_{max} 3390 cm^{-1}; 1H NMR (300 MHz, CDCl3): δ = 6.97 (d, *J* = 8.24 Hz, 2H), 6.61 (d, *J* = 8.24 Hz, 2H), 3.52 (bs, 2H), 2.24 (s, 3H); 13C NMR (75 MHz, CDCl3): δ = 143.7, 129.6, 127.6, 115.2, 20.3.

Entry 6: 3–Aminoacetaphenone:

Reaction temp: 110 °C; Time: 8 h,

Yield: 85%; Recrystallized from ethanol, yellow plates; mp 98 °C; lit[203] mp 97-99 °C, IR (neat): ν_{max} 3480, 3371, 2910, 2854, 1712, 1670, 1458, 1377 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 7.33–7.19 (m, 2H), 6.87(dd, 1H, *J*=2.4 &1.2 Hz), 6.85 (dd, 1H, *J* = 2.4 & 1.2 Hz), 3.85 (s, 2H), 2.54 (s, 3H); ^{13}C–NMR ($CDCl_3$, 75 MHz): δ = 198.5, 146.9, 138.3, 129.4, 119.7, 118.7, 114.0, 26.6.

Entry 7: 2–Amino benzaldehyde

Reaction temp: 120 °C; Time: 14 h,

Yield: 66%, (obtained as liquid); ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 9.85 (s, 1H), 7.65 (m, 1H), 7.44–7.10 (m, 2H), 6.87 (d, 1H, *J* = 8Hz), 4.05 (s, 2H).

Entry 8: Methyl 4–aminobenzoate

Reaction temp: 100 °C; Time: 6 h,

Yield: 90%, (solid) mp 115 °C; IR (neat): ν_{max} 3460, 3371, 2915, 2858, 1690, 1604, 1458, 1377, 1288 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 7.84 (d, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.7 Hz, 2H), 4.1 (br s, 2H), 3.84 (s, 3H); ^{13}C–NMR ($CDCl_3$, 75 MHz): δ = 167.13, 151.0, 131.0, 119.3, 114.0, 51.5.

Entry 9: 3–Nitroaniline

Reaction temp: 110 °C, Time: 10 h;

Yield: 92%, (pale yellow solid), mp 110–111 °C; lit[203] mp 114 °C; IR (nujol): ν_{max} 3433, 2915, 2858, 1624, 1519, 1458, 1350 cm^{-1}.

Entry 11: 1–Aminonapthalene

Reaction temp: 110 °C, Time: 10 h;

Yield: 77%, (solid), mp 49–50 °C; IR (nujol): ν_{max} 3390, 2900, 2854, 1624, 1458, 1377 cm^{-1}.

Entry 12: N-(3-Aminobenzyl)benzeneaminne

Reaction temp: 100 °C, Time: 12 h;

Yield: 66%; (solid); IR (nujol): ν_{max} 3400, 2935, 2850, 1614, 1530, 1450, cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 7.20–7.15 (m, 2H), 7.09-7.04 (m, 1H), 6.78–6.74 (m, 1H), 6.64–6.55 (m, 3H), 6.5 (s, 1H), 6.41-6.38 (m, 1H), 4.46 (s, 2H), 4.0 (bs, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.2, 141.7, 118.2, 129.6, 129.4, 115.0, 118.6, 117.3, 113.5, 48.5.

Section B

"Co-immobilized formate anion and palladium on a polymer surface: a novel heterogeneous combination for transfer hydrogenation"

I.B.1: Present Work: Background and Objectives

In the previous section, we have discussed the importance of metal–catalyzed transfer hydrogenation and modern trends in developing solid phase immobilized reagents and metal catalysts. The metal–catalyzed transfer hydrogenation using a stable H–donor has been found to be reliable, and the current emphasis on cleaner methods for chemical transformations requires high selectivity, low cost, easy separation and the production of minimum waste. From the practical point of view, a more attractive approach is to develop a heterogeneous catalyst that is efficient for this transformation. Immobilized reagents or immobilized catalyst can afford a clean transformation for laboratory to large–scale operations. While several immobilized reagents or immobilized catalysts have been demonstrated for numerous organic transformations,[7a,204] we envisaged that both the reagent and catalyst could be bound on the same polymer surface and employed for suitable transformations. Such an approach would provide further operational simplicity and economic control.

In CTH, either a source of palladium is required for each operation or it may be supported by a polymer framework and reused several times. We reasoned that the palladium catalyst might be anchored to the PSF so that it could be used and recycled. Palladium is usually attached to a solid surface either by absorption on polymeric surface, by coordination through the ligand or by the relatively new technique of microencapsulation.[11b,123,145,205] In this section, we describe that palladium can be immobilized on the PSF and used effectively in the CTH of a variety of functional groups. Furthermore, the formate (H–donor) and the palladium (the catalyst) supported on a polymeric surface (PSF–Pd) can be recycled at least four times without any appreciable loss of activity.

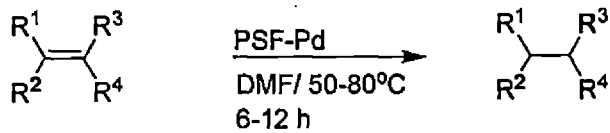
I.B.2: Present work: Results and Discussion

The polymer–supported formate (PSF) was prepared using Amberlyst resin (IRA® 420), the chloride form being exchanged with formic acid.[48] To a suspension of PSF (1 g) in DMF (5 ml) was added palladium acetate (10 mg) and the mixture magnetically stirred under nitrogen at room temperature for 2 h. The PSF beads turned black indicating that the Pd(II) species may have been reduced to Pd(0), and the solvent became colorless. The resulting mixture was filtered, washed with DMF and dried under vacuum overnight. The resulting black PSF beads of resin

supporting both the reagent and palladium catalyst (PSF–Pd) were used for reduction.

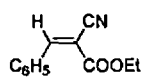
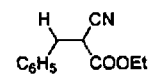
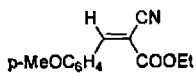
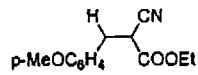
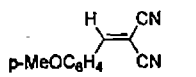
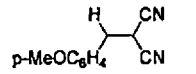
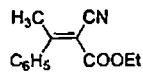
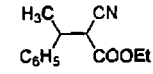
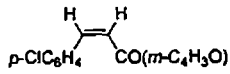
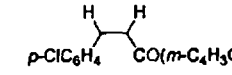
The efficiency and stability of these newly developed PSF–Pd was first examined in the reduction of electron deficient alkenes conjugated with ketones, nitrile and carboxylate ester (Scheme 66). An excess of the polymer supported formate/palladium catalyst (0.5 g of PSF–Pd per mmol of substrate) was employed, with the expectation that other functional groups would not react, to force the reaction to completion. The reduction of C=C double bond proceeded smoothly at 50–80 °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 and isolated in 75–86% yield (Table 4). Other reducible groups such as ketone, nitrile, or halogen and ester group remained unaffected under the reaction condition (entries 1–5 in Table 4).

Scheme 66



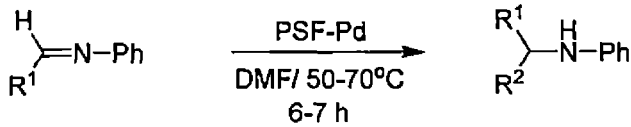
$R^1 = R^2$ = Ph, Ar, H
$R^3 = R^4$ = CN, COOEt, H, COAr'

Table 4

Entry	Substrate	Temp / time (°C / h)	Product	Yield (%)
1		65 / 8		82
2		70 / 8		80
3		50 / 6		86
4		70 / 7		78
5		80 / 12		75

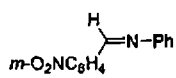
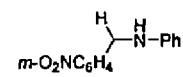
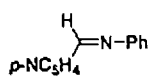
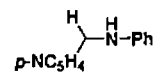
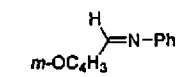
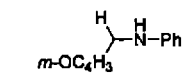
To extend the scope and the generality of the PSF–Pd in CTH, we explore reduction of C=N double bonds of imines (Scheme 67). Since the imines are generally derived from the corresponding aldehydes or ketones, the overall reaction in one pot constitutes a method for direct reductive amination and is an attractive synthetic route to secondary or tertiary amines. Using the PSF–Pd, the imines could be reduced efficiently at 50–70 °C (entries 1-3 in Table 5). A nitro group and a heteroaromatic moiety remained unaffected under the reaction conditions.

Scheme 67



R^1 = Ar

Table 5

Entry	Substrate	Temp. / time (°C / h)	Product	Yield (%)
1		70 / 7		80
2		50 / 6		87
3		60 / 6		78

The reduction of nitroarenes to anilines is a synthetically important transformation both in laboratory and in industry. To broaden the scope of PSF–Pd, reduction of the nitro groups was investigated with nitroarenes as the substrates (Scheme 68). While the nitro group was not reducible at lower temperature (70 °C) it could be reduced at 100–110 °C to yield the corresponding anilines (Table 6). Several other reducible groups such as a halogen, ester or ketone (entries 1–3 in Table 6) were inert to these conditions illustrating a clear advantage in terms of chemoselectivity.

Scheme 68

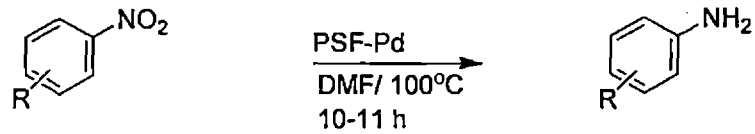
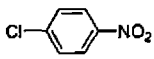
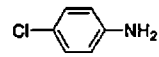
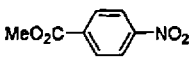
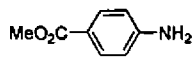
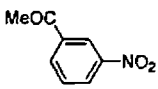
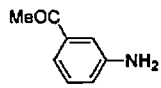
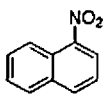
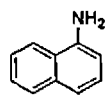
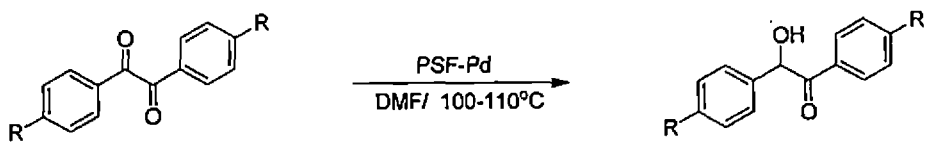


Table 6

Entry	Substrate	Temp / time (°C / h)	Product	Yield (%)
1		110 / 11		76
2		100 / 10		85
3		100 / 10		81
4		100 / 10		75

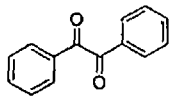
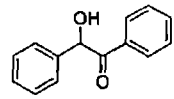
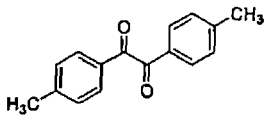
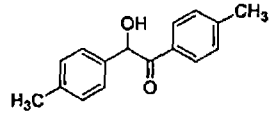
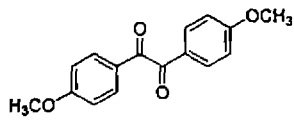
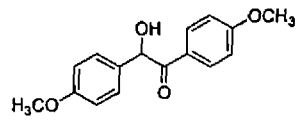
Further applications of this new heterogeneous reductive system were tested with 1, 2–dicarbonyl compounds (Scheme 69). When benzil or substituted benzils were used as the substrate, the reduction of one carbonyl group with PSF–Pd in DMF at 100 °C reached completion after 10–12 h to give corresponding α–hydroxyketone (benzoin) in a 77–88% isolated yield (entries 1-3 in Table 7).

Scheme 69



R = H, Me, OMe

Table 7

Entry	Substrate	Temp./Time	Product	Yield
1		100°C/ 12h		85
2		105°C/ 12h		77
3		110°C/14h		88

The novel combination PSF–Pd was easily used for four successive recycling runs without any significant drop of reactivity. With methyl 4–nitrobenzoate as the substrate, the reduction proceeded to completion giving excellent yields up to four runs.

I.B.3: *Conclusion*

In summary, formic acid as its formate anion and palladium catalyst from palladium acetate has been co-immobilized effectively on an inexpensive Amberlite ion exchange resin. This resin (PSF–Pd) proved to be a versatile and heterogeneous reductive combination for transfer hydrogenation of functionalized alkenes, imines, notroarenes and 1,2–diketones. This new technique also demonstrates high chemoselectivity in the reduction of alkenes, imines and nitro groups, thus establishing an efficient, environmentally benign, economically friendly and sustainable process.

I.B.4: Experimental Section

I.B.4.A: General Procedure: For the Reduction of 1,2-dicarbonyl Compounds

To a solution of 4,4'–dimethoxybenzil (2 mmol) in freshly distilled DMF (2 ml) was added PSF–Pd (1 g) and the reaction mixture was stirred at 110 °C for 10 h under N_2. The reaction mixture was diluted with water (10 ml) and filtered through a piece of cotton. The filtrate was extracted with ether (2 x 15 ml) and the combined organic layers were washed with brine (2 x 10 ml) and dried over Na_2SO_4. Evaporation of volatiles under reduced pressure afforded a residue, which was

purified through column chromatography over silica gel. Elution with ethyl ethyl acetate/light petroleum (1:5) afforded 4,4'–dimethoxy benzoin, as pale yellow crystalline solid in 88% yield. The solid was recrystallized from ethanol and its mp was checked.

I.B.4.B: *General Procedure: For the Reduction of Nitroarenes*

Methyl 4–nitrobenzoate (181 mg, 1 mmol) and 500 mg of PSF–Pd in freshly distilled DMF (1 ml) was taken in a screw capped sealed tube and purged with N_2 for 2–3 min. The screw–cap tube was tightened and placed in a pre–heated oil bath at 100 °C for 10 h. After that the reaction mixture was taken in water (5 ml), filtered through a cotton–bed and washed with ether (3 x 10 ml). The ethereal layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate/light petroleum (1:6) as eluent to furnish desired product (methyl 4–aminobenzoate) as colorless solid in 85% yield.

I.B.4.C: *General Procedure: For the Reduction of C=C Double Bond*

To a mixture of ethyl 2–cyano–3–phenylacrylate (202 mg, 1 mmol) in freshly distilled DMF (1 ml) was added 500 mg of PSF–Pd and the reaction mixture was purged with N_2 for 2–3 min. The screw–cap tube was tightened and placed in a pre–heated oil bath at 65 °C for 8 h. The reaction mixture was then taken in water (2 ml), filtered through a cotton–bed. The water layer was extracted with ether (3 x 10 ml). The organic layer was washed with brine, dried over anhydrous Na_2SO_4. Evaporation under reduced pressure left oil, which was purified through column chromatography over silica gel using ethyl acetate/light petroleum (1:99) as eluent to afford the desired product ethyl 2–cyano–3–phenylpropanoate as colorless oil in 82% yield.

I.B.4.D: *General Procedure: For the Reduction of C=N Double Bond*

N–((pyridin–4–yl)methylene)benzeneamine 182 mg (1 mmol) and 500 mg of PSF–Pd was taken in freshly distilled DMF (1 ml) then N_2 was purged for 2–3 minutes. After that the sealed tube was tightened and placed in a preheated oil bath at 50 °C for 6 h. the reaction mixture was cooled, diluted with water and extracted with ether (3 x 10 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel using with ethyl acetate–light petroleum (1:2) as eluent to furnish the desired product as a yellowish solid in 87% yield.

I.B.4.E: Spectral Analyses

Table: 4

Entry 1: Ethyl 2–cyano–3–phenylpropionate

Reaction time: 8 h, Temp: 65 °C;

Yield: 85%, (obtained as liquid); UV (MeOH): λ_{max} 258.0 nm; IR (neat): ν_{max} 2989, 2349, 2256, 1746, 1262, 1208, 701 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 7.36–7.25 (m, 5H), 4.21 (q, 2H, *J* = 9 Hz), 3.72 (dd, 1H, *J* = 9 and 6 Hz), 3.29–3.13 (m, 2H), 1.24 (t, 3H, *J* = 9 Hz); ^{13}C–NMR ($CDCl_3$, 75 MHz): δ = 165.5, 135.3, 129.1, 128.8, 127.8, 116.2, 62.9, 39.6, 35.7, 13.9.

Entry 2: Ethyl 2–cyano–3–(4–methoxyphenyl)propionate

Reaction time: 8 h, Temp: 70 °C;

Yield: 75% (obtained as liquid); UV (MeOH): λ_{max} 228.6 nm; IR (neat): ν_{max} 2226, 1720 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 7.18 (d, 2H, *J* = 6.7 Hz), 6.86 (d, 2H, *J* = 6.7 Hz), 4.2 (q, 2H, *J* = 7.14 Hz), 3.78 (s, 3H), 3.68 (dd, 1H, *J* = 8.3 6.1 Hz), 3.24–3.09 (m, 2H), 1.26 (t, 3H, *J* = 7.14 Hz); ^{13}C–NMR ($CDCl_3$, 75 MHz): δ = 165.5, 159.0, 130.1, 127.2, 116.2, 114.1, 62.7, 55.1, 39.8, 34.9, 13.8.

Entry 3: 4–Methoxybenzylmalononitrile

Reaction time: 6 h, Temp: 50 °C;

Yield: 80%, (solid) mp 90–92 °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, 2 H, *J* = 8.8 Hz), 6.85 (d, 2 H, *J* = 8.8 Hz), 3.79 (t, 1 H, *J* = 6.8 Hz), 3.7 (s, 3 H), 3.16 (d, 2 H, *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.

Entry 4: Ethyl 2–Cyano–3–phenylbutanoate

Reaction temp: 70 °C, Time: 7 h;

Yield: 78%; (obtained as liquid); UV (MeOH): λ_{max} 242.2 nm, IR (neat): ν_{max} 2243, 1747, 1595, 1446, 1250 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 7.43–7.22 (m, 5H), 4.12 (q, 2H, *J* = 7.1 Hz), 3.70–3.61 (m, 1H), 3.55–3.48 (m, 1H), 1.50 (d, 3H, *J* = 7.1 Hz).

Entry 5: 1–(4–Chlorophenyl)–3–(furan–2–yl)propan–1–one

Reaction temp: 80 °C, Time: 12 h;

Yield: 75%; (obtained as 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, 2 H, *J* = 7.8 Hz), 7.47 (d, 2 H, *J* = 7.8 Hz), 7.57 (m, 1 H), 7.44 (m, 1 H), 7.31 (m, 1 H), 3.34 (t, 2 H, *J* = 7.8 Hz), 3.09 (t, 2 H, *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.

Table: 4

Entry 1: N-(4-nitrobenzyl)benzeneamine

Reaction temp: 70 °C, Time: 7 h;

Yield: 80%; (orange solid), IR (neat): ν_{max} 3409, 2927, 2858, 1604, 1530, 1454, 1350 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 8.24 (s, 1H), 8.13–8.1 (m, 1H), 7.74–7.70 (m, 1H), 7.50 (t, 1H, *J* = 7.9 Hz), 7.20–7.15 (m, 2H), 6.78–6.74 (m, 1H), 6.64–6.61 (m, 2H), 4.46 (s, 2H), 2.17 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.0, 141.8, 133.3, 129.6, 129.4, 122.3, 122.2, 118.6, 113.3, 47.8.

Entry 2: N-((pyridin-4-yl)methyl)benzeneamine

Reaction temp: 50 °C, Time: 6 h;

Yield: 87%, (pale yellow solid), IR (neat): ν_{max} 3995, 2940, 2858, 1458, 1377 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 8.55 (d, 2H, *J* = 6 Hz), 7.13 (d, 2H, *J* =6 Hz), 7.17 (t, 2H, *J* = 7.5 Hz), 6.741 (t, 1H, *J* = 7.5 Hz), 6.59–6.55 (m, 2H), 4.39 (s, 2H), 1.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.6, 149.5, 147.4, 129.4, 122.2, 118.2, 112.9, 47.1.

Entry 3: N-((furan-3-yl)methyl)benzenamine

Reaction temp: 60 °C, Time: 6 h;

Yield: 78%, (obtained as liquid); IR (neat): ν_{max} 3402, 1604, 1504, cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 7.56 (dd, 1H, *J* =1.83 and 0.8 Hz), 7.24–7.16 (m, 2H), 6.77–6.67 (m, 3H), 6.31 (dd, 1H, *J* = 3.2 & 1.82 Hz), 6.23 (dd, 1H, *J* =3.2 & 0.8 Hz), 4.31 (s, 2H), 2.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.6, 147.4, 142.0, 129.2, 118.2, 113.2, 110.3, 107.1, 41.6.

Table: 6

Entry 1: 4-Chloro aniline

Reaction temp: 110 °C, Time: 11 h;

Yield: 76%, (solid) mp 69–70 °C; IR (nujol): ν_{max} 3379, 2920, 2862, 1612, 1490, 1458, 1373, 1281 cm^{-1}.

Entry 2: 4–Amino methyl benzoate

Reaction temp: 100 °C, Time: 10 h;

Yield: 85% (solid); mp 115 °C; IR (neat): ν_{max} 3460, 3371, 2915, 2858, 1690, 1604, 1458, 1377, 1288 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 7.84 (d, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.7 Hz, 2H), 4.1 (br s, 2H), 3.84 (s, 3H); ^{13}C–NMR ($CDCl_3$, 75 MHz): δ = 167.13, 151.0, 131.0, 119.3, 114.0, 51.5.

Entry 3: 3–Aminoacetaphenone

Reaction temp: 100 °C, Time: 10 h;

Yield: 81% (solid), mp 98 °C; IR (neat): ν_{max} 3480, 3371, 2910, 2854, 1712, 1670, 1458, 1377 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 7.33–7.19 (m, 2H), 6.87 (dd, 1H, *J* =2.4 &1.2 Hz), 6.85 (dd, 1H, *J* =2.4 & 1.2 Hz), 3.85 (s, 2H), 2.54 (s, 3H); ^{13}C–NMR ($CDCl_3$, 75 MHz): δ = 98.5, 146.9, 138.3, 129.4, 119.7, 118.7, 114.0, 26.6.

Entry 4: 1–Aminonapthalene

Reaction temp: 110 °C, Time: 10 h;

Yield: 77% (solid), mp 49–50 °C; IR (nujol): ν_{max} 3390, 2900, 2854, 1624, 1458, 1377 cm^{-1}.

Table: 4

Entry 1: Benzoin

Reaction temp: 100 °C, Time: 12 h;

Yield: 85%; (white solid), mp 136 °C; IR (nujol): ν_{max} 3409, 1681, 1458 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 7.91 (d, 2H, *J* =7.1 Hz), 7.52–7.47 (m, 1H), 7.40–7.10 (m, 7H), 5.95 (s, 1H), 4.58 (br s, 1H).

Entry 2: 4,4'–Dimethyl benzoin

Reaction temp: 105 °C, Time: 12 h;

Yield: 77%; (solid), mp 88 °C; IR (nujol): ν_{max} 3456, 3379, 1674, 1458 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 300 MHz): δ = 7.8 (d, 2H, *J* =8.2 Hz), 7.21 (d, 2H, *J*= 8 Hz), 7.12 (d, 2H, *J* =8.2 Hz), 7.07 (d, 2H, *J* =8 Hz), 5.89 (s, 1H), 4.45 (br. s, 1H), 2.28 (s, 3H), 2.23 (s,

3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6, 144.9, 138.3, 136.5, 131.0, 129.8, 129.4, 128.8, 127.7, 75.8, 21.7, 21.2.

Entry 3: 4,4'–Dimethoxy benzoin

Reaction temp: 110 °C, Time: 14 h;

Yield: 88%, (solid) mp 111–112 °C; FT–IR (nujol) ν_{max} 3466, 1666, 1597, 1512, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 9 Hz, 2H), 7.26 (d, *J* = 8.7 Hz), 6.87 (d, *J* = 9 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.87 (s, 1H), 4.85–4.3 (br s, 1H), 3.82 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 163.9, 159.6, 131.8, 131.5, 129.0, 126.2, 114.5, 113.9, 75.2, 55.4, 55.2.

Section C

"Palladium Supported on Poly-ionic Resins as Efficient, Ligand-free & Recyclable Catalyst for Heck, Suzuki-Miyaura and Buchwald-Hartwig Reactions"

I.C.1: Present Work: Background, Objectives and Strategy

Transition metal–catalyzed organic reactions constitute the central part of contemporary organic synthesis. In particular, palladium–catalyzed carbon–carbon and carbon–heteroatom (N and O) bond–forming processes represent the foremost reactions in the arena of organic process development.[72] While the Heck, Suzuki–Miyaura, Sonogashira reactions are excellent tools for carbon–carbon coupling reactions between aryl halides or triflates and suitable partners, Buchwald–Hartwig developed the expeditious means for carbon–heteroatom (N and O) bond–forming reactions.[72d] Over the last decade, commendable research has been done to achieve significant developments and to establish practical methodologies. Widespread uses of the palladium–catalyzed coupling reactions are found in modern organic synthesis, because the resulting coupled products often find good applications in the preparation of materials,[206] pharmaceuticals,[207] and other bioactive compounds.[208]

Since the common facet of these homo– and hetero–coupling reactions is the palladium, which act as the catalyst, numerous attempts have been made to employ it either as soluble homogeneous[16b,209] or as immobilized heterogeneous Pd–catalysts. [7a,74a,210] Whereas the soluble homogeneous Pd–catalysts are found to be significantly active in various coupling reactions, there are some drawbacks such as, less active or inactive colloidal species, unrecoverable and possibility of contamination with the products, cost etc. that are often encountered in the course of the reactions.[210] Consequently, several approaches have been explored utilizing various immobilization techniques on solid or colloidal supports, and aiming toward efficient recovery and reuse of the active catalysts. The major thrust for achieving success in designing and developing polymer–supported metal catalysts broadly include: improved stability within the polymer matrix, increased selectivity for reactions, enhanced regioselectivity, reusability for several runs and superior asymmetric induction due to site–specific chiral catalysts. Attempts have been made to surmount the problems pertaining to high reaction temperatures, separation of pure products, recovery and reuse of Pd–complexes by the use of heterogeneous palladium systems. Pd on carbon and Pd on different metal oxides,[74b,76b,212] silica,[92a,213] zeolites,[75c,155,158b,114] molecular sieves,[75b] hydrotalcite[162] and sepiolites[135-136,215] were found to be suitable catalysts for some reactions. Several groups have examined the use of polymer/dendrimer supported Pd–catalysts, where the immobilization of palladium has been achieved through covalent and non–covalent linkages and using coordinating phosphine ligands attached to the polymeric

framework.[109,112,216] A general review on heterogenization of transition metals (Pd, Ru, Rh etc.) under different modes have been presented in Section–I. However, there has been significant interest in the use of supported nanopalladium complexes as catalysts for C–C coupling reactions.[165,217] More recently, heterogeneous Pd–catalysts have been developed through microencapsulation technology, optionally with activating ligands, within a highly cross–linked polyurea matrix,[11b,145,95e,123,218] polystyrene and other copolymer (polymer incarcerated method to immobilize Pd),[219] cyclodextrine (CD),[220] and other dendrimer/polymer surfaces.[221] Advantages of such polymer–supported Pd–catalysts are focused with emphasis on several factors e.g. very low residual metal and ligand level in final products, easy recovery by filtration, re–use and recycling, high activity, selectivity and compatibility. While some of these supported catalysts exhibit excellent activity and selectivity in various reactions, most of them suffer from general compliance with the conditions and often require difficultly accessible and well–designed polymeric frameworks. Therefore, procedural complexity and versatile applicability have remained seemingly important and major thrust for further investigations in this field of research.

Recently, it has been shown that palladium could be immobilized on the surface of suitably designed ion–exchange resin.[222] The Amberlite® resin (chloride form) was first exchanged with formate anion to prepare the Amberlite resin formate (symbolized as ARF), which was then treated with catalytic amounts of $Pd(OAc)_2$ in dimethyl formamide (DMF). The grayish beads of ARF were soon found to turn black, possibly with the deposition of palladium on the resin surface. Since the resulting Amberlite resin formate soaked palladium complexes (symbolized and referred to herein as ARF–Pd) possess both the reducing source and suitable metal catalyst (at this time, the formate anion and the palladium), that was envisaged on using ARF–Pd in catalytic transfer hydrogenation. Indeed, ARF–Pd showed high efficiency in catalytic transfer hydrogenation of functionallzed C–C or C–heteroatom (N and O) double bonds. Thus, initial quest to explore the efficiency of the ARF–Pd in transfer hydrogenation revealed that it could be utilized as a stable hydrogen donor in presence of the palladium metal anchored to the polymeric matrix. As a result, ARF–Pd suffices to perform catalytic transfer hydrogenation (CTH) of a variety of functional groups, such as alkenes, nitroarenes, imines and 1,2–dicarbonyl compounds[221] (described in part I section B; page).

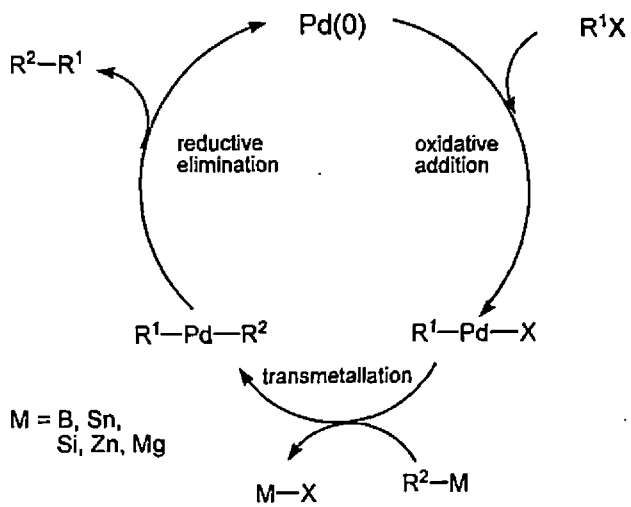
Motivated by the excellent activity of ARF–Pd as potential reductive system coupled with high selectivity and reusability in CTH and in view of low–cost starting

materials and its easy preparative procedures, it might be worth investigating further to develop this ARF–Pd as a viable heterogeneous phosphane– or *ligand–free* palladium–catalyst for various C–C & C–N coupling reactions. Moreover, use of ion–exchange resin for scavenging metals (preferably transition metals) and subsequent applications in catalysis has not been explored as compared to other types of polymeric surfaces.[79a-b,223] In general; carbon–carbon coupling reactions catalyzed by solid–supported palladium has been believed to follow the usual reaction mechanism, as shown for coupling of organometallics with organohalides or –triflates in scheme 70.[224]

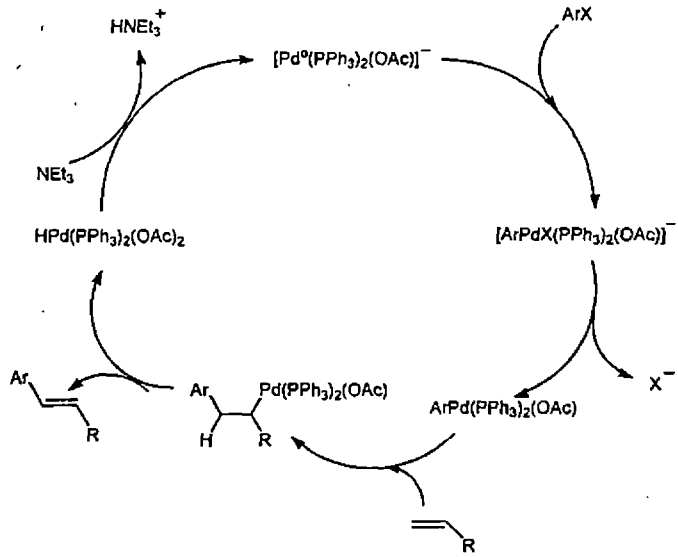
Each of the steps of the catalytic cycles can be rate–determining, depending on the type of substrate and catalyst. As far as the interaction of the palladium catalyst with the substrate and intermediates is concerned, several mechanisms have to be taken into consideration.[225] Thus the reaction can take place at the surface of solid[226] palladium as a truly heterogeneous reaction.

Scheme 70

General Catalytic Cycle for the Palladium Catalyzed Coupling Reaction



Palladium Catalyzed Heck Reaction Cycle Proposed by Amatore and Jutand



I.C.2: Present Work: Result and Discussion

I.C.2.A: Catalyst Preparation

The ARF was prepared by washing Amberlite® IRA 900 (Chloride form) packed in a column with 10% aqueous formic acid solution repeatedly until the washings gave a negative response for chloride ion (with aqueous $AgNO_3$ solution). Finally, the solid was washed several times with water and then dried under vacuum.[48] To obtain the palladium dispersion on the resin, both palladium acetate [$Pd(OAc)_2$] and sodium tetrachloropalladate [Na_2PdCl_4] were used. Thus, a suspension of ionic resin (1 g) was gently stirred at 50 °C in a solution of either $Pd(OAc)_2$ (5 μmol) or Na_2PdCl_4 (5 μmol) in DMF for 3 h. The orange or dark orange color of the solution became totally colorless, whereas the ARF beads became black. Such colour changes were not observed while using the Amberlite® IRA 900 (Chloride form) and $Pd(OAc)_2$ or Na_2PdCl_4 in control experiments, which led to suggest that palladium(II) species were reduced to palladium(0) in presence of the counter anion (formate as the reducing source) and then soaked on the resin surface. The black resin beads of the ARF–Pd were filtered and washed repeatedly with water, vacuum dried and used for subsequent studies.

I.C.2.B: Characterization of the ARF-Pd

While studying the catalytic efficiency in different cross-coupling reactions, vis-à-vis, characterization of this immobilized species [ARF–Pd] was undertaken by various spectroscopic and other methods in order to get an idea about the nature of

palladium distribution on the polymeric resin surface (ARF–Pd). Herein, characterization of the surface, mode of deposition of palladium, catalytic efficiency, recycling ability and leaching effect has been presented. The details of our findings along with possible interpretations have also been given.

I.C.2.B.1: FT-IR Spectroscopy

The ARF–Pd was first characterized by IR spectroscopy. Carboxylic acid salts are most accurately represented with the resonance stabilized carboxylate anions that contain two identical C---O bonds, and therefore give anti–symmetric and symmetric stretching absorptions. The FT–IR spectral data for the carboxylate anion of different formate salts, ARF and the ARF–Pd are given in Table 8. The spectrum of ARF–Pd was compared with those of ammonium formate ($HCOONH_4$), potassium formate (HCOOK) and the ARF. The absorptions due to anti–symmetric stretching of the carboxylate anions of $HCOONH_4$, HCOOK and ARF were observed in the range of 1595–1593 cm^{-1}, while that of ARF–Pd at 1653 cm^{-1}. Similar observations were noticed in the case of symmetric stretching of the carboxylate anions. The significant increase of ν_{max} for ARF–Pd indicated possible deposition and binding of the palladium metal with the formate carbonyl species.

Table 8: FT–IR data for the carboxylate anion (KBr)

Entry	Symmetric Stretching (ν_{max}) cm^{-1}	Anti–symmetric Stretching (ν_{max}) cm^{-1}
$HCOONH_4$	1354	1595
HCOOK	1348	1593
ARF	1344	1593
ARFPd	1404	1653

I.C.2.B.2: ^{13}C MAS NMR Spectroscopy

The MAS ^{13}C NMR spectra of ARF and ARF–Pd are recorded with special attention to the δ position of the carbonyl carbon (formate). As compared to the formate carbonyl carbon of ARF, the same has shown nearly δ 10 ppm upfield shift for ARF–Pd. Thus, the carbonyl carbon in ARF appeared at about δ 170 ppm (figure 2) while that of ARF–Pd displayed nearly at δ 160 ppm (figure 3). Such upfield

shifting in ARF–Pd may be attributed to binding of palladium with the formate carbonyl group.

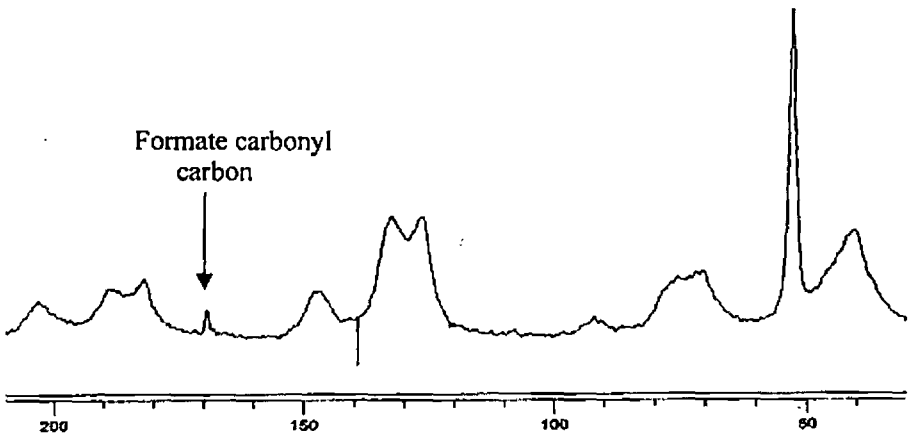


Figure 2: *^{13}C MAS NMR of ARF*

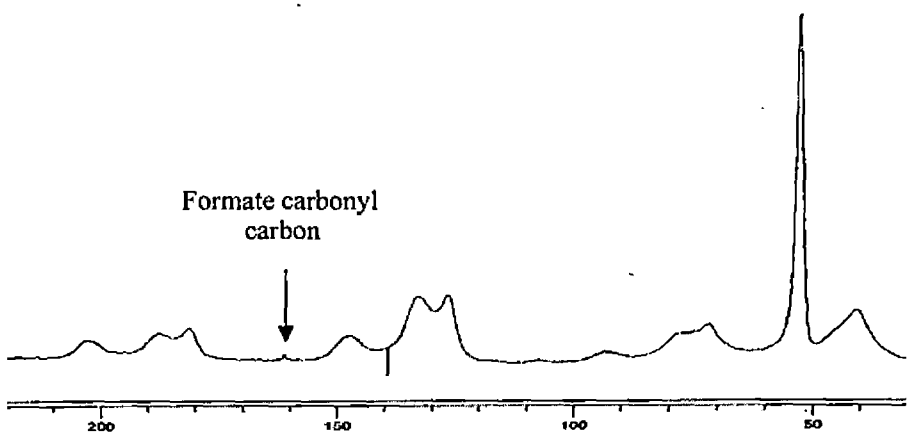
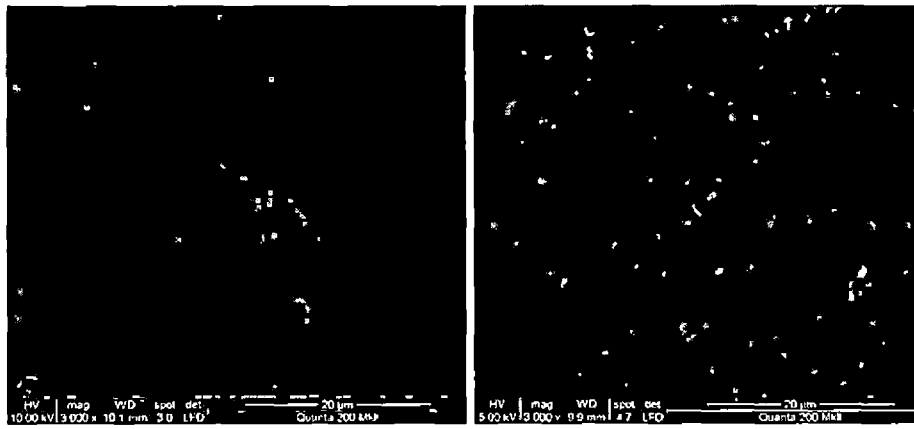


Figure 3: *^{13}C MAS NMR of ARF–Pd*

I.C.2.B.3: Scanning Electron Micrographs

Scanning electron micrograph (SEM) of ARF–Pd was examined at different magnifications using "Quanta 200, 50X50X25 Eucentric" scanning electron microscope. The SEM images illustrate clearly the differences in surface and shape characteristics and one might explain that palladium has been deposited in the surface of the resins (figure 4). From the SEM pictures of ARF–Pd at different magnifications, it has been found that the particle size of palladium is in the range from 0.375 to 1.857 μm. Comparative SEM images of ARF and ARF–Pd at same magnification (3000X) are shown below (figure 4).



ARF **ARF–Pd**

Figure 4: Comparative SEM micrograph images of ARF and ARF–Pd [prepared from $Pd(OAc)_2$ 10 mg/g ARF]

I.C.2.B.4: X-Ray Photoelectro Spectroscopic (XPS) Studies

The presence of palladium in the surface was confirmed by X-ray photoelectron spectroscopic (XPS) survey spectra. Binding energy (BE) of palladium 3d line indicates that the main component of palladium is in the metallic form (335.7 eV), while the minor part may be assigned to palladium(II) cation (337.8 eV). Two lines for palladium(0) [335.7 eV ($3d_{5/2}$) and 340.8 ($3d_{3/2}$) eV], which are observed in the XPS spectrum of ARF–Pd, conform to the observations reported in other related studies.[227] Minor presence of palladium(II) species might be possible from the fact that the palladium(II) salts were not completely reduced during the preparation of ARF–Pd.

XPS Survey Spectrum and Palladium 3d Spectrum of the Precatalyst ARF-Pd

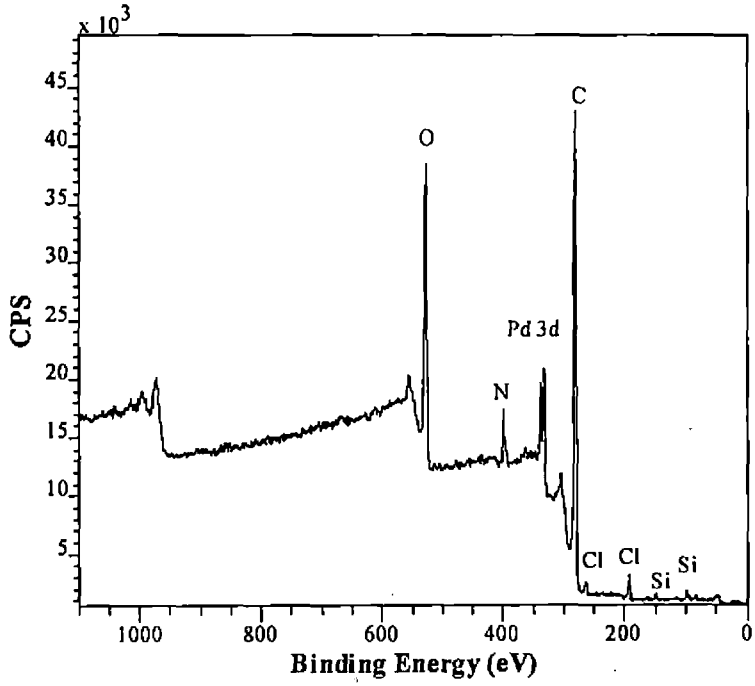


Figure 5: *Survey spectrum of ARF–Pd precatalyst prepared from $Pd(OAc)_2$ (10 mg/g ARF).*

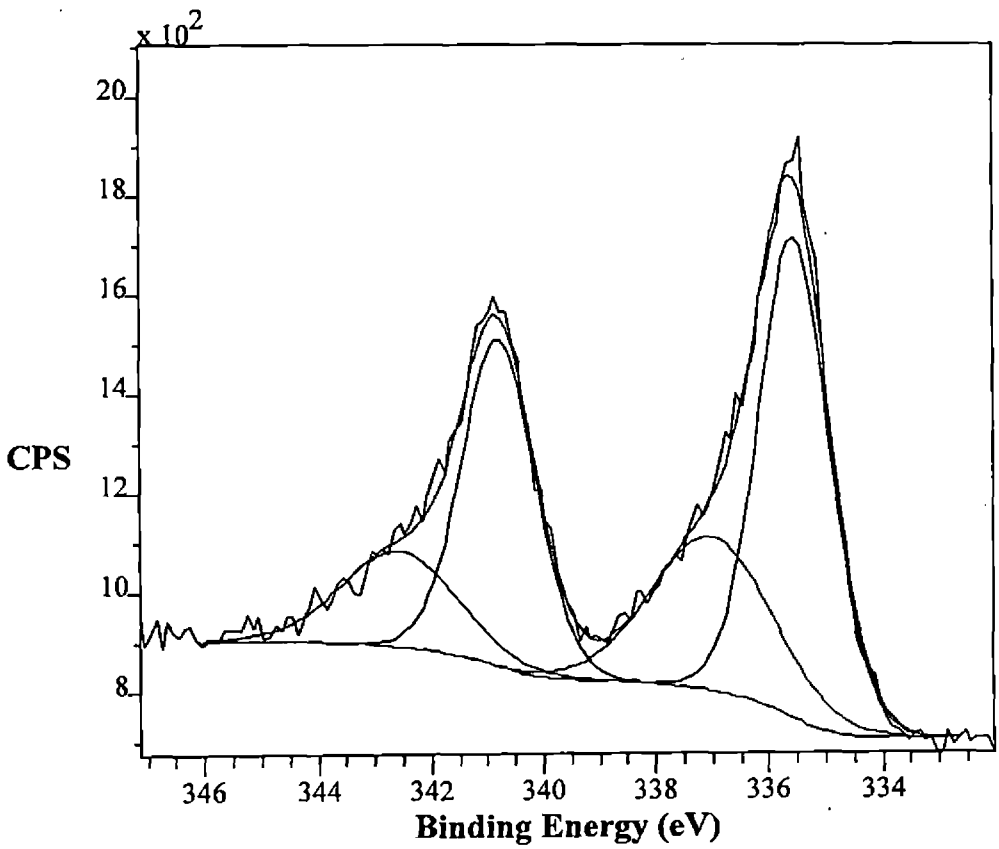


Figure 6: *Pd 3d spectrum of fresh ARF–Pd precatalyst prepared from $Pd(OAc)_2$ (10 mg/g ARF)*

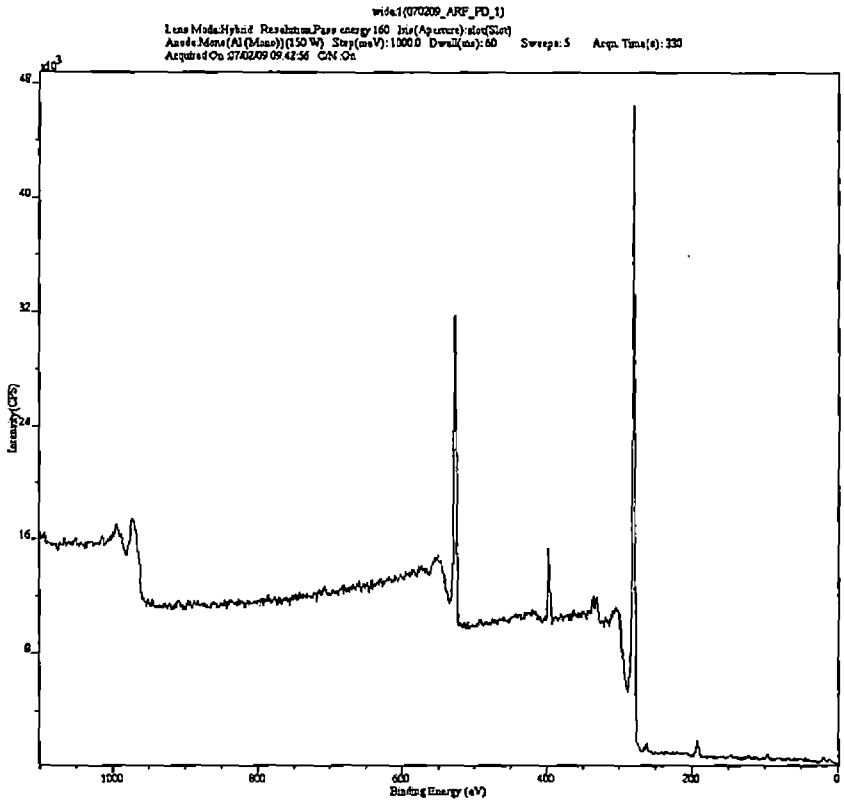


Figure 7: Survey spectra of ARF–Pd precatalyst prepared from $Pd(OAc)_2$ (7.5 mg/g ARF)

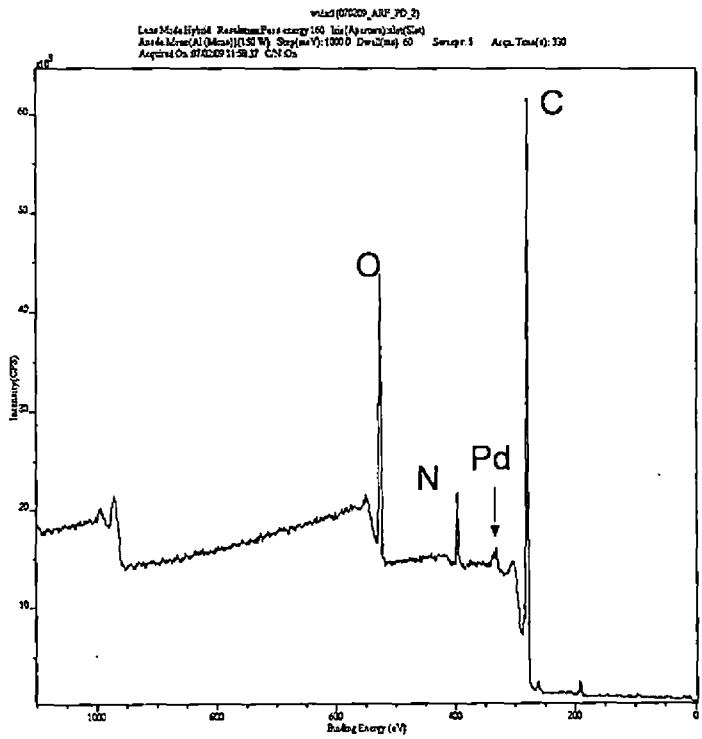


Figure 8: Survey spectra of ARF–Pd precatalyst prepared from $Pd(OAc)_2$ (7.5 mg/g ARF) after second treatment with DMF.

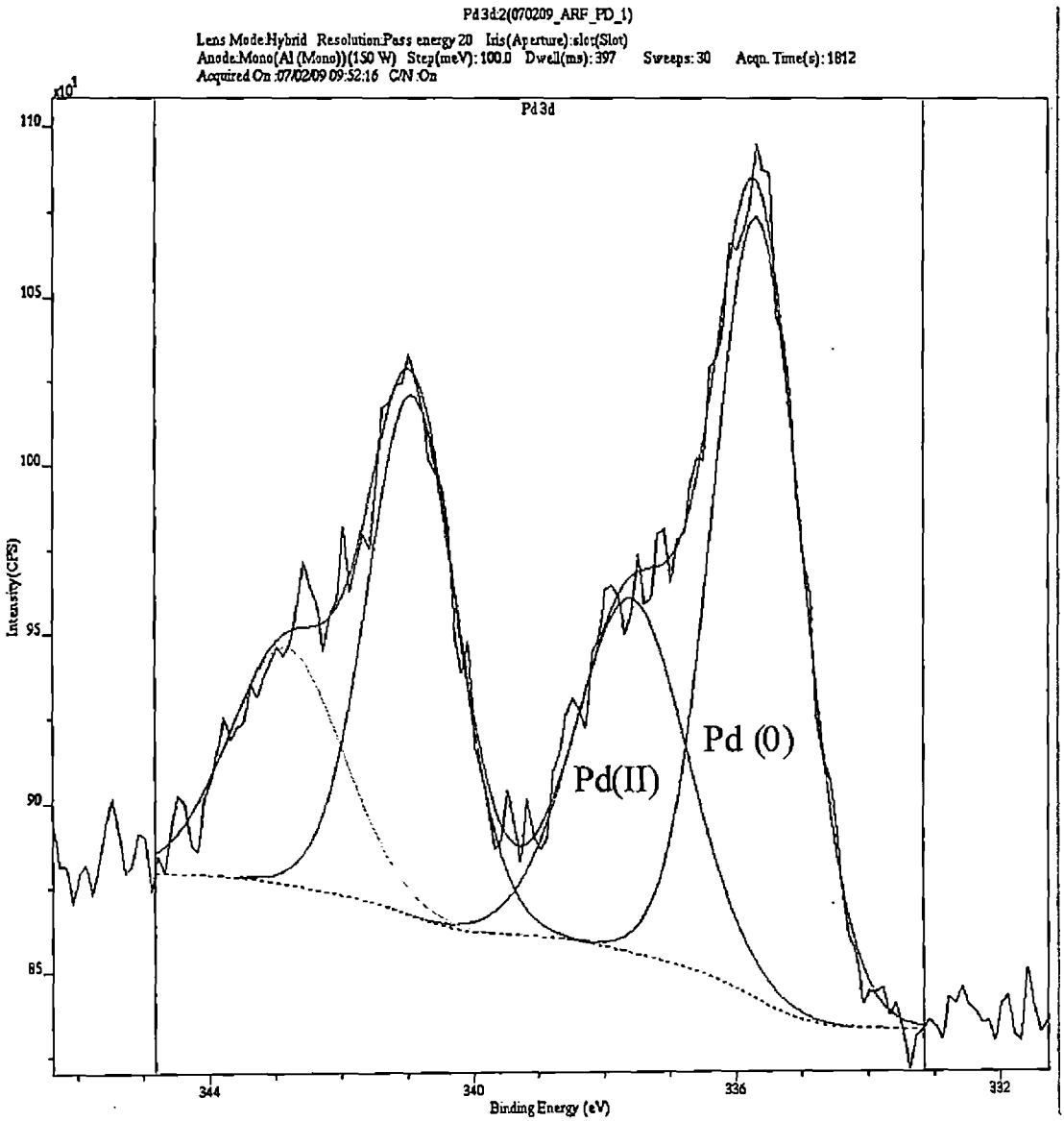


Figure 9: Pd 3d spectrum of fresh ARF–Pd

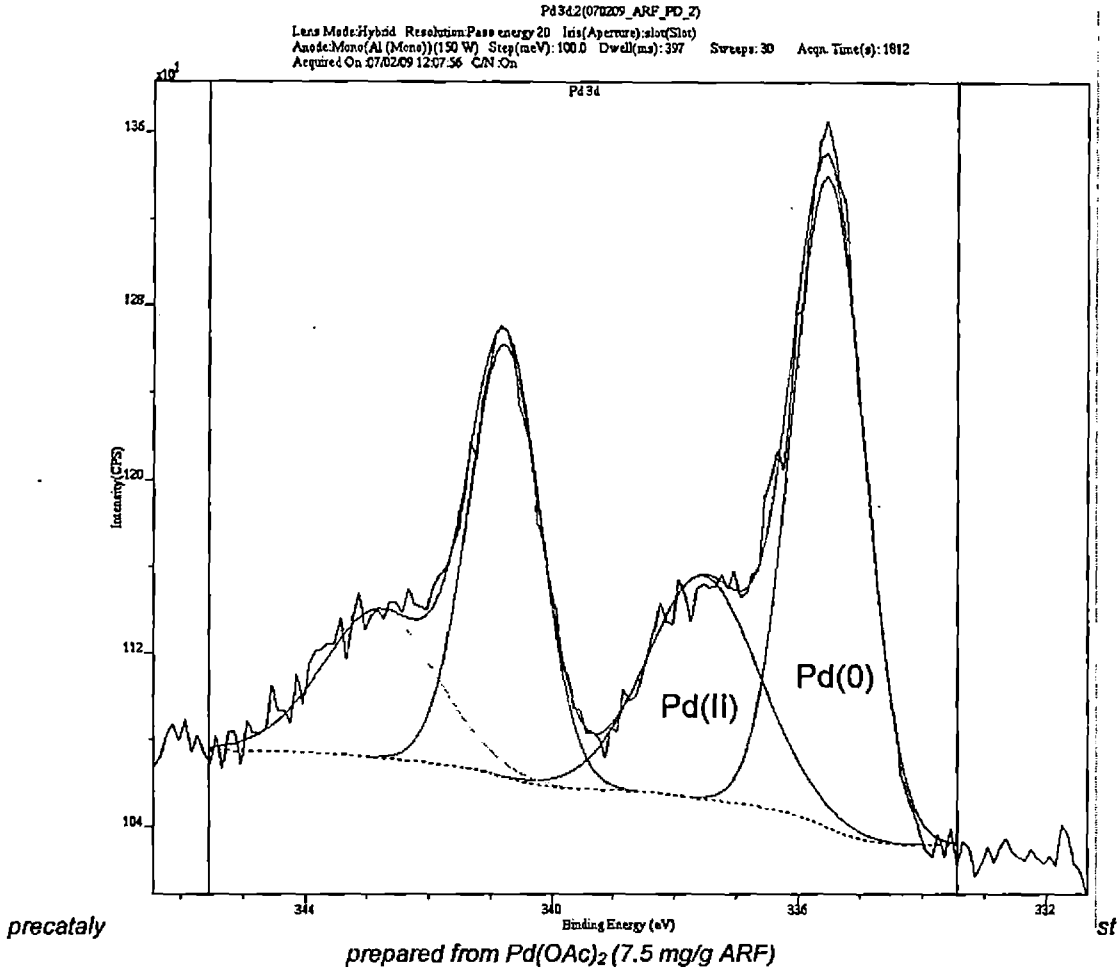


Figure 10: *Pd 3d spectrum of ARF–Pd precatalyst prepared from $Pd(OAc)_2$ (7.5 mg/g ARF) after second treatment with DMF*

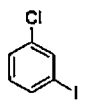
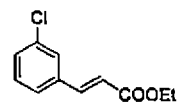
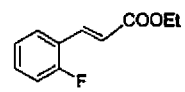
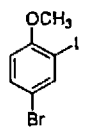
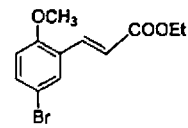
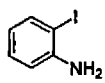
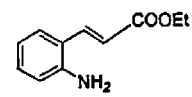
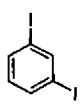
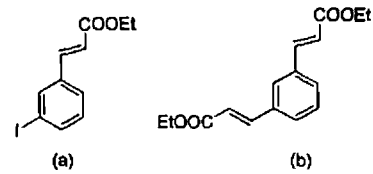
I.C.3: Catalytic Activity: Heck Coupling Reaction

The catalytic activity of ARF–Pd was first examined in the Heck coupling reactions (Scheme 71). As a first model case, we chose the reaction of 3–chloroiodobenzene with ethyl acrylate. The Heck coupling[207b] between these two coupling partners is known to give high yields of the coupled product in presence of both homogeneous and other heterogeneous palladium catalysts. Using our heterogeneous catalyst, ARF–Pd, and carrying out the reaction in presence of triethylamine and toluene, we were able to isolate *trans*–ethyl–3–chlorocinnamate in 86% yield. The *trans*–stereochemistry of the double bond was assigned on the basis of the value of the coupling constant (J = 15.9 Hz). As observed in some reports,[75d] we did not see any other products in this reaction when characterized by NMR. The product was isolated in pure form simply by filtering off the resin–bound catalyst

followed by chromatographic purification of the concentrated residue. Similar reactions were conducted with other substituted iodoarenes and the results are summarized in Table 9. In each case, the NMR spectra indicated *trans* double bonds of 2–aryl acrylates, the *J* values range from 15.6–16.2 Hz. Interestingly, the bromo–substituent remained unchanged, which is typically seen for other halogens like chloro or fluoro groups on the aromatic moiety, thereby allowing more selectivity in Heck coupling reaction. The *ortho*–substituent did not cause any steric inhibition, as usually experienced in other coupling reaction, which may be attributed to high activity of the catalyst. In the case of 3–diodobenzene, both the mono– and *bis*–coupled products were isolated in the ratio of 1:2, when performed the reaction at 100°C for 7 h.

Scheme 71

Table 9: Heck Coupling of aryl iodides with ethyl acrylate using ARF-Pd.

Entry	Haloaromatics	Conditions[a] Temp./ Time	Product(s)	Yield [%][b]
1		90°C/ 5h		86
2		90°C/ 5h		81
3		90°C/ 10h		90
4		95°C/ 9h		73
5		100°C/ 7h	 (a) (b)	30 (a) 65 (b)

[a] The reactions were carried out in toluene as the solvent; ARF-Pd was used 300 mg per mmol of the bromoarene.
[b] Yields are of isolated pure compounds, characterized by IR and NMR spectral data.

I.C.4: Catalytic Activity: Suzuki-Miyaura Coupling Reaction

The Suzuki–Miyaura coupling reaction between bromoarenes and aryl boronic acid is considered as one of the most important methods for preparing

biaryls.[71,207a] While discovery of this reaction dates back to over twenty five years, present interest is primarily associated with the development of the more potential and versatile catalysts. The use of highly active catalysts at low loadings not only minimizes the amount of palladium for reasons of cost but also offers advantages to put minimum efforts to obtain the products free from the catalyst. On attempting the Suzuki–Miyaura reaction (Scheme 72) with ARF–Pd, we first conducted coupling of 4–bromo–2–methyl anisole with phenyl boronic acid using the catalyst and base in DMF. Heating the mixture at 110°C for 5 h under N_2 followed by removal of ARF–Pd by filtration and chromatographic purification of the residue furnished the desired unsymmetrical biphenyl in 82% yield. High activity of the catalyst coupled with our interest in multi–couplings in one–pot reaction,[228] put our attention to evaluate the activity of ARF–Pd in one–pot sequential couplings of di– and tri–bromoarenes. Indeed, we were able to prepare *bis* and tris–coupled aryl benzenes in good to–excellent yields (entries 2-7 in Table 10), showing notable activity of the heterogeneous palladium–catalysts. In the case of 1,2–dibromobenzene, we were previously unsuccessful in *bis*–couplings in one–pot reaction using $Pd(OAc)_2$ as the source of palladium. The high activity of ARF–Pd made the coupling reactions successful thereby yielding the *bis*–product (*ortho*–terphenylene) in 55% yield. Similarly, 9,10–dibromoanthracene afforded the corresponding diphenylanthracene in 90% yield. The results are shown in Table 10.

Scheme 72

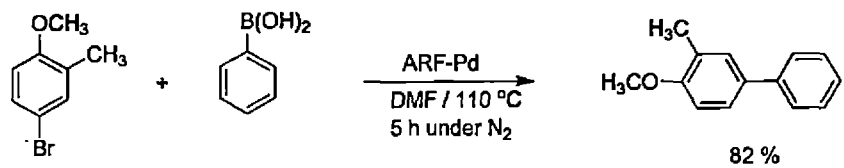
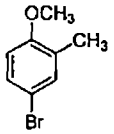
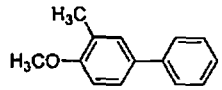
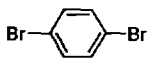
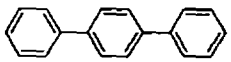
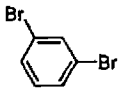
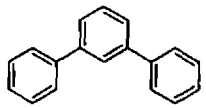
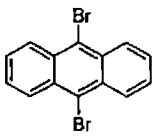
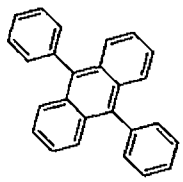
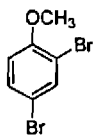
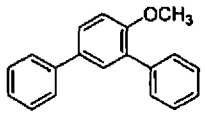
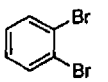
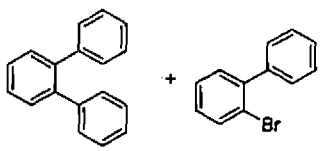
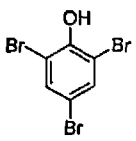
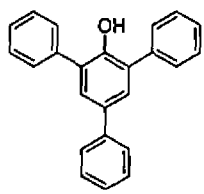


Table 10: Suzuki-Miyaura coupling between aryl bromide and aryl boronic acid using ARF-Pd.

Entry	Haloaromatics	Conditions[a] Temp./ Time	Products	Yield [%][b]
1.		110°C/ 5h		82
2.		110°C/ 5h		84
3.		110°C/ 2.5h		84
4.		115°C/ 8h		90
5.		110°C/ 5h		86
6		110°C/ 6h		55 & 30
7		120°C/ 6h		62

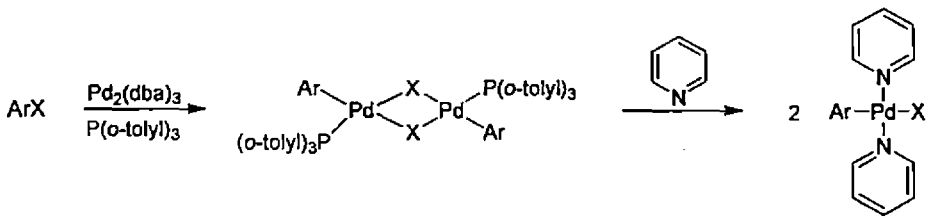
[a] The reactions were carried out in DMF; ARF-Pd (300 mg) was taken for 1 mmol of the bromoarenes.
[b] Yields are of isolated products, characterized by m.p.; IR and NMR spectral data.

I.C.5: Catalytic Activity: Buchwald-Hartwig (C-N) Coupling Reactions

Over the last decade, the palladium–catalyzed C–N coupling reactions, developed independently by Buchwald and Hartwig,[229] has become a versatile tool for preparing aryl amines from aryl halides, triflates etc. A brief introduction on the Pd–catalyzed Buchwald–Hartwig (C–N) coupling reaction has been presented in **Part–II** of this dissertation (pages 109-118). While employing similar coupling with halopyridines, Buchwald had experienced difficulty in achieving high yield of the product, possibly because of the formation of stable palladium complexes with pyridine (Scheme 73). Nitrogen- heterocycles are strongly binding ligands for late–transition metals. As a result, heteroaromatic halides with basic nitrogen atoms

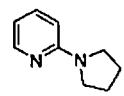
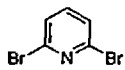
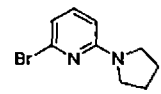
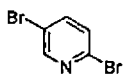
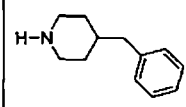
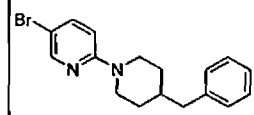
displaces weakly binding ligands such as, tri-*ortho*-tolylphosphine [P(*o*–tolyl)$_3$], so that the original catalystic system bearing P(*o*–tolyl)$_3$ as the ligand was ineffective for amination with heteroaromatic substrates. It has been shown in stoichiometric studies that pyridine displaces P(*o*–tolyl)$_3$ to form palladium–pyridine complexes (Scheme 73). Such problem of trapping Pd out of the catalytic cycle was, however, circumvented by using chelating *bis*–phosphine ligands, because chelating phosphanes are not displaced by pyridine and thus the amination of bromopyridines was accomplished successfully with Pd_2dba_3–BINAP and other such catalytic combinations.[230]

Scheme 73



Since aminopyridines are versatile intermediates as drugs and dyes, we were interested to apply our resin–bound palladium catalyst in the amination of bromopyridines. From our laboratory, it was previously reported that KF/alumina could serve as a potential basic surface for palladium–catalyzed amination of halopyridines under solvent–free conditions.[231] We first examined coupling of 2–bromopyridine with pyrrolidine on KF/alumina surface in presence of ARF–Pd. It was encouraging to observe that 2–aminopyridine could be obtained when a mixture of 2–bromopyridine and pyrrolidine and ARF–Pd was heated at 95°C for 2 h on KF/alumina surface. The product was isolated from the mixture by extraction with ether followed by chromatography over silica. The desired product 2–aminopyridine was obtained in 90% yield. Similar reactions were performed with dibromopyridines and amines using ARF–Pd as the catalyst were also successful. It is significant that no ligands (phosphines) are required for the amination, a major feature for industrial applications. However, further exploration of this methodology using ARF–Pd, studies on leaching effect and life–time of catalyst are currently underway. A partial result of the amination (C–N coupling) is presented in Table 11.

Table 11: Buchwald-Hartwig amination of bromopyridines with sec. amines using ARF-Pd.

Entry	Halopyridine	Amine	Conditions Temp./ Time	Product	Yield [%]
1			95°C/ 2h		90
2			90°C/ 1h		86
3			90°C/ 2.5 h		88

I.C.6: Minimum Concentration of Palladium on the Surface Required for Efficient Catalytic Activity

In order to find the minimum atomic concentration of palladium that is required to exhibit efficient catalytic activity, we chose the Suzuki–Miyaura coupling reaction as the model case. Different amounts of palladium acetate (1–10 mg) per 1 g of the ARF were used to immobilize palladium under various conditions and the resulting ARF–Pd was used in the Suzuki–Miyaura coupling of 1,4–dibromobenzene with phenylboronic acid. The results are summarized in Table 12. Loading of palladium from $Pd(OAc)_2$ used up to 5mg for 1 g of ARF seemed to decrease the catalytic efficiency in the second run of Suzuki–Miyaura coupling. Repeating the process of immobilization at different temperatures did not result any significant enhancement in catalytic activity. In fact, immobilization of palladium using 10 mg of $Pd(OAc)_2$ for 1 g of ARF at 50 °C for 3 h did show excellent catalytic activity even up to the fifth run with the formation of the coupled product in 80–84% yields. The minimum effective concentration of palladium in the surface of the resin was established as the use of 10 mg of $Pd(OAc)_2$ for 1 g of the ARF and prepared at 50 °C for 3 h in DMF.

Table 12 Minimum concentration of Palladium from $Pd(OAc)_2$.

Entry	$Pd(OAc)_2$	ARF	Temp./ Time/ Conditions[a]	%Yield in Suzuki - Miyaura coupling product[b]
1.	10.0mg	1g	50 °C /3h	84% (1st Run) 84% (2nd Run) 81% (3rd Run) 80% (4th Run) 80% (5th Run)
2.	5mg	1g	50 °C /2h	78% (1st Run) 50% (2nd Run)
3.[c]	5mg	1g	70 °C /2h	78% (1st Run) 35% (2nd Run)
4.	2.5mg	1g	50 °C /2h	76% (1st Run) 46% (2nd Run)
5.[d]	2.5mg	1g	50 °C /2h, then filtered and dried. Again taken in DMF, heated at 100°C for 1h, filtered and dried.	76% (1st Run) 46% (2nd Run)
6.	1.0mg	1g	50°C /2h,	< 5% (1st Run)

[a] Occasional shaking the suspension of ARF and Pd(OAc)2 in DMF. [b] SM reaction was studiedb etween thec oupling partners: 1,4-dibromobenzene(1 mmol) and phenylboronic acid (2.5 mmol). [c] To observe any change in catalytic activity when immobilization is performed ath igher temperature. [d]T o examine any leaching of Pd before applying in reaction.

I.C.7: Recycle Experiments and Leaching of Palladium

Recycle experiments were also verified taking the Suzuki–Miyaura couplings between 1,4–dibromobenzene and phenylboronic acid. After the reaction, the catalyst (ARF–Pd) was filtered off, washed with dichloromethane, water and finally dried under vacuum for further use. Consecutive five runs were tested to evaluate its activity. The results are presented in Table 13, which show that the catalyst is remarkably active even in the fifth run and thus the coupled product, *p*–terphenylene, was isolated without any significant drop of yields.

Table 13: Recycling Experiments in Suzuki-Miyaura Couplings using ARF-Pd.

Run	1	2	3	4	5
Yield [%]	84 (83)[b]	84 (81)	81 (78)	80	80
Time [h]	5	5	5	5	5

[a] Reagents & Conditions: 1,4-Dibromobenzene (2 mmol), Phenylboronic acid (4.5 mmol), ARF-Pd* = 600 mg, DMF (4 mL), 110 °C.
*ARF-Pd prepared from 10 mg of $Pd(OAc)_2$ for 1 g ARF (Entry 1, Table 12).
[b] Yields in the parenthesis represent use of ARF-Pd prepared from 7.5 mg of $Pd(OAc)_2$ for 1 g ARF (Entry 2, Table 10).

Leaching of palladium should generally depend on the nature of solvent used for a reaction. Although there is evidence that toluene as the solvent could prevent leaching of palladium, the poor solubility of the coupling partners and the extrinsic base (Na_2CO_3) in toluene might result in poor yield of the product.[153] We therefore carried out the Suzuki–Miyaura couplings between 1,4–dibromobenzene and phenylboronic acid in DMF as the solvent. The reaction was repeated using the recovered ARF–Pd and its palladium content was measured by XPS studies. In fact, leaching of palladium was followed by monitoring the change in Pd/N atomic ratio at the surface of catalyst after each cycle. The results show that the palladium content on surface seems to reach its steady–state after the second catalytic run and its catalytic activity remains notable up to the fifth run investigated. Detectable decrease in Pd/N atomic ratio may be caused by palladium leaching due to re–structuring of active particles during the course of the reaction.

Although the mechanism of involving palladium(0) species is generally accepted in homogeneously catalyzed coupling reactions, such thought for heterogeneous catalysts still remains under consideration. Choudary et al. have recently reported that the surface bound palladium(0) is the active species, analogous to homogeneously catalyzed coupling reactions, which undergoes oxidative addition to aryl C–halogen bonds.[227] As observed in XPS studies of ARF–Pd, the palladium spectra suggests the presence of both palladium(0) and palladium(II) species at the polymer surface. At this stage, we propose that the palladium(0) is the active species, soaked at the resin surface possibly through

reduction of palladium(II) salts by the carboxylate functions (formate) and that the palladium(II) species, which might come out of the surface during the reactions showing a low level leaching of palladium in the second catalytic run. No further leaching is observed in subsequent runs as the Pd/N ratio seems to attain a steady–state after the second catalytic run (figure 11).

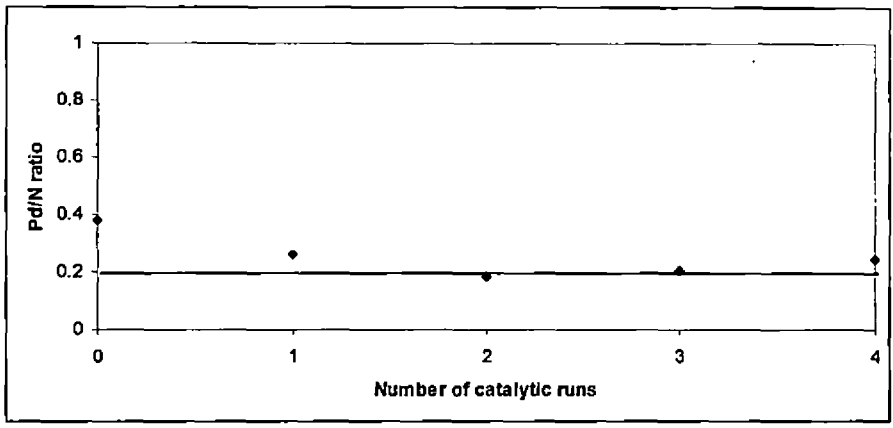


Figure 11: *Pd/N ratios in the ARF–Pd surface after various catalytic runs.*

I. C. 8: Conclusion

In summary, it has been demonstrated that suitably designed ion–exchange resins can be used as the potential polymeric surface to scavenge and immobilize palladium metal and the resulting palladium–soaked ionic resins can be used as efficient heterogeneous catalyst. The major advantage of using the formate as the counter anion is to facilitate reduction of paliadium(II) to palladium(0) in situ followed by deposition on the surface. The heterogeneous palladium–catalyst exhibits high catalytic efficiency in Heck, and Suzuki–Miyaura (C–C bond–forming) & Buchwald–Hartwig (C–N bond forming) reactions. The phosphane or ligand–free reaction conditions could be of potential interests for commercial applications of heterogeneous catalyst in C–C & C–N coupling reaction. Strict compliance with absence of air or moisture is not required and easy separation of the catalyst, isolation of the products in good to excellent yields and reuse of the ARF–Pd for at least five runs are attractive facets for the heterogeneous catalyst. The resin soaked catalyst can be stored for several weeks without any special protective arrangements like under–argon atmosphere or low temperatures.

I.C.9: Experimental Section: General

All the coupling reactions were carried out under nitrogen. Solvents were freshly distilled. Amberlite® IRA 900 (chloride form) was purchased from Acros Organics, Belgium and used as received. $PdCl_2$ and $Pd(OAc)_2$ were purchased from Fluka, Switzerland and used as received. The palladium–loaded resins were stored after drying without any precaution of absence of oxygen. Column chromatography: silica (60–200 μm) (SRL, India), tic on Merck plates coated with silica gel 60, F254. Solution NMR spectra of the organic compounds were recorded with a Bruker AV 300 spectrometer using TMS as the internal standard. FT–IR spectra were recorded on a Shimadzu–8300 spectrophotometer using KBr pellets. Solid–state ^{13}C MAS NMR spectra of ARF and ARF–Pd were recorded on a Bruker avance 500 spectrometer operating at a field of 125 MHz. The XPS spectra were collected with KRATOS Axis Ultra electron spectrometer under monochromatic A1 Kα radiation (1486.6eV). Analyses pass energy of 160 eV with a step size of 1 eV was used for survey scans whereas pass energy of 20 eV was used for narrow scans. The binding energy (BE) scale was referenced to the C 1s peak at 285.0 eV. Scanning Electron Micrograph images were taken with Quanta 200, 50X50X25 Eucentric.

I.C.9.A: Representative Procedure for Heck Reaction

To a suspension of ARF–Pd (300 mg, 2 mol% palladium) in toluene (2 mL) were added 4–bromo–1–iodo anisole (313 mg, 1 mmol), ethyl acrylate (220 mg, 2.2 mmol), triethyl amine (202 mg, 2 mmol) and the reaction mixture was heated under N_2 with gentle magnetic stirring at 90 ^{o}C for 10 h. The reaction mixture was passed through a cotton bed to isolate the catalyst followed by washing with dichloromethane. The combined washings were concentrated under reduced pressure leaving a residue, which was purified by column chromatography on silica gel. Elution with ethyl acetate/light petroleum (1:10) afforded ethyl 3–(5–bromo–2–methoxyphenyl)acrylate as color less solid (256 mg, 90% yield).

I. C. 9. B: Representative Procedure for Suzuki-Miyaura Reaction

A mixture of 1,3–Dibromobenzene (236 mg 1.0 mmol), phenylboronic acid 271 mg (2.2 mmol) and sodium carbonate (424 mg, 4 mmol) was taken in DMF (2 ml) and then added ARF–Pd (300 mg, 2 mol% palldium). The mixture was heated under nitrogen at 110°C for 2.5 h. After cooling, the reaction mixture was diluted with

10ml of cold water and filtered through a cotton bed. The filtrate was extracted with ether (3 x 30 ml) and the combined organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent left a solid residue, which was purified by column chromatography on silica gel (light petroleum) to give *m*–terphenyl as colorless solid (193 mg, 84% yield).

I.C.9.C: Representative Procedure for Amination of Halopyridines

2,5–Dibromopyridine (237 mg, 1 mmol) and 1 gm of KF/Al_2O_3 were mixed under nitrogen, then ARF–Pd (300 mg, 2 mol% Pd) and 4–benzyl piperidine (486 mg, 3 mmol) were added to it. The final mixture was covered under N_2 and placed on a pre–heated oil bath at 90 °C for 2.5 h. After cooling to room temperature, the solid mixture was transferred on a column of silica gel and elution with ethyl acetate/light petroleum (1:49) afforded 2–(4–benzylpiperidin–1–yl)–5–bromopyridine (291 mg, 88%).

I.C.9.D: Spectral Analysis

I.C.9.D.1: Spectral Data for the Heck–Coupled Product

Entry 1: *(E)*–ethyl 3–(3–chorophenyl)acrylate

Reaction temp: 90 °C; Time: 5 h,

Yield: 86%, (obtained as liquid); IR (Film): ν_{max} 1713, 1639, 1566 cm^{-1};

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.61 (d, 1H, *J* = 15.9), 7.50 (m, 1H), 7.41–7.27 (m, 3H), 6.43 (d, 1H, *J* = 15.9 Hz), 4.27 (q, 2H, *J* = 7.2 Hz), 1.34 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.5, 142.9, 136.4, 135.0, 130.13, 130.1, 127.8, 126.2, 119.9, 60.7, 14.3.

Entry 2: Ethyl 3–(2–fluorophenyi)acrylate

Temp: 90 °C, Time: 5 h;

Yield: 81%, (obtained as liquid); IR (Film): ν_{max} 1713, 1639, 1612, 1578 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.81 (d, 1H, *J* = 16.2 Hz), 7.53 (m, 1H), 7.33 (m, 1H), 7.17–7.05 (m, 2H), 6.53 (d, 1H, *J* = 16.2 Hz), 4.27 (q, 2H, *J* = 7.2 Hz), 1.34 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.7, 163.0, 159.6, 137.09, 137.05, 131.61, 131.49, 128.97, 128.93, 124.37, 124.32, 122.51, 122.35, 120.81, 120.72, 116.23, 115.94.

Entry 3: Ethyl 3–(5–bromo–2–methoxyphenyl)acrylate

Reaction temp: 90 °C; Time: 10 h,

Yield: 90%, (solid) mp 63–64 °C; IR (Nujol): ν_{max} 1713, 1632, 1589 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 300K): δ = 7.87 (d, 1H, *J* = 16.2 Hz), 7.59 (d, 1H, *J* = 2.4 Hz), 7.40 (dd, 2H, *J* = 8.7 & 2.4 Hz), 6.77 (d, 1H, *J* = 9 Hz), 6.48 (d, 1H, *J* = 16.2 Hz), 4.26 (q, 2H, *J* = 7.2 Hz), 3.85 (s, 3H), 1.33 (t, 3H, *J* = 7.2); ^{13}C NMR (75 MHz, $CDCl_3$, 300K): δ = 166.9, 157.1, 138.2, 133.6, 131.0, 125.3, 119.8, 113.1, 112.8, 60.8, 55.6, 14.2.

Entry 4: Ethyl 3–(2–aminophenyl)acrylate

Reaction temp: 95 °C, Time: 9 h;

Yield: 73%, (solid) mp 76–78 °C; IR (Nujol): ν_{max} 1693, 1616, 1570 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.83 (d, 1H; *J* = 15.6 Hz), 7.36 (dd, 1H; *J* = 7.8 & 1.5 Hz), 7.14 (d of ABq, *J* = 8.4 & 1.5 Hz), 6.76–6.67 (m, 2H), 6.34 (d,1H, *J* = 15.6 Hz), 4.25 (q, 2H, *J* = 7.2 Hz), 1.32 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.3, 145.6, 140.0, 131.2, 127.9, 119.7, 118.7, 117.8, 116.6, 60.4, 14.2.

Entry 5 (a): Ethyl 3–(3–iodophenyl)acrylate

Reaction temp: 100 °C, Time: 7 h,

Yield: 30%, (obtained as liquid); IR (Film): ν_{max} 1713, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.86 (d, 1H, *J* = 1.5 Hz), 7.69 (d, 1H, *J* = 8.1 Hz), 7.56 (d, 1H, *J* = 15.9 Hz), 7.46 (d, 1H, *J* = 7.8 Hz), 7.12 (ABq, 1H, *J* = 8.1 & 7.8 Hz), 6.41 (d, 1H, *J* = 15.9 Hz), 4.26 (q, 2H, *J* = 7.2 Hz), 1.33 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.5, 142.7, 138.9, 136.7, 130.5, 127.2, 119.7, 94.7, 60.6, 14.3.

Entry 5 (b): Ethyl 3–(3–(2–ethoxycarbonyl)vinylphenyl)acrylate

Reaction temp: 100 °C, Time: 7 h;

Yield: 86%, (solid) mp 50–52 °C; IR (Nujol): ν_{max} 1713, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.67 (d, 2H, *J* = 15.9 Hz), 7.64 (s, 1H), 7.52 (dd, 2H, *J* = 7.2 & 1.5 Hz), 7.42–7.37 (m, 1H), 6.46 (d, 2H, *J* = 15.9 Hz), 4.27 (q, 4H, *J* = 7.2 Hz), 1.34 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.5, 143.4, 135.0, 129.2, 127.4, 119.1, 60.4, 14.1.

I.C.9.D.2: Spectral Data for the Suzuki-Miyaura Coupled Product:

Entry 1: 4–Phenyl 2–methyl anisole

Reaction temp: 110 °C, Time: 5 h;

Yield: 82%, (solid) mp 74–75 °C; IR (Nujol): ν_{max} 1605, 1515, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.56– 7.53 (m, 2H), 7.42–7.36 (m, 4H), 7.30–7.21 (m, 1H), 6.89–6.86 (m, 1H), 3.85 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 157.4, 141.1, 133.4, 129.5, 128.7, 126.9, 126.8, 126.5, 125.4, 110.2, 55.4, 16.4.

Entry 2: 1, 4–Diphenylbenzene
Reaction temp: 110 °C, Time: 5 h;
Yield: 84%, (solid) mp 212–214 °C; IR (Nujol): ν_{max} 1454, 1377 cm^{-1} (lit.[232] 215–217 °C); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.67–7.63 (m, 8H), 7.48–7.43 (m, 4H), 7.38–7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.7, 140.1, 128.8, 127.5, 127.3, 127.0.

Entry 3: 1, 3– Diphenylbenzene
Reaction temp: 110 °C, Time: 2.5 h;
Yield: 84%, (solid) mp 87–88 °C (lit[233] mp 89 °C); IR (Nujol): ν_{max} 1454, 1377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 300K): δ = 7.78 (s, 1H), 7.62–7.28 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$, 300K): δ = 141.7, 141.1, 129.1, 128.7, 127.3, 127.20, 126.1.

Entry 4: 9, 10–Diphenylanthracene
Reaction temp: 115 °C, Time: 8 h;
Yield: 90%, (solid) mp 245–247 °C (lit.[234] 245–248 °C); IR (Nujol): ν_{max} 1458, 1377 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.72-7.66 (m, 4H), 7.62–7.46 (m, 10H), 7.34–7.29 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.1, 137.1, 131.3, 129.8, 128.4, 127.4, 126.9, 125.0.

Entry 5: 2, 4– Diphenylanisole
Reaction temp: 110 °C, Time: 5 h;
Yield: 86%, (solid) mp 93–94 °C;
IR (Nujol): ν_{max} 1600, 1510, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.59–7.50 (m, 6H), 7.44–7.25 (m, 6H), 7.01 (d, 1H, J = 8.4 Hz), 3.8 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.0, 140.6, 138.4, 133.8, 131.0, 129.7, 129.6, 128.7, 128.0, 127.0, 126.7, 115.1, 111.5, 55.7.

Entry 6: 1, 2– Diphenylbenzene
Reaction temp: 110 °C, Time: 6 h;

Yield: 55%, (solid) mp 54–56 °C (lit.[232] 58 °C);

IR (Nujol): ν_{max} 1600, 1578, 1480 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.46–7.33 (m, 4H), 7.22–7.01 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 141.5, 140.5, 130.6, 129.9, 127.8, 127.4, 126.4.

2–Phenylbromobenzene

Temp: 110 °C; Time: 6 h,

Yield: 30%; (obtained as liquid); IR (Film): ν_{max} 1600, 1545, 1498, 1419 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.56–7.12 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 142.5, 141.0, 133.1, 131.2, 129.3, 128.7, 127.9, 127.6, 127.3, 122.6.

Entry 7: 2, 4, 6– Triphenylphenol

Reaction temp: 120 °C, Time: 6 h;

Yield: 82%, (solid) mp 144–145 °C; IR (Nujol): ν_{max} 3512, 1595, 1227 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.61–7.26 (m, 17H), 5.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.9, 140.5, 137.5, 133.8, 129.4, 129.1, 128.9, 128.8, 128.6, 127.8, 126.9, 126.7.

I.C.9.D.3: Spectral data for the Buchwald-Hartwig (*C*-N) coupled product

Entry 1: 2–(Pyrrolidin–1–yl)pyridine

Reaction temp: 95 °C, Time: 2 h;

Yield: 90%, (obtained as liquid); IR (Film): ν_{max} 1597, 1555, 1501, 1485, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.06 (dd, 1H, *J* = 5.1 & 1.2 Hz), 7.33 (ddd, 1H, *J* = 8.7, 7.2 & 1.8 Hz), 6.41 (ddd, 1H, *J* = 6.3, 5.4 & 1 Hz), 6.25 (d, 1H, *J* = 8.7 Hz), 3.36 (t, 4H, J = 6.6 Hz), 1.91 (t, 4H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 157.2, 148.1, 136.9, 111.0, 106.5, 46.6, 25.5.

Entry 2: 2–Bromo–6–(pyrrolidin–1–yl)pyridine

Reaction temp: 90 °C, Time: 1 h;

Yield: 86%, (solid) mp 78–80 °C; IR (Nujol): ν_{max} 1589, 1535, 1493, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.13 (dd, 1H, *J* = 8.4 & 7.5 Hz), 6.55 (d, 1H, *J* = 7.5 Hz), 6.14 (d, 1H, *J* = 8.4 Hz), 3.33 (t, 4H, *J* = 6.6 Hz), 1.90 (t, 4H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 157.2, 140.4, 138.7, 113.7, 104.5, 46.7, 25.5.

Entry 3: 2–(4–Benzylpiperidin–1–yl)–5–bromopyridine

Reaction temp: 90 °C, Time: 2.5 h;

Yield: 88%, (solid) mp 75–77 °C; FT IR (Nujol) ν_{max}: 2920, 2846, 1581, 1392, 1242, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 300K): δ = 8.16 (d, 1H, *J* = 2.4 Hz), 7.47 (dd, 1H, *J* = 9 & 2.4 Hz), 7.3$\tilde{1}$7.13 (m, 5H), 6.51 (d, 1H, *J* = 9 Hz), 4.20 (d, 2H, *J* = 12.9 Hz), 2.8$\tilde{0}$2.70 (m, 2H), 2.55 (d, 2H, *J* = 6.9 Hz). 1.79–1.69 (m, 3H), 1.31–1.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 300K): δ = 157.9, 148.38, 140.2, 139.6, 129.1, 128.2, 125.9, 108.5, 106.7, 45.7, 43.2, 38.2, 31.5.

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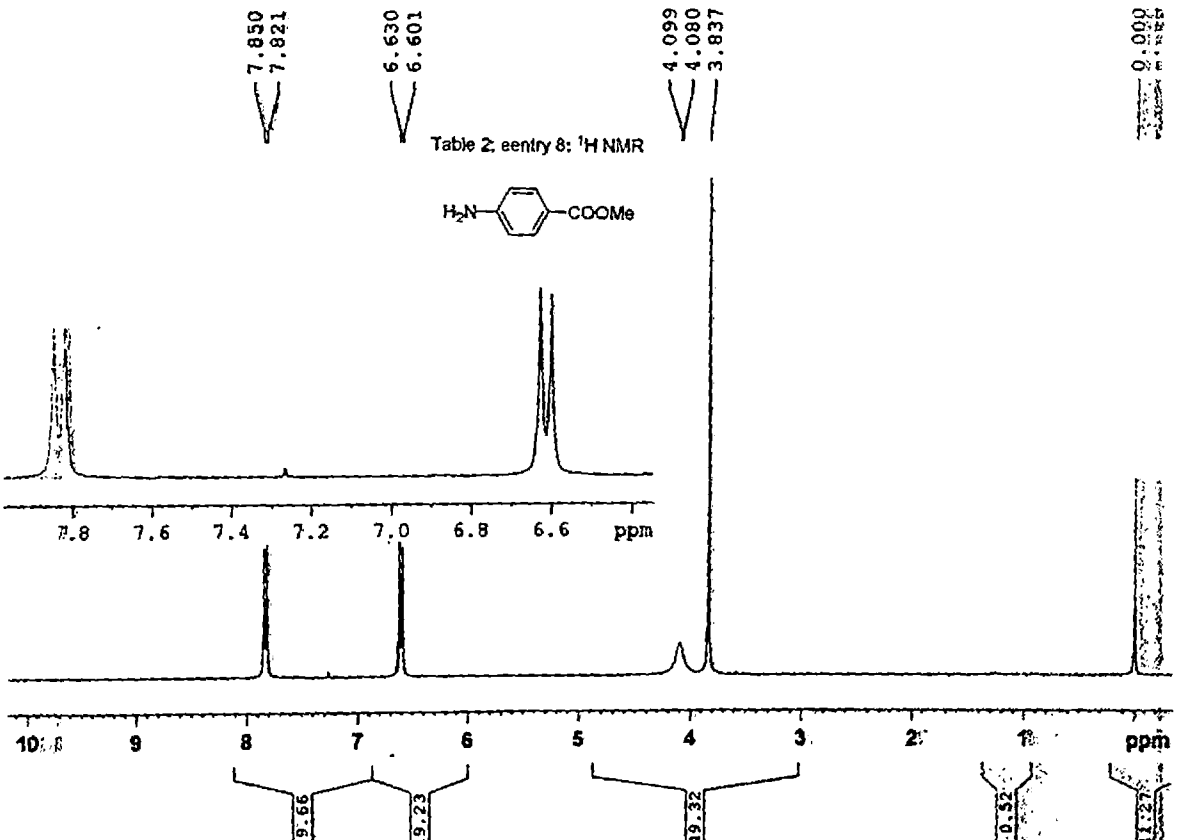
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COOMe
7.8
7.6
7.4
7.2
7.0
6.8
6.6
ppm
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9
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7
6
5
4
3
2
1
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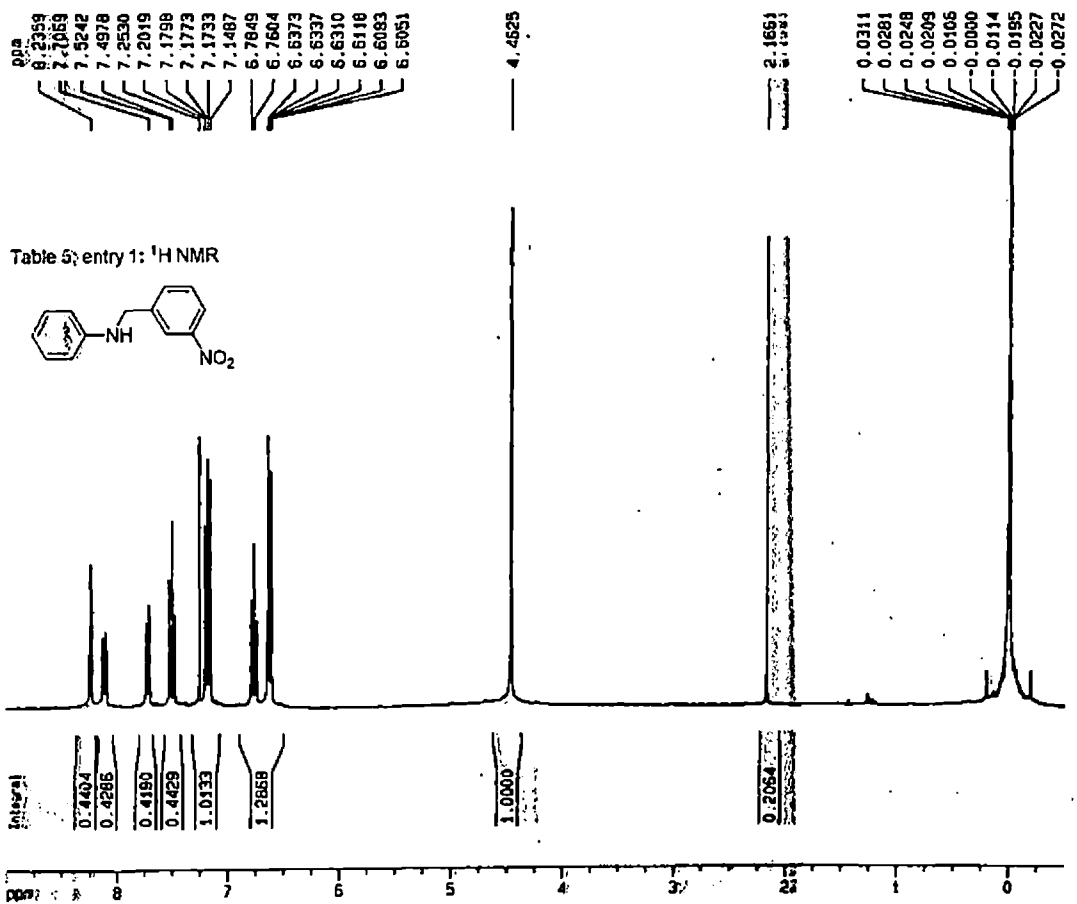


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GB                          0
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1D NMR plot parameters
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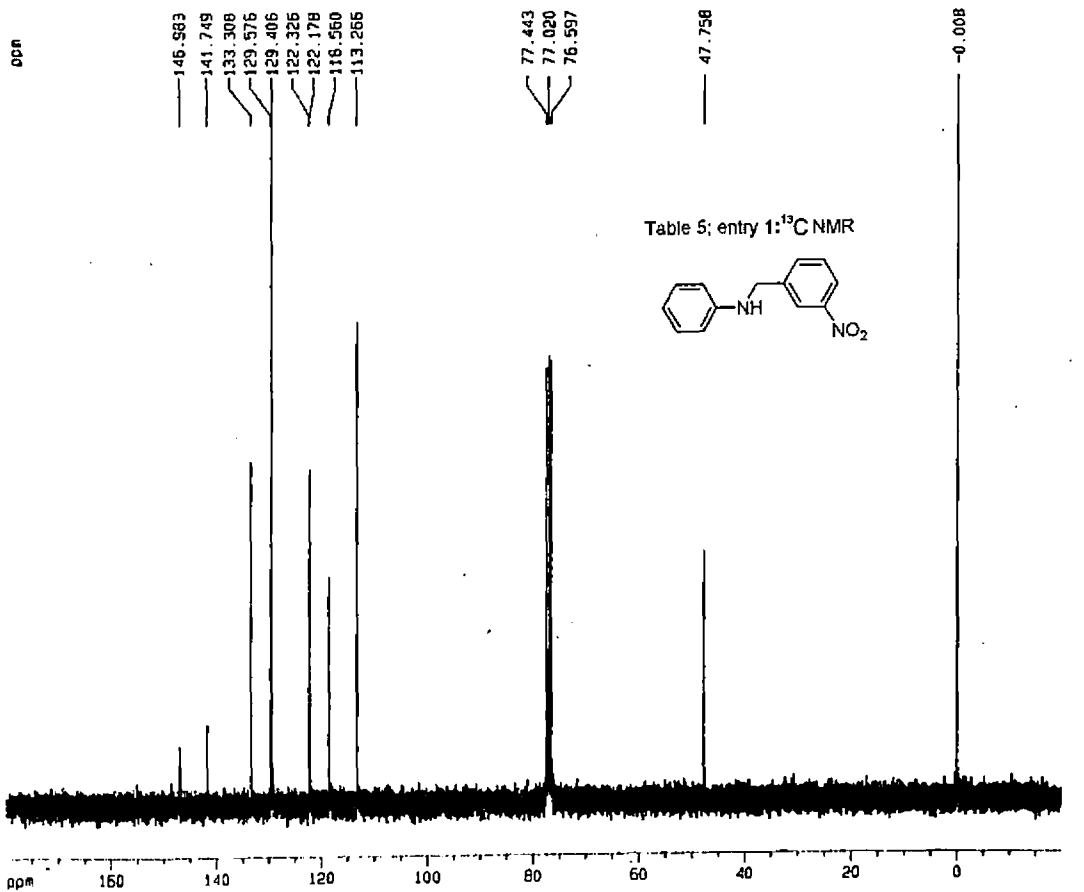

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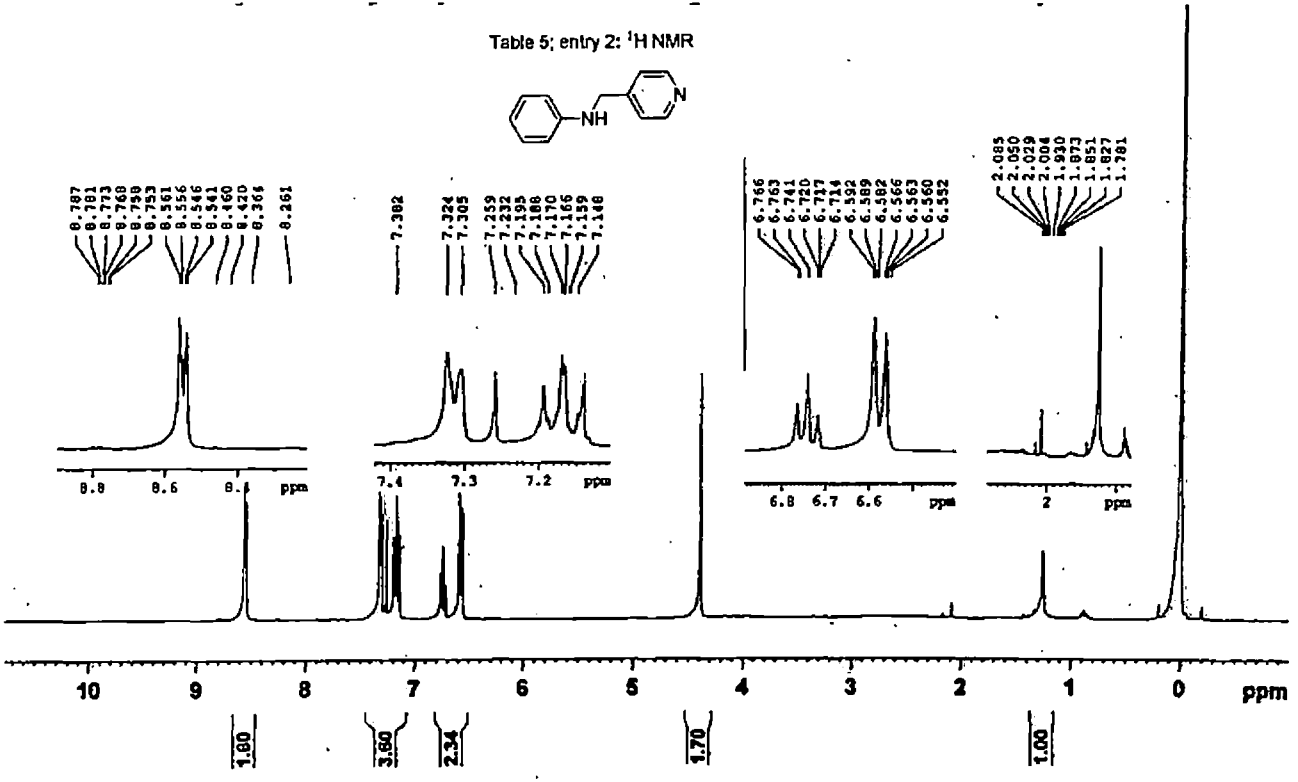
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8.546
8.541
8.460
8.420
8.364
8.261
7.382
7.324
7.305
7.259
7.232
7.195
7.188
7.170
7.166
7.159
7.148
6.766
6.763
6.741
6.720
6.717
6.714
6.592
6.589
6.582
6.566
6.563
6.560
6.552
2.085
2.050
2.029
2.004
1.930
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1.851
1.827
1.781
8.8
8.6
8.4
ppm
7.4
7.3
7.2
ppm
6.8
6.7
6.6
ppm
2
ppm
10
9
8
7
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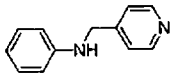

BRUKER

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MCREST	0.00000000	sec
MCWRK	0.01500000	sec

======== CHANNEL f1 ========

NDC1	13C	
P1	10.00	usec
PL1	-1.00	dB
SFO1	75.4752953	MHz

======== CHANNEL f2 ========

CPDPRG2	waltz16	
NUC2	1H	
PCPD2	80.00	usec
PL2	0.00	dB
PL12	16.00	dB
PL13	16.00	dB
SFO2	300.1312005	MHz

f2 - Processing parameters

SI	32768	
SF	75.4677488	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

Table 6; entry no. 3: ^{1}H NMR

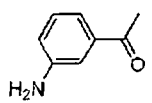
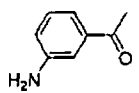
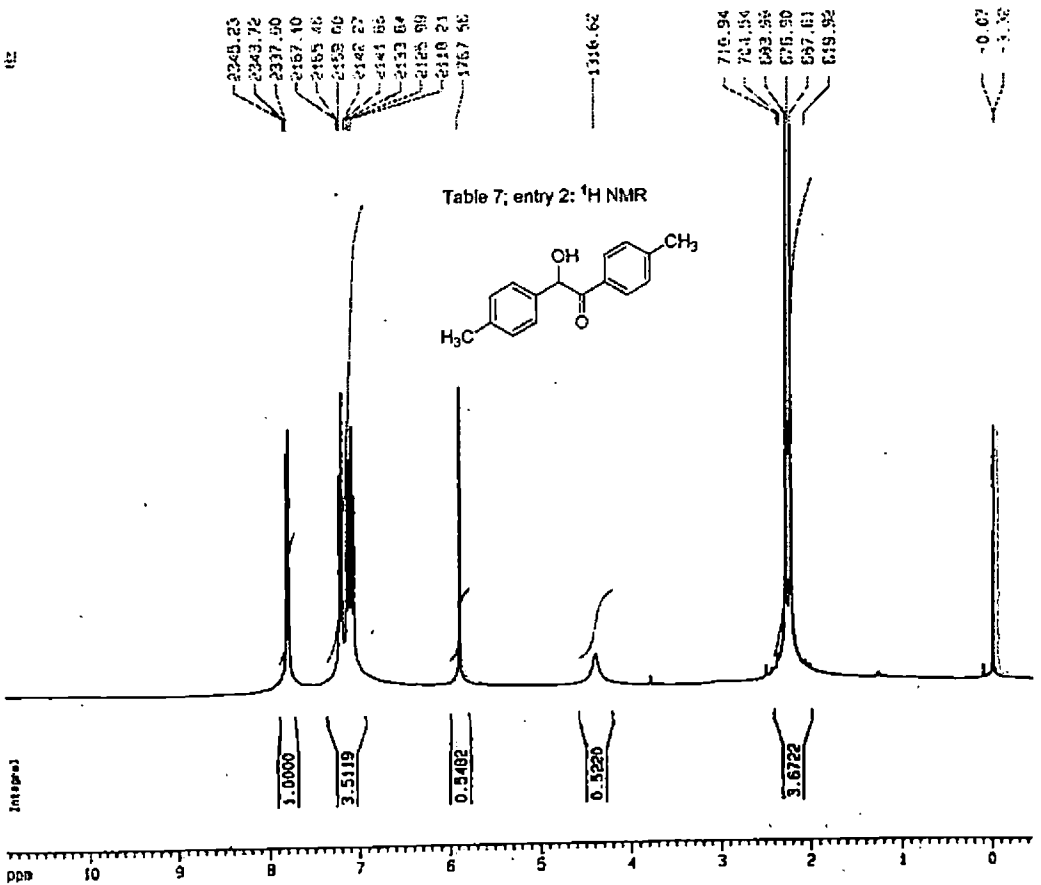


Table 6; entry no. 3: ^{13}C NMR



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Current Data Parameters
NAME            SS-II 130
EXPNO                  10
PROCNO                  1

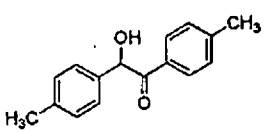
F2 - Acquisition Parameters
Date_         20050118
Time               11.04
INSTRUM            av300
PROBHD  5 mm BBO BB-1H
PULPROG            zg30
TD                32768
SOLVENT            CDCl3
NS                    64
DS                     0
SWH           5995.204 Hz
FIDRES        0.182959 Hz
AQ            2.7329011 sec
RG                  35.9
DW                83.400 usec
DE                 6.00 usec
TE                  0.0 K
D1            2.50000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

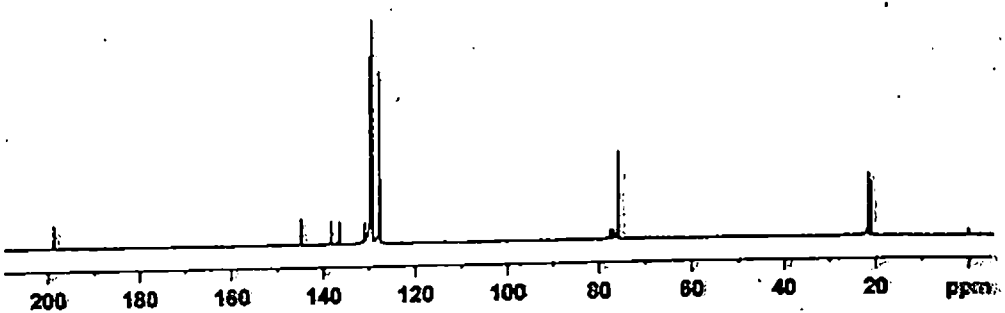
-------- CHANNEL f1 --------
NUC1                   1H
P1                 7.50 usec
PL1                -3.00 dB
SFO1          300.1323110 MHz

F2 - Processing parameters
SI                 16384
SF            300.1300179 MHz
WDW                   EM
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.40

1D NMR plot parameters
CX                 20.00 cm
CY                 14.00 cm
F1P               10.943 ppm
F1                3284.21 Hz
F2P               -0.446 ppm
F2                -133.90 Hz
PPMCM             0.56944 ppm/cm
HZCM           170.90533 Hz/cm
```

Table 7; entry 2: ^{13}C NMR





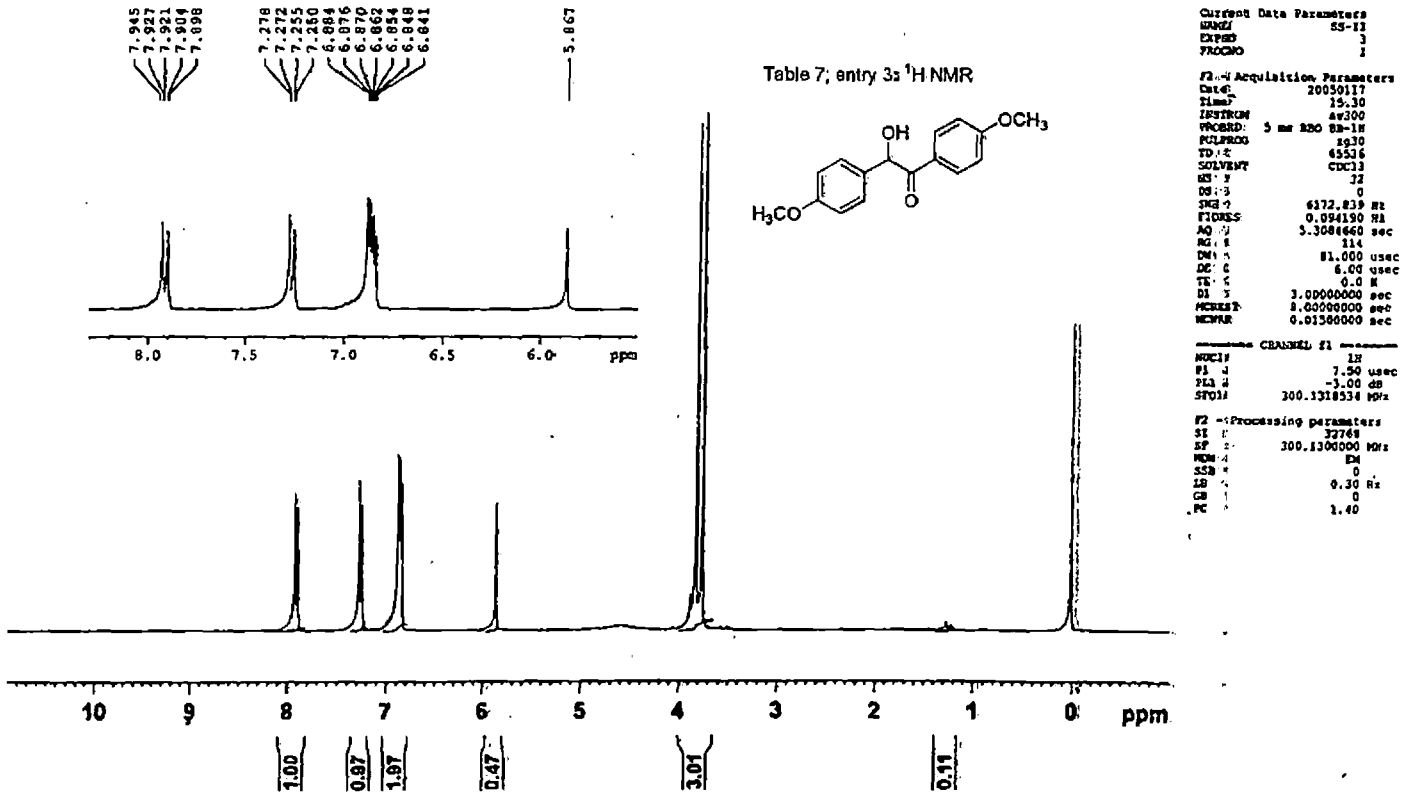

```
Current Data Parameters
NAME            SS-II 138C
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20050118
Time                  11.28
INSTRUM                av300
PROBHD  5 mm BBO BB-1H
PULPROG                zgpg
TD                     65536
SOLVENT               CDCl3
NS                       143
DS                         4
SWH               17985.611 Hz
FIDRES                0.274439 Hz
AQ                1.8219508 sec
RG                     16384
DW                   27.800 usec
DE                    6.00 usec
TE                     0.0 K
D1                2.00000000 sec
d11               0.03000000 sec
DELTA             1.89999998 sec
MCREST            0.00000000 sec
MCWRK             0.01500000 sec

======== CHANNEL f1 ========
NUC1                     13C
P1                    10.00 usec
PL1                   -1.00 dB
SFO1           75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2               waltz16
NUC2                      1H
PCPD2                 80.00 usec
PL2                    0.00 dB
PL12                  16.00 dB
PL13                  16.00 dB
SFO2          300.1312005 MHz

F2 - Processing parameters
SI                       32768
SF             75.4677490 MHz
WDW                         EM
SSB                          0
LB                    1.00 Hz
GB                           0
PC                    1.40
```



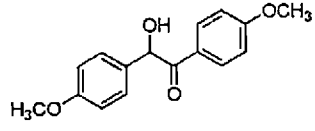
Current Data Parameters
NAME 55-II
EXPNO 3
PROCNO 1

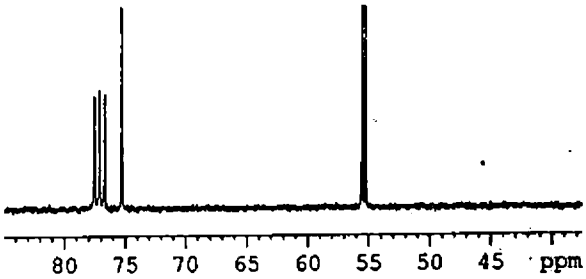
F2 - Acquisition Parameters
Date_ 20050117
Time 15.30
INSTRUM av300
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 0
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 114
DW 81.000 usec
DE 6.00 usec
TE 0.0 K
D1 3.00000000 sec
MCREST 8.00000000 sec
MCWRK 0.01500000 sec

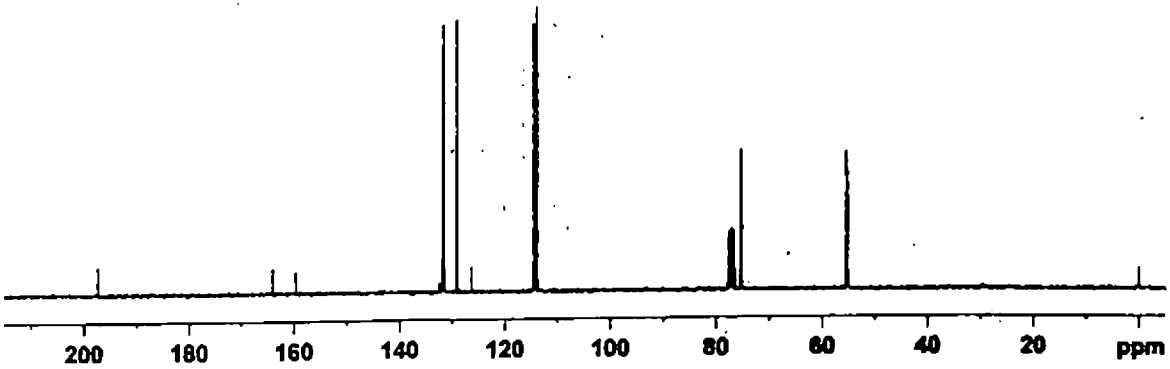
CHANNEL f1
NUC1 1H
P1 7.50 usec
PL1 -3.00 dB
SFO1 300.1318534 MHz

F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

Table 7; entry 3: ^{13}C NMR








```
Current Data Parameters
NAME                  SS-IIC
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_              20050117
Time                  16.10
INSTRUM                av300
PROBHD    5 mm BBO BB-1H
PULPROG                zgpg
TD                     65536
SOLVENT                CDCl3
NS                       448
DS                         4
SWH               17985.611 Hz
FIDRES                0.274439 Hz
AQ                1.8219508 sec
RG                     16384
DW                   27.800 usec
DE                    6.00 usec
TE                     0.0 K
D1                2.00000000 sec
d11               0.03000000 sec
DELTA             1.89999998 sec
MCREST            0.00000000 sec
MCWRK             0.01500000 sec

======== CHANNEL f1 ========
NUC1                     13C
P1                    10.00 usec
PL1                   -1.00 dB
SFO1             75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                 80.00 usec
PL2                    0.00 dB
PL12                  16.00 dB
PL13                  16.00 dB
SFO2            300.1312005 MHz

F2 - Processing parameters
SI                     32768
SF               75.4677490 MHz
WDW                       EM
SSB                        0
LB                    1.00 Hz
GB                         0
PC                    1.40

1D NMR plot parameters
CX                    20.00 cm
CY                    12.50 cm
F1P                  147.418 ppm
F1                 11125.32 Hz
F2P                  104.482 ppm
F2                  7885.01 Hz
PPMCM                2.14682 ppm/cm
HZCM               162.01553 Hz/cm
```

Table 9: Entry 12: ^{1}H NMR

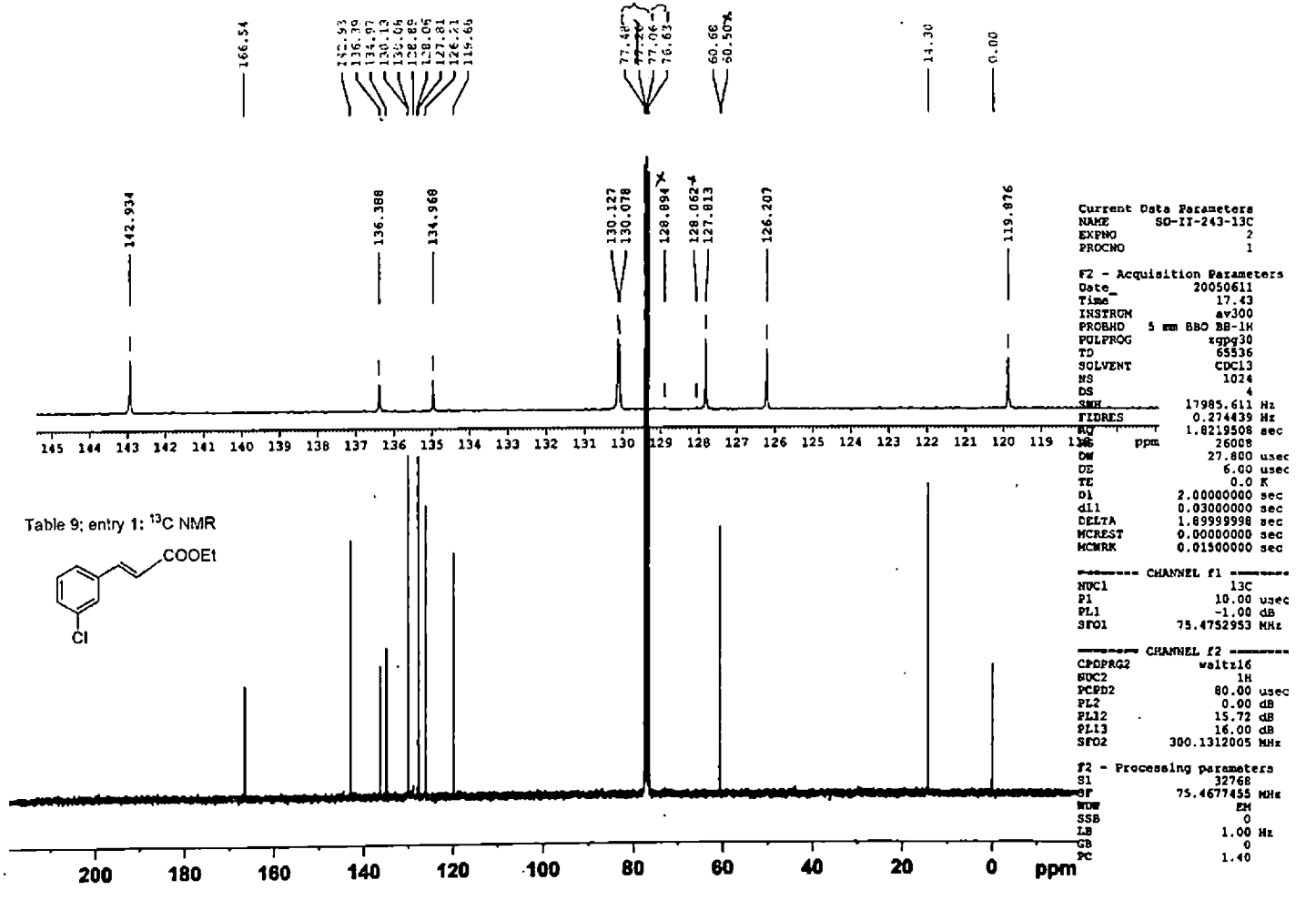
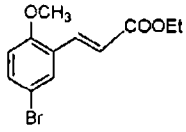


Table 9; entry 1: ^{13}C NMR

Table 9; entry 3: ^{1}H NMR



BRUKER

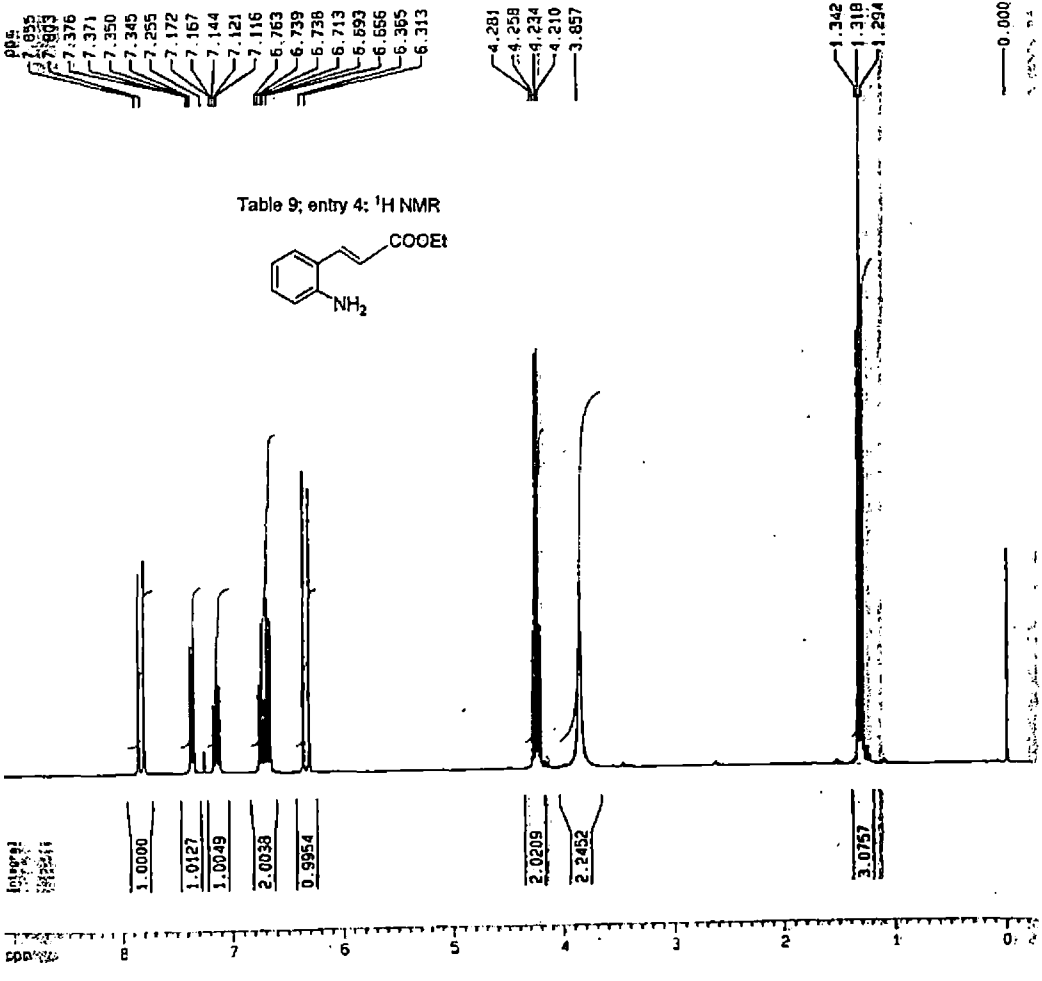
```
Current Data Parameters
NAME      Jun21-2005-basu
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20050621
Time              13.57
INSTRUM           av300
PROBHD   5 mm BBO BB-1H
PULPROG         zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    4
SWH           17985.611 Hz
FIDRES        0.274439 Hz
AQ            1.8219508 sec
RG              18390.4
DW               27.800 usec
DE                6.00 usec
TE                 0.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                13C
P1                10.00 usec
PL1               -1.00 dB
SFO1        75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              16.00 dB
PL13              16.00 dB
SFO2       300.1312005 MHz

F2 - Processing parameters
SI                32768
SF         75.4677494 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```



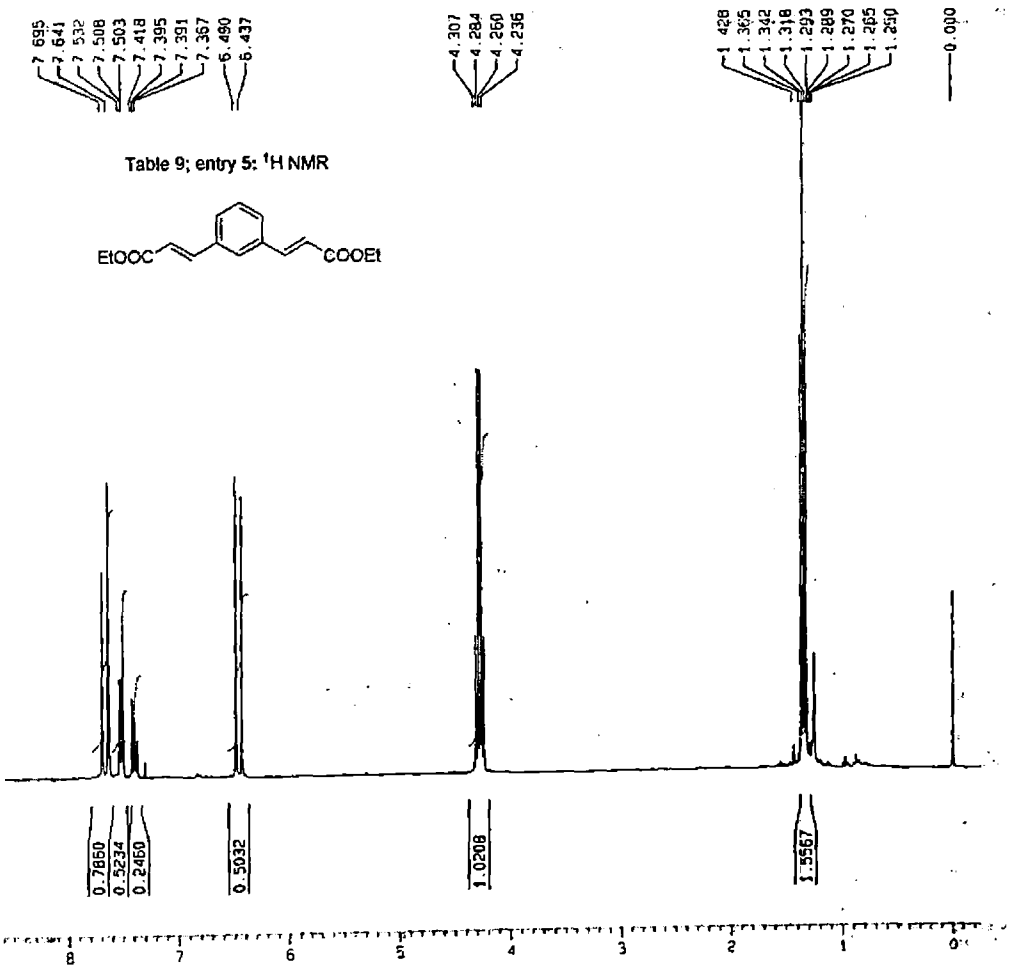
Current Data Parameters
NAME Jul07-2005-basu
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20050707
Time 12.39
INSTRUM av300
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 0
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084560 sec
RG 45.3
DW 81.000 usec
DE 6.00 usec
TE 0.0 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 13.10 usec
PL1 0.00 dB
SFO1 300.1318534 MHz

F2 - Processing parameters
SI 32768
SF 300.1300073 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
CY 15.00 cm
F1P 9.093 ppm
F1 2729.11 Hz
F2P -0.233 ppm
F2 -70.07 Hz
PPMCM 0.45633 ppm/cm
HZCM 139.95895 Hz/cm



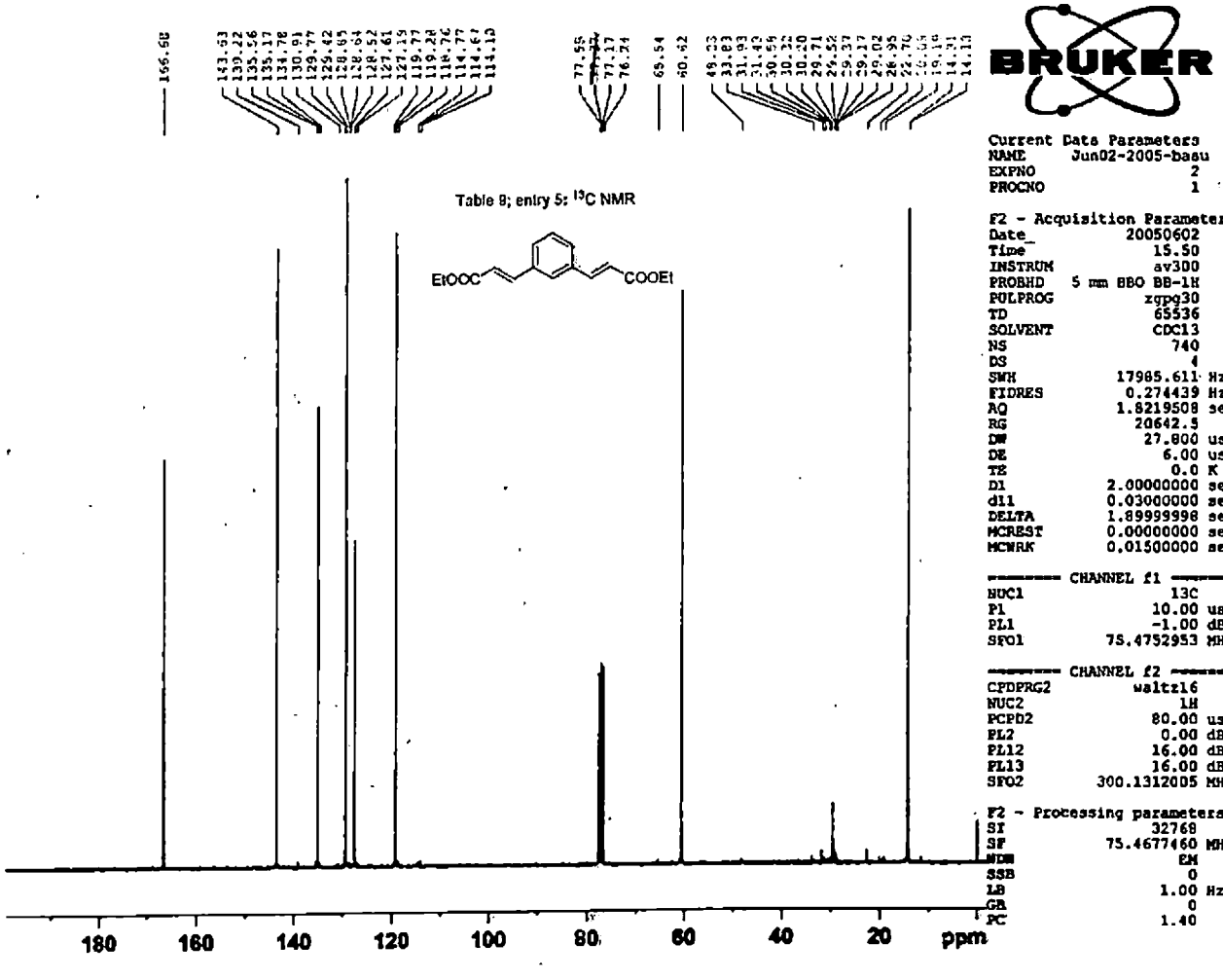
Current Data Parameters
NAME Jun02-2005-basu
EXPNO 1
PROCNO 1

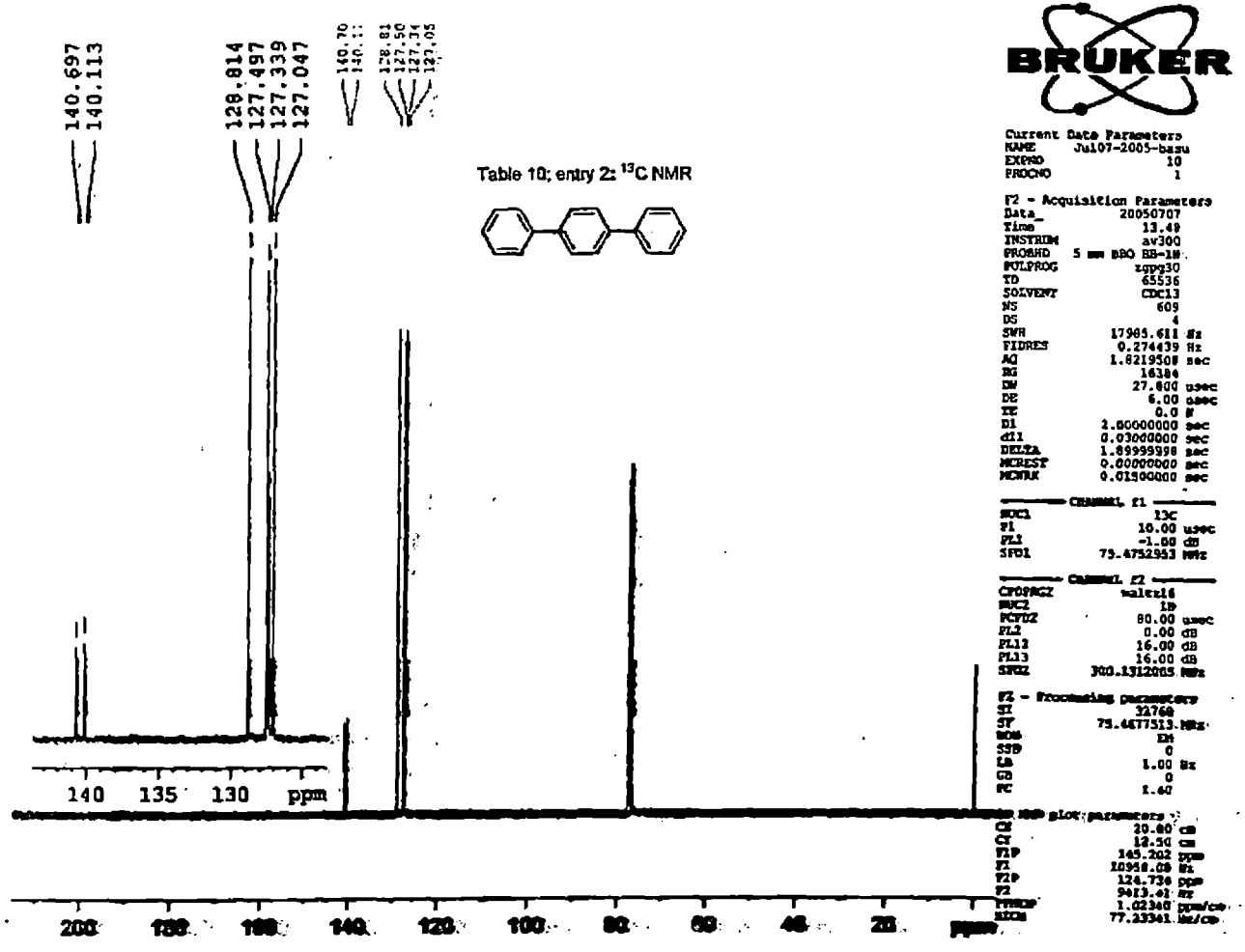
F2 - Acquisition Parameters
Date_ 20050602
Time 15.22
INSTRUM av300
PROBHD 5 mm SBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 0
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084560 sec
RG 35.9
DW 81.000 usec
DE 6.00 usec
TE 0.0 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

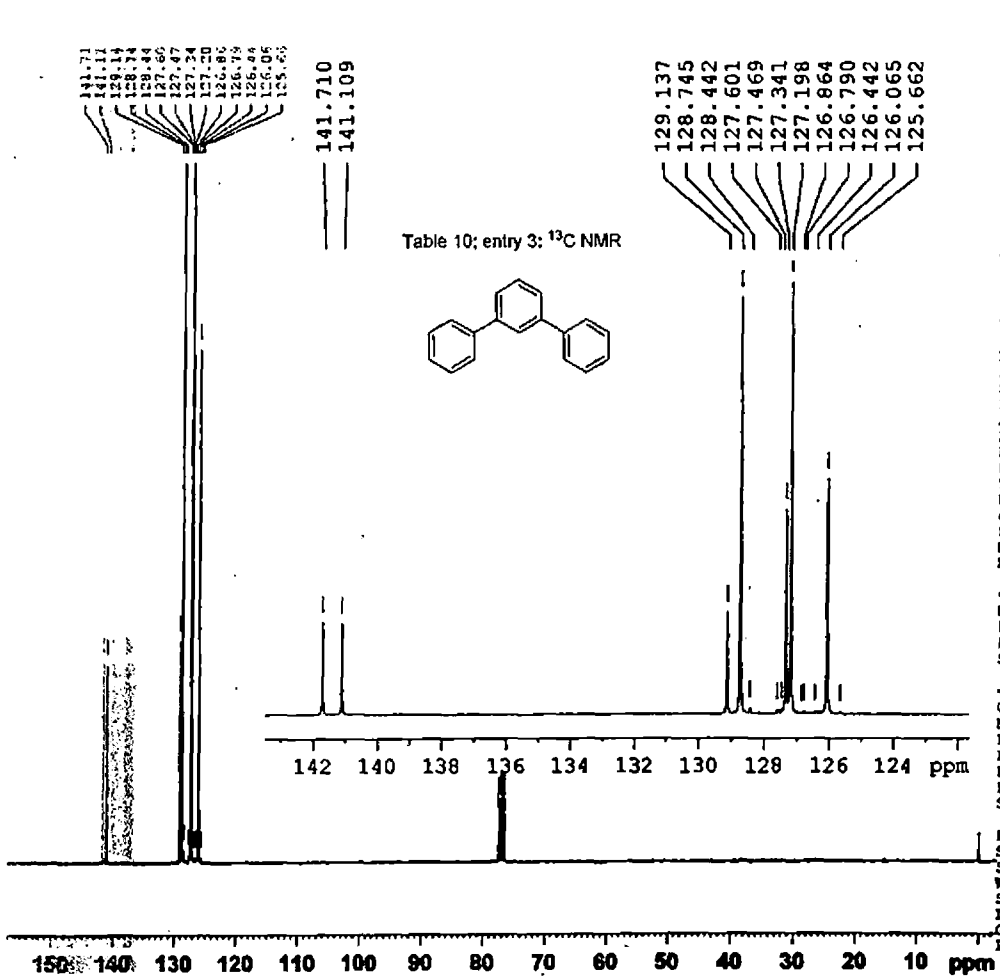
-------- CHANNEL f1 --------
NUC1 1H
P1 13.10 usec
PL1 0.00 dB
SFO1 300.1318534 MHz

F2 - Processing parameters
SI 32768
SF 300.1299931 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
CY 16.00 cm
F1P 9.044 ppm
F1 2714.48 Hz
F2P -0.259 ppm
F2 -77.86 Hz
PPMCM 0.46515 ppm/cm
HZCM 139.60666 Hz/cm


166.68
143.53
139.22
135.56
135.17
134.78
130.91
129.77
129.42
128.95
128.64
128.52
127.61
127.15
119.77
119.28
118.76
114.77
114.67
114.13
77.55
77.17
76.24
60.54
60.42
49.53
33.83
31.93
31.43
30.56
30.32
30.20
29.71
29.52
29.37
29.17
29.02
26.95
22.70
19.16
14.31
14.13
Table 8; entry 5: ^{13}C NMR
EtOOC
COOEt
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME Jun02-2005-basu
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050602
Time 15.50
INSTRUM av300
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 740
DS 4
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 20642.5
DW 27.800 usec
DE 6.00 usec
TE 0.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 10.00 usec
PL1 -1.00 dB
SFO1 75.4752953 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 16.00 dB
PL13 16.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677460 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


140.697
140.113
128.814
127.497
127.339
127.047
140.70
140.11
128.81
127.50
127.34
127.05
Table 10; entry 2: ^{13}C NMR
140
135
130
ppm
200
160
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME Jul07-2005-basu
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Data_ 20050707
Time 13.49
INSTRUM av300
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 609
DS 4
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 16384
DW 27.800 usec
DE 6.00 usec
TE 0.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 10.00 usec
PL1 -1.00 dB
SFO1 75.4752953 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 16.00 dB
PL13 16.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677513 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F2 - Plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 145.202 ppm
F1 10958.08 Hz
F2P 124.736 ppm
F2 9413.41 Hz
PPMCM 1.02340 ppm/cm
HZCM 77.23341 Hz/cm



BRUKER

Current Data Parameters
NAME Jul07-2005-basu
EXPNO 7
PROCNO 1

F2 - Acquisition Parameters

Date_	20050707
Time	13.27
INSTRUM	av300
PROBHD	5 mm BBO BB-1H
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	323
DS	4
SWH	17985.611 Hz
FIDRES	0.274439 Hz
AQ	1.8219508 sec
RG	16384
DW	27.800 usec
DE	6.00 usec
TE	0.0 K
D1	2.00000000 sec
d11	0.03000000 sec
DELTA	1.89999998 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	10.00 usec
PL1	-1.00 dB
SFO1	75.4752953 MHz

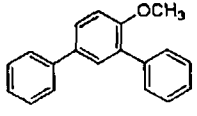
======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	16.00 dB
PL13	16.00 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

SI	32768
SF	75.4677680 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

Table 10; entry no. 5: ^{13}C NMR




```
Current Data Parameters
NAME      Jul08-2005-basu
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20050708
Time                13.04
INSTRUM           av300
PROBHD  5 mm BBO BB-1H
PULPROG          zgpg30
TD                65536
SOLVENT             CDCl3
NS                    486
DS                      4
SWH           17985.611 Hz
FIDRES        0.274439 Hz
AQ            1.8219508 sec
RG                  26008
DW                27.800 usec
DE                 6.00 usec
TE                  0.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.69999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                 10.00 usec
PL1                -1.00 dB
SFO1          75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               16.00 dB
PL13               16.00 dB
SFO2          300.1312005 MHz

F2 - Processing parameters
SI                    32768
SF            75.4677501 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40

1D NMR plot parameters
CX                   20.00 cm
CY                   12.50 cm
F1P                160.647 ppm
F1                 12123.69 Hz
F2P                109.548 ppm
F2                 8267.34 Hz
PPMCM              2.55497 ppm/cm
HZCM             192.81767 Hz/cm
```

Part II

"Palladium-Catalyzed Selective Amination of Haloaromatics on KF-Alumina Surface"

II.1: Introduction

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

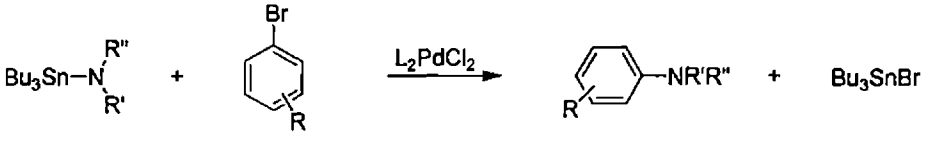
The historical importance of aromatic amines, which is also reflected in their industrial relevance, spurred interest in developing methods for their production. Over the years a number of cleverly designed and extremely useful methods of aryl C–N bond formation have been reported.[6] Most of the early preparative methods for aromatic amines involve electrophilic nitration and subsequent reduction, alkylation and dealkylation of amines, rearrangement, hydrogenolysis, aromatic nucleophilic substitution by S_NAr, benzyne or $S_{RN}1$ reactions.[9]

The catalytic amination of aryl halides represents a mild alternative to classical methods of aryl C–N bond formation and has many potential applications for the synthesis of aniline derivatives which are inaccessible through other routes.[10] Palladium–catalyzed amination reactions are fundamentally important organic transformations that have received tremendous attention over the past few years.[11] The transition metal–mediated coupling of amines with aryl halides is regeoselective, does not require activating groups, and occurs under relatively mild conditions. Recently, Buchwald *et al.*[12] and Hartwig *et al.*[13] have demonstrated a valuable palladium catalyzed *N*–arylation of various amines with aryl halides and triflates as a powerful tool for the formation of an aromatic nitrogen bond in the synthesis of a variety of arylamines. The reactions can be carried out at a lower temperature under mild conditions than the copper–mediated classical Ullmann condensation. Elegant work by Buchwald,[12] Hartwig,[13] and others[14] has led to significant improvements in amination methodology since its discovery by Migita and co–workers[15] in 1983. Most of the reported methods employ electron–rich phosphine ligands,[16] possessing either

a ferrocene[17] or a biphenyl backbone,[18] or bulky nucleophilic *N*–heterocyclic carbenes (sometimes referred to as "phosphine mimics").[19] Chelating phosphines such as 1,1'–*bis*(diphenylphosphino)ferrocene (DPPF)[20] and 2,2'–*bis*(diphenylphosphino)1,1'–binaphthayl (BINAP)[21] have been demonstrated to exhibit improved catalytic activity in this type of transformation. Commonly used bases in Pd–catalyzed aminations are *t*–BuONa,[12] Cs_2CO_3,[22] K_3PO_4,[13] MeONa and *i*-PrONa.[23] The combination of Pd / rac. BINAP has been found to be an excellent catalyst system for the coupling of primary amines with aryl bromides.[21] Additionally, the BINAP catalyst system functions well in the presence of the weak base Cs_2CO_3, allowing for a high level of functional group tolerance.[22] Although a general protocol had been developed for the Pd–catalyzed cross coupling of primary and secondary amines with aryl bromides using sodium *tert*–butoxide,[22] this base causes problems with a number of common functional groups such as, esters, aldehydes, enolizable ketones, nitriles and nitro groups. The scope of this method was further expanded by the use of Cs_2CO_3,[22] allowing the coupling of aryl bromides, which were incompatible with *t*–BuONa.

Kosugi and Migita first reported the C–N coupling of aryl halides with tin amides (Scheme 1) using palladium catalysts containing tri–*o*–tolylphosphine as ligand.[15,24] Although these reactions were limited in scope and possessed problems from the toxicity and environmental instability of tin amides, the potential for palladium complexes to catalyze aromatic carbon–nitrogen bond formation in a synthetically valuable fashion was suggested.

Scheme 1

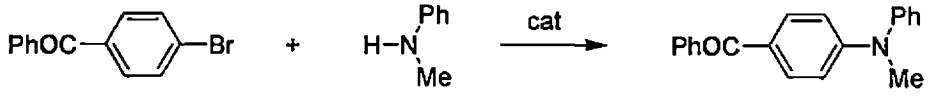


$L_2PdCl_2 = [PdCl_2\{P(o\text{-toyl})_3\}_2]$

Guram and Buchwald[25] subsequently developed methodology in which the Migita process was generalized and greatly simplified. The use of stoichiometric amounts of organo tin compounds is the main disadvantage of this method both for ecological reasons and with regard to practicability. Independently, Buchwald *et al.*[26] and Hartwig *et al.*[27] reported the first catalytic amination of aryl bromides with free amines (Scheme 2). Instead of isolation or generation of a tin amide *in situ*, the amination reactions were conducted by reaction of an aryl halide with the

combination of amine and stoichiometric amounts of sterically hindered base such as, *t*–BuONa or silylamide base in toluene or THF at temperature 65–100 °C.

Scheme 2

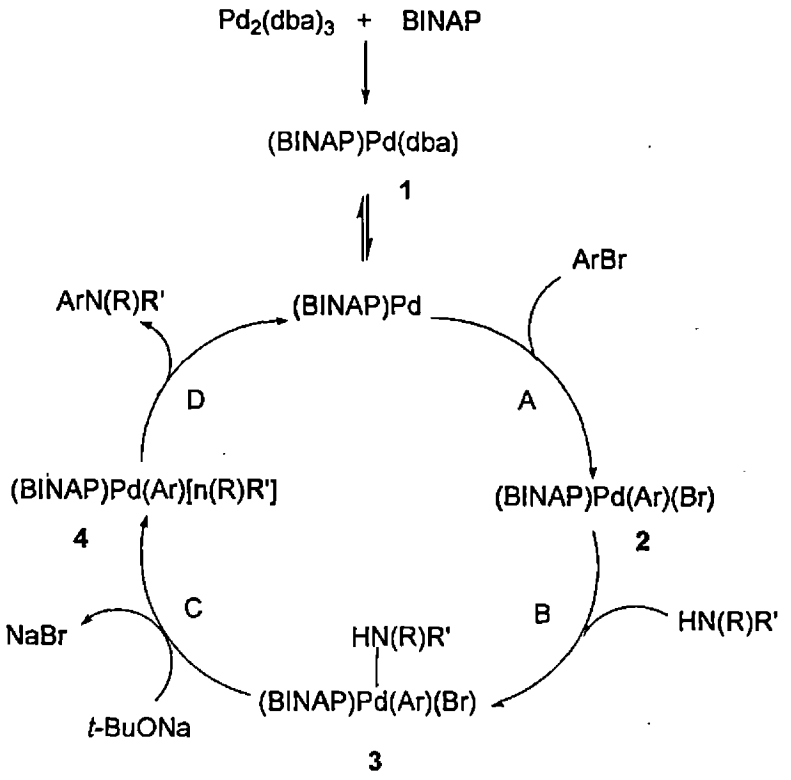


89 %

cat = $Pd_2(dba)_3$ / P(*o*-tolyl)$_3$ or $PdCl_2[P(o\text{-tolyl})_3]_2$

Palladium–catalyzed cross coupling of aryl bromides with amines have stressed the need to employ P(*o*–tolyl)$_3$ as a ligand in order to obtain reasonable yields of the desired aniline products.[15,25–28] The importance of this ligand was attributed to its steric bulk, which is believed to hinder the formation of *bis*(phosphine) palladium complexes as intermediates. Hartwig has demonstrated through kinetics studies that oxidative addition, palladium–nitrogen bond formation, and reductive elimination proceed through mono-phosphine palladium complexes when P(*o*–tolyl)$_3$ is used as the ligand.[29] One drawback of the use of these P(*o*–tolyl)$_3$/Pd catalyst systems is that they typically give poor results when applied to the cross coupling of primary amines with aryl bromides. In general, low yields of the desired aniline are realized, and large amounts of arene side products are produced which result from β–hydride elimination from a palladium–amido intermediate. In a number of transition metal complexes, the use of the chelating *bis*(phosphine) ligand has been found to inhibit β–hydride elimination. Hartwig's results rendered this alternative unattractive since it appeared that a chelating ligand would cause difficulty in accessing the requisite three–coordinate monophosphine complexes. In conjunction, Buchwald et al .[21a] used BINAP as a supporting ligand for palladium–catalyzed carbon–nitrogen bond forming reactions. The use of BINAP as a ligand for coupling secondary amines with ortho–substituted halides also resulted in much higher yields than were obtained when P(*o*–tolyl)$_3$ was employed. The effectiveness of $Pd_2(dba)_3$/BINAP suggests that any or all of steps A–D (Scheme 3) may occur from intermediates without prior phosphine dissociation. In particular, coordination of the amine to **2** would form pentacoordinate **3**.[30] Deprotonation of the coordinated amine by *t*-BuONa would give **4** which reductively eliminates to give (BINAP)Pd and the aniline product. Structural features specific to BINAP may be the key to the success of this catalyst system.

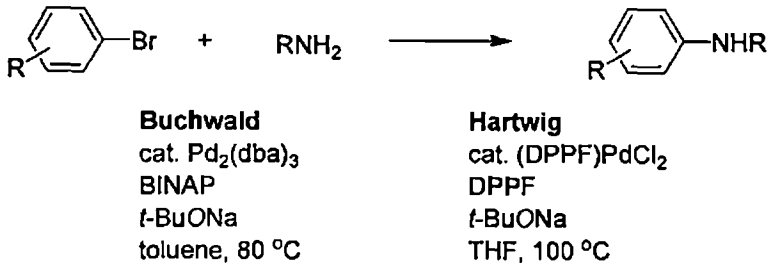
Scheme 3

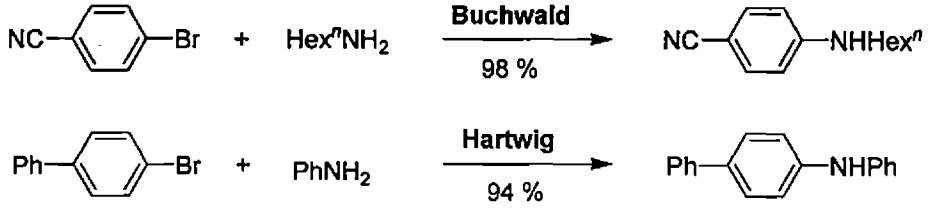


The research groups of Buchwald[21a] and Hartwig[20] reported amination reactions with palladium complexes of BINAP and DPPF as catalysts. These palladium complexes provided aminations of aryl bromides and iodides with primary alkyl amines, with cyclic secondary amines, and with anilines. It is ironic that the amination chemistry was first discovered upon use of a particular labile phosphane, but dramatically improved by the use of chelating ligands.

The Buchwald group found that a combination of $Pd_2(dba)_3$ and BINAP in the presence of *t*–BuONa performed as a superior catalyst for the cross coupling of amines with aryl bromides to afford aniline derivatives.[21a] The efficiency of BINAP as a ligand may be attributed to its ability to inhibit the formation of catalytically inactive palladium *bis*(amine) aryl halide complexes. This remarkable protocol is illustrated by the catalytic cross–coupling of 4–cyanobromobenzene with n–hexylamine to give the aminated product in 98% yield using only 0.05 mol% of catalyst.

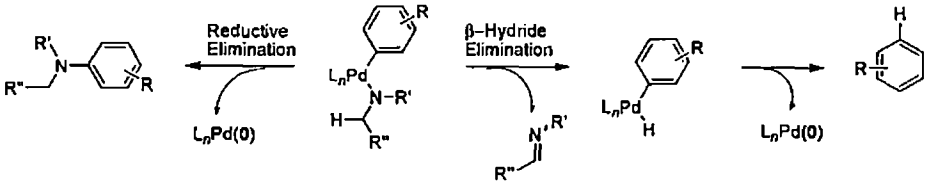
Scheme 4



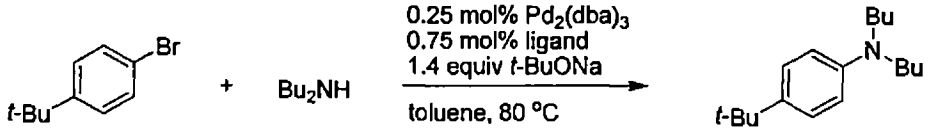


The Hartwig group discovered that $(DPPF)PdCl_2$ catalyst provided high yields of mixed, secondary arylamines from aryl halides and primary amines, notably in examples that gave low to moderate yields with the Pd(0)/P(*o*–tolyl)$_3$ catalyst system.[20] This study revealed several important concepts; first, the catalytic cycle involves *bis*(phosphine) intermediates. Second, sterically encumbered phosphines are not necessary for the high–yielding, intermolecular amination of aryl halides and finally the favorable selectivity for reductive elimination over β–hydrogen elimination results from chelation and large bite angle, rather than from steric effects. The methods, based on the use of the monophosphine ligand P(*o*–tolyl)$_3$ or *bis*–phosphine ligands BINAP and DPPF, lead to efficient coupling of primary amines and secondary cyclic amines, the arylation of secondary acyclic amines remains problematic; the corresponding tertiary aromatic amines are generally formed in low yields. This was especially true when electron–rich arenes were used as coupling partners.[12b] These reactions are usually plagued by the reduction of the starting aryl bromide, leading to the formation of the byproduct arene via a β–hydride elimination pathway from amido–palladium intermediate (Scheme 5). To surmount such problem Buchwald *et al.*[12b] tested that palladium complexes derived from ligands (*rac*)–PPFA[31] and (*rac*)–PPF–OMe[31,32] are highly effective for the aryl amination reaction of acyclic secondary amines (Scheme 6).

Scheme 5

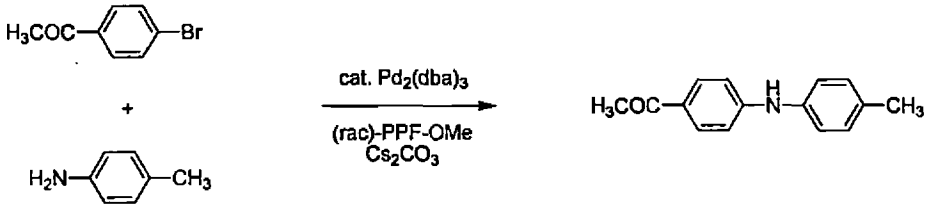


Scheme 6



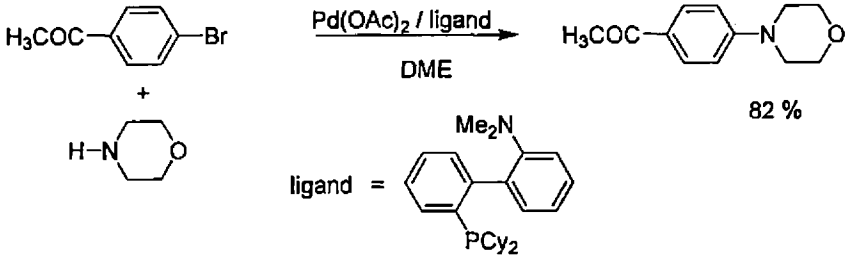
It was noted that the combination of $Pd_2(dba)_3$ and (*rac*)–PPF–OMe allowed the reaction to tolerate the presence of methyl and ethyl esters aldehydes, enolizable ketones and nitro groups, which are incompatible with reaction conditions which employ *t*–BuONa as the stoichiometric base (Scheme 7).[22]

Scheme 7



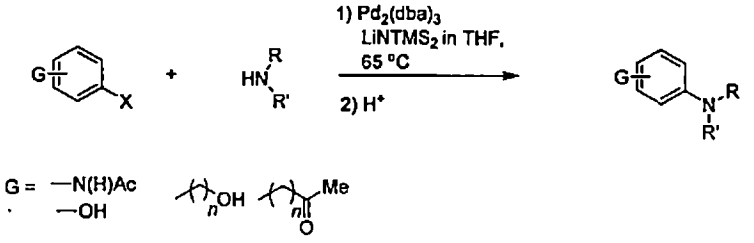
Buchwald *et al.*[18a,33] reported the palladium catalyzed amination of 4–bromoacetophenone with morpholine in the presence of $Pd(OAc)_2$, ligand, K_3PO_4 in DME(Scheme 8).

Scheme 8



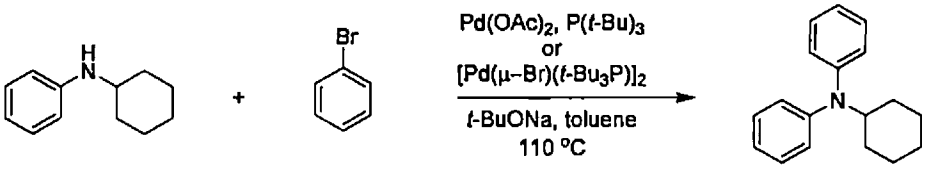
Recently, Buchwald *et al.*[34] described a method for the coupling reaction of amines with aryl halides containing alcohol, phenol, amide, or keto groups in the presence of $LiN(TMS)_2$ (Scheme 9).

Scheme 9



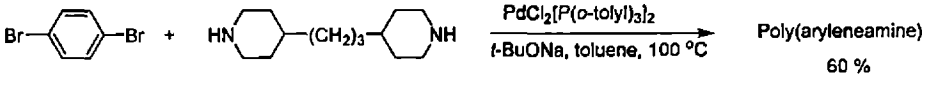
Very recently, Prashad *et al.*[35] reported an efficient palladium catalyzed amination of aromatic bromides with hindered N–alkyl substituted anilines either using the combination of $Pd(OAc)_2$ and P(*t*–Bu)$_3$ or a palladium(I) tri–*tert*–butylphosphine bromide dimer (Scheme 10), $[Pd(\mu\text{–}Br)(t\text{–}Bu_3P)]_2$, a new, commercially available, and easily handled catalyst.

Scheme 10



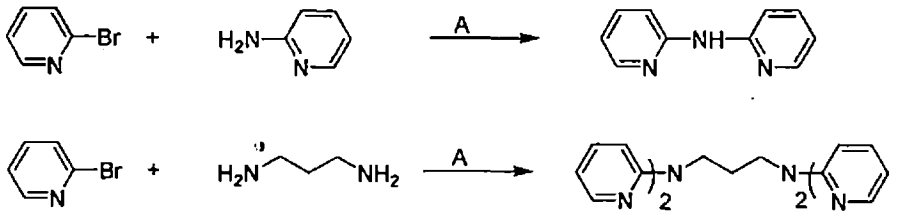
The amination methodology has recently found application in polymer synthesis. The reaction of aryl dibromide with secondary amine (Scheme 11) proceeds smoothly in the presence of stoichiometric *t*–BuONa and catalytic $PdCl_2[P(o\text{–tolyl})_3]_2$ to give new poly(aryleneamine).[38]

Scheme 11



The Buchwald groups have revealed that the palladium catalyzed amination strategy can be effectively applied to the synthesis of amino pyridines and this protocol represents a significant improvement relative to existing procedures which often require activated substrates and harsh reaction conditions.[37] The reaction of 2–bromopyridine with 2–aminopyridine (sheme 12) produced the interesting product in 87% yield. This was also an effective strategy for preparing diarylated diamines.

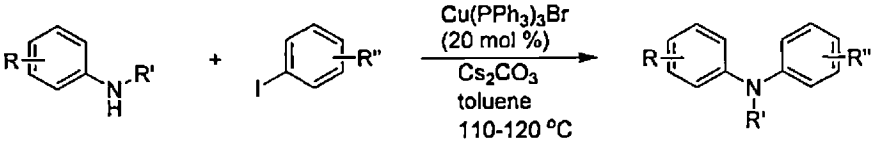
Scheme 12



A = $Pd_2(dba)_3$, BINAP, $NaOBu^t$, toluene, 70 °C

One of the most widely used methods for the synthesis of arylamines is the Ullmann condensation, in which an amine is condensed with an aryl halide in the presence of base and a copper catalyst.[8e] Traditionally, copper–catalyzed Ullmann coupling protocols necessitate the use of high temperature (200 ^{0}C) providing low to moderate yield of amines and often require the use of stoichiometric amounts of copper reagents, which, on scale, leads to problems of waste disposal.[38] Additionally, they have been plagued by poor substrate scope. However, there has been a resurgence of more economical copper–mediated systems that circumvent or overcome the limitations of classical Ullmann–Goldberg type couplings, which are known to require harsh reaction conditions.[39] Recently, milder Ullmann–type processes for C–N bond formation such as N–arylation of anilines,[40] amides,[41] imidazoles,[42] indoles,[43] and hydrazines[44] have been reported. Progress in the arylation of aliphatic amines, however, has been realized only in the context of chelating substrates,[39b] such as α– and β–amino acids[45] and β–amino alcohols[48] or in strategies utilizing less convenient or more costly arylating agents.[47] Gujadhur *et al.*[40b–c] have found that the copper complex $Cu(PPh_3)_3Br$, is active for amination of mono– and diarylamines to di– and triarylamines, respectively, using Cs_2CO_3 as a base at 120 ^{0}C (Scheme 13).

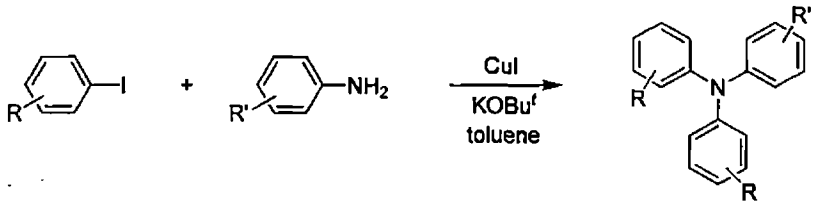
Scheme 13



Similarly Goodbrand and Hu[39a] have reported ligand–accelerated single–step catalytic synthesis of triarylamines with high selectivity using CuCl/1,10–phenanthroline catalyst system and KOH as a base at 125 ^{0}C. Chaudhari *et al.*[40a]

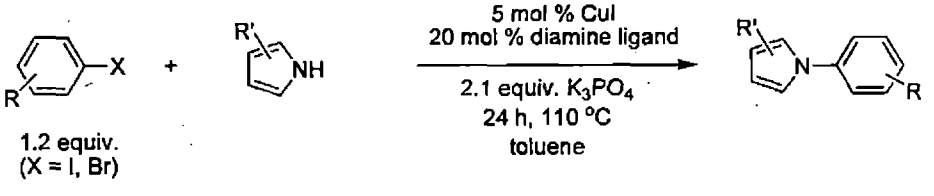
described a simple and efficient methodology for the synthesis of triarylamines in a single step using a ligand–free CuI catalyst and potassium tertiary butoxide as the base (Scheme 14).

Scheme 14



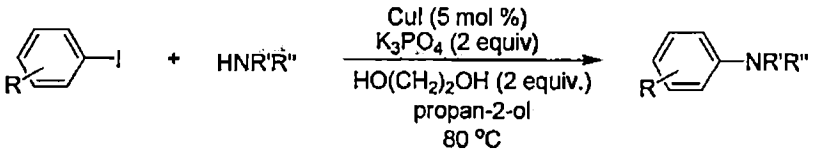
Kang *et al.*[47a] demonstrated the Cu–catalyzed *N*–arylation of amines with hypervalent iodonium compounds with secondary aliphatic amines, at room temperature in presence of weak base. Later on they[41b] also described the Cu–catalyzed N–arylation of benzamides or nitrogen heterocycles with catalytic CuI (10 mol %) in the presence of ethylene diamine (10 mol %) as a ligand and K_3PO_4 or Cs_2CO_3 as a base under mild conditions. After that a variety of diamine ligands have been used by Buchwald group[48] for copper–catalyzed N–arylation of π–excessive nitrogen heterocycles (Scheme 15). The coupling of either aryl iodides or aryl bromides with common nitrogen heterocycles (pyrroles, pyrazoles, indazoles, imidazoles, and triazoles) was successfully performed in good yield with catalysts derived from diamine ligands and CuI. It has been found that the functional groups such as aldehydes, ketones, alcohols, primary amines, and nitriles on the aryl halide or heterocycle remain unaffected after reaction.

Scheme 15



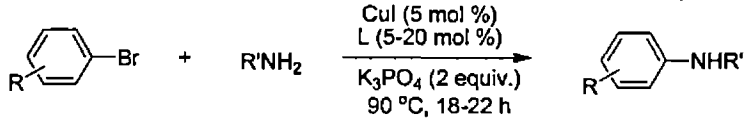
Recently, Buchwald *et al.*[43c] reported a mild, practical Cu–catalyzed amination of functionalized aryl iodides using air stable CuI as the catalyst, ethylene glycol as the ligand and unpurified propan–2–ol as the solvent (Scheme 16). These reactions can be performed without protection from air or moisture.

Scheme 16



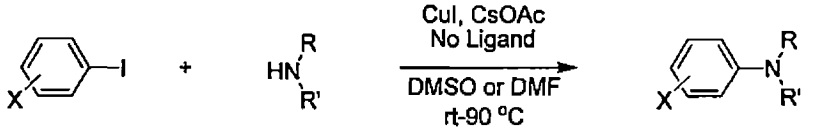
Very recently, Kwong and Buchwald[49] reported a mild Cu–catalyzed coupling of primary amines to functionalized aryl bromides using air–stable CuI as the catalyst and structurally simple salicylamides as ligands (Scheme 17).

Scheme 17



A unique combination of CuI and cesium acetate was found to mediate intermolecular amination of aryl halides under mild conditions (Scheme 18).[50]

Scheme 18



R, R = H, alkyl, aryl, Ns

II.2: Present work: Background, Objective and strategy

The palladium–catalyzed amination of aryl halides[12,13b,21a,20,26,27] has become an important method for the synthesis of arylamines found in pharmaceuticals,[51] materials with important electronic properties,[36,52] and ligands for early metal catalysts.[6] Because of the importance of this synthetic method, there has been extensive effort to find catalysts that provide high turnover numbers,[16a,53] fast reaction rates,[17b,33] high functional group compatibility,[22] and increased scope of the aromatic C–N bond formation. The Buchwald–Hartwig reaction has emerged during the last decade as a very powerful tool for the synthesis of aryl amines. The hetero cross–coupling reaction is normally carried out in presence of a palladium catalyst, most commonly a *bis*–phosphine ligand and a base (3–5 equiv), preferably sodium *tert*–butoxide.[26] Many advances have been made in this palladium–catalyzed amination reaction since it was reported by Buchwald and Hartwig.[14b,54] The use of sodium *tert*–butoxide as the base has limitations with a number of common functional groups such as esters, enolizable ketones, aldehydes, nitriles and nitro groups, and efforts

have been made to replace it with a milder base. In presence of other base such as KOH or Cs_2CO_3, the double amination proceeds slowly and leads to an increased amount of the reductive product.[13b,21b,55] Furthermore, several groups employed this protocol to synthesize polyanilines[52k-l,56] and polyaminosubstituted benzenes.[55,57] Although anilines gave high yields of double amination products, primary amines did not afford the desired *bis*–amination due to competing reductive debromination. While studying double amination of *o*–dibromobenzene with primary amines, Diver *et al.* reported formation of imine besides concomitant reductive debromination as the byproducts.[55] From our laboratory, it was previously reported that KF–alumina could serve as a potential basic surface for palladium–catalyzed amination of halopyridines.[58] The solvent free dry media reaction has been found to have advantages in the case of halopyridines. While extending the preparative advantages for amination of haloaromatics, we conducted KF–alumina mediate palladium–catalyzed C–N cross–coupling should be studied with polyhalobenzenes to extend the scope and the amelioration of the various parameters of this amination process.

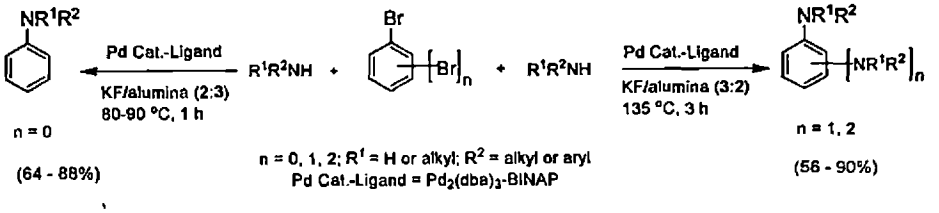
II.3: Present Work: Results and Discussion

The catalytic amination of aryl halides represents a mild alternative to classical methods of aryl C–N bond formation and has many potential applications for the synthesis of aniline derivatives, which are inaccessible through other routes.[10,12,13b] The most commonly used catalysts for this transformations are based on chelating phosphine such as BINAP and DPPF,[13b] aryl bromide are the most frequently employed substrates[10,12,13b] Recent reports have described the use of other catalyst system based on bulky, electron–rich, phosphine ligands.[16,17b,18,33,53,59] However, the BINAP catalyst system remains the most active and general catalyst for the coupling of aryl bromide with primary and secondary amines. Additionally, the BINAP catalyst system functions well in the presence of the weak base KF/Al_2O_3, allowing for a high level of functional group tolerance. In this part, we have described our studies on the scope and limitations of the Pd/BINAP–catalyzed amination of aryl bromides. Certain types of secondary amines were also efficiently arylated using the Pd/BINAP catalyst system. These reactions provided the best results when conducted without solvent. Considerably improved results were obtained for several substrate combinations that gave low yields with catalysts supported by P(*o*–tol)$_3$ and 1,2–*bis* (diphenylphosphino)ethane ligands. For example, the reaction of Piperidine with 1,3–dibromobenzene (entry 15 table 1) afforded the desired *bis*–aminated

product in 78% and mono–aminated product 12% isolated yield using 2 mol% of the $Pd_2(dba)_3$/BINAP catalyst. In comparison, the $Pd_2(dba)_3$/P(*o*–tol)$_3$ and $Pd_2(dba)_3$/1,2–*bis* (diphenylphosphino)ethane catalyst did not produce the desired product even when other conditions remain same. In above similar case $Pd(OAc)_2$/BINAP combination gives major mono–aminated product in 71% and *bis*–aminated product in 12% isolated yield.

In the course of developing synthetic protocol towards amination of polyhaloaromatics on KF–alumina surface, we first employed similar conditions that we had developed for mono–amination of bromopyridines [amine (2 mmol), KF–alumina (1:4; 1 g/mmol), palladium–phosphine catalyst (2 mol%) for bromopyridines (1 mmol)]. Although amination of bromobenzene with *sec.* amines did work well under the conditions, the primary amines showed sluggish reactions and poor yields. The conditions were optimized and the best results are achieved when KF impregnated on alumina was used in the ratio of (2:3). In presence of $Pd_2(dba)_3$–BINAP as the catalytic system, bromobenzene underwent amination with both primary (entries 3 and 4) and secondary amines (entries 1 and 2) quite rapidly at moderate temperatures (80–90 °C/1 hour) yielding the corresponding anilines in 73–88% yields (Table 1). Since the use of other bases can affect groups like enolizable ketones, we tested amination of *p*–bromoacetophenone using the solvent–free KF–alumina surface. Gratifyingly, amination occurred effectively without any changes to the base–sensitive functionality (entry 5). In a typical experiment, the catalyst $Pd_2(dba)_3$–BINAP (2 mol%) was admixed intimately with KF–alumina (2:3; 2g), heated at 80–90 °C for 15 min. and then treated with the mixture (2 mmol aryl bromide and 5mmol amine) was stirred at 80–90 °C for 1 hour (Scheme 19). The desired product was then isolated by column chromatography over silica gel.

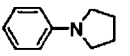
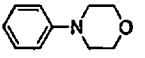
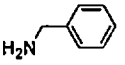
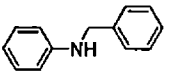
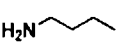
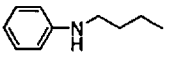
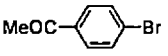
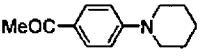
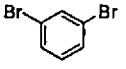
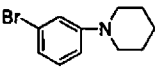
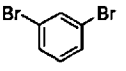
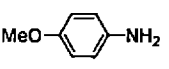
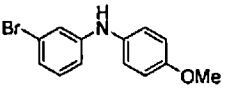
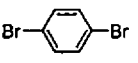
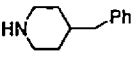
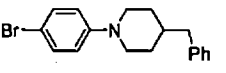
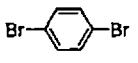
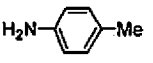
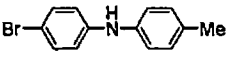
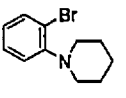
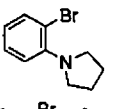
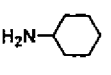
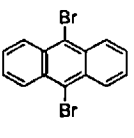
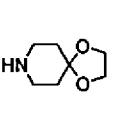
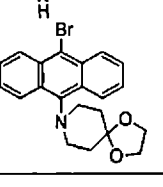
Scheme 19



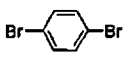
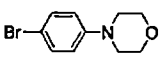
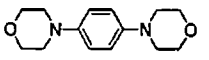
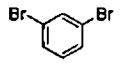
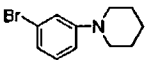
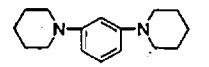
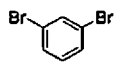
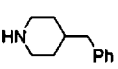
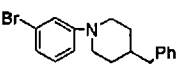
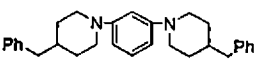
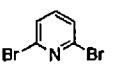
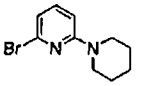
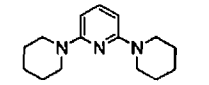
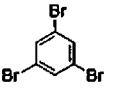
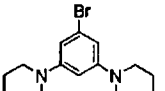
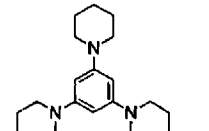
Since poiyaminobenzenes are important compounds for various industries, we wanted to employ the reaction conditions to effect polyamination of polyhaloaromatics. While applying similar conditions to dibromobenzenes, we ended up with mono–aminated products only (entries 6-9, and 13). Earlier we observed

similar results in case of dibromopyridines. In order to obtain the *bis*–aminated products, we examined various proportions of KF–alumina and different catalytic systems. The combination of KF–alumina in the ratio of (3:2) and $Pd_2(dba)_3$–BINAP as the catalyst was found to be suitable for *bis*–, or *tris*–amInations in one–pot reactions (entries 14, 15 and 16). Using the similar conditions, 2,6–dibromopyridine and 1,3,5–tribromobenzene yielded the corresponding *bis*– and *tris*–aminated products (entry 17 and 18) in 90% and 67% yields respectively. Neither reductive debrominatIon nor the formation of imine was observed under this condition, indicating that the possible β–elimination might not be favourable, and thus avoids contamination with any other byproducts. The amination occurs quite rapidly for mono–amination (1 hour) while polyamination requires longer times (3 hour) and higher temperatures (135 °C). In the case of polyaminations, partial mono–aminated products remained in the reaction mixtures, which were easily isolated by column chromatography (Table 1). Interestingly, 1,2–dibromobenzene did not produce the 1,2–*bis*–amines in either condition, possibly due to steric crowding (entries 10–12). Several variations in terms of the catalytic system, the surface (KF–alumina) and temperatures did not change the course of the reactions.

Table: 1 Palladium-catalyzed selective amination of haloaromatics on KF-alumina surface

Entry	Aryl bromide	Amine	Conditions	Product (s)[a]	Yield [%]
1			A		83
2			A		88
3			A		78
4			A		73
5			A		80
6			A		86
7			A		75
8			A		90
9			A		80
10			A or B		90
11			A or B		80
12			A or B		65
13			A		64

Continued from previous page: Table 1

Entry	Aryl bromide	Amine	Conditions	Products		Yield (%)
14			B		17		72
15			B		12		78
16			B		14		73
17			B		5		80
18			B		18		67

II.4: Conclusion

In summary, we have demonstrated that it is possible to effect palladium–catalyzed amination of halobenzenes on a solvent–free surface of KF–alumina without using any strong bases such as sodium *tert*–butoxide. The base–sensitive functional groups remained unaffected under this condition. The procedure is also effective for one–pot mono– or poly–aminations selectively, depending on the conditions used, and thus constitutes a mild and benign method for the synthesis of polyaminobenzenes. No reductive bromination leading to other by products has been observed in this procedure.

II.5: Experimental

II.5.A: Preparation of Activated KF–Al_2O_3 (2:3)

A mixture of basic alumina (Activity I according to Brockmann) (6 g) and KF (4 g) was mixed intimately with a grinder and then activated at 250°C under reduced pressure (0.5 mm of Hg) for 30 min. Then cooled under reduced pressure and opened under a weak flow of N_2 and was used for performing the reactions. The activated KF–alumina may be kept in a glass–stopper flask flashed with N_2 for 2–3 weeks, without any loss of activity.

Activated KF–Al_2O_3 (3:2) was prepared according to the above procedure and changing the proportions only.

II.5.B: General Procedure for the Amination Reactions

Conditions [A]: A mixture of $Pd_2(dba)_3$ (2 mol%) and BINAP (4 moi%) was admixed intimately with KF–alumina (2:3; 2 g) and heated at 80–90 °C for 15 min. Aryl bromide (2 mmol) and an amine (5mmol) were added to the solid surface and the mixture was stirred at 80–90 °C for 1 h. An orange color was developed while mixing and gradually disappeared during one hour. The solid mass was then cooled, packed on a column of silica gel and eluted with EtOAc: light petroleum (1:9) to afford the mono aryl amines. All the products were identified by IR, ^1H and ^{13}C NMR spectral data.

Conditions [B]: The reaction conditions were identical except the amine was taken in 7–8 equivalent; KF–alumina was used in the ratios of (3:2) and the solid mixture was heated at 135 °C for 3 hours. Pure *bis*–amines were obtained by chromatography over silica gel and elution with EtOAc: light petroleum (1:9). The spectral data were consistent with the assigned structures.

II.5.C: A Representative procedure for Mono-amination using KF- Al_2O_3 (2:3)

A mixture of (*rac*)–BINAP (25 mg, 0.04 mmol) and $Pd_2(dba)_3$ (18 mg 0.02 mmol) was mixed intimately with KF–Al_2O_3 (2:3) (2 g) under nitrogen and then heated at 80 °C for 15 min. It was cooled under nitrogen and treated with a mixture of piperidine (680 mg, 8 mmol) and 4–bromo acetophenone (398 mg, 2 mmol). The solid mixture was heated under nitrogen at 80 °C for 1 h. An orange colour, immediately developed on mixing, was gradually disappeared indicating completion of the reaction. After cooling to room temperature, the solid reaction mixture was stacked on a column of silica gel (60–120 mesh) and the desired product was isolated by eluting with petroleum ether: ethyl acetate (19:1) to give 325 mg 1–(4–piperidin–1–yl–phenyl)ethanone (entry 5) with 80% yield.

II.5.D: Spectral Analysis

Entry 1: 1–Phenyl–pyrrolidine
Temp: 90 °C; Time: 1 h,
Yield: 83%; (obtained as lquid); UV (MeOH): λ_{max} 203.6, 254.6 nm; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.2–7.17 (m, 5H), 3.4–3.35 (m, 4H), 1.98–1.93 (m, 4H).

Entry 2: 4–Phenyl–morpholine
Reaction temp: 90 °C; Time: 1 h,

Yield: 88%; (solid) mp 54–58 °C (lit.[60] mp 57 °C); UV (MeOH): λ_{max} 248.0, 283.6 nm; IR (Nujol): ν_{max} 2962.5, 2744.5, 1600.8, 1498.6, 1232.4, 1122.5, 927.7, 759.9 cm^{-1}; ^1H–NMR ($CDCl_3$, 300 MHz) δ = 7.21 (t, 2H, *J* = 7.2 Hz), 6.89–6.80 (m, 3H), 3.8 (t, 4H, *J* = 4.8 Hz), 3.1 (t, 4H, *J* = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 129.1, 120.3, 115.8, 66.7, 49.5.

Entry 3: Benzyl–phenyl–amine
Reaction temp: 90 °C, Time: 1 h;
Yield: 78%, (solid) m.p. 36–40 °C (lit.[61] mp 36 °C); UV (MeOH): λ_{max} 206.8, 246.8, 295.4 nm; IR (Nujol): ν_{max} 3419.6, 3053.1, 1600.8, 1506.3, 1452.3, 983.6, 748.3 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.33–7.12 (m, 7H), 6.70–6.59 (m, 3H), 4.3 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.1, 139.4, 129.2, 128.6, 127.5, 127.2, 117.2, 112.9, 48.3.

Entry 4: Butyl–phenyl–amine
Reaction temp: 90 °C, Time: 1 h;
Yield: 73%; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.17 (d, 2H, *J* = 6.6 Hz), 6.43 (d, 2H, *J* = 6.9 Hz), 3.0 (t, 2H, *J* = 7.1 Hz), 1.57–1.48 (m, 2H) 1.40–1.28 (m, 2H), 0.874 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 132.0, 115.1, 44.4, 31.2, 20.2, 13.9.

Entry 5: 1–(4–piperidin–1–yl–phenyl)ethanone
Reaction temp: 80 °C, Time: 1 h;
Yield: 80%, (solid) mp 87–89 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ=7.85 (d, 2H, *J* = 8.7 Hz), 6.85 (d, 2H, *J* = 8.7 Hz), 3.4 (m, 4H), 2.7–2.5 (s, 3H), 1.8–1.57 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=196.4, 154.4, 130.5, 126.7, 113.3, 48.7, 26.0, 25.3, 24.4.

Entry 7: (3–Bromo–phenyl)–(4–methoxy–phenyl)–amine
Reaction temp: 90 °C, Time: 1 h;
Yield: 75%, m.p. 139–143 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.22–6.87 (m, 8H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 131.0, 123.9, 122.4, 118.0, 115.2, 114.1, 96.0, 55.0.

Entry 8: 4-benzyl-1-(4-bromophenyl)piperidine
Reaction temp: 90 °C, Time: 1h;
Yield: 90%; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.22–7.07 (m, 7H), 6.69 (dd, 2H, *J* = 6.9 & 2.1 Hz), 3.50 (d, 2H, *J* = 12.3 Hz), 2.58–2.47 (m, 4H), 1.67–1.52 (m, 3H), 1.37-1.32

(m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 150.7, 140.4, 131.8, 129.2, 128.3, 126.0, 118.1, 111.3, 49.7, 43.1, 37.8, 31.8.

Entry 9: 8–(10–Bromo–anthracene–9–yl)–1,4–dioxa–8–aza–spiro [4,5] decane

Reaction temp: 90 °C, Time: 1 h;

Yield: 64%, mp 136–138°C; UV (MeOH): λ_{max} 220.0, 257.8 nm; IR (Nujol): ν_{max} 1122.5 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.56 (d, 2H, *J* = 8.7 Hz), 8.48 (d, 2H, *J* = 8.5 Hz), 7.60–7.48 (m, 4H), 4.10 (s, 4H), 3.57 (t, 4H, *J* = 5.3 Hz), 2.05 (t, 4H, *J* = 5.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=131.4, 131.2, 128.3, 126.9, 125.3, 125.2, 107.6, 64.4, 49.9, 36.4.

Entry 10: 1–(2–Bromo–phenyl)–piperidine

Reaction temp: 135 °C, Time: 3 h;

Yield: 82%, (liquid); UV (MeOH): λ_{max} 211.4, 256.2 nm; IR (Nujol): ν_{max} 2935.5, 2850.6, 2804.3, 1473.5, 1232.4, 1022.2, 756.0 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.54 (d, 1H, *J* = 7.9 Hz), 7.24 (t, 1H, *J* = 7.5 Hz), 6.86 (t, 1H, *J* = 7.5 Hz), 2.95 (t, 4H, *J* = 4.6 Hz), 1.57–1.61 (m, 2H), 1.71–1.78 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 133.7, 128.1, 123.8, 121.0, 120.1, 53.3, 26.2, 24.2.

Entry 11: 1–(2–Bromo–phenyl)–pyrrolidine

Reaction temp: 135 °C, Time: 3 h;

Yield: 80%, (obtained as liquid); UV (MeOH): λ_{max} 209.6, 255.0 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.51 (d, 1H *J* = 9.2 Hz), 7.2 (t, 1H, *J* = 8.3 Hz), 6.98 (m, 1H), 6.76 (t, 1H, *J* = 7.4 Hz), 3.37 (t, 4H, *J* = 6 Hz), 1.95 (t, 4H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.5, 129.6, 123.3, 120.1, 120.0, 115.7, 53.2, 26.9.

Entry 12: (2–Bromo–phenyl)–cyclohexyl–amine

Reaction temp: 135 °C, Time: 3 h;

Yield: 65%, (obtained as liquid); UV (MeOH): λ_{max} 208.6, 246.2, 308.0 nm; IR (Nujol): ν_{max} 3404.1, 2931.6, 2852.5, 1593.1, 1508.2, 1321.1, 1016.4, 738.7 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.40 (d ,1H , *J* = 8.8 Hz), 7.14(t,1H, *J* = 7.1 Hz), 6.6 (d, 1H, *J* = 8.1 Hz), 6.5 (t, 1H, *J* = 7.0 Hz), 1.79–2.1 (m, 2H), 4.26 (s, 1H), 1.79–2.1 (m, 2H), 1.75–1.79 (m, 2H), 1.67–1.63 (m, 1H), 1.44–1.20 (m, 6H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 144.0, 132.5, 128.3, 117.1, 111.8, 109.8, 51.6, 33.0, 25.8, 24.8.

Entry 13: (4–Bromo–phenyl)–*p*–tolyl–amine

Reaction temp: 135 °C, Time: 3 h;

Yield: 80 %; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.3 (d, 2H, *J* = 8.7 Hz), 7.1 (d, 2H *J* = 8.0 Hz), 6.97 (d, 2H, *J* = 7.9 Hz), 6.86 (d, 2H, *J* = 8.5 Hz), 2.3 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 132.0, 131.0, 120.2, 119.4, 118.9, 20.6.

Entry 14: 1,4–dimorpholino benzene

Reaction temp: 135 °C, Time: 3 h;

Yield: 72%, mp 186–190 °C; UV (MeOH): λ_{max} 204.0, 259.0 nm; IR (Nujol): ν_{max} 2829.4, 1515.9, 1234.4, 1120.6, 923.8 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 6.85 (s, 4H), 3.8 (t, 8H, *J* = 4.8 Hz), 3.01 (t, 8H, *J* = 4.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 150.2, 117.3, 66.8, 50.4.

4–(4-bromophenyl)morpholine

Reaction temp: 135 °C; Time: 3 h,

Yield: 17%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.28 (d, 2H, *J* = 9 Hz), 6.7 (d, 2H, *J* = 9 Hz), 3.77 (t, 4H, *J* = 4.8 Hz), 3.04 (t, 4H, *J* = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.8, 129.1, 117.2, 115.8, 66.7, 49.5.

Entry 15: 1,3–dipiperidino benzene

Reaction temp: 80 °C, Time: 1 h;

Yield: 78%, (obtained as liquid); UV (MeOH): λ_{max} 233.2 nm; IR (Nujoi): ν_{max} 2931.6, 2850.6, 2790.8, 1595.0, 1498.6, 1201.6, 1124.4 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.15 (t, 1H, *J* = 8.1 Hz), 6.61 (s, 1H), 6.49 (d, 1H, *J* = 2.25 Hz), 3.16 (t, 8H, *J* = 5.4 Hz), 1.78–1.70 (m, 8H0, 1.62–1.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=155.9, 132.0, 11.4, 108.8, 53.9, 28.7, 27.1.

Entry 16: 1-(3-bromo-5-(piperidin-1-yl)phenyl)piperidine

Reaction temp: 135 °C, Time: 3 h;

Yield: 14%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 6.57 (s, 2H), 6.50 (s, 1H), 3.13 (t, 8H, *J* = 5.4 Hz), 1.70-1.63 (m, 8H), 1.60-1.53 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 123.5, 111.0, 103.9, 50.7, 25.6, 24.1.

1,3–Di (4–Benzyl piperidin–1–yl)–benzene

Reaction temp: 135 °C, Time: 3 h;

Yield: 73%, (solid) mp 80–83 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.31–7.11 (m, 11H), 6.60–6.46 (m, 3H), 3.62 (d, 4H, *J* = 12 Hz), 2.70–2.57 (m, 8H), 1.76–1.43 (m, 10H),

Entry 17: 3,4,5,6,3",4",5",6"–Octahydro–2H,2"H–[1,2',6',1"]terpyridine
Reaction temp: 135 °C, Time: 3 h;
Yield: 90%, (solid) mp 35–38 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.21 (t, 1H, *J* = 8.0 Hz), 5.9 (d, 2H, *J* = 8.01 Hz), 3.38–3.40 (m, 8H), 1.61–1.47 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.5, 138.8, 95.3, 46.3, 25.5, 24.8.
2-Bromo-6-(piperidIn-1-yl)pyridine
Reaction temp: 135 °C; Time: 3 h,
Yield: 5%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.22 (dd, 1H, *J* = 8.1 & 7.2 Hz), 6.65 (d, 1H, *J* = 7.5 Hz), 6.48 (d, 1H, *J* = 8.4 Hz), 3.50 (t, 4H, *J* = 6.0 Hz), 1.66-1.56 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.2, 140.1, 139.2, 114.8, 104.6, 45.9, 25.1, 24.5.
Entry 18: 1,3,5–Tripiperidino benzene
Reaction temp: 135 °C, Time: 3 h;
Yield: 55%, (solid) mp 178–180°C; UV (MeOH): λ_{max} 240.8 nm; IR (Nujol): ν_{max} 2935.5, 2790.8, 1541.0, 1448.4, 1199.6, 1122.5 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 6.14 (s, 3H), 3.10 (t, 12H, *J* = 5.3 Hz), 1.78–1.66 (m, 12H), 1.58–1.51 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 153.7, 99.2, 51.5, 26.0, 24.3.

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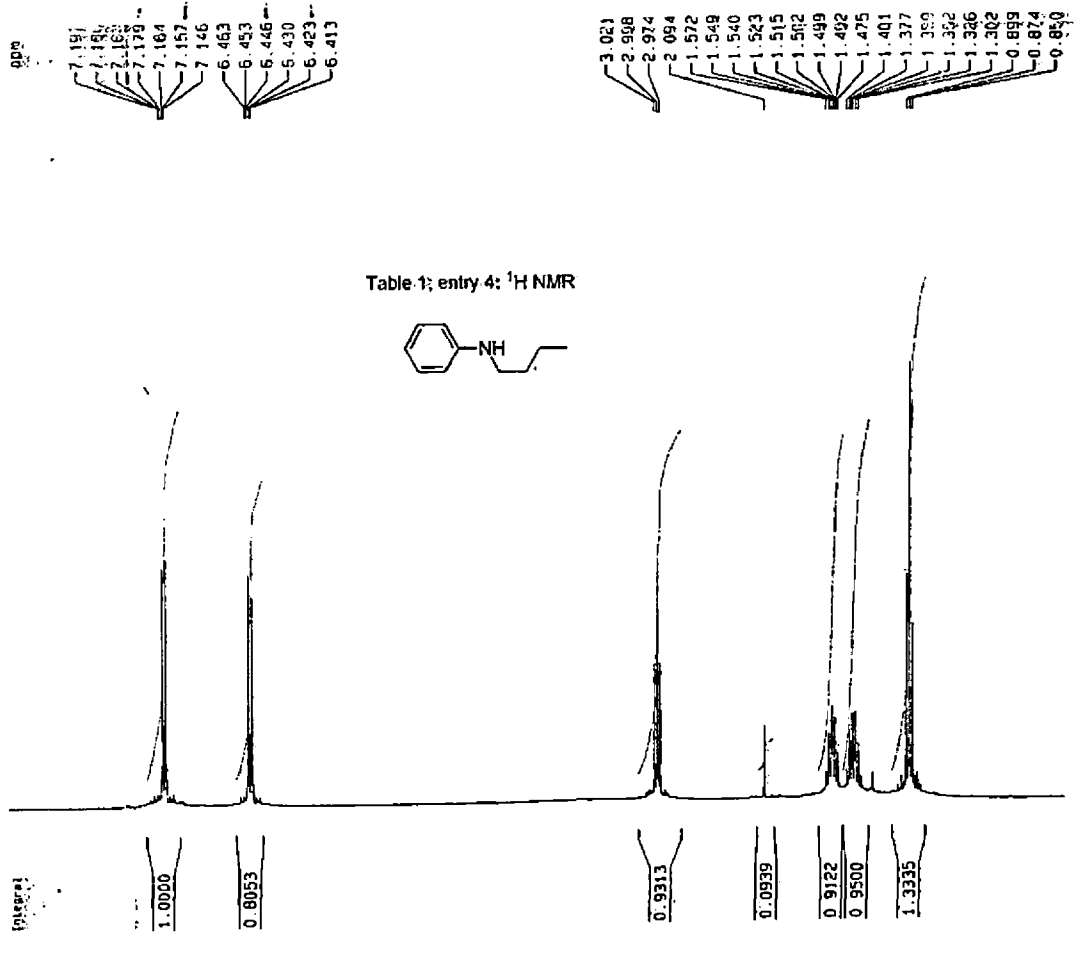

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PROCNO 1

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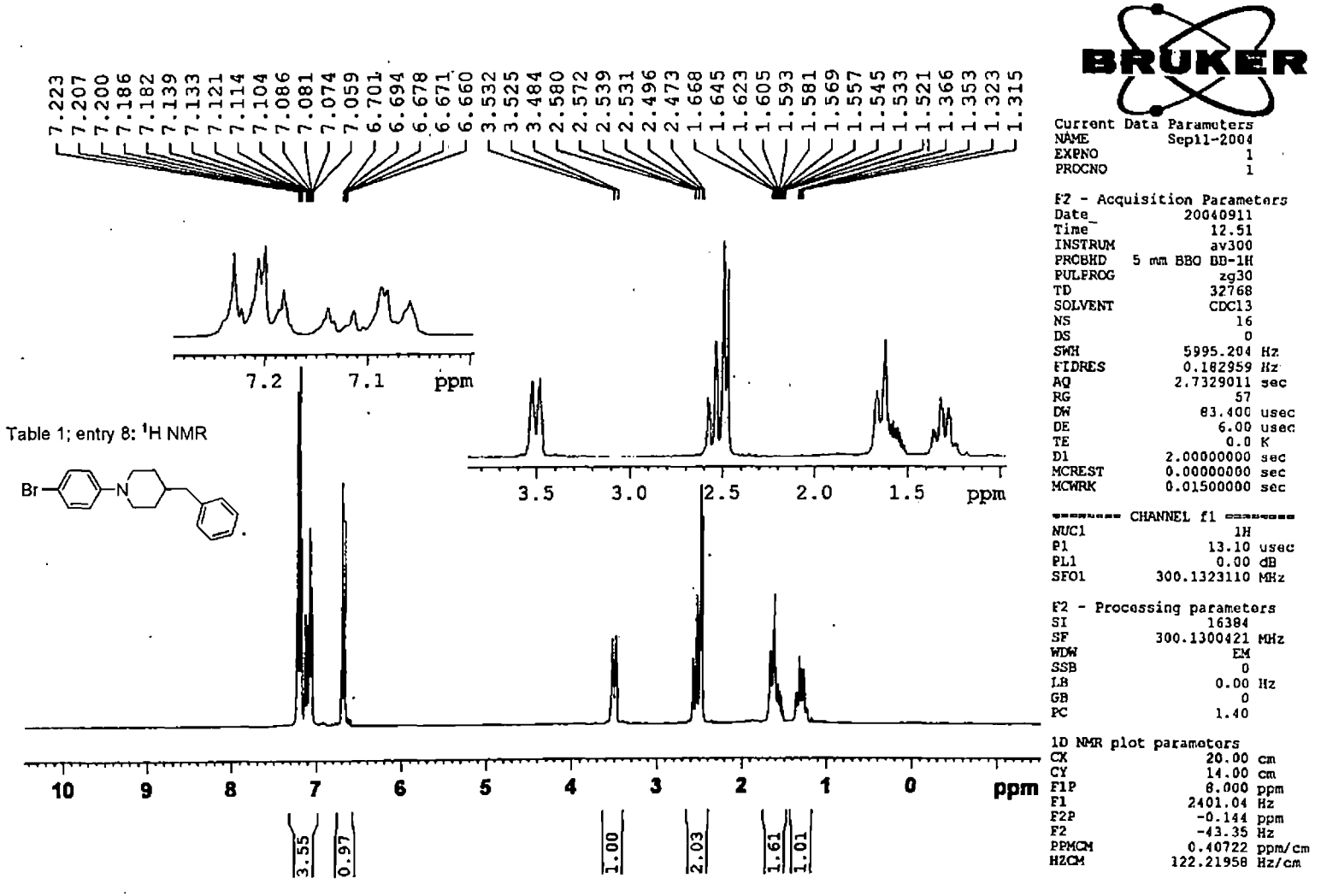

BRUKER

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F2 - Processing parameters

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GB	0
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1D NMR plot parameters

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CY	14.00 cm
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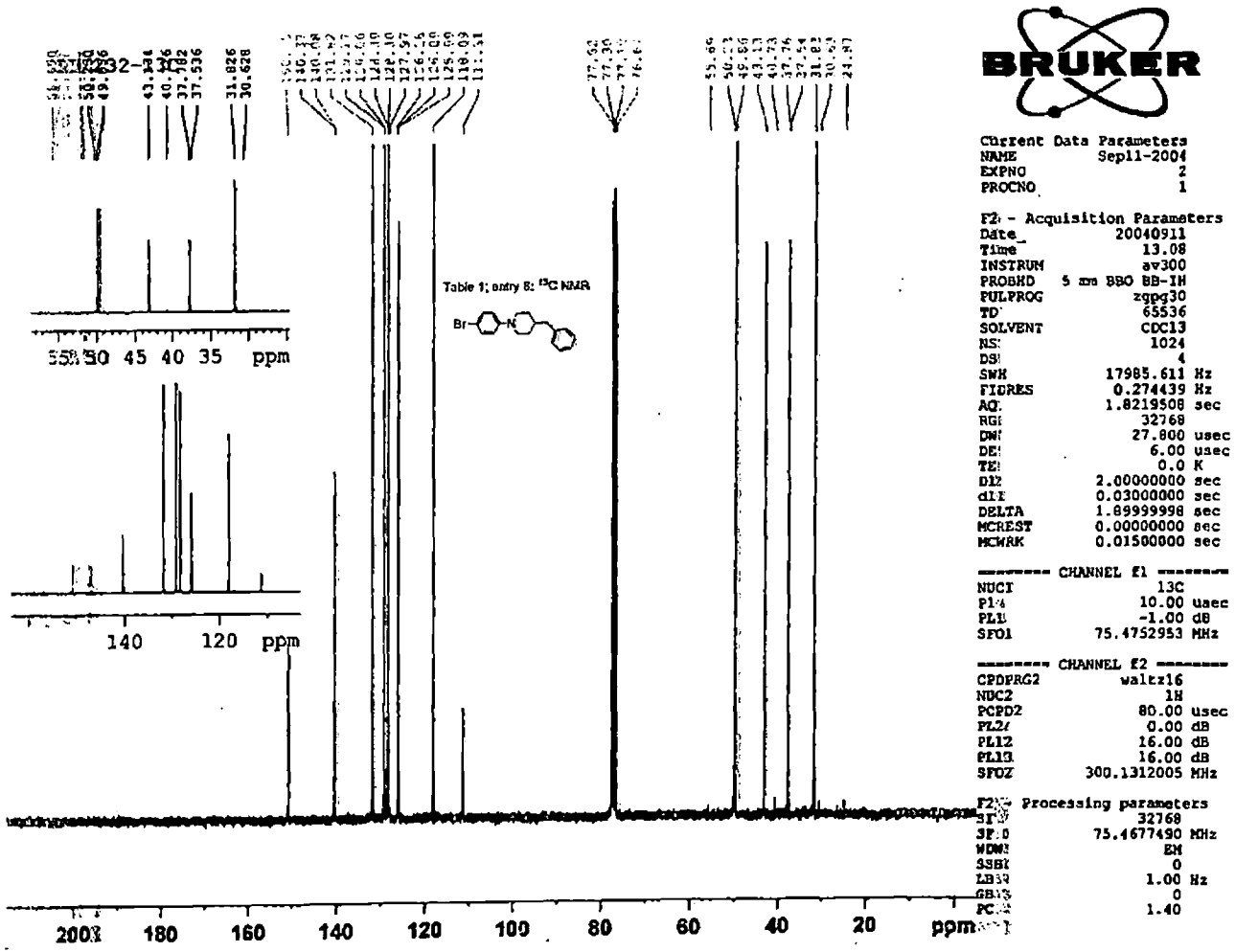
F1	2401.04 Hz
F2P	-0.144 ppm
F2	-43.35 Hz
PPMCM	0.40722 ppm/cm
HZCM	122.21958 Hz/cm



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PL12 16.00 dB
PL13 16.00 dB
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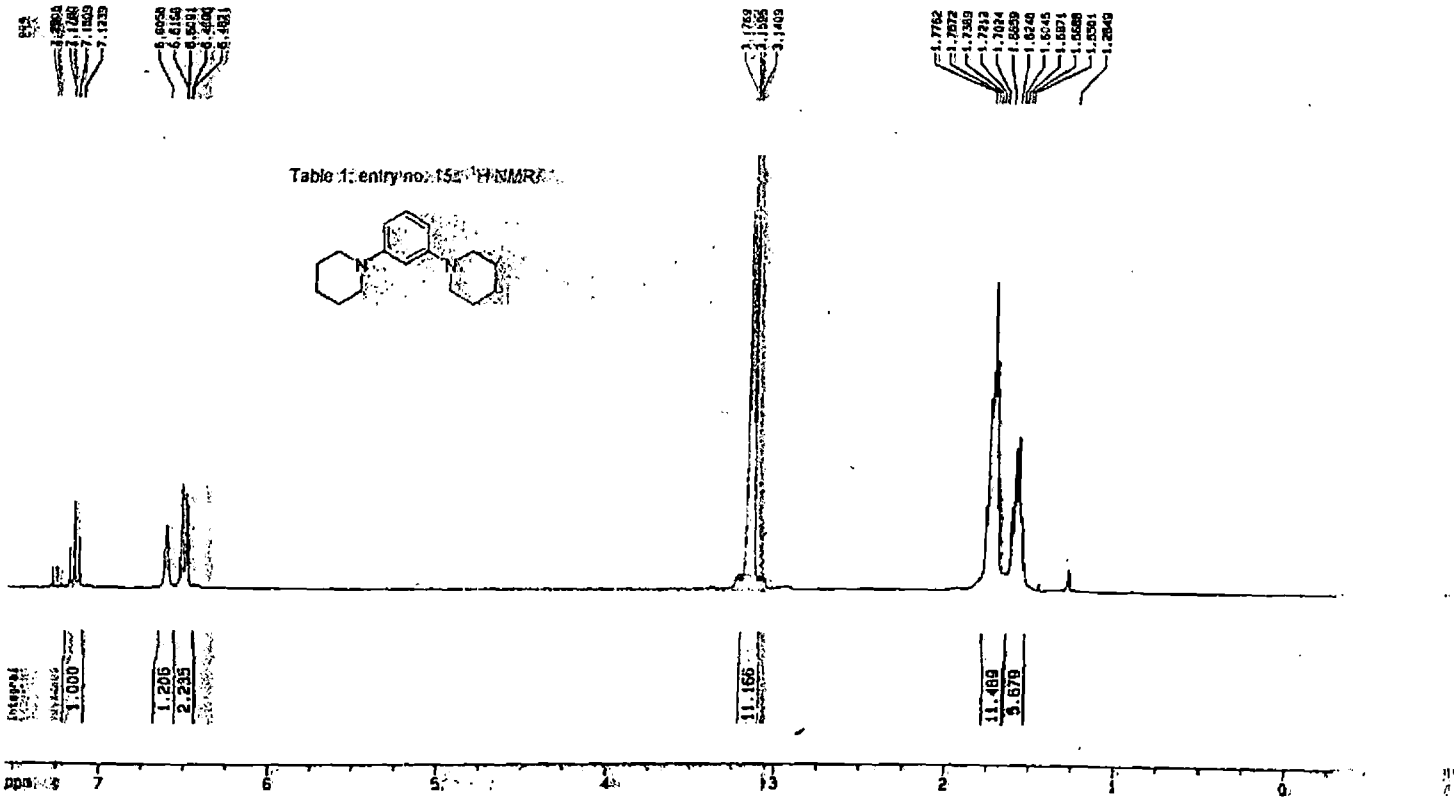
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5.679
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6
5
4
3
2
1
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Table 1; entry no. 15; ^{13}C NMR

Table 1; entry no. 17: ^{1}H NMR

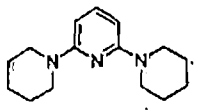
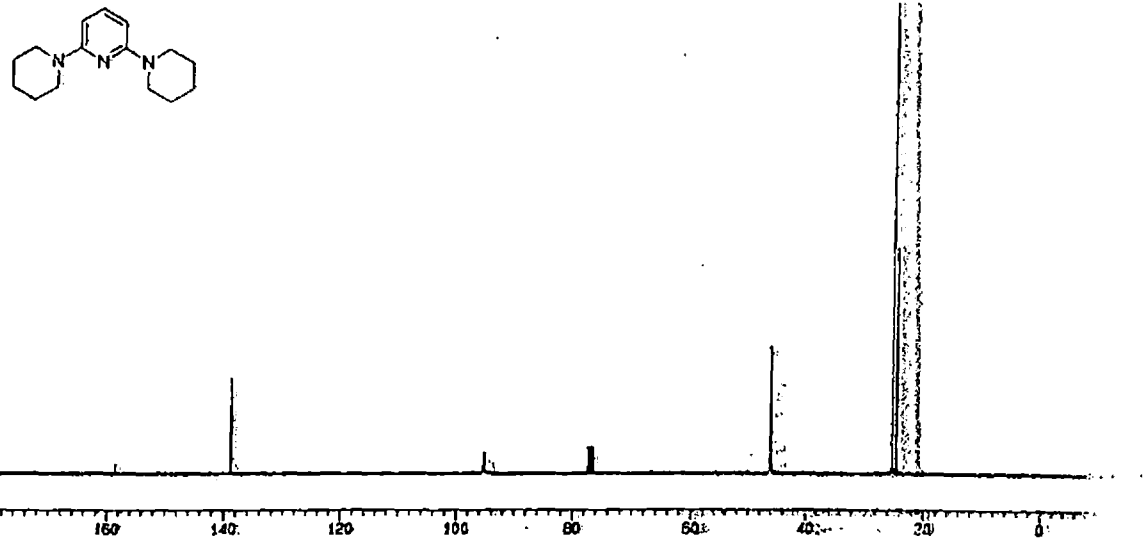


Table 1: entry no. 17: ^{13}C NMR



ppm
153.673
99.215
77.347
76.923
76.501
51.490
25.943
24.298
Table 1; entry 18; ^{13}C NMR
ppm
160
140
120
100
80
60
40
20
0

Molecular Diversity (2005) 9: 259–262
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Short communication

Transfer hydrogenation using recyclable polymer-supported formate (PSF): Efficient and chemoselective reduction of nitroarenes

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Key words: aniline, ion-exchange resin, nitroarene, palladium acetate, polymer-supported formate, transfer hydrogenation

Summary

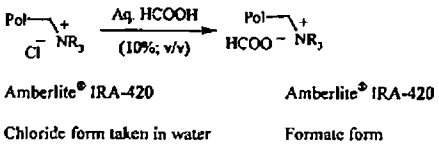
Nitroarenes can be reduced in high yields to the corresponding anilines by transfer hydrogenation using a stable H-donor, polymer-supported formate (PSF) in combination with palladium acetate (catalytic). The reactions occur at 100–120 °C in dimethyl-formamide and the PSF can be recycled for at least three runs. The procedure is chemoselective for nitro group; ester, ketone, aldehyde, and halide substituents on aromatic ring remain unaffected.

Introduction

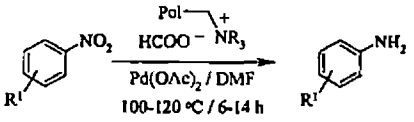
Reduction of nitroarenes to anilines is a synthetically important transformation, both in the laboratory and in industry [1–4]. The resulting aromatic amines are widely used as dyes, medicinal supplies, agrochemicals and electronic materials [5–8]. Furthermore, anilines are often converted into diazonium salts, which can be substituted for many other functional groups [9]. A large number of methods have therefore been developed for the reduction of nitro groups [1–4]. The reagents that are generally employed for the reduction include catalytic hydrogenation [10–11] with Pd/C, Raney Ni and PtO_2 or dissolving metal reduction, for example, with Sn/HCl [12], Fe/HCl [13] and Fe/AcOH [14]. Reduction of aromatic nitro compounds with indium powder in ethanolic ammonium chloride [15] or SmI_2 [16–17] results in selective reduction. Most of these methods require high pressure, specific hydrogenation apparatus, harsh reaction conditions or use of expensive metals and therefore lack the desired generality for true synthetic utility. Moreover, poor selectivity was reported in the reduction of aromatic nitro compounds bearing other potentially reducible groups such as carbonyl and halogen substituents.

Catalytic transfer hydrogenation (CTH) with the aid of a stable H-donor is a useful alternative method to catalytic hydrogenation by molecular hydrogen [18–20]. In transfer hydrogenation, several organic molecules such as hydrocarbons, primary and secondary alcohols, and formic acid and its salts have been employed as the hydrogen source. The use of a H-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 for pressure vessels and other equipment. Formic acids and its salts are frequently employed as hydrogen donor in CTH reactions and nitroarenes can be reduced to anilines using ammonium formate and Pd-C or Raney nickel [21–23]. However, reductive elimination of halogen substituents on the aromatic nucleus and formation of *N*-formyl derivatives instead of arylamines are the major drawbacks on using ammonium formate/Pd-C [24]. On the other hand, combination of $NaBH_4$ with Cu(II), Co(II) or Rh(III) halides has been used to reduce the nitro group, which is inert to $NaBH_4$ itself [11]. Metal hydrides are, however, water-sensitive as well as expensive chemicals.

Synthetic applications of solid phase organic chemistry have received, in recent years, an enormous boost from the expeditious development of the combinatorial approach [25–27]. The use of solid phase-bound reagents and catalysts allows much simpler work-up procedures and, in many cases, eliminates the need for strict control of reagent ratios [28–29]. In addition, reagents immobilized on insoluble matrices offer advantages for recycling thus becoming cost effective. Borohydride exchange resin (BER), an immobilized hydride reagent, in combination with transition metal salts has been shown to reduce the nitro group selectively [30]. In connection with our interest in CTH reactions [31–32], we have recently demonstrated that resin-bound formate (PSF) can function as stable H-donor and be utilized in palladium-catalyzed transfer hydrogenation of functionalized alkenes [33]. We have also shown that several other reducible groups such as cyano, carbonyl, ester can be tolerated the process. In continuation of our interest, we wish to report herein that



Scheme 1.



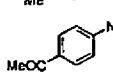
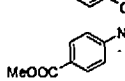
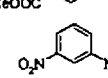
Scheme 2.

the PSF can also serve as a stable H-donor in reducing the nitroarenes to anilines. The reaction conditions have been optimized so that the aromatic nitro group can be reduced in a chemoselective manner where the other groups such as ketone, aldehyde and halide substituents on aromatic ring remain unaffected.

The PSF was prepared using Amberlyst resin (IRA® 420), the chloride form being exchanged with formic acid, according to our procedure reported previously [33] (Scheme 1). When the PSF was treated with catalytic amount of palladium acetate (2 mol% with respect to the substrate) in DMF, an efficient reductant is generated that can be used for efficient reduction of nitroarenes (Scheme 2).

The reduction of nitro group was carried out using 2 mol% $Pd(OAc)_2$ and formylated (aminomethyl)polystyrene (PSF) in a minimum quantity of DMF at 100–120 °C for 6–14 h (Table 1). After filtration, extraction with ether followed by

Table 1. Reduction of nitroarenes to anilines using PSF and Pd-catalyst[a]

Entry	Nitroarene	Temp (°C) / Time (h)	Anilines	Yield[b], (%)
1		100 / 8		82
2		110 / 8		77
3		120 / 12		71
4		100 / 10		76
5		100 / 8		70
6		110 / 8		85
7		120 / 14		68
8		100 / 8		90
9		110 / 10		92
10		120 / 12		No reaction
11		110 / 10		77
12		100 / 12		66

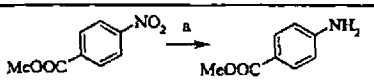
[a]Reaction conditions: Nitroarene (2 mmol), $Pd(OAc)_2$ (0.04 mmol), PSF (1 g) in DMF (2 mL).
[b]Yield refers to isolated product by column chromatography and average of 2–3 runs.

chromatographic purification afforded the desired anilines in good yields. The anilines in most cases were identified by comparison of spectroscopic data and/or melting points with literature values. Initially, reduction of nitrobenzene leading to aniline was performed in 82% yield. Concomitant reductive elimination of halogen on aromatic nucleus is often associated with transfer hydrogenation [34] and therefore poor selectivity was observed in the reduction of aromatic nitro compounds bearing halogen substituent. In our conditions, however, *o*- and *p*-chloronitrobenzene underwent reduction of the nitro group chemoselectively leading to corresponding chloroanilines in 71 and 77% yield, respectively. *p*-Nitrophenol and *p*-nitrotoluene also underwent smooth reduction of the nitro group leading to the desired anilines. The selective and rapid reduction of nitro groups in the presence of carbonyl functionalities is also a highly valuable transformation in organic synthesis. The development of an efficient solid phase-bound reagent to achieve this goal has attracted considerable effort recently. We therefore investigated reduction of *m*-nitroacetophenone, *o*-nitrobenzaldehyde and methyl *p*-nitrobenzoate. The results showed that the formylated (aminomethyl)polystyrene (PSF) can effect highly efficient reduction of nitro groups in the presence of carbonyl functionalities. In transfer reduction of polynitrobenzenes, it was reported that use of much greater proportions of catalyst to substrates afforded only aminonitroarenes [20]. In a typical case, dinitroarenes (*o*-, *m*-, *p*-) are reported to yield corresponding nitroanilines in 90% yields. At our hand, reduction of *p*-dinitrobenzene gave *p*-nitroaniline in 92% yield and further reduction to *p*-diaminobenzene was not possible. Previously, we observed reduction of the C=N bond of imine using PSF and catalytic $Pd(OAc)_2$ [33]. The imine bearing a nitro group was examined under this condition and we obtained reduction of nitro group in addition to the imino group.

To explore the efficiency and stability of the H-donor (PSF), recycling was examined with methyl *p*-nitrobenzoate as a substrate. Reduction proceeds to completion giving excellent yields through three successive recycle runs (Table 2). It should be noted that after separation of the Amberlite resin at the end of the three successive runs, the PSF can be easily generated and could be reused in further reductions.

In summary, we have demonstrated that polymer-supported formate (PSF) can efficiently perform reduction of nitroarenes leading to anilines under palladium-catalyzed transfer hydrogenation conditions in small-scale. The procedure is chemoselective for nitro group; and several other potentially reducible functionalities such as ketone, aldehyde, ester, and halide substituents on aromatic ring remain unaffected. Other advantages are clean work-up, high yields, and reusability of the PSF for at least three times and regeneration of PSF by reusing the recovered resin. Further applications of PSF in reduction of other organic functional groups are under active pursuit.

Table 2. Recycling experiments



Run	1	2	3
Yield (%)	90	90	84
Time/h	6	7	8

[a]Reagents and conditions: 2 mol% $Pd(OAc)_2$/PSF (0.5 g/1 mmol nitro compound)/DMF (1 mL)/100 °C.

Experimental section: General

All reactions were performed in screw cap sealed tubes flashed with nitrogen. The minimal reaction times were determined by monitoring TLC of the reaction mixture. Silica gel (60–120 mesh) was used for chromatographic purifications. DMF was dried by distillation over P_2O_5. ^{1}H-NMR and ^{13}C-NMR were recorded at 300 MHz and 75 MHz respectively using Bruker AV-300 spectrometer. Amberlite® IRA-420 (Cl) standard grade (14–52 mesh) and palladium acetate were purchased from commercial suppliers and were used directly.

General procedure for reduction of nitroarene to aniline

To a mixture of nitroarene (2 mmol) and palladium acetate (0.04 mmol, 2 mol%) in freshly distilled DMF (2 mL) was added PSF (1 g) and the reaction mixture was purged with N_2 for 2–3 min. The screw-cap tube was tightened and placed in a pre-heated oil bath for several hours (Table 1). After completion of the starting material as analyzed by TLC, the reaction mixture was taken in water, filtered through a cotton-bed and washed with ether. The ethereal layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified either by column chromatography over silica gel or by crystallization to afford the desired aniline.

Acknowledgements

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Co-immobilized formate anion and palladium on a polymer surface: a novel heterogeneous combination for transfer hydrogenation

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Dedicated to Professor Debabrata Mukherjee on the occasion of his 65th birthday

Abstract—A novel heterogeneous combination of a formate reagent and palladium catalyst co-immobilized on a resin support has been developed and shown to be highly efficient and recyclable for transfer hydrogenation of alkenes, imines, nitroarenes and 1,2-dicarbonyl compounds.

Catalytic transfer hydrogenation (CTH) with the aid of a stable hydrogen donor is a useful alternative method for catalytic hydrogenation by molecular hydrogen.[1] In transfer hydrogenation, organic molecules such as hydrocarbons,[2] primary and secondary alcohols[3] and formic acid and its salts[4] have been employed as the hydrogen source. The use of a 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 for pressure vessels and other equipment. Although metal-catalyzed transfer hydrogenation using a stable H-donor has been found to be reliable, the current emphasis on cleaner methods for chemical transformations requires high selectivity, low cost, easy separation and the production of minimum waste. From a practical point of view, a more attractive approach is to develop a heterogeneous catalyst that is efficient for this transformation. Immobilized reagents and immobilized catalysts can afford clean transformations for laboratory to large-scale operations. While several immobilized reagents or immobilized catalysts have been demonstrated for numerous organic transformations,[5] we envisaged that both the reagent and the catalyst could be bound on the same polymer surface and employed for suitable transformations. Such an approach would provide further operational simplicity and economic control.

As a part of a continuous effort to develop solid phase organic reactions, we recently reported that polymer-supported formate (PSF) could be used as a potential H-donor in palladium-catalyzed transfer hydrogenation of alkenes, imines and aromatic nitro compounds.[6] The conditions appeared to be mild and selective for many functional groups such as ketones, esters, halogens and nitriles. The reactions were performed using catalytic palladium acetate (2 mol %) in DMF and it was assumed that the palladium catalyst worked as a homogeneous catalyst. The high degree of chemoselectivity in palladium-catalyzed transfer hydrogenation using HCOOH or its salts has been explained on the basis that the hydrogen is delivered directly from a Pd formate species which has much stronger hydridic nature compared to that of a Pd hydride species.[7] The combination of formic acid and palladium acetate is known to undergo anionic ligand exchange to form a palladium diformate complex, eventually producing Pd(0) through decarboxylation and loss of molecular hydrogen.[8] In CTH, either a source of palladium is required for each operation or it may be supported by a polymer framework and reused several times. We reasoned that the palladium catalyst might be anchored to the PSF so that it could be used and recycled. Palladium is usually attached to a solid surface either by adsorption on the polymeric surface, by

Keywords: Transfer hydrogenation; Polymer-supported formate; Supported palladium catalyst; Alkenes; Imine; Nitroarenes; 1,2-Diketones.
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coordination through the ligand or by the relatively new technique of microencapsulation.[9] In this latter,[4] we report that palladium can be immobilized on the PSF and used effectively in the CTH of a variety of functional groups. Furthermore, the formate (the H-donor) and palladium (the catalyst) supported on a polymeric surface (PSF-Pd) can be recycled at least four-times without any appreciable loss of activity. To the best of our knowledge, this approach, where both the reagent and the catalyst are co-immobilized on same polymeric backbone, has not previously been reported.

The overall procedure is simple and straightforward. The polymer-supported formate (PSF) was prepared using Amberlyst resin (IRA® 420), the chloride form being exchanged with formic acid, according to our previously reported procedure.[6] To a suspension of PSF (1 g) in DMF (5 ml) was added palladium acetate (10 mg) and the mixture magnetically stirred under nitrogen at room temperature for 2 h. The PSF beads turned black indicating that the Pd(II) species may have been reduced to Pd(0), and the solvent became colourless. The resulting mixture was filtered, washed with DMF and dried under vacuum overnight. The resulting black PSF beads of the resin supporting both the reagent and palladium catalyst (PSF-Pd) were used for the reduction.[10]

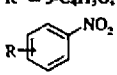
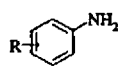
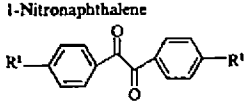
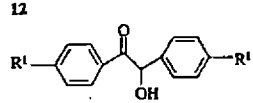
Table 1. FT-IR data (KBr) for the carboxylate anion

Formate	Stretching vibration (ν_{max}) cm^{-1}	Anti-symmetrical/symmetrical vibration (ν_{max}) cm^{-1}
$HCOONH_4$	1354	1595
HCOOK	1348	1593
PSF	1344	1593
PSF-Pd	1404	1653

The PSF-Pd was characterized by IR spectroscopy. The FT-IR spectral data for the carboxylate anion of different formate salts, PSF and PSF-Pd are given in Table 1. The FT-IR spectrum of PSF-Pd was compared with those of ammonium formate, potassium formate and the PSF. The absorptions of the carboxylate anions of $HCOONH_4$, HCOOK and PSF were observed at 1595, 1593 and 1593 cm^{-1}, respectively, while that of PSF-Pd occurred at 1653 cm^{-1}. The significant increase of ν_{max} for PSF-Pd clearly indicated binding of the palladium metal through complexation with PSF.[11]

The efficiency and stability of this newly developed PSF-Pd was first examined in the reduction of electron-deficient alkenes conjugated with ketones, nitriles and carboxylate esters (entries 1–5 in Table 2). An excess of the polymer-supported formate/palladium catalyst (0.5 g of PSF-Pd per mmol of the substrate) was em-

Table 2. Catalytic transfer reduction using PSF-Pd

Entry	Substrate	Conditions[a] temperature (°C)/time (h)	Product	Yield (%)[b]
				
1.	R^1 = Ph; R^2 = H; R^3 = CN; R^4 = COOEt	65/8	1	82
2.	R^1 = 4-MeOC$_6$H$_4$; R^2 = H; R^3 = CN; R^4 = COOEt	70/8	2	80
3.	R^1 = 4-MeOC$_6$H$_4$; R^2 = H; R^3 = R^4 = CN	50/6	3	86
4.	R^1 = Ph; R^2 = Me; R^3 = CN; R^4 = COOEt	70/7	4	78
5.	R^1 = 4-ClC$_6$H$_4$; R^2 = H; R^3 = H; R^4 = CO(3-C$_4$H$_3$O)	80/12	5	75
				
6.	R^1 = 3-NO$_2$; R^2 = H; R^3 = Ph	70/7	6	80
7.	R^1 = 4-C$_5$H$_4$N; R^2 = H; R^3 = Ph	50/6	7	87
8.	R^1 = 3-C$_4$H$_3$O; R^2 = H; R^3 = Ph	60/6	8	78
				
9.	R = 4-Cl	110/11	9	76
10.	R = 4-COOMe	100/10	10	85
11.	R = 3-COMe	100/10	11	81
12.	1-Nitronaphthalene	100/10	12	75
				
13.	R^1 = H	100/10	13	85
14.	R^1 = Me	110/12	14	77
15.	R^1 = OMe	110/10	15	88

[a] 0.5 g of PSF-Pd per 1 mmol of the substrate in DMF (1 cm^3).

[b] Yields are based on at least two runs and the products were isolated as pure compounds after column chromatography. All products showed satisfactory IR, ^{1}H NMR and ^{13}C NMR spectral data.

ployed, with the expectation that other functional groups would not react, to force the reaction to completion. The reduction of the C–C double bond proceeded smoothly at 50–80 °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 and isolated in 75–86% yield. Other reducible groups such as the ketone, nitrile or halogen and ester groups remained unaffected under the reaction conditions.

To extend the scope and generality of the PSF-Pd in CTH, we explored reduction of the C–N double bonds of imines. Since imines are generally derived from the corresponding aldehydes or ketones, the overall reaction in one-pot constitutes a method for 'direct reductive amination' and is an attractive synthetic route to secondary and tertiary amines. Using the PSF-Pd, the imines could be reduced efficiently at 50–70 °C (entries 6–8 in Table 2). A nitro group and heteroaromatic moiety remained unaffected under the reaction conditions.

The reduction of nitroarenes to anilines is a synthetically important transformation both in the laboratory and in industry. To broaden the scope of PSF-Pd, reduction of the nitro group was investigated with nitroarenes as the substrates. While the nitro group was not reducible at a lower temperature (70 °C) it could be reduced at 100–110 °C to yield the corresponding anilines (entries 9–12 in Table 2). Several other reducible groups such as a halogen, ester or ketone were inert to these conditions illustrating a clear advantage in terms of chemoselectivity.

Further applications of this new heterogeneous reductive system were tested with 1,2-dicarbonyl compounds. When benzil or substituted benzils were used as the substrate, the reduction of one of the carbonyl groups with PSF-Pd in DMF at 100 °C reached completion after 10–12 h to give the corresponding α-hydroxyketone (benzoin) in a 77–88% isolated yield (entries 13–15 in Table 2).

The novel combination PSF-Pd was easily used for four successive recycling runs without any significant drop of reactivity. With methyl 4-nitrobenzoate as the substrate, the reduction proceeded to completion giving excellent yields for up to four runs.

In summary, formic acid as its formate anion and a palladium catalyst from palladium acetate have been co-immobilized effectively on an inexpensive Amberlyst ion-exchange resin. This resin (PSF-Pd) proved to be a versatile and heterogeneous reductive combination for transfer hydrogenation of functionalized alkenes, imines, nitroarenes and 1,2-diketones. This new technique also demonstrates high chemoselectivity in the reduction of alkenes, imines and nitro groups, thus establishing an efficient, environmentally benign, economically friendly and sustainable process. Further studies on structural aspects and the reaction behaviour (leaching of the palladium) of PSF-Pd along with newer applications for other transformations are currently underway.

Acknowledgements

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10. *A representative procedure for the CTH of 1,2-diketones using PSF-Pd*: To a solution of 4,4′-dimethoxybenzil (2 mmol) in freshly distilled DMF (2 cm^3) was added PSF-Pd (1 g) and the reaction mixture was stirred at 110 °C for 10 h. The reaction mixture was diluted with ether (15 cm^3) and filtered through a bed of cotton. The filtrate was extracted with ether (2 × 15 cm^3) and the combined organic layers were washed brine (2 × 10 cm^3) and dried (Na_2SO_4). Evaporation under reduced pressure and purification by column chromatography afforded 4,4′-dimethoxybenzoin as a pale yellow solid (88% yield); mp 111–112 °C; FT IR (Nujol): ν_{max} 3466, 1666, 1597, 1512, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.91$ (d, $J = 9$ Hz, 2H), 7.26 (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 9$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 5.87 (s, 1H), 4.85–4.3 (br s, 1H), 3.82 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.3$, 163.9, 159.6, 131.8, 131.5, 129.0, 126.2, 114.5, 113.9, 75.2, 55.4, 55.2.
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Palladium-Catalyzed Selective Amination of Haloaromatics on KF-Alumina Surface

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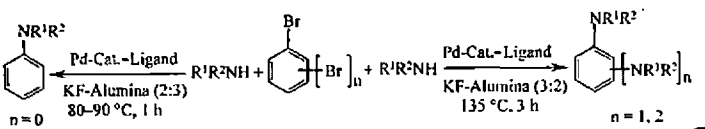
Abstract: An effieient palladium-catalyzed amination, including polyaminations of aromatic bromides mediated on a surface of KF-alumina, is reported. The solvent-free one-pot protocol avoids the use of a strong base (sodium *tert*-butoxide) making it applicable to substrates containing a base-sensitive functional group. It proceeds without concomitant reductive bromination and provides access to selective amination of polyhaloaromatics.

Key words: aryl halides, aryl amines, amination, palladium, KF-alumina

Aromatic amines are an integral part of pharmaceuticals, dyes, polymers, organic materials with important electronic properties, and ligands for transition metals.[1] The preparation of aryl amines is therefore important to synthetic organic chemists. The palladium-catalyzed cross-coupling of aryl halides with amines, developed independently by Buchwald[2] and Hartwig,[3] represents a mild alternative to the classical construction[4] of aryl amines. The Buchwald–Hartwig reaction has emerged during the last decade as a very powerful tool for the synthesis of aryl amines. The hetero cross-coupling reaction is normally carried out in the presence of a palladium catalyst, most commonly a bis-phosphine ligand and a base (3–5 equiv), preferably sodium *tert*-butoxide.[2d] Many advances have been made in this palladium-catalyzed amination reaction since it was reported by Buchwald and Hartwig.[5] The use of sodium *tert*-butoxide as the base eliminates a number of common functional groups such as esters, enolizable ketones, aldehydes, nitriles and nitro groups, and efforts have been made to replace it with a milder base. In the presence of other bases such as KOH or Cs_2CO_3, the double amination proceeds slowly and leads to an increased amount of the reductive product.[6,8a] Furthermore, several groups have employed this protocol to synthesize polyanilines[1d,7] and polyamino-substituted benzenes.[8] Although anilines gave high yields of double amination products, primary amines did not afford the desired *bis*-amination due to competing reductive debromination. While studying double amination of *o*-dibromobenzene with primary amines, Diver et al. reported formation of imine as the byproduct besides concomitant reductive debromination.[8a] Recently, we reported a procedure for palladium-catalyzed amination of heteroaryl halides using KF-alumina as the base.[9] The solvent-free dry reaction has been found to have advantages in the case of halopyridines. While extending the preparative advantages for amination of haloaromatics, we conducted KF-alumina mediated palladium-catalyzed C–N cross couplings between the aryl bromides and amines. We envisaged that the Buchwald–Hartwig C–N couplings should be studied with polyhalobenzenes to extend the scope and the amelioration of the various parameters of this amination process. We report herein our observations, which finally constitute not only a mild and efficient procedure for amination of aromatic bromides on a solvent-free surface of KF-alumina but also provide an expedient route for selective amination of polyhaloaromatics.

In the course of developing synthetic protocol toward amination of polyhaloaromatics on a KF-alumina surface, we first employed similar conditions to those developed for mono-amination of bromopyridines [amine (2 mmol), KF-alumina (1:4; 1 g/mmol), palladium-phosphine catalyst (2 mol%) for bromopyridines (1 mmol)]. Although amination of bromobenzene with secondary amines worked well under the conditions, the reaction with



n = 0, 1, 2; R^1 = H or alkyl; R^2 = alkyl or aryl
Pd-Cat.-Ligand = $Pd_2(dba)_3$–BINAP

Scheme 1

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primary amines was sluggish and poor yields were obtained. The conditions were optimized and the best results were achieved with KF impregnated on alumina was used in a ratio of 2:3. In the presence of $Pd_2(dba)_3$/BINAP as the catalytic system, bromobenzene underwent amination with both primary (Table 1, entries 3 and 4) and secondary amines (Table 1, entries 1 and 2) quite rapidly at moderate temperatures (80–90 °C/1 h) yielding the corresponding anilines in 73–88% yields (Table 1). Since the use of other bases can affect groups like enolizable ketones, we tested the amination of *p*-bromoacetophenone using the solvent-free KF-alumina surface. Gratifyingly, amination occurred effectively without any changes to the base-sensitive functionality (Table 1, entry 5). In a typical experiment,[10] the catalyst $Pd_2(dba)_3$/BINAP (2 mol%) was admixed intimately with KF-alumina (2:3; 2 g), heated at 80–90 °C for 15 minutes, and then treated with a mixture of aryl bromide (2 mmol) and amine (5 mmol). The solid mixture was stirred at 80–90 °C for 1 hour. The desired product was then isolated by column chromatography over silica gel.

Table 1 Palladium-Catalyzed Selective Amination of Haloaromatics on KF-Alumina Surface

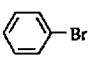
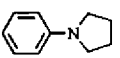
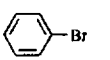
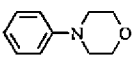
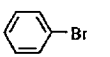
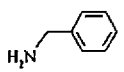
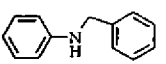
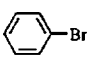
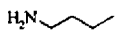
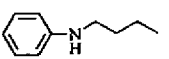
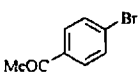
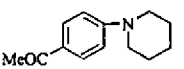
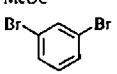
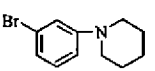
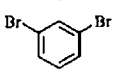
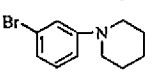
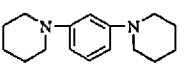
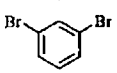
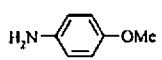
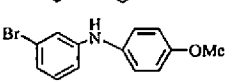
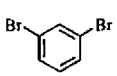
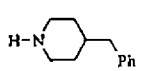
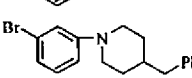
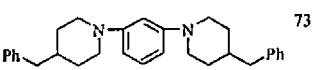
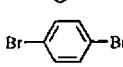
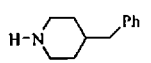
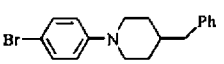
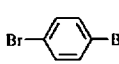
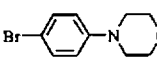
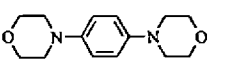
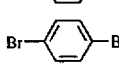
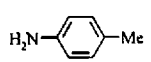
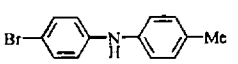
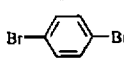
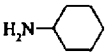
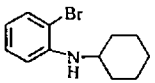
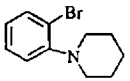
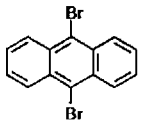
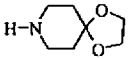
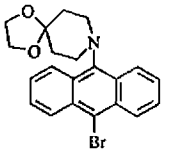
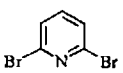
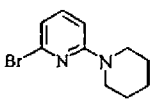
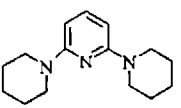
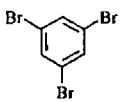
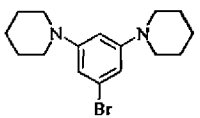
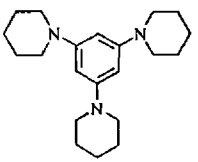
Entry	Aryl bromide	Amine	Conditions[a]	Products[b]			
				Monoamine	Yield (%)	Bisamine	Yield (%)
1			A		83		
2			A		88		
3			A		78		
4			A		73		
5			A		80		
6			A		86		
7			B		12		78
8			A		75		
9			B		14		73
10			A		90		
11			B		17		72
12			A		80		
13			B		23		56
14			A or B		80		

Table 1 Palladium-Catalyzed Selective Amination of Haloaromatics on KF-Alumina Surface (continued)

Entry	Aryl bromide	Amine	Conditions[a]	Products[b]			
				Monoamine	Yield (%)	Bisamine	Yield (%)
15			A or B		65		
16			A or B		90		
17			A		64		
18			B		5		90
19			B		18		67

[a] A: KF-Al_2O_3 (1:4 or 2:3), Pd_2dba_3/BINAP, 80–90 °C, 1 h; B: KF-Al_2O_3 (3:2), Pd_2dba_3/BINAP, 135 °C, 3 h.
[b] Isolated products; structure determined by IR, ^1H NMR, and ^{13}C NMR spectra.[11]

Since polyaminobenzenes are important compounds for various industries, we wanted to employ the reaction conditions to effect polyamination of polyhaloaromatics. While applying similar conditions to dibromobenzenes, mono-aminated products only resulted (Table 1, entries 6, 8, 10, 12, and 17). Earlier we observed similar results in the case of dibromopyridines.[8] In order to obtain the bis-aminated products we examined various proportions of KF-alumina and different catalytic systems. The combination of KF-alumina in the ratio of 3:2 and $Pd_2(dba)_3$/BINAP as the catalyst was found to be suitable for bis-, or tris-aminations in a one-pot reaction (Table 1, entries 7, 9, 11, and 13). Under similar conditions, 2,6-dibromopyridine and 1,3,5-tribromobenzene yielded the corresponding bis- and tris-aminated products (Table 1, entry 18 and 19) in 90% and 67% yields, respectively. Neither reductive debromination nor the formation of imine was observed under these conditions, indicating that the possible β-elimination might not be favorable, and thus contamination with any other byproducts is avoided. The amination occurs quite rapidly for mono-amination (1 h) while polyamination requires a longer time (3 h) and higher temperatures (135 °C). In the case of polyaminations, partial mono-aminated products remained in the reaction mixtures, which were easily isolated by column chromatography (Table 1). Interestingly, 1,2-dibromobenzene did not produce the 1,2-bis-amines in either condition, possibly due to steric crowding (Table 1, entries 14–16). Several variations in terms of the catalytic system, the surface (KF-alumina), and temperatures did not change the course of the reactions.

In conclusion, we have demonstrated that it is possible to effect palladium-catalyzed amination of halobenzenes on a solvent-free surface of KF-alumina without using any strong bases such as sodium *tert*-butoxide. The base-sensitive functional groups remained unaffected under this condition. The procedure is also effective for one-pot mono- or poly-aminations selectively, depending on the conditions used, and thus constitutes a mild and benign method for the synthesis of polyaminobenzenes. No reductive bromination leading to other byproducts has been observed in this procedure.

Acknowledgment

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(10) **General Procedure for the Amination Reactions:**
A: A mixture of $Pd_2(dba)_3$ (2 mol%) and BINAP (4 mol%) was admixed intimately with KF-Alumina (2:3; 2 g) and heated at 80–90 °C for 15 min. Aryl bromide (2 mmol) and amine (5 mmol) were added to the solid surface and the mixture was stirred at 80–90 °C for 1 h. An orange color developed while mixing and gradually disappeared over 1 h. The solid mass was then cooled, packed on a column of silica gel and eluted with EtOAc–light petroleum (1:19) to afford the mono-aryl amines. All the products were identified by IR, ^1H and ^{13}C NMR spectral data.
Condition B: The reaction conditions were identical except the quantity of amine was increased to 7–8 equiv, KF-alumina was used in the ratio of 3:2, and the solid mixture was heated at 135 °C for 3 h. Pure bis-amines were obtained by chromatography over silica gel and elution with EtOAc–light petroleum (1:9). The spectral data were consistent with the assigned structures.

(11) **Selected Spectral Data for Mono- and Bis-Coupled Products**
Table 1, Entry 5: 1-(4-Piperidin-1-yl-phenyl)ethanone: IR (Nujol): 1675, 1206.5 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.65 (m, 6 H), 2.50 (s, 3 H), 3.34 (m, 4 H), 6.84 (d, 2 H, J = 9.0 Hz), 7.85 (d, 2 H, J = 9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.3, 25.3, 26.0, 48.6, 113.3, 126.7, 130.5, 154.4, 196.4.
Table 1, Entry 7: 1, 3-Dipiperidino Benzene: IR (Nujol): 1201.6, 1124.4 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.55–1.62 (m, 4 H), 1.70–1.78 (m, 8 H), 3.16 (t, 8 H, J = 5.4 Hz), 6.49 (dd, 2 H, J = 8.1, 2.2 Hz), 6.61 (s, 1 H), 7.15 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.4, 26.0, 51.2, 106.1, 108.7, 129.3, 153.2.
Table 1, Entry 11: 1,4-Dimorpholino Benzene: IR (Nujol): 1234.4, 1120.6 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.01 (t, 8 H, J = 4.7 Hz), 3.80 (t, 8 H, J = 4.7 Hz), 6.85 (s, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 50.5, 66.9, 117.4, 145.8.
Table 1, Entry 13: 1,4-Di-[8-(1,4-dioxa-8-aza-spiro[4,5]decane)]benzene: IR (Nujol): 1125 cm^{-1}. ^1H NMR (acetone-d_6, 300 MHz): δ = 1.76 (t, 8 H, J = 5.7 Hz), 3.16 (t, 8 H, J = 5.7 Hz), 3.94 (s, 8 H), 6.88 (s, 4 H). ^{13}C NMR (acetone-d_6, 75MHz): δ = 34.7, 48.6, 63.9, 107.5, 117.9.
Table 1, Entry 15: (2-Bromophenyl)cyclohexylamine: IR (Nujol): 1321.1, 1016.4 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.20–1.44 (m, 6 H), 1.75–1.79 (m, 2 H), 2.02–2.1 (m, 2 H), 3.30 (m, 1 H), 4.26 (br s, 1 H), 6.5 (m, 1 H), 6.6 (d, 1 H, J = 8.1 Hz), 7.14 (m, 1 H), 7.40 (d, 1 H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.8, 25.8, 33.0, 51.6, 109.8, 111.8, 117.1, 128.3, 132.5, 144.
Table 1, Entry 17: 8-(10-Bromoanthracene-9-yl)-1,4-dioxa-8-aza-spiro[4,5]decane: IR (Nujol): 1122.5 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.05 (t, 4 H, J = 5.3 Hz), 3.57 (t, 4 H, J = 5.3 Hz), 4.10 (s, 4 H), 7.48–7.60 (m, 4 H), 8.48 (d, 2 H, J = 8.7 Hz), 8.56 (d, 2 H, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 36.4, 49.9, 64.4, 107.6, 125.2, 125.3, 126.9, 128.3, 131.2, 131.4, 134.1, 145.3.
Table 1, Entry 19: 1,3,5-Tripiperidino Benzene: IR (Nujol): 1199.6, 1122.5 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.51–1.58 (m, 6 H), 1.66–1.73 (m, 12 H), 3.10 (t, 12 H, J = 5.3 Hz), 6.14 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.3, 26.0, 51.5, 99.2, 153.7.