Poly Ionic Resins Supported Reagents and Catalysts: Applications to C-C & C-Heteroatom Bond-Forming Reactions

Thesis submitted for the degree of Doctor of Philosophy in Science (Chemistry)
under the University of North Bengal

Submitted by

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(M.Sc. in Chemistry)

Under The Supervision of

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February, 2012

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Dedicated

to

My Parents

Declaration

The research work embodied in this thesis entitled "**Poly Ionic Resins Supported Reagents and Catalysts: Applications to C-C & C-Heteroatom Bond-Forming Reactions**" has been carried out in the Department of Chemistry, North BengalUniversity, Darjeeling under the supervision of Prof. Basudeb Basu, Department of Chemistry, 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: 20th February 2012

Sekhar Kundu

Place: University of North Bengal (SEKHAR KUNDU)

Acknowledgement

I take this opportunity to express my deep and sincere gratitude to my honourable supervisor Dr. B. Basu, Professor, Department of Chemistry, North Bengal University, Darjeeling, for his constant guidance, encouragement and inspiration throughout my research work. His extensive knowledge and his logical way of thinking have been of great value for me. His truly scientist intuition has made him as a constant oasis of ideas and passions in science, which exceptionally inspire and enrich my growth as a student, a researcher and a scientist that I aspire to be. I am indebted to him more than he knows.

I wish to express my warm and sincere thanks to Dr. A. K. Nanda, Associate professor, Dr. P. Ghosh, Associate professor and Dr. A. K. Panda, Associate professor, Head, Department of Chemistry, NBU for the valuable advice and cooperation I received from them throughout the period of my research work. I would also like to express my warm thanks to Dr. A. Majumder of this department for helping me in recording the IR spectra.

I warmly thank all the faculties, staff members and all the research scholars of this department from whom I have always received complete cooperation.

I wish to thank my friends Dr. Sajal Das, Dr. Bablee Mandal, Ms. Susmita Paul, Ms. Sangita Mitra Mustafy, Mr. Sujit Ghosh, Mr. Kinkar Biswas and Ms. Babli Roy for their help in my laboratory works and for always being there to share my happy and sad moments.

I would like to thank my parents, brothers, brother in law, my wife Debashree and son Sanway, without their constant selflessness, love, and support, I would not be half the person that I am today.

Finally, I would like to express my thanks to The University of North Bengal for providing the infrastructural facilities.

ABBREVIATION

1.	NBS	N-bromo succinamide
2.	DIC	N,N′-Diisopropylcarbodimide
3.	MCPBA	m-chloro per benzoic acid
4.	NMP	N-methyl pyrolidone
5.	DMF	Dimethyl formamide
6.	DMSO	Dimethyl sulfoxide
7.	THF	Tetrahydrofuran
8.	PANI	Polyaniline
9.	CTAB	Cetyl tetramethyl ammonium bromide
10.	TBAB	Tetramethyl ammonium bromiode
11.	DME	Dimethoxy ethane
12.	BINAP	2,2′-bis(diphenylphosphino)-1,1′-binapthyl
13.	DBA	Dibenzylacetone
14.	DPPE	Diphenylphosphinoethane
15.	DPEP	Deoxophylloerythroetioporphyrin
16.	DMEDA	N,N′-dimethylethylenediamine
17.	DMAC	Dimethyl acetamide
18.	TMAD	N,N,N′,N′-Tetramethylazodicarboxamide
19.	DPPF	1,1′-*bis*(diphenylphosphino)ferrocene
20.	AIBN	Azo bis isobutyronitrile
21.	MC	Microencapsulated
22.	NMO	N-methylmorpholine-N-oxide
23.	TFA	Trifluro acetic acid

Contents
Part I

"An Introduction to Green Chemistry"

Part I

Section A

"Poly-ionic Resin Supported Phenylating Agent for Base-free Suzuki-Miyaura Coupling Reaction"

Part 1

Section B

Highly effective alternative aryl trihydroxyborate salts for a ligand-free, on-water Suzuki–Miyaura coupling reaction

Part II

"Catechol Violet as Novel and Efficient Ligand for Cu (I)-Catalyzed C–S Coupling Reactions"

List of Publications and Poster Presentations

List of Publications:

1. **Polyionic Heterogeneous Phenylating Agent for Base-Free Suzuki–Miyaura Coupling Reaction.** Basudeb Basu, Sajal Das, **Sekhar Kundu**, Bablee Mandal *Synlett,* **2008**, 255-259.
2. **Catechol Violet as Novel and Efficient Ligand for Cu(I)-Catalyzed C–S Coupling Reactions.** Basudeb Basu, Bablee Mandal, Sajal Das, **Sekhar Kundu**
   Tetrahedron Letters 2009, 50, 5523-5528.
3. **Highly Effective Alternative Aryl Trihydroxyborate Salts for a Ligand-free, on-water Suzuki–Miyaura Coupling Reaction.** Basudeb Basu, Kinkar Biswas, **Sekhar Kundu**, Sujit Ghosh. *Green Chem.*, **2010,** *12*, 1734–1738.

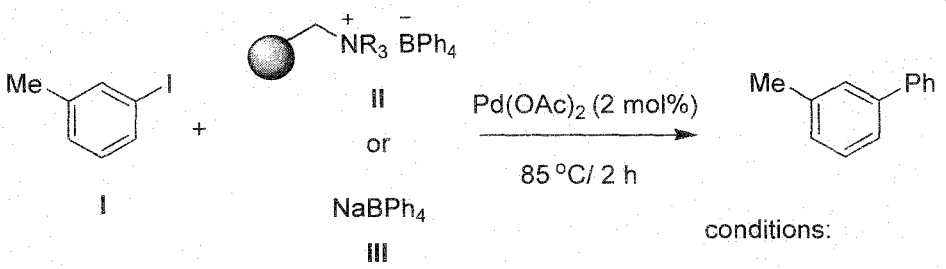
Papers presented in Symposia/ Conferences:

1. **Catechol Violet as Novel and Efficient ligand for Cu(I)-Catalyzed C-S coupling Reactions** Kinkar Biswas, Bablee Mandal, Sajal Das, Susmita Paul, **Sekhar Kundu**, Sujit Ghosh and Basudeb Basu *11th CRSI "International Symposium in Chemistry (NSC-11)*, held at National Chemical Laboratory, Pune, Feb 06-08, 2009.
2. **"Highly Efficient, Recyclable Rhodium Catalyst Immobilized on Poly-Ionic Resins: Application in the Heck-type Coupling reactions"** Susmita Pal, Bablee Mandal, Sajal Das, **Sekhar Kundu**, Sangita Mustafy, Basudeb Basu, *10th National Symposium in Chemistry (NSC–10)*, CRSI, 2008 held at IISC. Bangalore –110 007, February 1–3, 2008.
3. **"Poly–Ionic Heterogeneous Arylating Agent for Suzuki–Miyaura Coupling Reaction: Synthesis of Biphenyls"** Sajal Das, **Sekhar Kundu**, Basudeb Basu. *9th National Symposium in Chemistry (NSC–9)*, CRSI, 2007 held at Delhi University, New Delhi–110 007, February 1–3, 2007.

Summary

The research work embodied in this thesis entitled was initiated on December, 2005 in the Department of Chemistry, North Bengal University, Darjeeling – 734 013, under the supervision of Prof. B. Basu, Department of Chemistry, North Bengal University. The studies described in this thesis are primarily directed towards development of immobilized reagents and their manifold applications in various organic transformations. The thesis has been divided into two parts.

Part I: Section A is entitled as ***"Poly-ionic Heterogeneous Phenylating Agent for Base-Free Suzuki–Miyaura Coupling Reaction"***. This section deals with a new poly-ionic resin-bound tetraphenylborate that has been prepared and can serve as efficient phenylating agent in Pd-catalyzed Suzuki–Miyaura (SM) coupling with aryl halides in absence of any base. The conditions are mild, operationally simple and the poly-ionic resins can be recharged and reused for several runs.

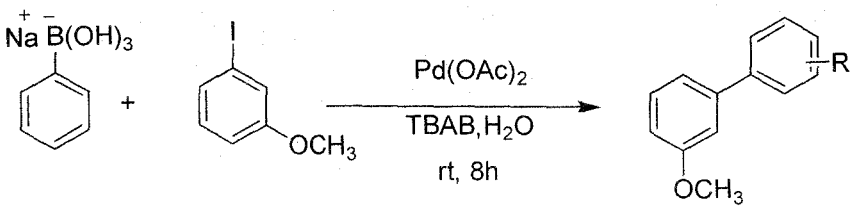


conditions:

(a) **I/II**/Na_2CO_3 = 1:1 g/mmol:1; 90%
(b) **I/III**/Na_2CO_3 = 1:1:1; 43%
(c) **I/III**/Na_2CO_3 = 1:2.5:1; 88%
(d) **I/III** = 1:2.5; 88%
(e) **I/II** = 1:1 g/mmol; 96%

A brief account of this work has been published in *Synlett*, **2008**, 255-259.

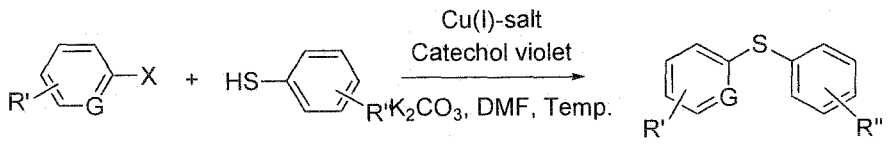
Part I: Section B is entitled as ***"Highly effective alternative aryl trihydroxyborate salts for a ligand-free, on-water Suzuki–Miyaura coupling reaction"***. We have presented here an efficient easily accessible and air-stable sodium aryl trihydroxyborates which can be effectively used as an alternative source of organoboron species in ligand free Pd-catalyzed SM cross-coupling reactions in water under an aerobic atmosphere and at room temperature. The protocol has been found to be broadly applicable to a variety of aryl halides (X = Br, I) and also to aryl chlorides bearing electron withdrawing groups.

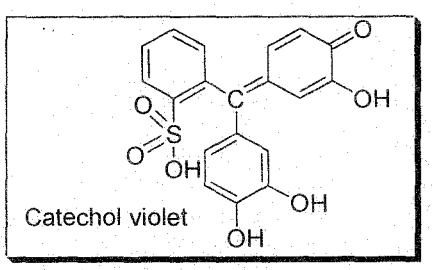


A brief account of this work has been published in *Green Chem.*, **2010**, *12*, 1734–1738

A brief account of this work has been published in *Green Chem.*, **2010**, *12*, 1734–1738

Part II: This part is entitled as ***"Catechol Violet as Novel and Efficient Ligand for Cu(I)-Catalyzed C–S Coupling Reactions"***. We have presented here an efficient copper(I) catalyzed C-S coupling reaction protocol, where a wide variety of aromatic halides such as aryl iodides, bromo-pyridines, activated aryl chlorides and vinyliodide undergo coupling with aromatic or aliphatic thiols to afford the corresponding thioether in good to excellent yields. Presence of catechol violet (CV) (only catalytic amount), which is stable in air, greatly accelerated the reaction. Wide variety of functional group tolerance has also been observed in this reaction methodology.





A brief account of this work has been published in *Tetrahedron Lett.* **2009,** *50*, 5523-5528.

Green Chemistry:

1.1. Introduction:

The term green chemistry is defined as the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances. Green chemistry, also called sustainable chemistry, is a philosophy of chemical research and engineering that encourages the design of products and processes that minimize the use and generation of hazardous substances. Whereas environmental chemistry is the chemistry of the natural environment, and of pollutant chemicals in nature, green chemistry seeks to reduce and prevent pollution at its source. As a chemical philosophy, green chemistry applies to organic chemistry, inorganic chemistry, biochemistry, analytical chemistry, and even physical chemistry. Although the focus of green chemistry is on industrial applications but it also has wide spread application in other field of chemistry. The focus is on minimizing the hazard and maximizing the efficiency of any chemical choice. It is distinct from environmental chemistry which focuses on chemical phenomena in the environment.

Another aspect of the definition of green chemistry is found in the phrase "use and generation". Rather than focusing only on those undesirable substances that might be inadvertently produced in a process, green chemistry also includes all substances that are part of the process. Therefore, green chemistry is a tool not only for minimizing the negative impact of those procedures but also aims at optimizing efficiency, although clearly both impact minimization and process optimization are legitimate and complementary objectives of the subject. Green chemistry, however, also recognizes that there are significant consequences to the use of hazardous substances, ranging from regulatory, handling and transport, and liability issues, to name a few. To limit the definition to deal with waste only would be to address only part of the problem. Green chemistry is applicable to all aspects of the product life cycle as well.

Finally, the definition of green chemistry includes the term "hazardous". It is important to note that green chemistry is a way of dealing with risk reduction and pollution prevention by addressing the intrinsic hazards of the substances rather than those circumstances and conditions of their use that might increase their risk.

1.1.1. Importance of green chemistry to adopt a hazard-based approach:

To understand this, we have to revisit the concept of risk. Risk, in its most fundamental terms, is the product of hazard and exposure: Risk = Hazard X Exposure.

A substance manifesting some quantifiable hazard, together with a quantifiable exposure to that hazard, will allow us to calculate the risk associated with that substance. Virtually all common approaches to risk reduction focus on reducing exposure to hazardous substances. Regulations often require increases in control technologies and treatment technology, and in personal

protective equipment such as respirators, gloves, etc., in order to reduce risk by restricting exposure.

The definition of green chemistry also illustrates another important point about the use of the term "hazard". This term is not restricted to physical hazards such as explosiveness, flammability, and corrodibility, but certainly also includes acute and chronic toxicity, carcinogenicity, and ecological toxicity.

1.1.2. Principles of Green Chemistry:

1. **Prevention**

   It is better to prevent waste than to treat or clean up waste after it has been created.

2. **Atom Economy**

   Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. **Less Hazardous Chemical Syntheses**

   Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. **Designing Safer Chemicals**

   Chemical products should be designed to affect their desired function while minimizing their toxicity.

5. **Safer Solvents and Auxiliaries**

   The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

6. **Design for Energy Efficiency**

   Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. **Use of Renewable Feed stocks**

   A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. **Reduce Derivatives**

   Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. **Catalysis**

   Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. **Design for Degradation**

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. **Real-time analysis for Pollution Prevention**

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. **Inherently Safer Chemistry for Accident Prevention**

Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires. Therefore, green chemistry applications include the use of supercritical water oxidation, on water reactions, solid supported media reactions etc. These are shortly described here.

1.2. Solid Supports in Organic Synthesis:

Homogeneous palladium catalysis has gained enormous relevance in various coupling reactions such as Heck, Stille, Suzuki, Sonogashira, and Buchwald-Hartwig reactions. Many products could be synthesized by this methodology for the first time or in a much more efficient way than before. The massive increase in use and the boardening range of applications for 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 the need to remove residual metals.[1]These problems have to be overcome in the application of homogeneous Pd-catalyzed coupling reactions in industry and are still a challenge. In order to address these problems, heterogeneous Pd catalysis is a promising option. Organic synthesis has played a vital role in changing the world and will undoubtedly continue to do so into the future. The benefits afforded by synthesis already considerably enrich our lives, from the development of drugs in the ongoing fight against disease to the more aesthetic aspects of society with preparation of perfumes and cosmetics. Furthermore, the quality and quantity of our food supply relies heavily upon synthesized products, as do almost all aspects of our modern society ranging from paints, pigments, and dyestuffs to plastic, polymers, and materials of all kinds. For the prevention of environment from hazardous chemical, chemists deserve to be regarded as trendsetters in recycling of the reagent as well as the catalyst tends to developments of ligand-free Pd catalysts have provided interesting and practically important alternatives to ligand assisted methodologies. On the other hand, 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 loss of expensive metal as well as ligands to impurities in the products and the need to remove residual metals. In order to overcome these problems, heterogeneous Pd

catalysis is a promising option for Suzuki coupling. Pd is fixed to a solid support, [2] such as activated carbon,[3]zeolites and molecular sieves,[4]metal oxides,[5] mainly silica or alumina, KF-Al_2O_3 but also MgO, ZnO, TiO_2, ZrO_2), clays, [6] alkali and alkaline earth salts ($CaCO_3$, $BaSO_4$, $BaCO_3$, $SrCO_3$), porous glass, [7] organic polymers or polymers embedded in porous glass. Basic supports such as basic zeolites, layered double hydroxides, KF-Al_2O_3 or sepiolites can play a similar supporting role as phosphines in homogeneous catalysis,[8] or can act as bases, [9] that is, no external bases are necessary in these cases. Due to their controlled pore size, microporous and mesoporous materials, such as zeolites, can be advantageous over simple metal oxides. Pd (0) clusters can be encapsulated in these pores. The pore size and structure of such supports can have an important impact on the reactivity and selectivity of those catalysts. Thus, cases were reported where a larger pore size of mesoporous silica allowed reaction of larger substrates as compared with microporous supports. The characterization of a heterogeneous Pd catalyst on a molecular level is still a problem, although TEM, X-ray diffractometry, and IR spectroscopy allow important insights into the structure. Often, heterogeneous catalysts are still chosen on an empirical basis without understanding why a given catalyst is superior to another one. There are also cases included where Pd is fixed to an inorganic solid support (e.g., silica or iron oxide) by the help of organic ligands, that is, as a complex. Such ligands can be part of a polymer, for example, in glass/polymer composites.[10] Supported reagents are reactive species which are associated with a support material. They transform a substrate (or substrates) to a new chemical product (or products) and the excess or spent reagent may be removed by filtration. Reuse of heterogeneous catalyst is often possible but is sometimes limited due to leaching of the Pd without redeposition (leaching up to 14% Pd from Pd/C was observed in Heck reactions, [11] changing of crystallite structure of the Pd on the support surface, [12] chemical change of Pd ligands (e.g., oxidation of phosphanes leading to high leaching of Pd) grafted to the solid support, or congesting the catalyst surface, for example, by salts formed as by-products in the coupling reaction.[13] There were cases reported where the catalytic activity dropped considerably in the second run, while marginal losses of catalytic activity were observed in the following runs. Reuse of catalytic Pd can also be achieved, when colloidal Pd is formed by leaching from the support and these colloidal particles are separated and submitted to another run. Interestingly, there are a few cases reported where the recycled catalyst exhibited higher activity than the original one.

The concept of solid-phase synthesis was first realized by Merrifield, [14] in 1963 with the preparation of large number of peptide compound via attachment of the intermediates to polymer backbone. Organic chemists Leznoff and Frechet established the validity of small-molecule solid-phase synthesis in the 1970s, [15] the focus today is on applying solid-phase

synthesis in combinatorial discovery efforts. In this regard, the majority of small molecules synthesized on solid phase have been heterocyclic in nature. The solid-phase organic synthesis of small organic molecules depends greatly on the adaptation of solution reactions to solid phase. Now these methods are revolutionizing pharmaceutical, agrochemical sectors. SPOS offers some advantages as compared to solution chemistry. Purification is facilitated by simple filtration, avoiding time-consuming separation techniques; consequently, building blocks and reagents can be added in excess to drive reactions to completion. Amenability to automate and the less favourable interference between functionalities linked to the solid support are other benefits of this chemistry. Again solid phase techniques allow the use of high-boiling solvents because their evaporation is not an issue. A wide variety of supports were investigated.[16]The importance of the correct choice of reaction solvent, the ideas of site isolation, and examples of micro environmental effects were identified, studied, and substantially understood.[17]

1.3. Synthesis of functionalized polystyrene Resin:

Several strategies have been examined for the synthesis of polystyrene resin (Figure 1): (1) using heterogeneous cross-linked polystyrene in different formats or preparing the polymer in such a way that the functional groups are concentrated toward the surface of the resin, (2) using a cross-linker other than divinylbenzene to heterogenize polystyrene in order to modulate the physical and chemical properties of the resin, (3) adding functional groups to the polystyrene backbone that provide desired properties, and (4) grafting polystyrene onto a heterogeneous support and the use of the graft as the point of substrate/reagent/catalyst attachment in order to reduce the importance of resin swelling.

Scheme 1

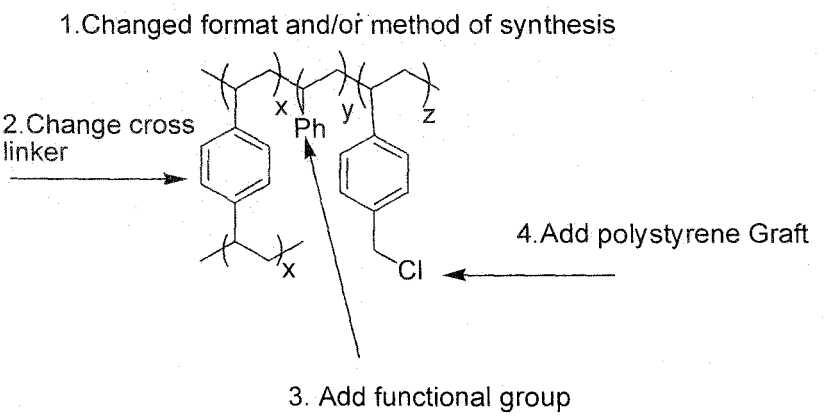
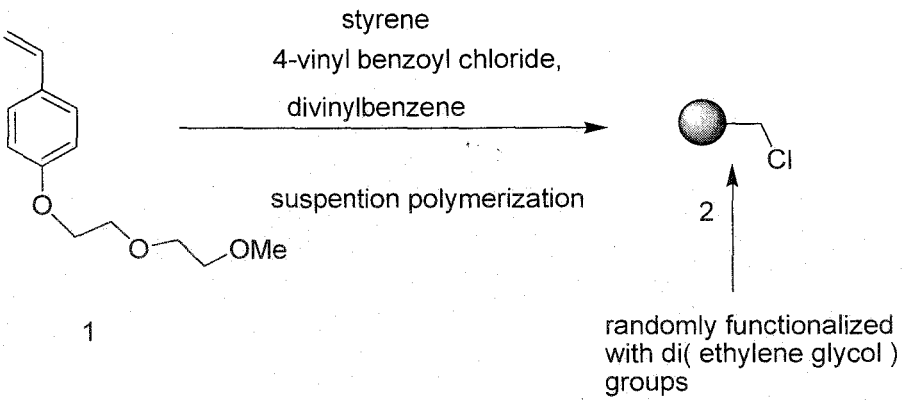


Figure 1

Use of PEG derivatives to cross-link polystyrene led to resins that performed well in solid-phase peptide synthesis, presumably due in part to their good swelling in the required solvents. This inspired Bradley to develop a complimentary strategy and add short oligo (ethylene

glycol) groups to the backbone of divinylbenzene cross-linked polystyrene to make the resin beads more compatible with polar solvents.[18] \

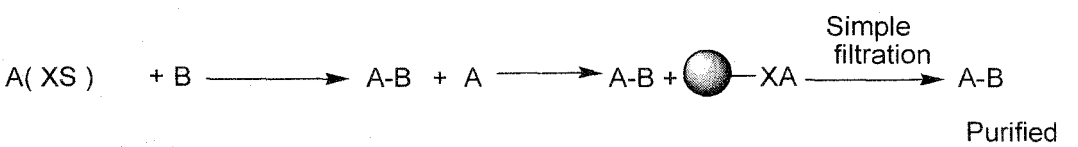
Scheme 2



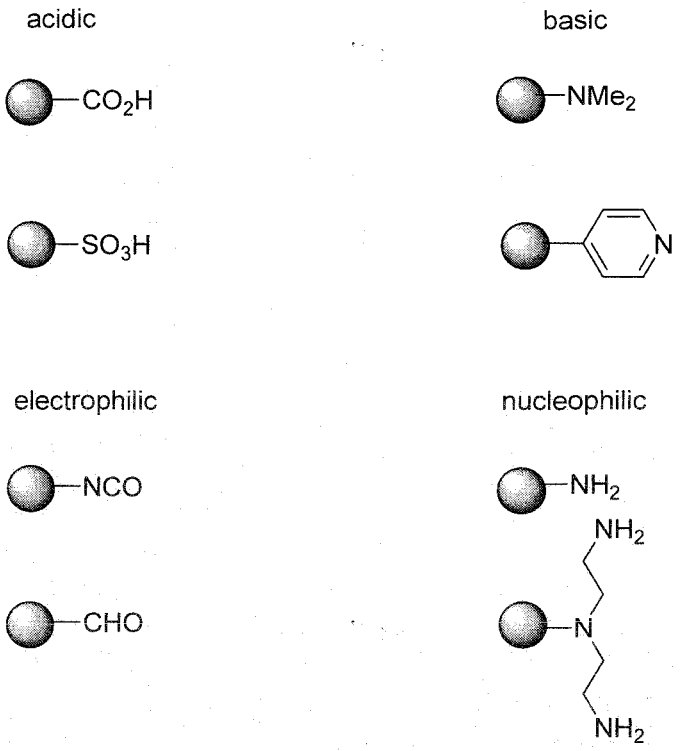
I.3.1. Reagents/Catalyst Supported onto Polymers and Applications:

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. Use of solid-supported reagents, [19] a novel extension has recently been reported by several groups and its subsequent application towards more efficient solution phase combinatorial chemistry. This technique involves traditional solution phase chemical synthesis in which the reaction mixture is purified by using a solid support. These solid supported reagents can be used to remove an excess of reactants and thus give the required product in high yield and in a single operation (Scheme 3). This technique offers many of the advantages of solid supported organic synthesis in the ease of reaction workup, and product purification with the additional advantages associated with traditional solution phase synthesis. Previously this strategy has been referred to as a solid-supported scavenger (SSS), polymer-supported quench (PSQ), or complementary molecular reactivity and molecular recognition (CMR/R), [20] wherein such reagents will be referred to as polymeric scavenger reagents (PSRs). There are only two different classes of scavenger available; those that are ionic (acidic and basic reagents) in origin and those that are covalent (electrophilic and nucleophilic reagents) (Scheme 3).

Scheme 3



Schematic representation of a reaction involving a polymer scavenger



Representative examples of the four different classes of polymeric scavengers

Catalyst and reagent 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 complementary resin sites (d) adsorption method. By far, the 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).Immobilization can also be affected by micro–encapsulation, where 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.[21] 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.

1.4. Covalent Binding of Reagents: linkers

In the solid phase synthesis requires a covalent linker group sometimes referred to as a "handle", to attach the small molecule onto the polymeric resin. Currently a wide variety of

linkers exist, many of which are based upon chemistry originally developed for oligomeric solid phase synthesis.

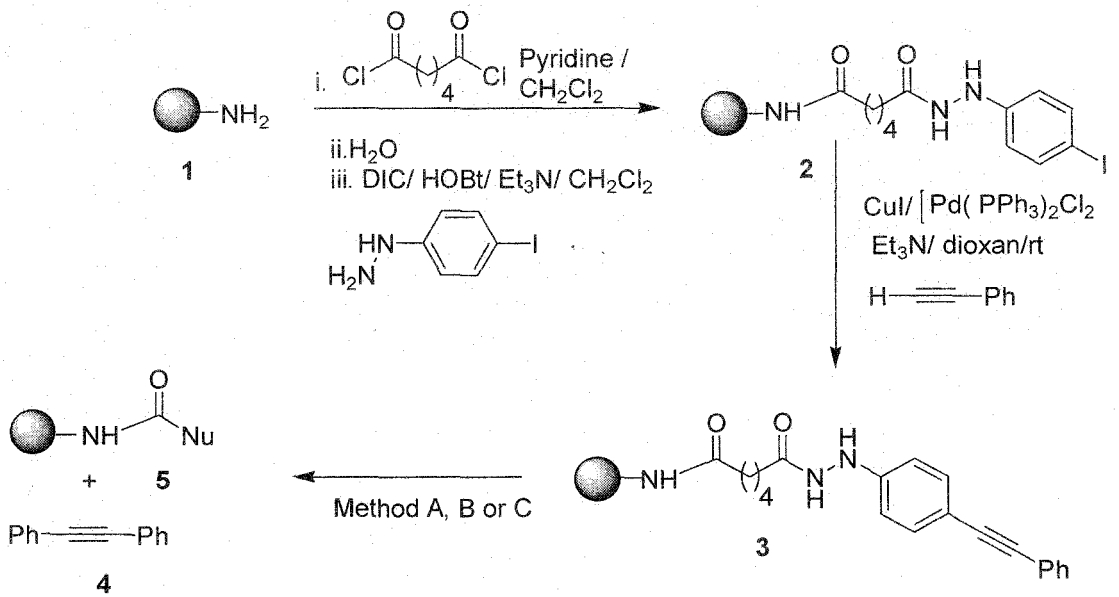
1.4.1. Traceless linkers:

Functional groups have a dramatic outcome on the potential medicinal efficiency on the final drug-like target molecules. Keeping this idea in mind chemists designed ''traceless linkers".

1.4.1. A: Nitrogen linkers

An aryl hydrazine oxidation labile traceless linker has been reported.[22] Different amino functionalized polymers **1** (polystyrene-NH_2, Tentagel-NH_2, Argopore-NH_2) were loaded with 4-iodophenylhydrazine to give **2**. This was subjected to Heck, Suzuki, Sonagashira, or Stille couplings, the example shown being the Sonagashira coupling with phenylacetylene, to give **3**. Three different cleavage methods were used (Method A, Cu $(OAc)_2$/MeOH/pyridine/RT/2 h; Method B, $Cu(OAc)_2$/*n*-propylamine/RT/2 h, Method C, NBS/ pyridine/CH_2Cl_2/RT/45 min then MeOH) to give stilbene.

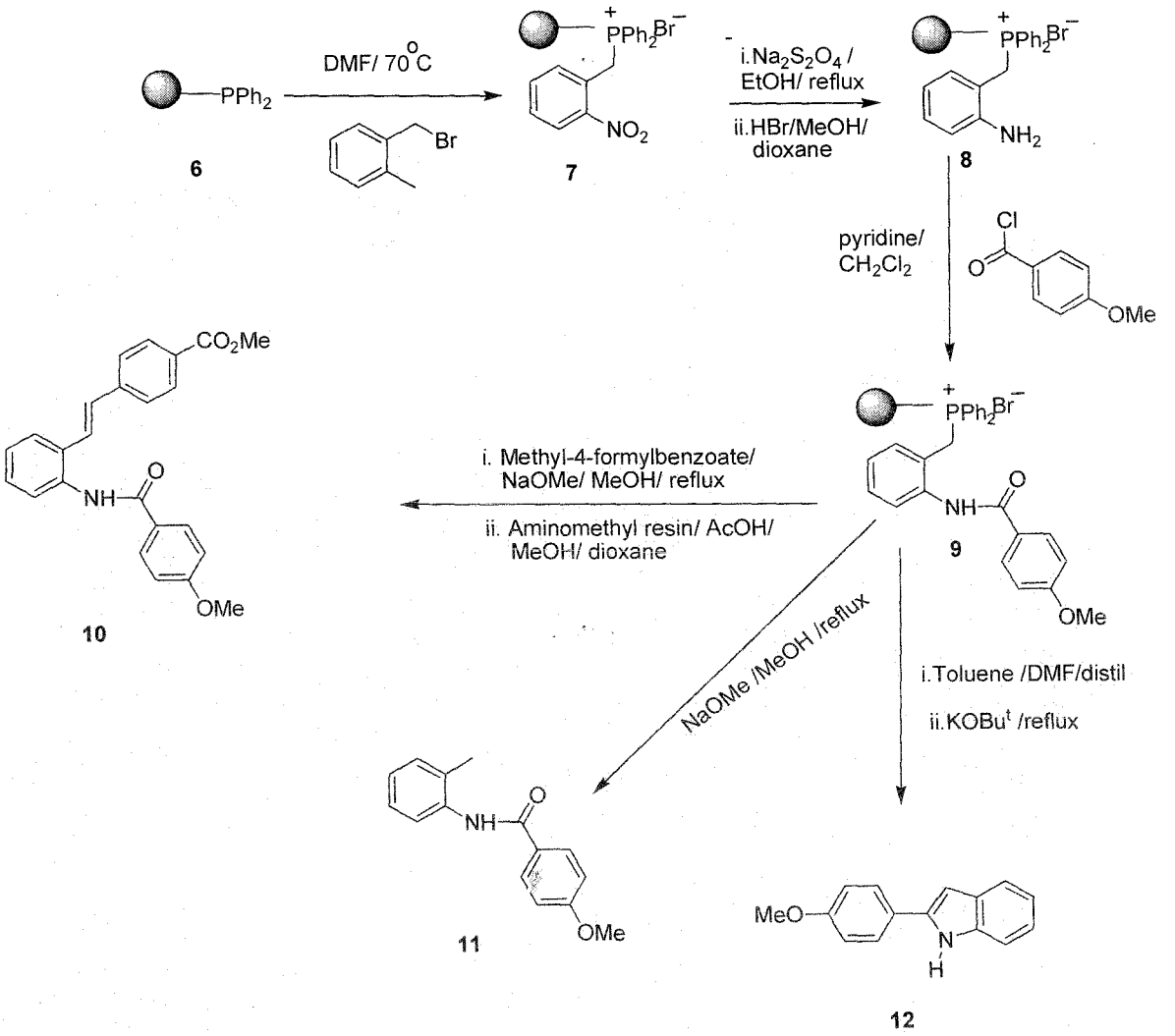
Scheme 4



1.4.1. B: Phosphorus Linker

Phosphorus as a traceless linker was employed by Hughes.[23] Commercially available polystyrene-bound phosphine **6** was loaded with 2-nitrobenzylbromide to give the resin-bound phosphonium salt **7** , which was converted to the aniline **8** then acylated giving the phosphonium resin **9**. Cleavage could then be facilitated by intermolecular Wittig reaction giving a 3:1 *E/Z* mixture of **10**. The aminomethyl resin was used as a solid-phase scavenger reagent for the excess aldehyde used. Hydrolysis of the carbon-phosphonium bond generated the 2-methylanilide **11**. Intramolecular Wittig reaction occurred upon distillation prior to adding base, giving indole **12**.

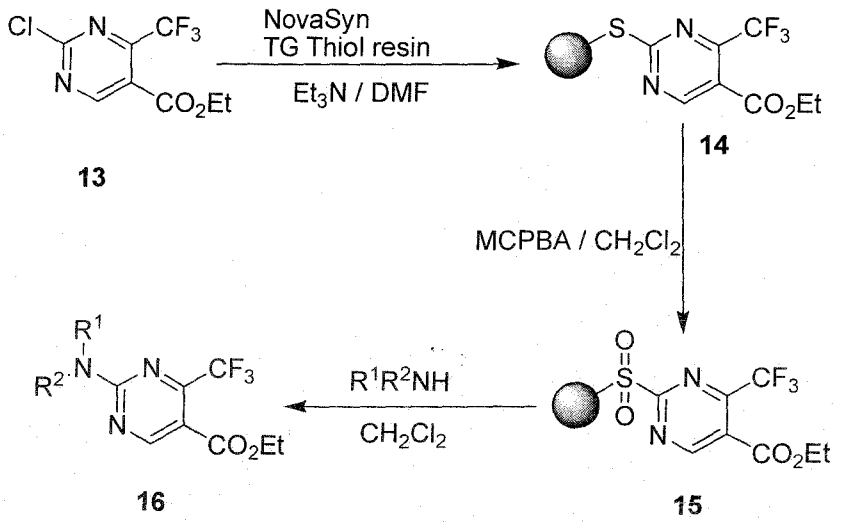
Scheme 5



1.4.1. C: Sulfur Linker:

The first example of a sulfur-based traceless linke was introduced by Suto.[24] Oxidative activation of a sulfide to a sulfone allowed nucleophilic displacement of the sulfone, incorporating further diversity into the final compound. Suto used this technique to synthesize functionalized pyrimidines **16** (Scheme 6). The 2-chloropyrimidine **13** was loaded onto Tentagel thiol resin, a PEG resin. The sulfide resin **14** is oxidized using MCBPA to the sulfone **15**, which was cleaved from the resin using primary and secondary amines to give pyrimidines **16** in 50-93% yield. The purity of the cleaved compounds were generally excellent (mainly >90%). The ester was also manipulated to synthesize amides and ethers. Using highly reactive sulphonamide linkers solid phase synthesis of carboxylic acids or amines has also been synthesized.

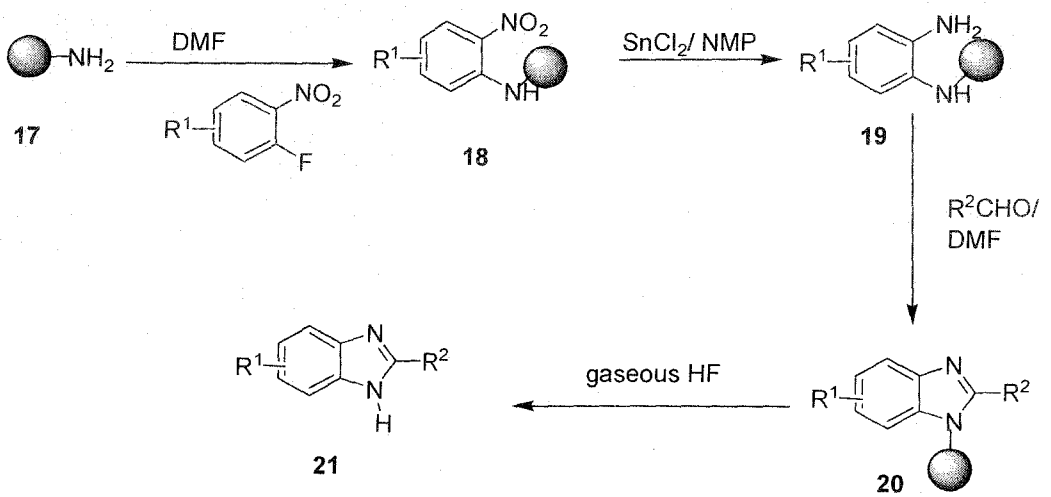
Scheme 6



1.4.1. D: Protecting-Group-Based Traceless Linkers:

The linkers were based on the chemistry of a particular element and its use in solid-phase traceless synthesis. This section will concentrate on linkers based around protecting groups, auxiliaries, or chemically specific traceless linkers. MBHA polystyrene has been used in the synthesis of benzimidazoles.[25] MBHA polystyrene **17** was loaded with 2-fluoronitrobenzene derivatives to give **18**. Reduction of the nitro group gave resin-bound aniline **19**, which was condensed with aldehydes to produce the resin bound benzimidazoles **20**. Cleavage was achieved using gaseous HF to give benzimidazoles **21**.

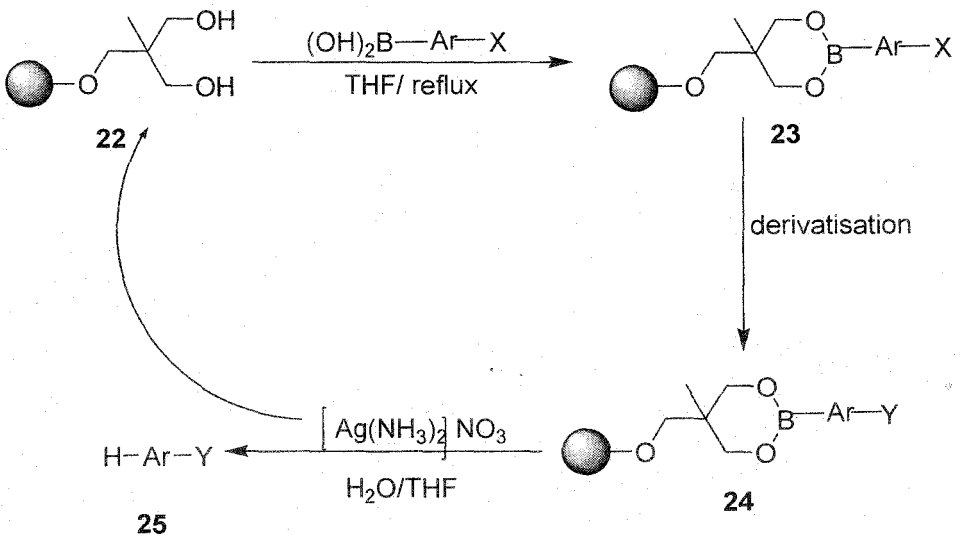
Scheme 7



1.4.1. E: Boron linker:

A novel boronate linker,[26](Scheme 8) was developed from **22**, which allows boronic acids to be attached to give **23**. A function X was then derivatized in a number of ways including ester and amide formation, reductive amination, and an Ugi four-component condensation, giving derivatized boronate **24**. A mild protodeboronation cleavage protocol was developed using silver diamine nitrate in water and THF to release the functionalized aromatic compound **25**, regenerating the initial linker **22**.

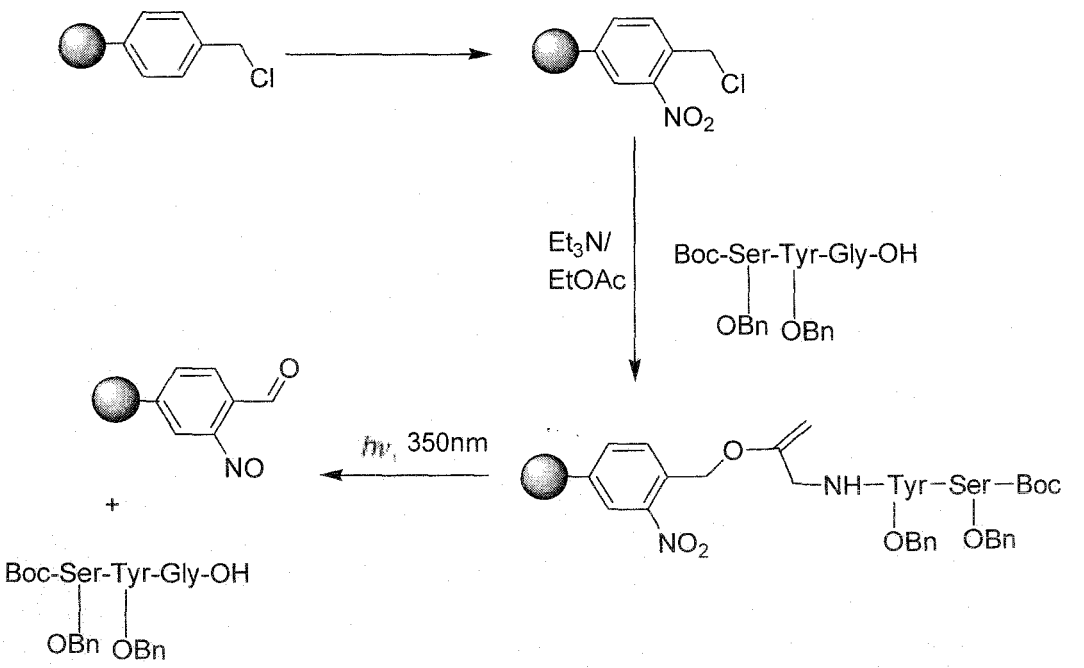
Scheme 8



1.4.1. F: Photolabile Linkers:

Photolabile linkers are very useful in the generation of combinatorial libraries as they offer compound cleavage under mild conditions directly into a solvent suitable for biological testing. The first account of a photolabile linker to bind a substrate to a solid support was published in 1973 by Rich *et al.*[27] and was based on the *o*-nitrobenzyl alcohol derivatives introduced by Patchornik.[28] Its preparation was extremely easy, and took advantage of the already present chloromethyl group on the resin aromatic framework: simple nitration of chloromethylated polystyrene beads was followed by heating the resulting benzylic chloride with an amino acid (or a peptide fragment) and a base (Scheme 9). Photolysis (350 nm) gave a tripeptide with an overall yield of 62%.

Scheme 9



1.5. Solid Supported Catalysts:

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. Palladium can be deposited on a solid support in different ways.[29] The preferred mode of deposition depends also on the type of support. The surface of the support can be covalently functionalized by ligands, such as phosphines, pyridines, or mercaptans, which form complexes with dissolved metal salts. This methodology is widely used in polymer,[30] and silica-supported,[31] palladium catalysts. Grafting of Pd complexes to the solid support by starting with a Pd complex bearing linker groups in the ligands is another method to prepare solid-supported Pd catalysts.[32] The support usually has an impact on the activity of the catalytic system. Particle size, surface area, pore structure, and acid-base properties are important parameters of the support. Sol-gel processes can also be used for the preparation of solid-supported Pd catalysts, mainly for silica- and alumina supported Pd catalysts. The support is generated from a monomer, such as tetraethoxysilane or aluminum isopropoxide in the presence of a soluble Pd compound, such as $PdCl_2$, Pd $(NH_3)_4Cl_2$, or Pd (acac) $_2$ (coprecipitation) and eventually a linker. In this way, usually amorphous materials are obtained, where a part of the Pd is encapsulated. Basic supports such as basic zeolites, layered double hydroxides, or sepiolites can play a similar supporting role as phosphines in homogeneous catalysis or can act as bases, that is, no external bases are necessary in these cases. Due to their controlled pore size, microporous and

mesoporous materials, such as zeolites, can be advantageous over simple metal oxides. Pd (0) clusters can be encapsulated in these pores. The pore size and structure of such supports can have an important impact on the reactivity and selectivity of those catalysts.[33] Thus, cases were reported where a larger pore size of mesoporous silica allowed reaction of larger substrates as compared with microporous supports.The characterization of a heterogeneous metal catalyst on a molecular level is still a problem, although TEM, X-ray diffractometry, and IR spectroscopy allow important insights into the structure. Often, heterogeneous catalysts are still chosen on an empirical basis without understanding why a given catalyst is superior to another one.

Poly-ionic resins have been addressed in the section ion exchange resin.

1.5.1. Covalent binding of catalyst:

Silica, a neutral oxide, is totally hydroxylated and the hydroxyl layer covered with physically absorbed water.[34] Removal of water,[35] at higher temperature results an amorphous porous,[36] 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,[37] 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)] and 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, Suzuki reaction and the catalyst can be reused in these reactions without noticeable loss of activity. The systematic use of immobilization of organ functional groups has increased in the past three decades, mainly on silica, because this support offers pronounced advantages over other organic/inorganic supports as listed below:

(a) Immobilization on silica results in great variety of silylating agents, allowing pendant functional groups in the inorganic framework.[38]

(b) Attachment is easier on silica surface than on organic polymeric supports, which have a high number of cross-linking bonds, requiring hours to reach equilibrium for surface activation.[39]

(c) Silica gel being the most popular substrate for surface studies because it is the first commercially available high specific surface area substrate with constant composition, enabling easy analysis and interpretation of results

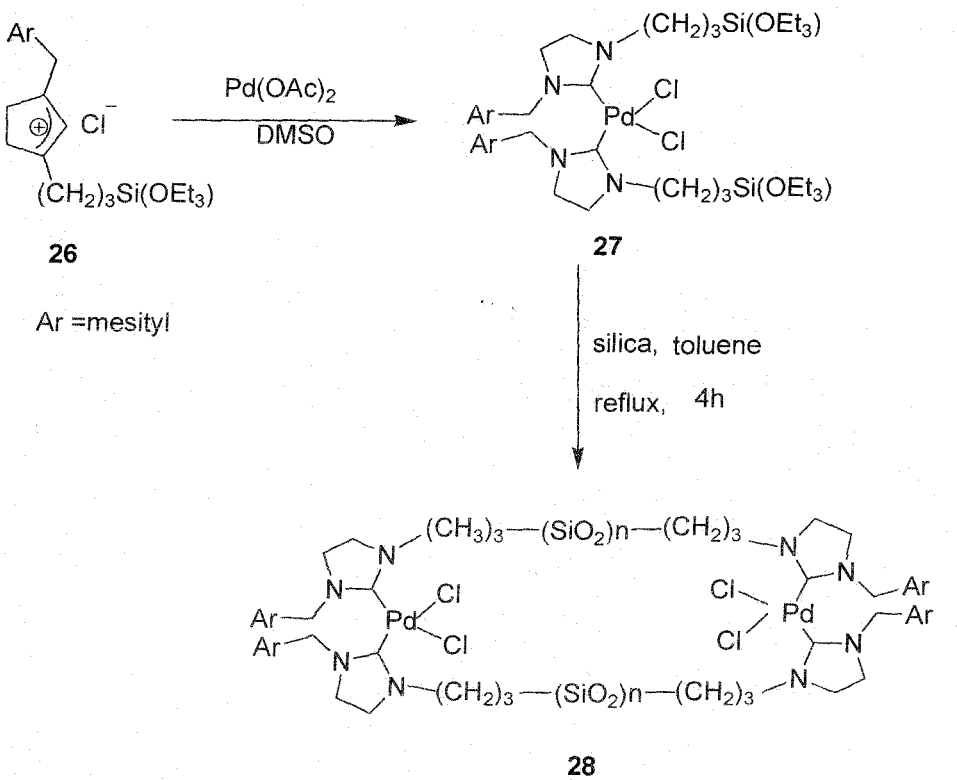
(d) Silica gel has high mass exchange characteristics and no swelling.[40]

(e) Silica support has great resistance to organic solvents

(f) Silica has very high thermal resistance.[41]

Example an electron-rich imidazolidine carbene Pd (II) complexes **27** could be grafted onto mesoporous silica via a propyltriethoxysilane linker (Scheme 10).[42] The resulting catalyst **28** exhibited excellent activity in Suzuki and Heck coupling.

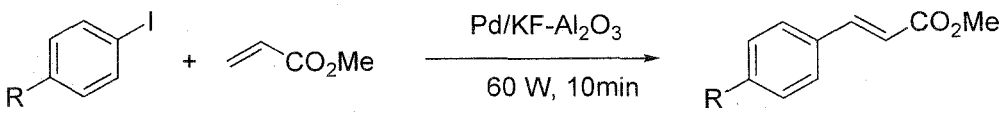
Scheme 10



1.5.2. Palladium on metal oxide other than silica:

The first report about a heterogeneous Heck reaction using Pd supported on metal oxide was published by Kaneda *et al.* in 1990.[43] Chlorobenzene was coupled with styrene in methanol at 150°C using Pd/MgO as catalyst and Na_2CO_3 as base. Later on several metal oxides (MgO, Al_2O_3, TiO_2, ZrO_2, ZnO, mixed MgLaO, etc.) have been used as supports for Pd catalysts in Heck reactions. Ar-X with X) I, Br, Cl, OTf, COCl, SO_2Cl, or N_2BF_4 were coupled with acrylates,[44] acrylonitrile,styrene,[45] vinyl alkyl ther,[46] terminal alkenes.[47] Biffis and co-workers reviewed palladium metal catalysts in Heck reactions in 2001.[48] Microwave irradiation can be applied to Heck reaction catalyzed by Pd on several metal oxides as shown in the coupling of iodobenzene with 1-decene.[49] Slightly higher yields were achieved in the microwave-mediated solvent less Heck reaction of aryl iodides with methyl acrylate in the presence of palladium on KF/alumina (Scheme11).

Scheme 11



R=H, 62% ; R= OMe, 68%

1.6. Ion Exchange resins:

Ion exchange materials are insoluble substances containing loosely held ions which are able to be exchanged with other ions in solutions which come in contact with them and normally obtained as beads of 1-2 mm diameter. These exchanges take place without any physical alteration to the ion exchange material. Ion exchangers are insoluble acids or bases which have salts which are also insoluble, and this enables them to exchange either positively charged ions (cation exchangers) or negatively charged ones (anion exchangers). Many natural substances such as proteins, cellulose, living cells and soil particles exhibit ion exchange properties which play an important role in the way they function in nature. Synthetic ion exchange materials based on coal and phenolic resins were first introduced for industrial use during the 1930s. A few years' later resins consisting of polystyrene with sulphonate groups to form cation exchangers or amine groups to form anion exchangers were developed. The most typical ion exchange resins are based on cross linked polystyrene and the required active groups can be introduced after polymerization, or substituted monomers can be used. For example, the cross linking is often achieved by adding 0.5-25% of divinylbenzene to polystyrene at the polymerization process. Non-cross linked polymers are used only rarely because they are less stable. Cross linking decreases ion- exchange capacity of the resin and prolongs the time needed to accomplish the ion exchange processes. Particle size also influences the resin parameters; smaller particles have larger outer surface, but cause larger head loss in the column processes.

Their insolubility renders them environmentally compatible since the cycle of loading/regeneration/reloading allows them to be used for many years. Ion-exchange resins have been used in water softening, removal of toxic metals from water in the environment, wastewater treatment, hydrometallurgy, sensors, chromatography, and biomolecular separations. They have also been used as catalysts, both in place of homogeneous catalysts such as sulfuric acid and to immobilize metallic catalysts.

1.6.1. Types Ion Exchange resins:

There are four types of ion exchange resins and these ares-

- Strong cation exchange resins, containing sulphonic acid group or the corresponding salts.
- Weak cation exchange resins, containing carboxylic acid groups or the corresponding salts.

- Strong anion exchange resins, containing quaternary ammonium groups.
- Weak anion exchange resins, containing primary, secondary, and/or ternary amino groups, e.g. polyethelene amine.

The affinity for a series of anions with this resin was determined to be: citrate > sulfate > oxalate > iodide > nitrate > chromate > bromide > thiocyanate > chloride > formate > hydroxyl > fluoride > acetate.[50]

1.6.2. Properties:

A. Cross linkage:

The amount of cross linking depends on the proportions of different monomers used in the polymerization step. Resins with very low cross linking tend to be watery and change dimensions markedly depending on which ions are bound. Copolymers of styrene containing low amounts of divinylbenzene (1-4%) are characterized as follows:

- Large moisture content
- Lower capacity on a wet volumes basis
- High equilibrium rates
- Reduce physical stability
- Decreased selectivity for various ions, but ability to accommodate larger ions is increased.
- Thermally stable.
- Selectivity for various ions is decreased, but ability to accommodate larger ions is increased. Copolymers of styrene containing high amounts of divinylbenzene (12-16%) exhibit characteristics in the opposite direction.

B. particle size:

The physical size of the resin particles is controlled during the polymerization step. A higher mesh number means more and finer wires per unit area and thus a smaller opening. Screens are used to sieve resins to get a fairly uniform range of sizes. The particle size affects the equilibrium and flow rate of the ion-exchange process as follows:

- Decrease in particle size shortens the time required for equilibration
- Decrease in flow rates with decreasing particle sizes.

C. Uses of Ion Exchange resins:

Ion exchange resins are widely used in different separation, purification and decontamination process examples are: Water softening, Water purification (Removal of Herbicides from Water; Sorption of Phenol, Removal of Herbicides from water, [51] Uranium recoveries from seawater, Inversion of sucrose. Sugar Cane Juice Processing and many other relatively uses.

- Recover of radioactive metal
- Sorption of Gases

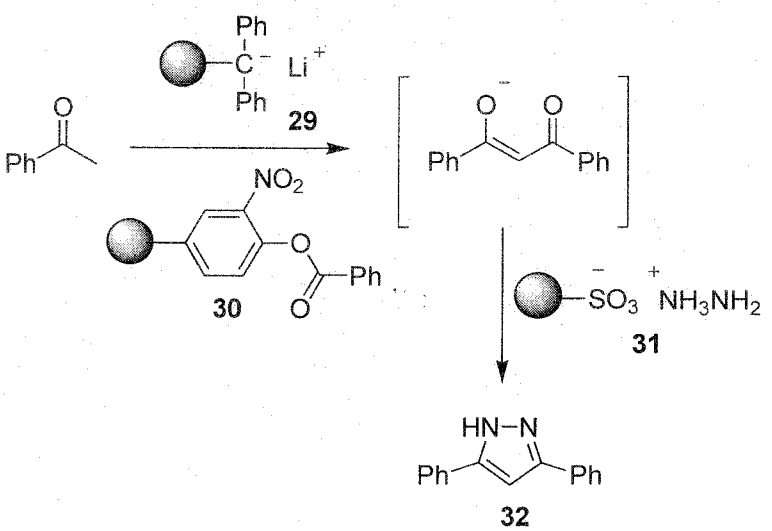
- Olefin/Paraffin Separations in industries
- Manufacture of various pharmaceuticals and also for isolating and purifying pharmaceutical product.
- In chemistry as metal scavengers and catalysts in organic reaction.

1.7. Catalytic activity of ion exchange resin in organic reactions: A few Applications are presented here.

A. **Cation Exchange Resin:**

Scheme 12 describes the "wolf and lamb" technique utilized by the Cohen group.[52] It involves the use of a polymer-bound trityllithium base **29** to remove an acidic proton from acetophenone. The anion generated then undergoes a *C*-acylation reaction with a benzoyltransfer polymer **30** and is passed without isolation into Amberlyst® A-15 resin (hydrazine form), affording 3,5- diphenylpyrazole when filtered from the spent polymer reagent.

Scheme 12



B. Anion Exchange Resin:

A. **Reduction using polymer supported reagents:**

The selective reduction of functional groups is a common need in organic synthesis. Borohydride exchange resin, [53](BER) was introduced in the 1970s and has since proven to be of considerable value in the reduction of organic compounds. This reagent reduces both ketones and aldehydes readily to corresponding alcohol (Scheme 13).

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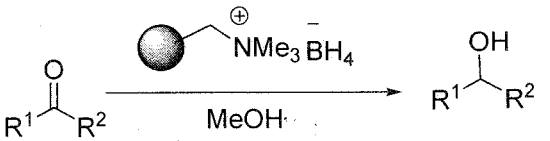
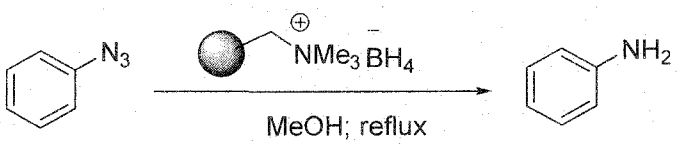
Scheme 13



R' = H or any alkyl group

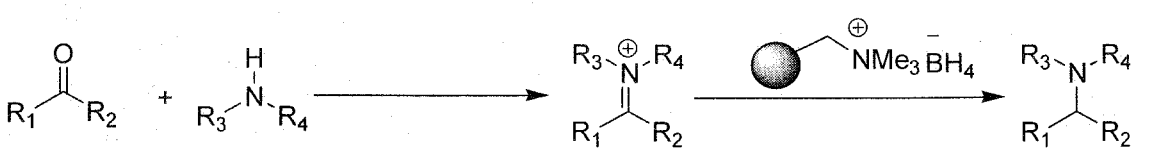
Complete reduction of benzaldehydes to the corresponding hydrocarbons can be accomplished using BER-Ni(OAc)$_2$. Less reactive aromatic aldehydes, such as those with two electron-donating groups, are reduced only to the benzyl alcohols. $CuSO_4$ has also been used as an additive to increase the reactivity of BER.[54]Alkyl and aryl halides (not chloro) can be reduced to hydrocarbons under certain conditions. Azides and nitro compounds are cleanly reduced to give amines in high yields the reduction of azides to amines is a synthetically useful process. BER in MeOH reduces aryl azides and sulfonyl azides to the corresponding aryl amines and sulfonamides, respectively.[55]

Scheme 14



Alkyl azides are either not reduced at all, or the reactions proceed in poor yield. The reactivity of $NaBH_4$ can be enhanced by combining it with certain transition metal salts. The same is true of BER, and a system employing BER-Ni(OAc)$_2$ reduces both alkyl and aryl azides in high yields.[56] Primary, secondary, and tertiary azides are all reduced under these conditions. BER can also reduce imines, and has proven to be useful as a reducing agent in the reductive amination of aldehydes and ketones[57] (scheme15). Aldehydes are reductively aminated cleanly with both primary and secondary amines. Ketones react well with less hindered aliphatic amines, and give lower yields with aromatic amines.

Scheme 15

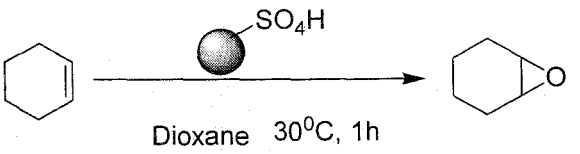


B. Oxidation using polymer-supported reagent:

Medicinal chemists often need to perform mild and selective oxidation reactions. A variety of polymer-supported oxidizing agents have been developed which offer some advantages over more traditional oxidants. Per acid type resins (PARs) prepared from polymer-bound carboxylic acids perform for epoxidation reactions (scheme 16), oxidation of sulfides or

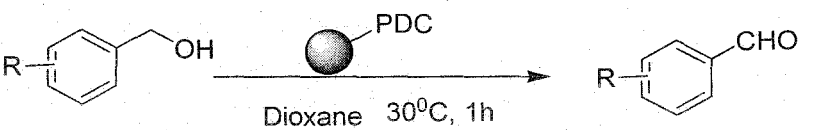
sulfoxides to sulfones, and conversion of ketones to esters.[58] The PARs are quite stable, and can be easily regenerated after each use.

Scheme 16



Frechet and colleagues developed poly (vinylpyridinium dichromate) (PVPDC) as an inexpensive, convenient to use, recyclable oxidant.[59] Oxidations of alcohols to carbonyl compounds performed with this reagent (scheme 17).

Scheme 17

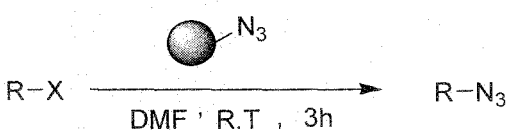


Polymer-supported periodate, can be used for the oxidation quinols to quinones, 1, 2-diols are cleaved to the corresponding carbonyl compounds, sulfides are oxidized to sulfoxides.

C. **Substitution reactions using polymer supported nucleophiles or reagents**:

Alkyl azides are useful intermediates in organic synthesis, and can be prepared using a polymeric quaternary ammonium azide. This reagent allows for the conversion of activated and nonactivated alkyl halides into azides at room temperature[60] (scheme 18). The reaction proceeds most rapidly in polar solvents such as DMF and acetonitrile, but reasonable reaction rates are also obtained in a variety of other solvents. This reagent has also been used to open epoxides of polycyclic aromatic hydrocarbons to give azidohydrins.[61]

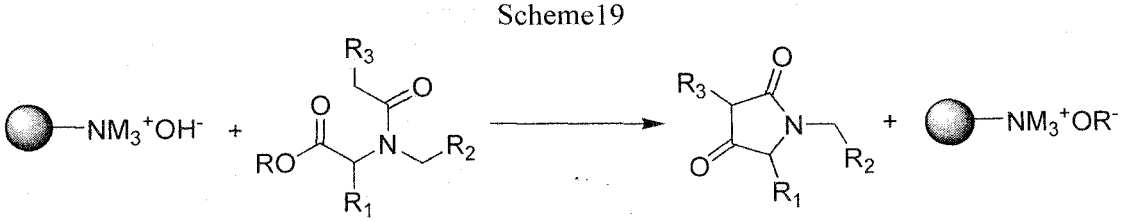
Scheme 18



D. Cyclization process using polyionic resin:

Ganesan, *et al.* are used poly ionic resin hydroxide form of Amberlyst A-26 as a catalyst for the Dieckman cyclization to give 2, 4-pyrrolidinediones (Scheme19).[62]

Scheme19



1.8. Micro-encapsulation:

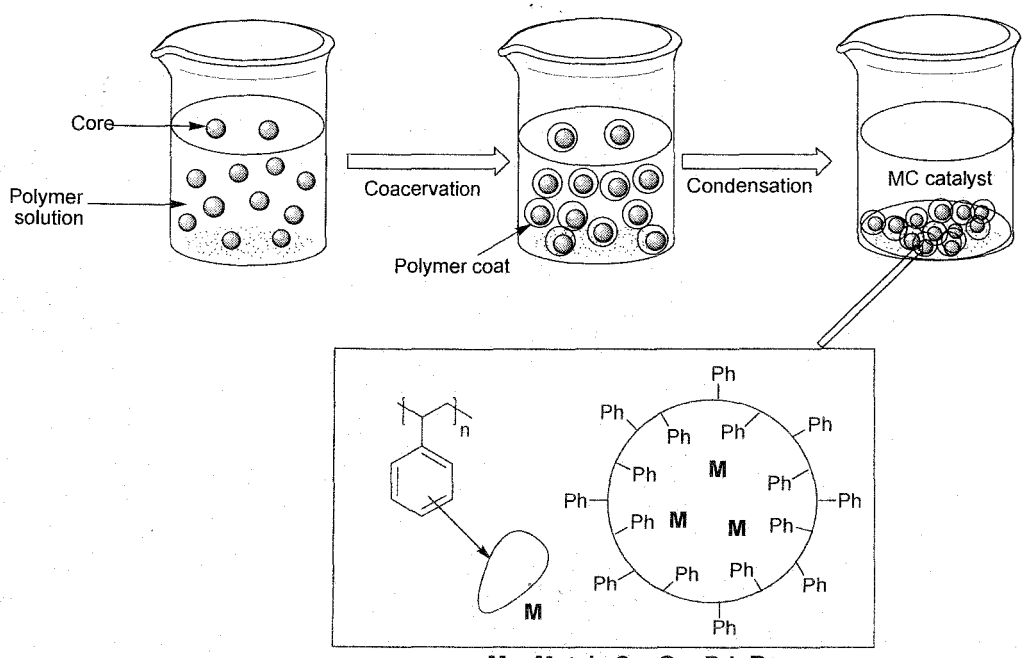
Micro-encapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules many useful properties. In a relatively simplistic form, a microcapsule is a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. Most microcapsules have diameters between a few micrometers and a few millimeters. Microencapsulation technique has found application in-

- Drug delivery systems.
- Radiation therapies
- Cell entrapment
- Controlled release technique

Recently, microencapsulation technique has been applied to the immobilization of catalysts on to polymers. Here the catalysts would be physically enveloped by thin films of polymer, and at the same time immobilized by the interaction between π- electrons of benzene rings of the polystyrene used as a polymer backbone and vacant orbitals of the catalyst. Microencapsulation is widely practiced industrially and has found use in such diverse applications as drug delivery systems,[63] radiation therapies,[64] cell entrapment,[65] and the controlled release of pesticides.[66]

1.8.1. Microencapsulated and Related Catalysts for Organic Chemistry

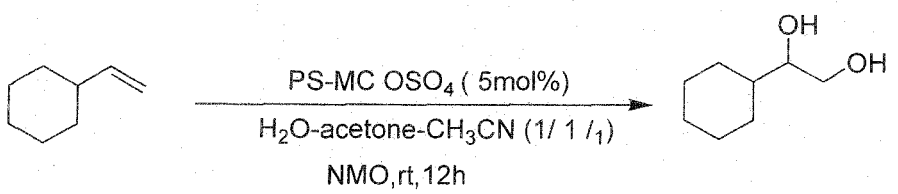
"Green Chemistry" is spreading all over the world. Green Chemistry (environment-friendly chemistry) is chemical technology for eradication of environmental pollution by changing from conventional processes to environmentally friendly processes, which do not produce or use environmental pollutants or dangerous substances, and also by replacing conventional chemical products with environmentally friendly or harmless ones. And for continuous development of human beings, realization of symbiosis in chemistry and the environment is the most important subject in this century. In this era chemist are developed a new method for immobilizing metal catalysts onto polymers, the microencapsulation method was first introduced in 1998.[67] The idea of the new method is to apply the microencapsulation technique for immobilization of catalysts onto polymers (Figure 1).That is, catalysts would be physically enveloped by thin films of polymers (polystyrene derivatives in many cases) and at the same time immobilized by interaction between π electrons of the benzene rings of the polystyrenes, which are used as a polymer backbone, and vacant orbitals of the catalysts (metal compounds). The catalysts were new types of heterogeneous catalysts and were named as "microencapsulated (MC) catalysts". Their application to medicine and pharmacy was extensively studied.



1.8.1. A: Microencapsulated OSO_4

PS-MC OsO_4 has been successfully applied to asymmetric dihydroxylation at room temperature for 6-48 hours and it is less toxic, nonvolatile and easily recovered.[68]

Scheme 20

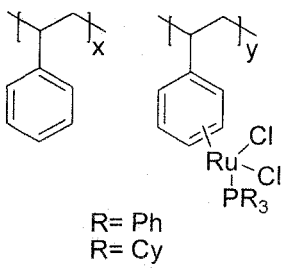


NMO = N-methylmorpholine N-Oxide

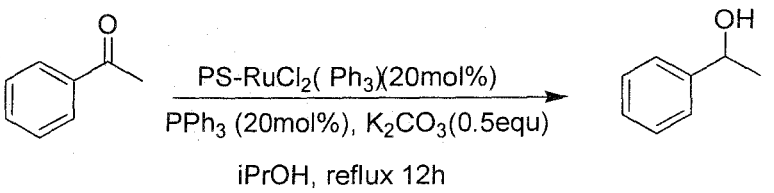
1.8.1. B: Microencapsulated Ru:

PS-$RuCl_2(PPh_3)$, this is the first example of a polymer-supported ruthenium catalyst in which the benzene rings of the polymer coordinated to the ruthenium to immobilize the catalyst onto the polymer, has been successfully used in the smooth reduction of acetophenone to the corresponding alcohol in high yield.

Scheme 21

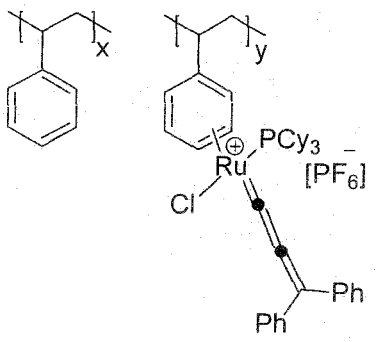


PS-$RuCl_2$(PPh_3)

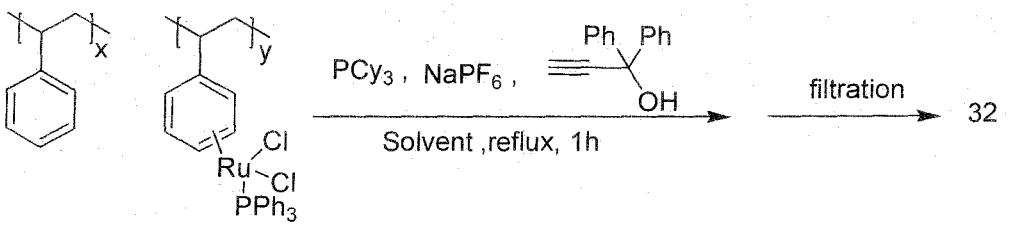


An activated polymer supported ruthenium catalyst (**33**) prepared when PS- $RuCl_2(PPh_3)$, tricyclohexylphosphine(PCy_3),1,1-diphenyl-2-propynol and sodium hexafluorophosphate ($NaPF_6$) were mixed in several solvents, and the mixture was stirred for 1 h under reflux conditions. This activated PS Ru-catalyzed ring-closing metathesis of olefins.

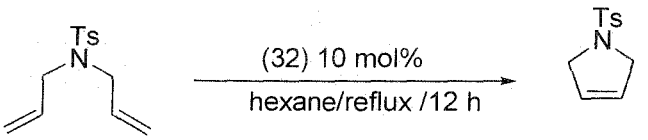
Scheme 22



(**33**)

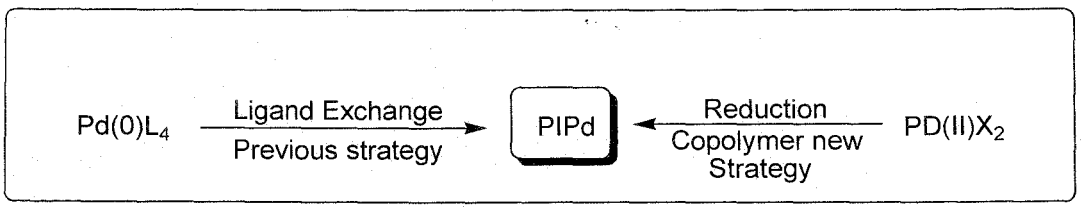


Scheme 23



1.8.1. C: Encapsulated palladium (0):

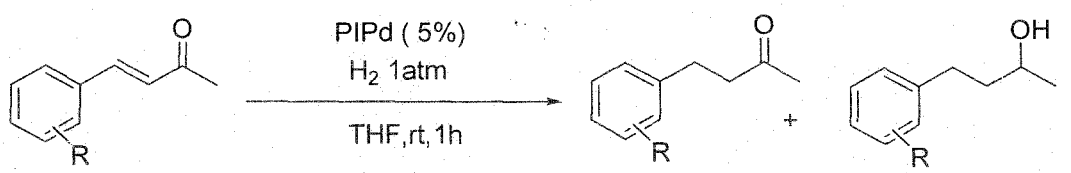
Several polymer-supported palladium catalysts have been developed for allylic substitution, oligomerization, decarboxylation, hydrogenation, isomerization, telomerization, Suzuki coupling, the Mizoroki-Heck reaction, etc. Palladium catalyst was successfully immobilized onto a polymer using the microencapsulation technique. There have two strategies for the polymer incarcerated method.



Hydrogenation:

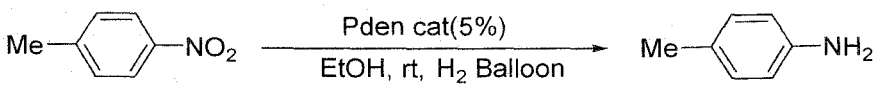
PIPd was tested in hydrogenation of benzalacetone (scheme 24).[69] The reduction was completed within 1 h in THF under ordinary pressure, the reactions proceeded smoothly to afford the desired products in high yields and it should be noted that the catalyst was recovered quantitatively by simple filtration and that the same yields were obtained even after the fifth use.

Scheme 24



Polyurea microcapsules160 another type of microencapsulated catalyst was found to be suitable by virtue of their chemical structure a backbone of urea functionality that could ligate and thus retain catalytically active metal species. Polyurea microcapsules containing palladium acetate (Pd EnCat) were also applied to hydrogenation reactions.[70] Pd-EnCat was prereduced under H_2 (50 bar) for two days, and hydrogenations were then carried out with this reduced catalyst. The reactions were performed on a 1 mmol scale (with respect to substrate) using 5 mol % of prereduced Pd EnCat under an atmosphere of H_2 maintained by an inflated balloon or under higher pressure using an autoclave. The studies carried out revealed that these Pd microcapsules are effective in the hydrogenations of alkenes, alkynes, and imine and nitro functionalities (scheme 25).

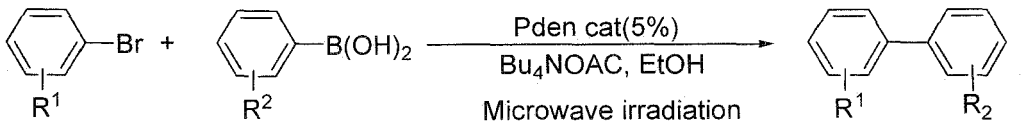
Scheme 25



Suzuki reaction:

Ley *et al.* carried out Suzuki reactions in ethanol (scheme26) where the catalyst used as Pd^0Encat. The catalyst system is highly efficient when used in conjunction with microwave heating, showing enhanced reactivity and a prolonged lifetime.[71]

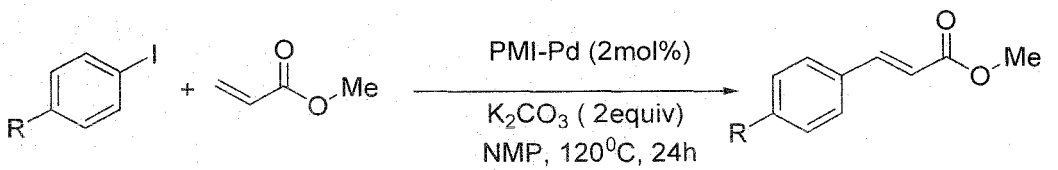
Scheme 26



Heck Reaction:

Polymer micelle incarcerated palladium are effective and stable cross-coupling catalysts.[72] Chemists have demonstrated its catalytic activity in a Heck reaction of iodobenzene with ethyl acrylate. They observed high conversions at low loading (0.5 mol %) at 100-120°C in all cases. The loading of Pd was determind by XRF analysis after decomposition.

Scheme 27



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Part I

Section A

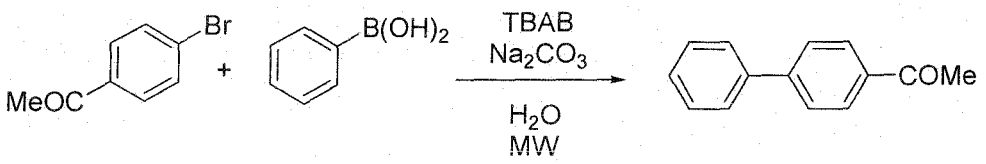
"Poly-ionic Resin Supported Phenylating Agent for Base-free Suzuki-Miyaura Coupling Reaction"

1. A.1. Intoduction

Solid phase organic synthesis (SPOS) is now routinely used for the preparation of combinatorial libraries of low molecular weight organic molecules.[1] Recently much of this effort has been focused towards optimisation of biologically active frameworks within the pharmaceutical industry.[2] Use of solid-supported reagents,[3] a novel extension has recently been reported by several groups and its subsequent application towards more efficient solution phase combinatorial chemistry. This technique involves traditional solution phase chemical synthesis in which the reaction mixture is purified by using a solid support (scavenger). These solid supported reagents can be used to remove an excess of reactants and thus give the required product in high yield and in a single operation. This technique offers many of the advantages, such as easy reaction workup, and product purification with the additional advantages associated with traditional solution phase synthesis. Previously this strategy has been referred to as either a solid-supported scavenger (SSS), polymer-supported quench (PSQ), or complementary molecular reactivity and molecular recognition (CMR/R)[4] and now such reagents will be referred to as polymeric scavenger reagents (PSRs). The development of suitable polymer support to immobilize the reagents/catalysts followed by its applications to various organic transformations constitutes an attractive area of "Green Chemistry". It has become the backbone of modern combinatorial chemistry. The chemical transformation which has received much attention in the modern era is polymer-assisted solution-phase (PASP) Suzuki-Miyaura reaction. The Suzuki-Miyaura reaction has proven to be an extremely versatile and useful in the formation of carbon-carbon bonds, especially the formation of aryl-aryl or vinyl aryl bonds. The Suzuki-Miyaura reaction has gained popularity due to the mild reaction conditions, commercial availability of diverse boronic acids, and the tolerance of a wide range of functional groups that are environmentally safer than the other organometallic reagents[5]. Due to the low toxicity,[6] air and moisture stability of organoboranes makes this method more attractive alternative over other methods. This coupling reaction generally employ organic solvents such as DMF, THF, CH_3CN etc, in the presence of base, ligand and Pd-catalysts which are soluble in these solvents, the catalysts may also be used on the solid surface in different ways.[7] Aryl halides and triflates substituted with electron-withdrawing groups (EWGs) are suitable substrates for the cross-coupling reaction. The relative reactivity of leaving groups is normally in the order $I^- > OTf^- > Br^- >> Cl^-$. The most commonly used base in the SM cross-coupling reaction is K_2CO_3 but this is often ineffective with sterically demanding substrates. In such instances, $Ba(OH)_2$ or K_3PO_4 has been used to generate good yields of the cross-coupled products. Other bases utilised in the SM coupling reaction include Cs_2CO_3, K_2CO_3, TlOH, KF and NaOH.[8] It is well known that the base is involved in the coordination

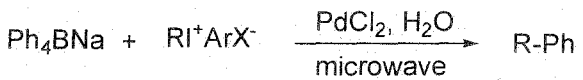
sphere of the palladium and the formation of the Ar-PdL_2–OR from Ar-PdL_2–X is known to accelerate the transmetallation step. The biaryl motif is found in a range of pharmaceuticals, herbicides, and natural products, liquid crystalline materials, nanotechnology & in conducting polymers. So the development and improvement of the conditions for Suzuki-Miyaura reaction has received much attention. In the past few years, great advances have been made in developing the active and efficient catalyst by modifying the traditional ligands and discovering new ones. Among the variations of the catalyst and the base, Leadbeater *et al.*[9] reported SM coupling reactions using very low levels of Pd (50 ppb). (Scheme 1)

Scheme 1



Yan and coworkers have recently reported base-free SM reaction using hypervalent iodonium aryl salts instead of aryl halides.[10]

Scheme 2



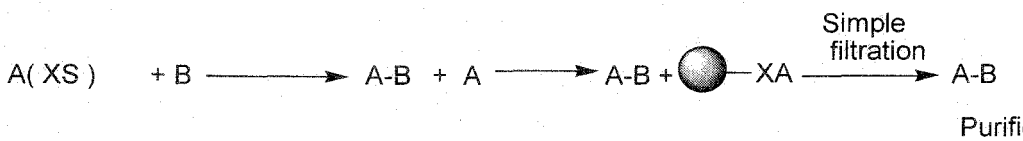
Functionalized solid supports like polymers loaded with homogeneous catalysts and polymer supported reagent are well established in organic synthesis.[11] Simple purification of the products and easy recyclability of the catalysts as well as reagent are major advantages of heterogeneous reactions. In general, arylboronic acids are good nucleophilic organoboron reagents in this coupling reaction.[12]However, boronic acids are never ideal because they exhibit several drawbacks, such as the partial formation of dimeric and cyclic trimeric boroxines (which depend on storage water content).[13]Many functionalized boronic acids are waxy solids that are difficult to purify and electron-deficient heteroaryl-boronic acids, have a short shelf life owing to their tendency to undergo facile proto-deboronation. This instability often requires their storage at low temperatures. Protodeboronate tendency is quite often manifests itself during cross-coupling reactions carried out in polar protic solvents.[14]This structural ambiguity affects the stoichiometry of boronic acids added to the intended reaction and use of excess boronic acids in cross-coupling reactions. In view of the several aspects required for the development of new variants of the organoboron species, the catalyst and the base in the SM coupling reaction and the optimizing process have remained challenging areas of research.

1. A.2. Background and Objective:

In the era of 1990-2000, the concept of a resin-capture-release technique generating the polymer-bound reactive species has been established as a potential method for several organic

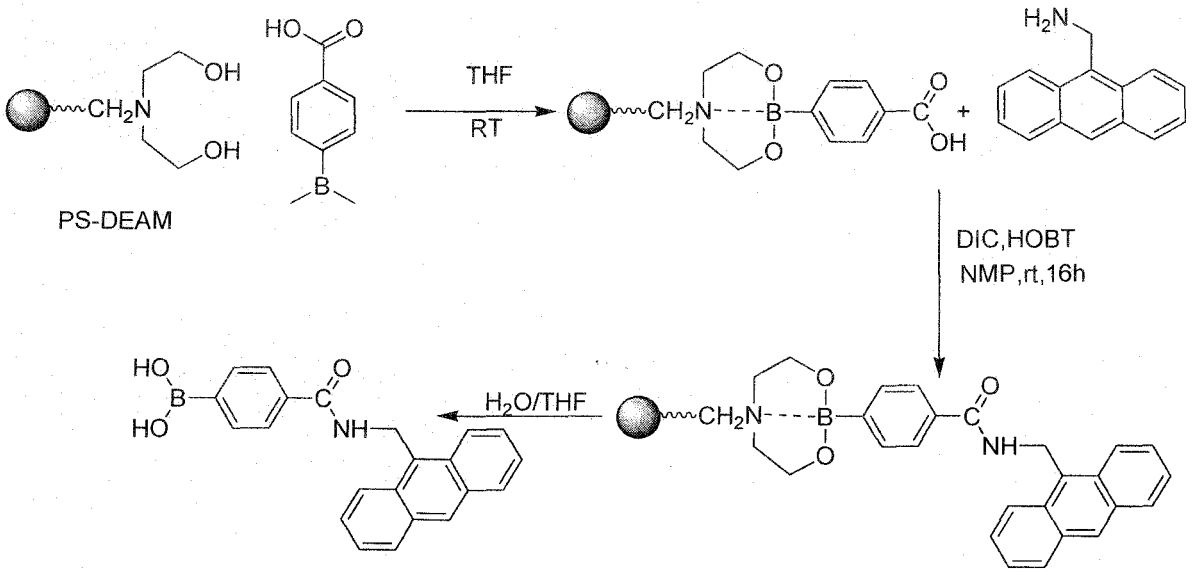
transformations,[15] mand the first report of an application of a polymer supported reagent in synthesis was accounted by Keating and Armstrong.[16]Considerable effort has been devoted to the development of new techniques which assist in the rapid purification of solution phase reactions. The solid supported reagents can be used to remove an excess of reactants by simple filtration and thus give the required product in high yield in a single operation step (Scheme 3) without further purification.

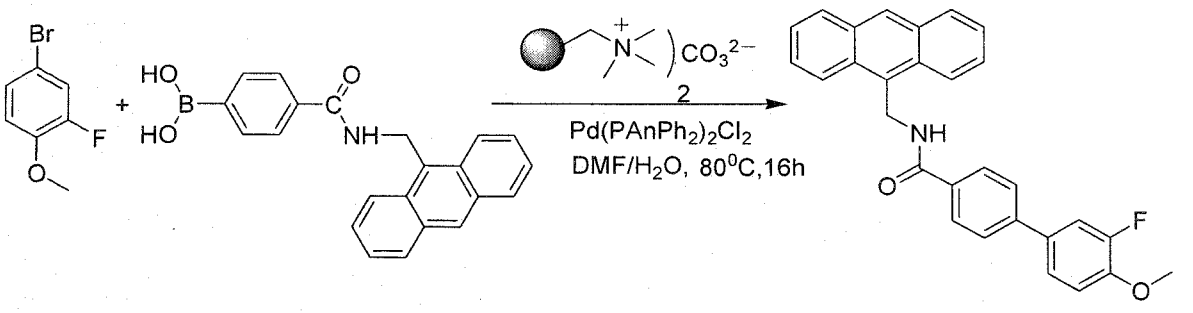
Scheme 3



Polymer-bound boronic acids were first reported in 1976[17]& in 1994, that supported bornic acid was used in SM coupling reaction with the aid of combinatorial chemistry. A variety of techniques to immobilize different components of SM reactions on macroporous solids clearly revealed the lack of application of polyionic resins soaked with organoboron species. Parlow and co-worker[18] synthesized anthracene-tagged boronic acid using polymer supported *N,N*-diethanolaminomethyl polystyrene and applied it for Suzuki-Miyaura reaction to afford > 90% yield of the coupled product, as shown in Scheme 4.

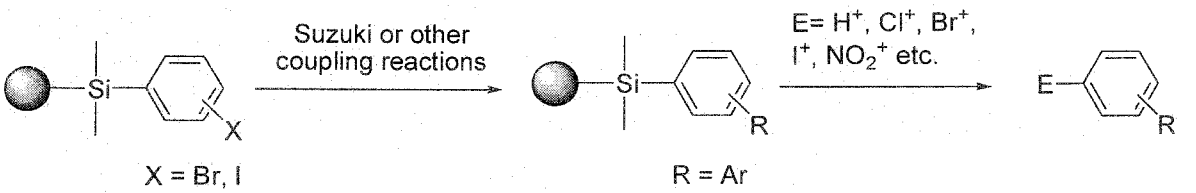
Scheme 4





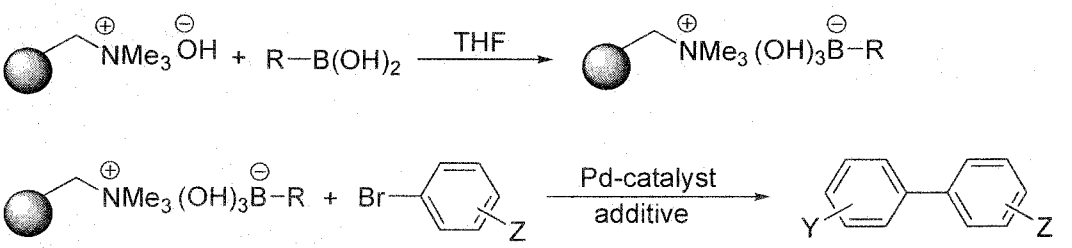
Han *et al.*[19] reported the silicon-based linking technology where the polymer-bound arylsilane linker reacts with a variety of arylboronic acids under the SM reaction conditions. The coupled resin is then cleaved by different electrophiles to give the *ipso*-substituted products in good yields.

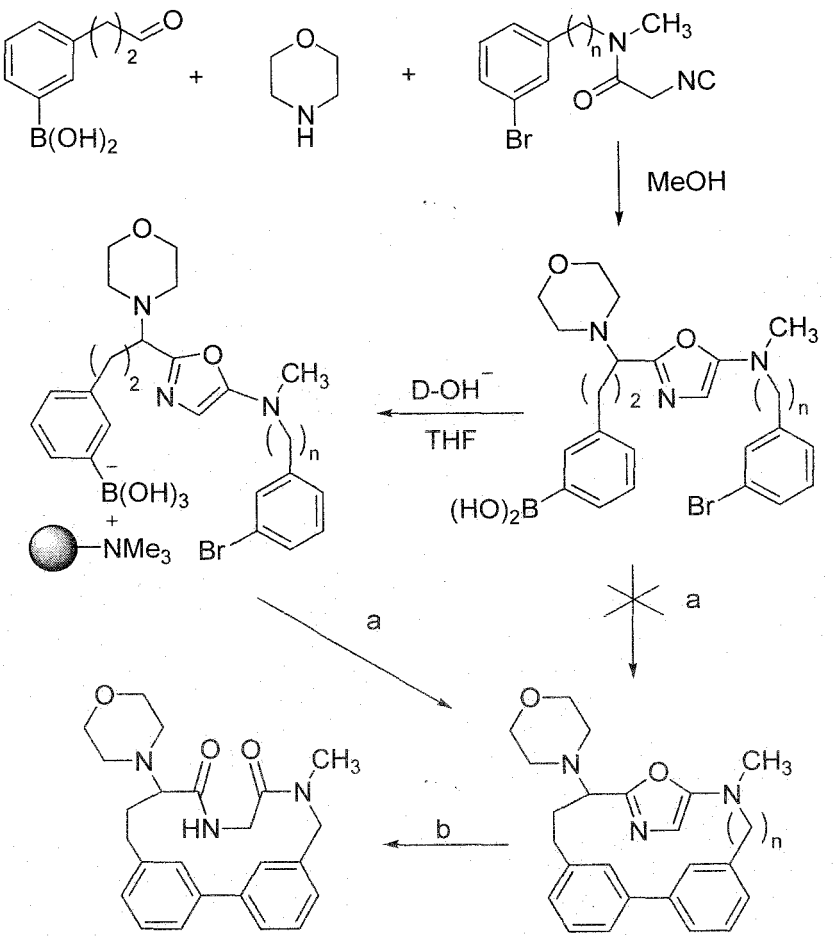
Scheme 5



Lobregat *et al* showed that arylboronic acid may be trapped by an ammonium hydroxide from Doex® ion-exchange resin and the resulting species can be used for macro hetero cyclization under SM conditions, as outlined in Scheme 6.[20]

Scheme 6

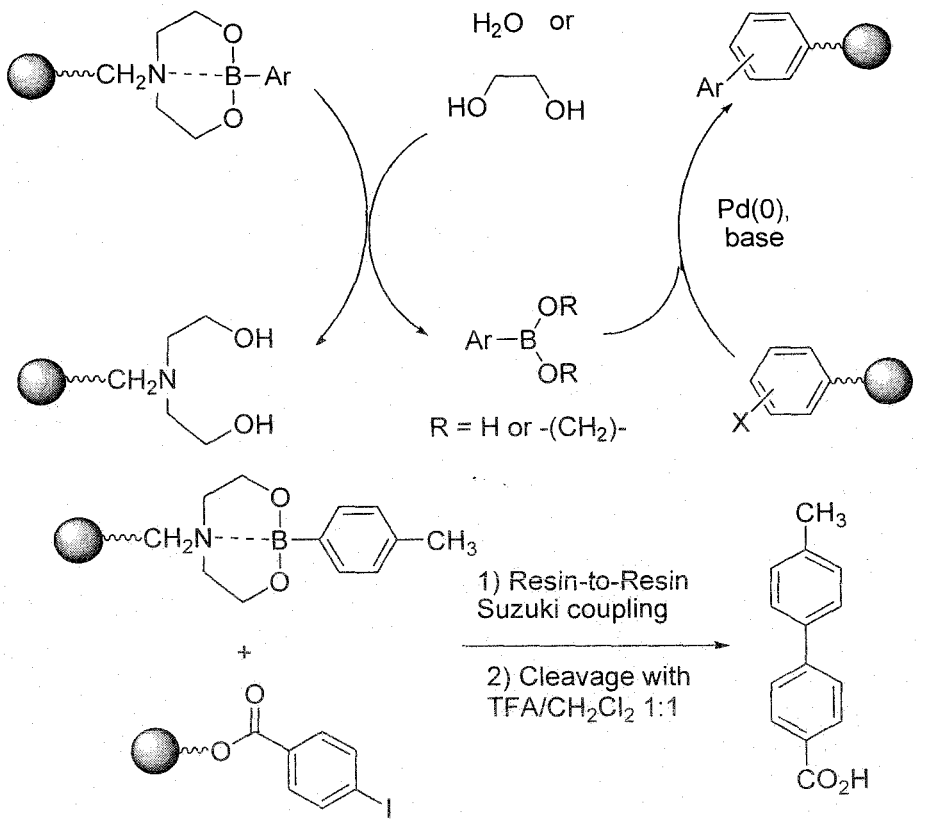




(a) D-Br$^-$ (1 eq), cat. $Pd(OAc)_2$ (5 mol%), TPPDS (20 mol%), THF-H_2O (4:1), 40 °C, 40 h; (b) TFA (120 eq), H_2O (30 eq), rt, 2 h

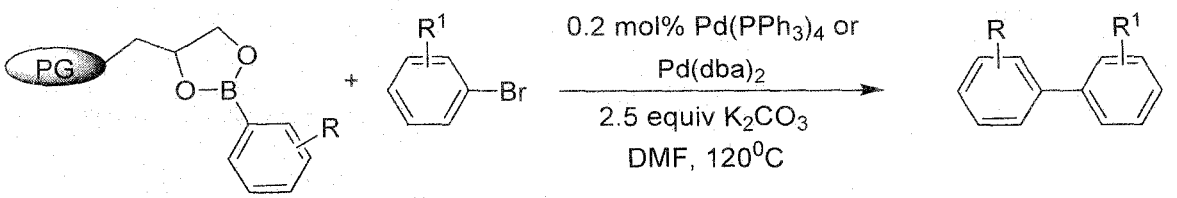
The first resin-to-resin transfer reaction [RRTR] for the formation of carbon-carbon bonds described by Hall *et al.*[21] is the Suzuki-Miyaura RRTR system which allows the convergent solid-phase synthesis of un-symmetrically functionalized biphenyl compound that would have been difficult to access using a linear solid-phase strategy. They used DEAM-PS resin to generate libraries of several new arylboronic acids as coupling partners.

Scheme 7



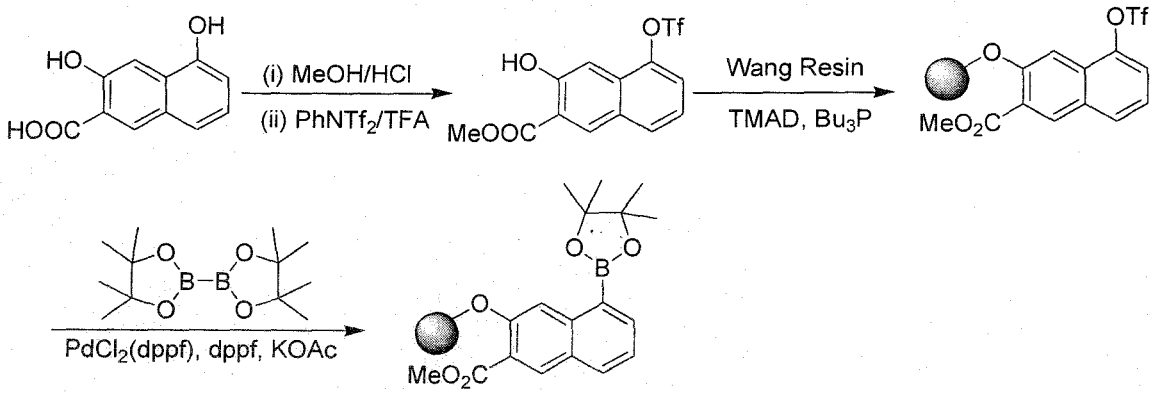
Haag *et al.*[22] first synthesized the soluble high-loading polyglycerol support for functionalized boronic acids or ester and subsequently employed in homogeneous Suzuki-Miyaura cross-coupling reactions & isolated high yields (84-91%) of functional biaryls with minimal amounts of the Pd catalyst.

Scheme 8



Kim *et al.* has prepared polymer bound napthyl boronate[23]in different way which is used for Suzuki-Miyaura cross coupling reaction.

Scheme 9

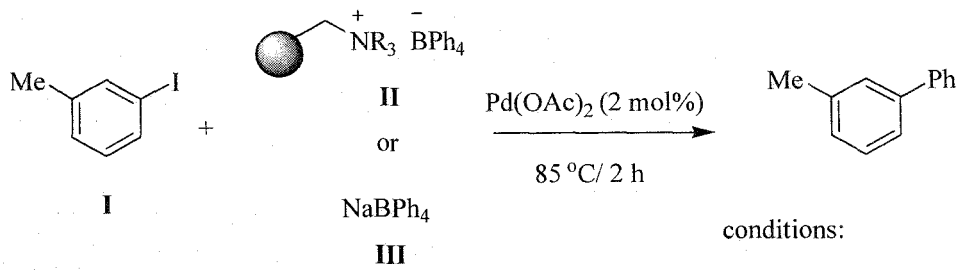


1. A.3. Results and discussion:

In connection with our interest in the development of ionic resin-bound reagents and/or catalysts,[24] we have an idea to develop an ion-exchange resin-supported borate species as a heterogeneous phenylating agent. Our initial studies began with Amberlite® IRA-900 (chloride form) ion-exchange resins, which were exchanged with tetraphenylborate anion (Ph_4B^-) by continuous rinsing with an aqueous solution of $NaBPh_4$ until the washings gave negative response to chloride anion (monitored with $AgNO_3$ solution followed by addition of aqueous ammonia). The exchange resin beads were then washed successively with water (to make it free from sodium ions), acetone and finally dried under vacuum for several hours to afford the Amberlite resin (Ph_4B^- form). Loading of the borate anion was determined by differential weighing between the quantities of dried resin (chloride form) initially taken and recovered after several washings with aqueous solution of $NaBPh_4$, water, acetone and drying.

The Amberlite (Ph_4B^-) resin thus prepared was used directly for the SM coupling with 3-iodotoluene in the presence of $Pd(OAc)_2$ (2 mol%) and Na_2CO_3 (1 equiv) and the corresponding unsymmetrical biphenyl was isolated in 90% yield (Scheme 10, conditions a). Similar coupling of 3-iodotoluene and $NaBPh_4$ in the presence of Na_2CO_3 afforded only 43% yield of the coupled product (Scheme 10, conditions b). However, on increasing the quantity of $NaBPh_4$ in 3-iodotoluene–$NaBPh_4$ (1:2.5), the resulting coupled product could be isolated in 88% yield (Scheme 10, conditions c). A further interesting observation was that the yield of the coupled product was not influenced by the absence of base (Scheme 10, conditions d and e). Such base-free conditions for SM reactions offer significant practical advantages and have not previously been reported with the organoborate ion immobilized onto polymers.

Scheme10



I

conditions:

(a) **I/II**/Na_2CO_3 = 1:1 g/mmol:1; 90%
(b) **I/III**/Na_2CO_3 = 1:1:1; 43%
(c) **I/III**/Na_2CO_3 = 1:2.5:1; 88%
(d) **I/III** = 1:2.5; 88%
(e) **I/II** = 1:1 g/mmol; 96%

The common mechanism of SM coupling reactions (i.e., sequential oxidative addition, transmetalation, and reductive elimination includes a base, [25] which is believed to be involved inseveral steps of the catalytic cycle, most notably the transmetalation process.[26]

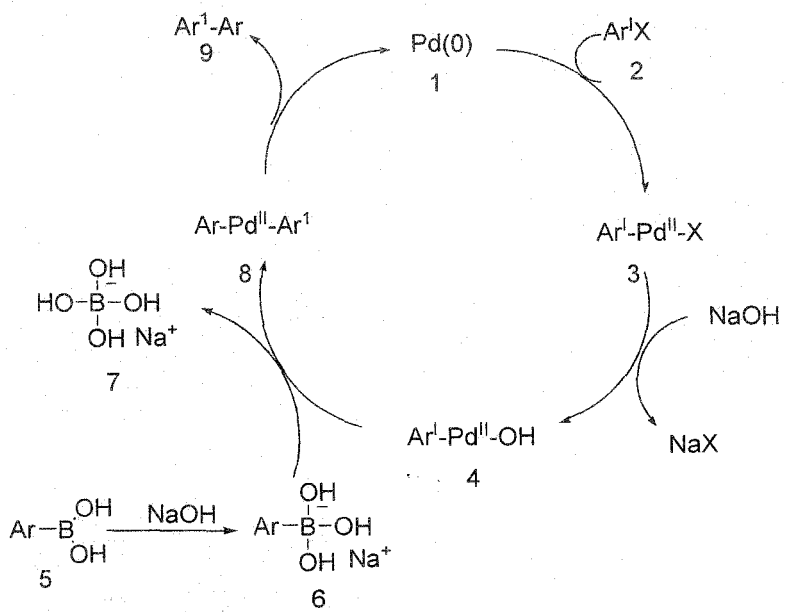
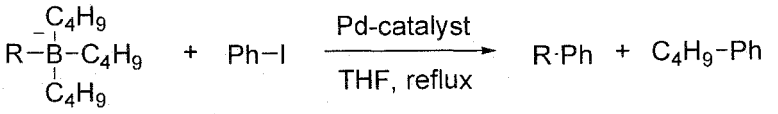


Fig. 1 A general catalytic cycle for Suzuki–Miyaura coupling reaction

The efficiency of palladium originates from its ability, when it is zerovalent, to activate C-X bonds (X=I, Br, Cl) by an oxidative addition which provides an organopalladium (II) complex prone to react with nucleophiles.[27] This is followed by the transmetallation step between the organopalladium (II) complex and the organoboron compound in the presence of a base. The transmetalation between organopalladium (II) halides and organoboron compounds does not occur readily due to the low nucleophilicity of organic group on boron atom.[28] However, the nucleophilicity of organic group on boron atom can be enhanced by quarternization of the

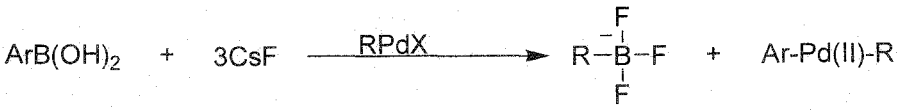
boron with negatively charged bases giving the corresponding "ate" complexes.[29] It is reported that such "ate" complexes undergo a clean coupling reaction with organic halide[30] (Scheme 11).

Scheme 11

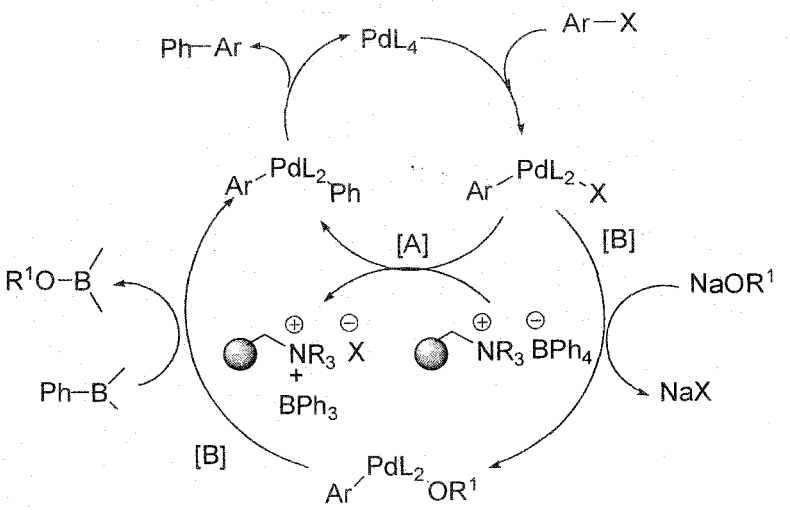


The final step is reductive elimination which takes place giving the product and regenerating the Pd(0) species. Recently, fluoride salts have been found to affect to the cross-coupling reactions of 1-alkenyl and arylboronic acids (scheme 12)[31]. The species that undergoes transmetalation is assumed to be organo(trifluoro) borate ion.

Scheme 12



The reaction protocol reported herein precludes the use of any base. Hence we propose a plausible base-free mechanism vis-à-vis the catalytic cycle using a base as shown below.



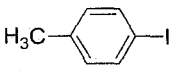
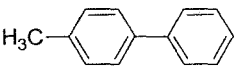
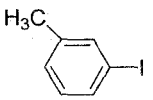
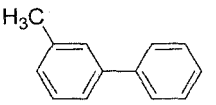
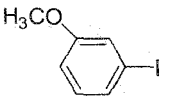
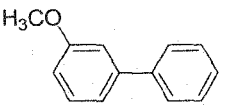
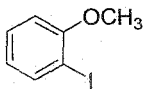
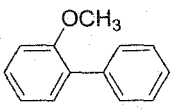
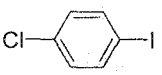
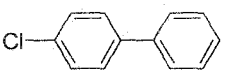
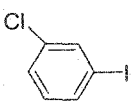
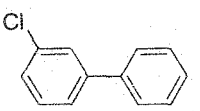
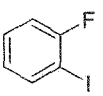
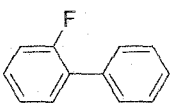
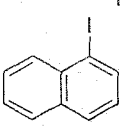
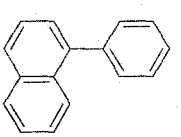
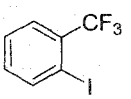
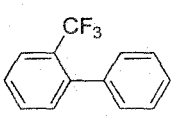
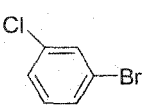
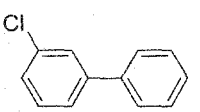
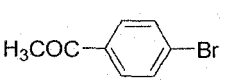
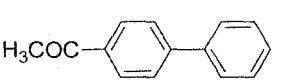
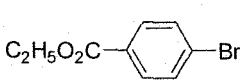
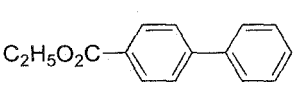
[A] Proposed catalytic cycle for cross-coupling of aryl halide with organoborane species without any base.
[B] Catalytic cycle for cross-coupling of aryl halides with organoborane species using base.

Fig. 2 - Plausible mechanism for the Suzuki-Miyaura coupling reaction using the borate resin

The transmetalation process releases triphenylborane, which being water-sensitive may be hydrolyzed during work-up producing phenylboronic acid. Indeed new isolated and characterised phenylboronic from the reaction mixture. Therefore it may be proposed that the

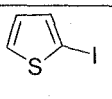
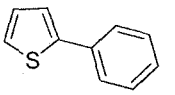
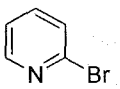
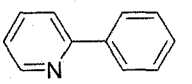
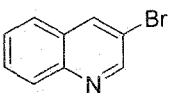
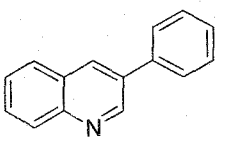
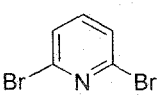
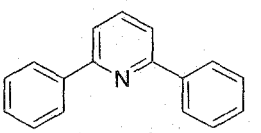
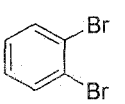
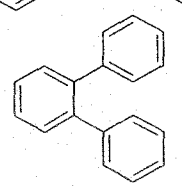
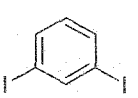
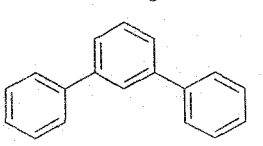
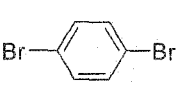
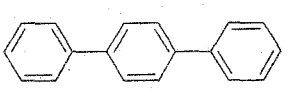
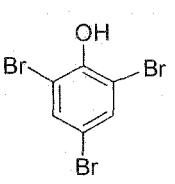
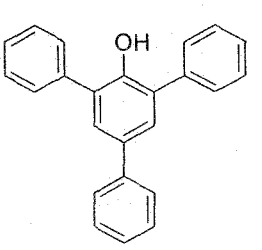
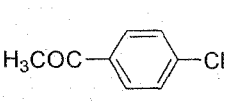
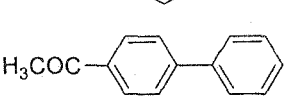
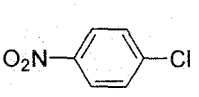
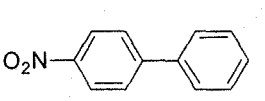
resin-supported tetraphenyl borate not only serves as an efficient phenylating agent but also acts as a suitable nucleophile requisite in the transmetalation process. A variety of aryl bromides and iodides bearing electron donating or withdrawing groups as well as heteroaryl halides underwent SM coupling in either DMF or water at 80-90 °C. Many examples have been illustrated in Table 1. Typical problems encountered during SM coupling reactions using the base, such as saponification of esters or aldol-type condensations of carbonyl compounds were successfully overcome using our reaction protocol (Table 1, entries 11, 12). Bis- and tris-aryl halides underwent SM cross-coupling with ease giving the desired adducts in good yields (Table 1, entries 19, 20). Activated aryl chlorides are known to undergo SM coupling reactions.[32]Using the immobilized borate we performed base-free couplings with activated aryl chlorides successfully (Table 1, entries 21 and 22) in presence of one equivalent of tetrabutylammonium salts (TBAB).[33]

Table 1: Suzuki-Miyaura Couplings Using Amberlite Resin (Tetraphenylborate Form)

Entry No.	Aromatic Halide [a]	Temp./ Time	Product [b]	% of Yield [c]
1		80 °C / 2 h		91 (91)
2		85 °C / 2 h		96 (95)
3		85 °C / 3 h		89
4		90 °C / 4 h		76
5		80 °C / 2.5 h		95 (92)
6		80 °C / 2 h		95
7		90 °C / 3 h		88
8		85 °C / 4 h		91
9		80 °C / 6 h		71
10		80 °C / 2 h		86 (88)
11		80 °C / 3 h		92
12		80 °C / 3 h		83

Continued.....

Table 1: Suzuki-Miyaura Couplings Using Amberlite Resin (Tetraphenylborate Form)

Entry No.	Aromatic Halides [a]	Temp/ Time	Products [b]	% of yield [c]
13		80 °C / 3 h		90
14[d]		85 °C / 6 h		80 (75)
15[d]		80 °C / 4 h		97
16[d]		90 °C / 3 h		84
17		90 °C/ 4 h		77
18		80 °C / 3 h		78 (85)
19		85 °C / 3 h		87
20		90 °C / 8 h		58
21[e]		90 °C / 5 h		(88)
22[e]		85 °C / 5 h		(95)

[a] 1 mmol aryl halide : 1 g resinTPB : 2 mol% $Pd(OAc)_2$ in DMF or water.
[b] All compounds were characterized by known mp; IR, ^1H- and ^{13}C-spetral data.
[c] Yields in the parentheses represent reactions carried out in water.
[d] 1.5 mol% of $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$.
[e] TBAB (1 Equiv.) and Na_2CO_3 (1 Equiv.) were required.

1. A.4. Conclusion

Many of the methods employed for C-C bond formation involve the direct coupling of highly reactive organometallic reagents with aryl halides in the presence of various catalysts. Suzuki-Miyaura coupling reaction is one of the example where C-C bond formation occur under ordinary comdition. Here tetraphenylborate ions are immobilize on polyionic resin surface and the resulting species can be used as phenylating reagents in SM coupling reactions as well as it also fulfils the function of base . Attaching of tetraphenylborate to a solid phase has many advantages compared to running the reaction in solution, not only in terms of simplified purification but also in minimizing contamination of the final product. Easy isolation of the desired coupled product in high yields along with base- and ligand-free conditions offer distinct advantages over the direct use of the corresponding metal salt and phenyl boronic acid. Aryl chlorides are also arylated under this reaction conditions.

A limitation of the process is that although there are four Ph-groups on the immobilized tetraphenylborate, it was possible to utilize only one in the arylation whereas the other three get converted to phenylboronic acid during the work-up. Another drawback is that the resin functions only as a phenylating agent. In order to introduce other aryl groups the protocol needs some improvement. This can be done by immobilizing substituted phenyl borates onto the resin which would indeed broaden the scope of our methodology. Further exploration regarding this work is underway in our laboratory.

1. A.5. Experimental Section:

All reactions were performed in round bottom flask in airing and refluxing condition. 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. ^1H 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.

1. A.6. Preparation of Polymer Supported Borate (PS-Borate)

Amberlite® IRA-900 resin (chloride form; 2.50 g) was stirred with aq. $NaBPh_4$ (1.73 g) until complete exchange as judged by Cl^- loss (tested with $AgNO_3$). The exchanged resin was washed with H_2O, acetone and dried to give the tetraphenylborate$^-$ form resin (3.92 g). The mass difference between product and starting materials (ca. 310 mg) was comparable with the calculated difference (296 mg). The resulting borate-bound resin thus contained a 1.14 mmol g^{-1} loading of the borate ions and was used directly in the SM coupling reactions.

1. A.7. General Reaction Procedure

A mixture of aryl halide (1 mmol), Amberlite resin (Ph_4B^- form) (1 g, 1.14 mmol) and $Pd(OAc)_2$ (4.5 mg, 2 mol%) was taken in DMF (2 mL) and heated in an oil bath at 85 °C for 2 h. After cooling, the reaction mixture was diluted with H_2O (5 mL) and the resin was filtered off. The filtrate was extracted with Et_2O (3 × 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent left an oily residue, which was passed through a short column of silica gel (60–120 mesh) and eluting with light petroleum to afford 3-phenyltoluene as a colourless liquid.

1. A.8. Physical Properties and Spectral Data of Compounds:

Entry 1: 4-Methyl biphenyl

Reaction temp: 80^0c; Time: 2h; Yield: 91%, mp. 46-48 °C

IR (nujol): ν_{max} 2924, 2858, 2360, 2337, 1458, 1377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52-7.10 (m, 9H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.1, 138.3, 136.9, 129.5, 128.7, 128.6, 127.0, 126.9, 21.1.

Entry 2: 3-Methyl biphenyl

Reaction temp: 85^0c; Time: 2h; Yield: 96%, (obtained as liquid).

IR (nujol): ν_{max} 3031, 2900, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.87-7.43 (m, 9H), 2.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.3, 141.2, 138.2, 128.6, 127.9, 127.8, 127.2, 127.1, 126.7, 124.2, 21.4.

Entry-3: 3-Methoxy biphenyl

Reaction temp: 85^0c; Time; 3h; Yield: 89%, (obtained as liquid).

IR (neat): υ_{max} 1574, 1610 cm-1. ^1H NMR ($CDCl_3$): δ = 3.75 (s, 3H,); 6.77–6.81 (m, 1H), 7.03–7.10 (m, 2H), 7.21–7.36 (m, 4H), 7.47–7.51 (m, 2H); ^{13}C NMR ($CDCl_3$), δ = 55.2, 112.6, 112.8, 119.6, 127.1, 127.4, 128.7, 129.7, 141.0, 142.7, 159.9.

Entry 5: 4-Chloro biphenyl

Reaction temp: 80^0c; Time; 2h; Yield: 91%, mp. 77-78 °C.

IR (nujol): ν_{max} 2924, 2854, 2357, 2337, 1454, 1377 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.60-7.31 (m, 9H). ^{13}C NMR ($CDCl_3$): δ = 140.0, 139.7, 133.4, 128.96, 128.94, 128.4, 127.7, 127.0.

Entry 6: 3-Chlorobiphenyl.

Reaction temp: 80 °C, Time: 2 h, Yield: 95% (obtained as liquid).

IR (neat): ν_{max} 3062, 3032, 2360, 2341, 1593, 1566 cm^{-1}; ^1H NMR ($CDCl_3$): δ= 7.60-7.30 (m, 8H); ^{13}C NMR ($CDCl_3$): δ = 140.0, 139.7, 133.4, 129.0, 128.9, 128.4, 127.6, 127.0.

Entry 7: 2-Fluorobiphenyl.

Reaction temp: 90 °C, Time: 3 h, Yield: 88%; mp 70-72 °C.

IR (nujol): ν_{max} 2924, 1716 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.15 – 7.57(m, 9H); ^{13}C NMR (CDCl3): δ = 159.76, 135.82, 130.8, 130.7, 129.2, 129.0, 128.9, 128.7, 128.4, 127.6, 124.3, 116.2.

Entry 8: 1-Phenyl naphthalene

Reaction temp: 85°c; Time: 4h, Yield: 91% (obtained as liquid).

IR (neat): ν_{max} 3059, 1493, 1396 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.00-7.98 (m, 1H), 7.94-7.87 (m, 2H), 7.65-7.34(m, 9H). ^{13}C NMR ($CDCl_3$): δ= 141.0, 140.5, 134.1, 131.9, 130.3, 129.1, 128.5, 127.9, 127.5, 127.4, 127.2, 126.3, 126.0, 125.6.

Entry 9: 2-Trifluoromethyl biphenyl

Reaction temp: 80 °C, Time: 6 h, Yield: 71% (obtained as liquid).

IR (neat): ν_{max} 3067, 2360, 1481, 1450, 1315, 1126, 767 cm^{-1}; ^1H NMR ($CDCl_3$): δ = (dd, 2H, j = 7.8 & 0.9 Hz); 7.58-7.26 (m, 8H); ^{13}C NMR ($CDCl_3$) : δ = 141.4, 141.2, 139.9, 132.0, 131.2, 129.0, 128.8, 128.7, 127.8, 127.6, 127.3, 127.2, 126.2, 126.1, 126.0, 125.9, 122.4, 118.8, 30.3,29.8.

Entry 12: 4-Phenylethyl benzoate

Reaction temp: 80° C; Time: 8 h; Yield: 83%; mp 38 °C.

IR (nujol): ν_{max} 2930, 2346, 1780,1681, cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.11 (d, 2H, J = 8.4 Hz), 7.67-7.61 (m, 4H), 7.49-7.38 (m, 3H), 4.40 (q, 2H, J = 7.2 Hz), 1.41 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 166.5, 145.5, 140.1, 130.1, 129.2, 128.9, 128.1, 127.0, 60.9, 14.4.

Entry: 14: 2- Phenylpyridine

Reaction temp: 85 °C; Time: 6h; Yield: 80% (obtained as liquid)

IR (nujol): ν_{max} 3060, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23-7.27 (m, 1H), 7.42-7.46 (m, 3H); 7.49-7.51 (m, 2H); 7.75-7.78 (m, 2H); 7.98-8.01 (m, 1H);. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 149.5, 139.2, 137.0, 129.1, 128.8, 127.0, 122.2, 120.7.

Entry 15: 3-Phenyl quinoline

Reaction temp: 80 °C; Time: 4 h; Yield: 97% (obtained as liquid)

IR (nujol): ν_{max} 3074, 2935, 2341, 1500 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.01-7.98 (m, 1H), 7.94-7.87 (m, 2H), 7.65-7.37 (m, 9H); ^{13}C NMR ($CDCl_3$): δ = 141.0, 140.5, 134.1, 131.9, 130.3, 129.0, 128.5, 127.5, 127.4, 127.2, 126.3, 126.0, 125.6.

Entry 17: 1, 2– Diphenylbenzene

Reaction temp: 90 °C, Time: 4 h; Yield: 77%, (solid) mp 54–56 °C (lit.[34] 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.

Entry 18: 1, 3-Diphenylbenzene

Reaction temp: 80 °C, Time: 3 h; Yield: 78%, (solid) mp 87–88 °C (lit[35] 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 19: 1, 4-Diphenyl benzene

Reaction temp: 85°C; Time: 3 h; Yield: 87%; mp 212–214 °C. (lit[34])

IR (nujol): ν_{max} 1454, 1377 cm^{-1}; ^1H NMR ($CDCl_3$,): δ = 7.60–7.54 (m, 8H), 7.41–7.36 (m, 4H), 7.31–7.26 (m, 2H); ^{13}C NMR ($CDCl_3$,): δ = 140.7, 140.1, 128.8, 127.5, 127.4, 127.0.

Entry 20: 2, 4, 6-Triphenyl phenol

Reaction temp: 90 °C; Time: 8 h; Yield: 58%; mp. 144–145 °C.

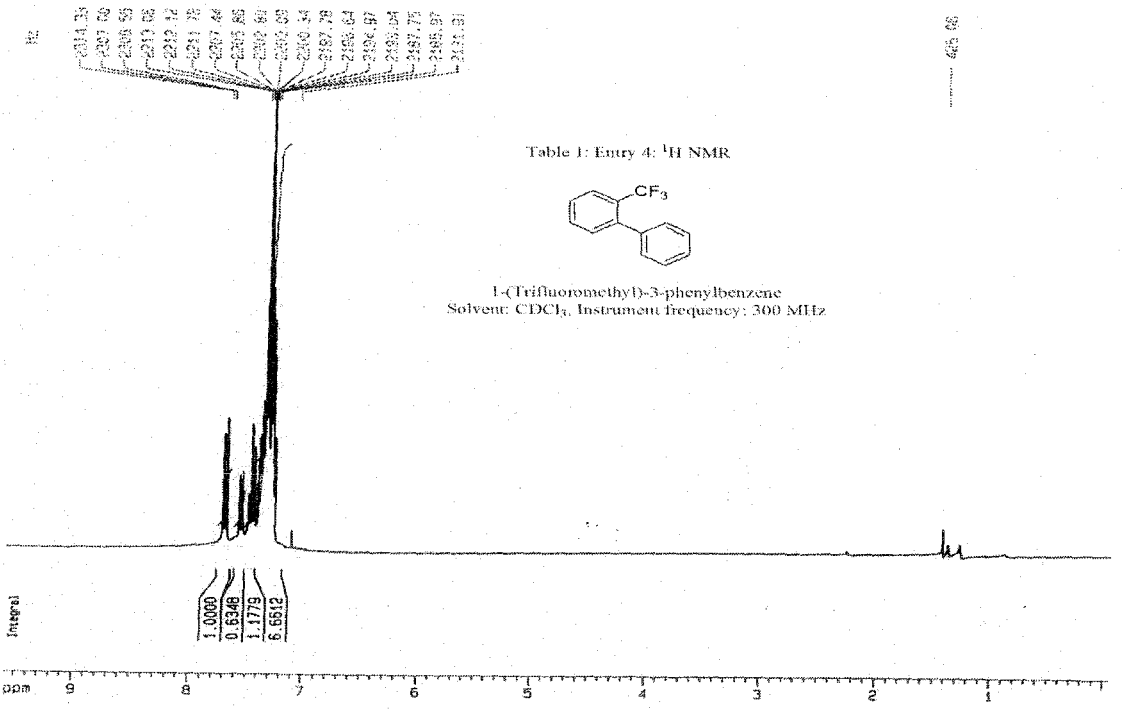
IR (nujol): ν_{max} 3512, 1595, 1227 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.61–7.26 (m, 17H), 5.43 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 148.9, 140.5, 137.5, 133.8, 129.4, 129.1, 128.9, 128.8, 128.6, 127.8, 126.9, 126.7.

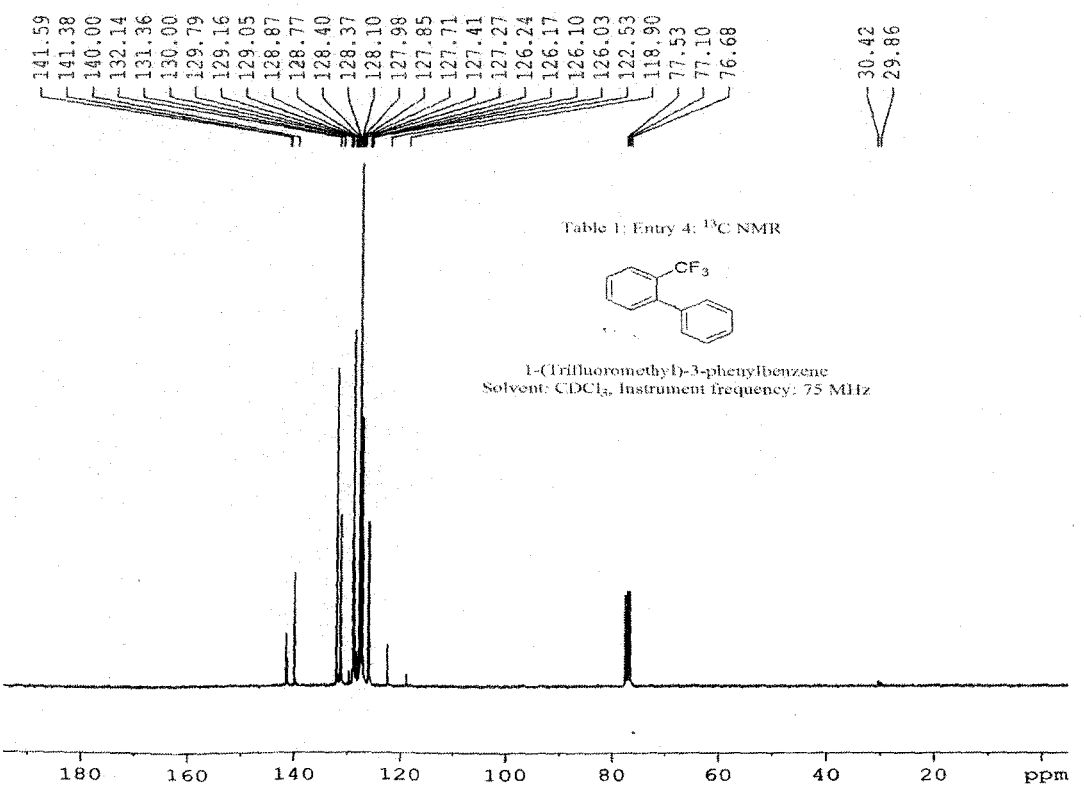
Entry 22: 4-Nitro biphenyl

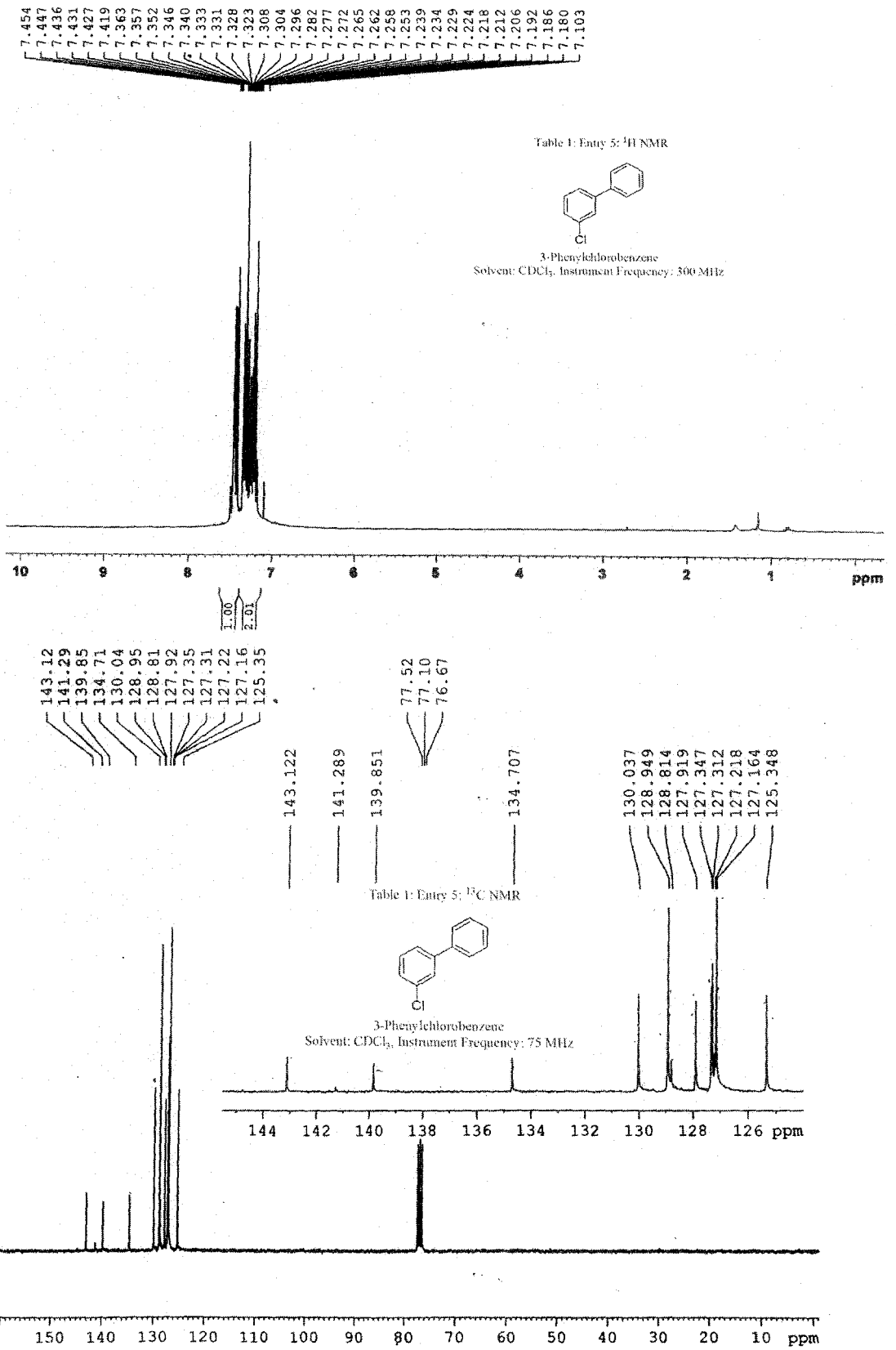
Reaction temp: 85 °C; Time: 5h; Yield: 95%; (solid) mp. 112-113 °C. (lit[36])

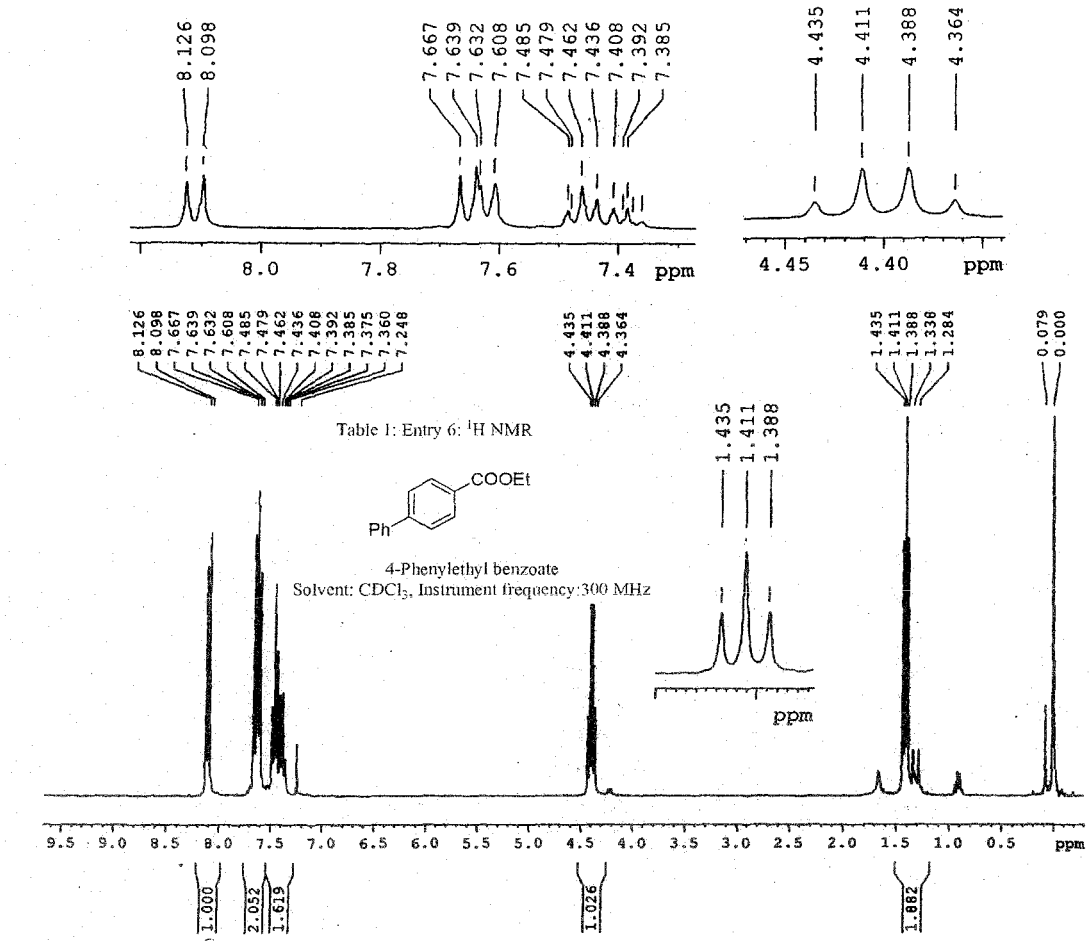
IR(nujol): ν_{max} 2924, 2855, 2360, 2337, 1512, 1458, 1346 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.29 (td, 2H, J = 9 & 2.1 Hz), 7.73 (td, 2H, J = 8.7 & 1.8 Hz), 7.64-7.61 (m, 2H), 7.53-7.44 (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 147.6, 147.1, 138.8, 129.2, 128.9, 127.8, 127.4, 124.1.

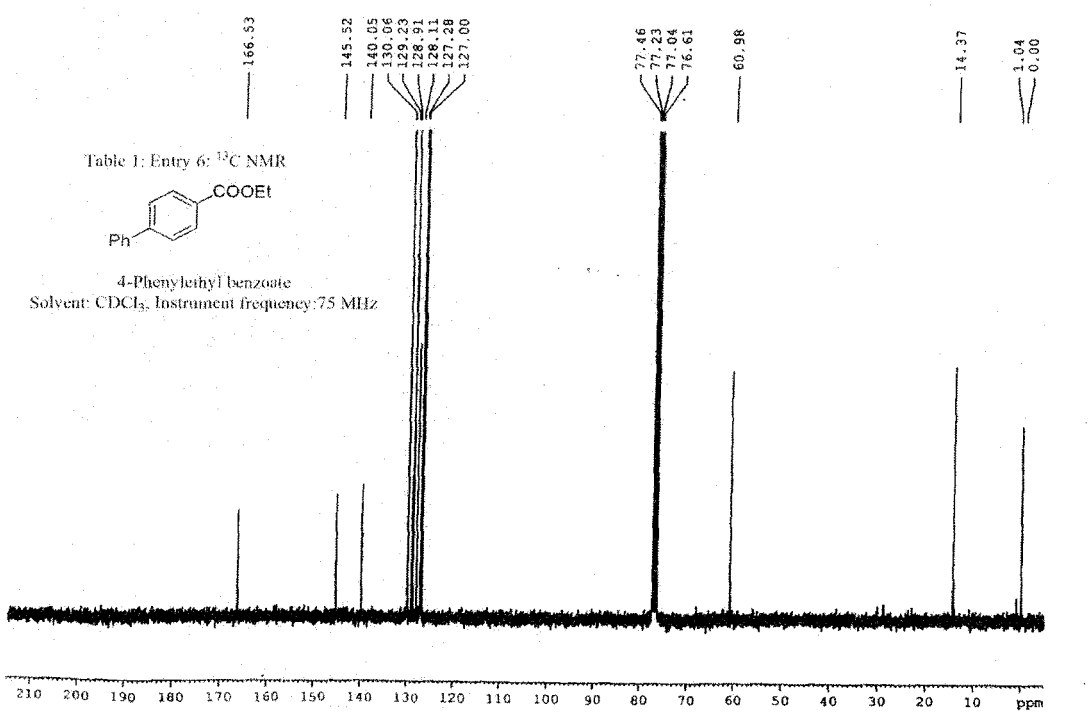
NMR Spectra of Some Selected Compounds

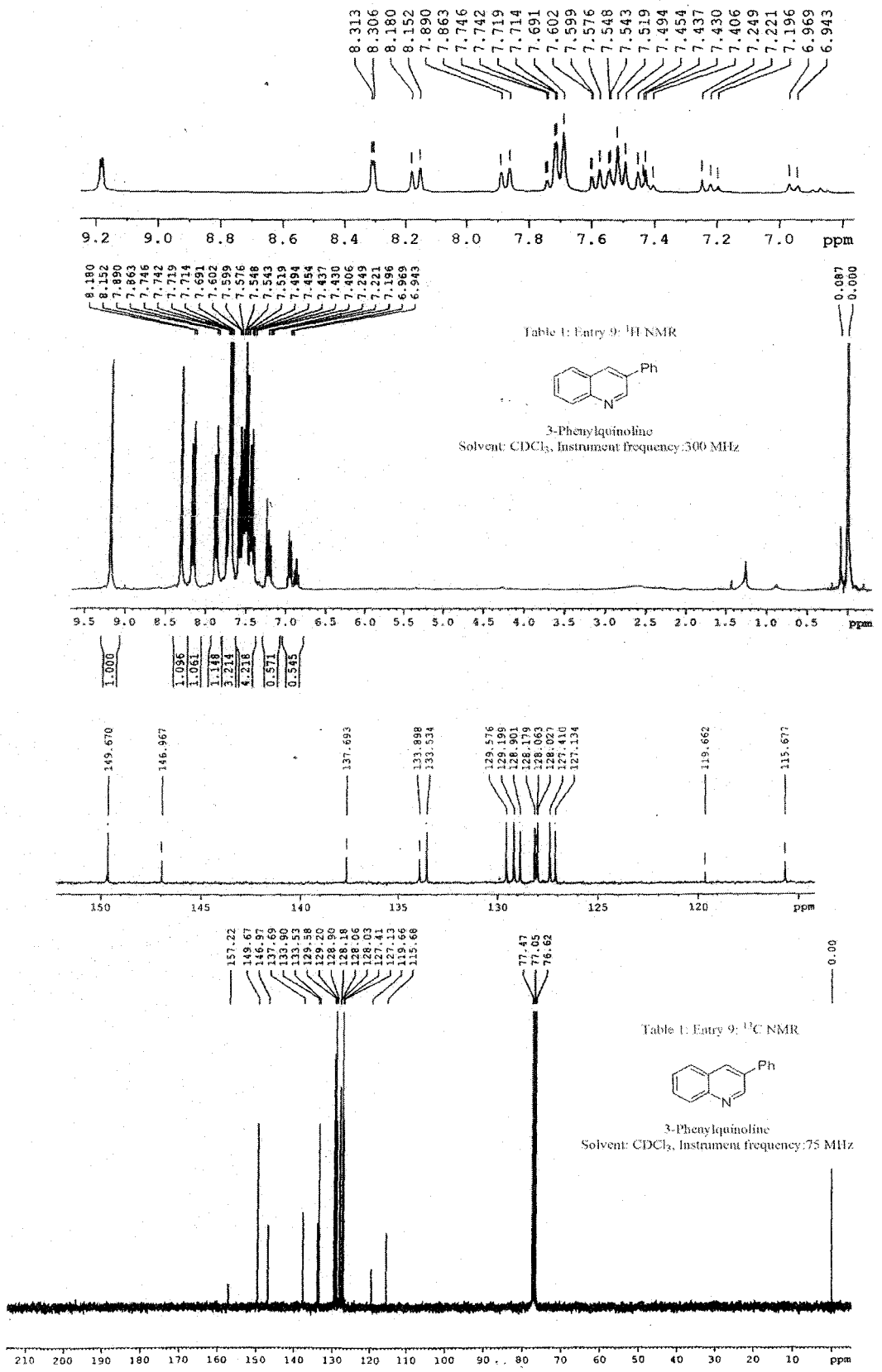





7.454
7.447
7.436
7.431
7.427
7.419
7.363
7.357
7.352
7.346
7.340
7.333
7.331
7.328
7.323
7.308
7.304
7.296
7.282
7.277
7.272
7.265
7.262
7.258
7.253
7.239
7.234
7.229
7.224
7.218
7.212
7.206
7.192
7.186
7.180
7.103
Table 1: Entry 5: ^{1}H NMR
Cl
3-Phenylchlorobenzene
Solvent: $CDCl_3$, Instrument Frequency: 300 MHz
10
9
8
7
6
5
4
3
2
1
ppm
1.00
2.01
143.12
141.29
139.85
134.71
130.04
128.95
128.81
127.92
127.35
127.31
127.22
127.16
125.35
77.52
77.10
76.67
143.122
141.289
139.851
134.707
130.037
128.949
128.814
127.919
127.347
127.312
127.218
127.164
125.348
Table 1: Entry 5: ^{13}C NMR
Cl
3-Phenylchlorobenzene
Solvent: $CDCl_3$, Instrument Frequency: 75 MHz
144
142
140
138
136
134
132
130
128
126 ppm
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


8.126
8.098
7.667
7.639
7.632
7.608
7.485
7.479
7.462
7.436
7.408
7.392
7.385
4.435
4.411
4.388
4.364
8.0
7.8
7.6
7.4 ppm
4.45
4.40
ppm
Table 1: Entry 6: ^{1}H NMR
COOEt
Ph
4-Phenylethyl benzoate
Solvent: $CDCl_3$, Instrument frequency:300 MHz
1.435
1.411
1.388
1.338
1.284
0.079
0.000
ppm
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.000
2.052
1.619
1.026
1.882


166.53
145.52
140.05
130.06
129.23
128.91
128.11
127.28
127.00
77.46
77.23
77.04
76.61
60.98
14.37
1.04
0.00
Table 1: Entry 6: ^{13}C NMR
COOEt
Ph
4-Phenylethyl benzoate
Solvent: $CDCl_3$, Instrument frequency:75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.313
8.306
8.180
8.152
7.890
7.863
7.746
7.742
7.719
7.714
7.691
7.602
7.599
7.576
7.548
7.543
7.519
7.494
7.454
7.437
7.430
7.406
7.249
7.221
7.196
6.969
6.943
9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 ppm
0.087
0.000
Table 1: Entry 9: ^{1}H NMR
Ph
N
3-Phenylquinoline
Solvent: $CDCl_3$, Instrument frequency:300 MHz
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.000
1.096
1.061
1.148
3.214
4.218
0.571
0.545
149.670
146.967
137.693
133.898
133.534
129.576
129.199
128.901
128.179
128.063
128.027
127.410
127.134
119.662
115.677
150 145 140 135 130 125 120 ppm
157.22
149.67
146.97
137.69
133.90
133.53
129.58
129.20
128.90
128.18
128.06
128.03
127.41
127.13
119.66
115.68
77.47
77.05
76.62
0.00
Table 1: Entry 9: ^{13}C NMR
Ph
N
3-Phenylquinoline
Solvent: $CDCl_3$, Instrument frequency:75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

1. A. 9. References:

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Part 1

Section B

Highly effective alternative aryl trihydroxyborate salts for a ligand-free, on-water Suzuki-Miyaura coupling reaction

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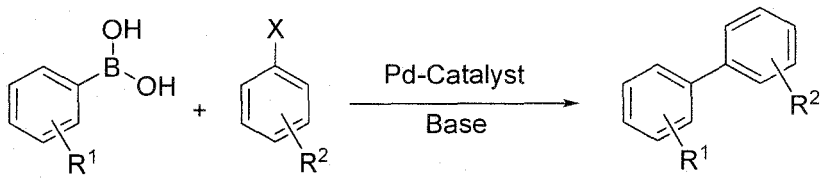
Highly effective alternative aryl trihydroxyborate salts for a ligand-free, on-water Suzuki-Miyaura coupling reaction

1. B.1. Introduction

The cross-coupling reaction of alkenyl and aryl halides with organoborane derivatives in the presence of a palladium catalyst and a base is known as the Suzuki–Miyaura reaction. Although Davidson and Triggs[1] discovered in 1968 that arylboronic acids reacted with palladium (II) acetate to give corresponding biaryls, and Garves,[2] in 1970 accounted that arylsulfinic acids could be coupled to biaryls using Pd(II), it was not until 1979 when biaryls could efficiently be prepared by a palladium- catalyzed reaction. Miyaura and Suzuki[3] reported that cross-coupling reactions between alkenylboranes and organic halides were efficiently catalyzed by a catalytic amount of tetrakis (triphenylphoshine) palladium $Pd(PPh_3)_4$ in the presence of a suitable base. Pd-catalysed Suzuki–Miyaura (SM) coupling reaction is one of the most efficient methods for the construction of C–C bonds. Several other methods (e.g. Kharasch coupling, Negishi coupling, Stille coupling, Himaya coupling, Liebeskind–Srogl coupling and Kumada coupling) are available for this purpose, the SM crosscoupling reaction which produces biaryls has proven to be the most popular in recent times. All reaction types have drawbacks that limit the use in synthesis. Suzuki–Miyaura cross coupling has, on the other hand, fewer limitations than the other reactions mentioned. In the Heck reaction, for example, where an aryl or vinyl halide and an alkene are converted to a more highly substituted alkene under Pd catalysis, the intermolecular reaction often proceeds well when the alkene is electrophilic. With nucleophilic substituents, the reaction gives less satisfactory results. The Kumada coupling is very sensitive to air and the presence of radical inhibitors and this has limited the use of the reaction in aqueous media. In the Stille reaction, stannates are used as substrates, and many of these are environmentally hazardous. The SM reaction has gained prominence in the last few years because the conditions developed for the cross-coupling reaction have many desirable features for large-scale synthesis and are unwilling to the industrial synthesis of pharmaceuticals and fine chemicals. The SM cross-coupling reactions generally employ organic solvents such as tetrahydrofuran, di-methyl formamide, toluene and diethyl ether in the presence of Pd(II) or Pd(0) catalysts. Aryl halides (bromides or iodides) and triflates substituted with electron-withdrawing groups (EWGs) are suitable substrates for the cross-coupling reaction. The most commonly used base in the SM cross-coupling reaction is Na_2CO_3 but this is often ineffective with sterically demanding substrates. In such instances, $Ba(OH)_2$ or K_3PO_4 has been used to generate good yields of the cross-coupling products. Other bases utilised in the SM coupling reaction include Cs_2CO_3, K_2CO_3, TlOH, KF and NaOH. It is known that the base is involved in the coordination sphere of the palladium and the formation of the Ar-PdL_2–OR from Ar-PdL_2–X is known to accelerate the transmetallation step.

Scheme 1



A typical catalytic cycle of the Suzuki–Miyaura reaction involves an oxidative addition, transmetallation and reductive elimination pathway (Fig. 1).

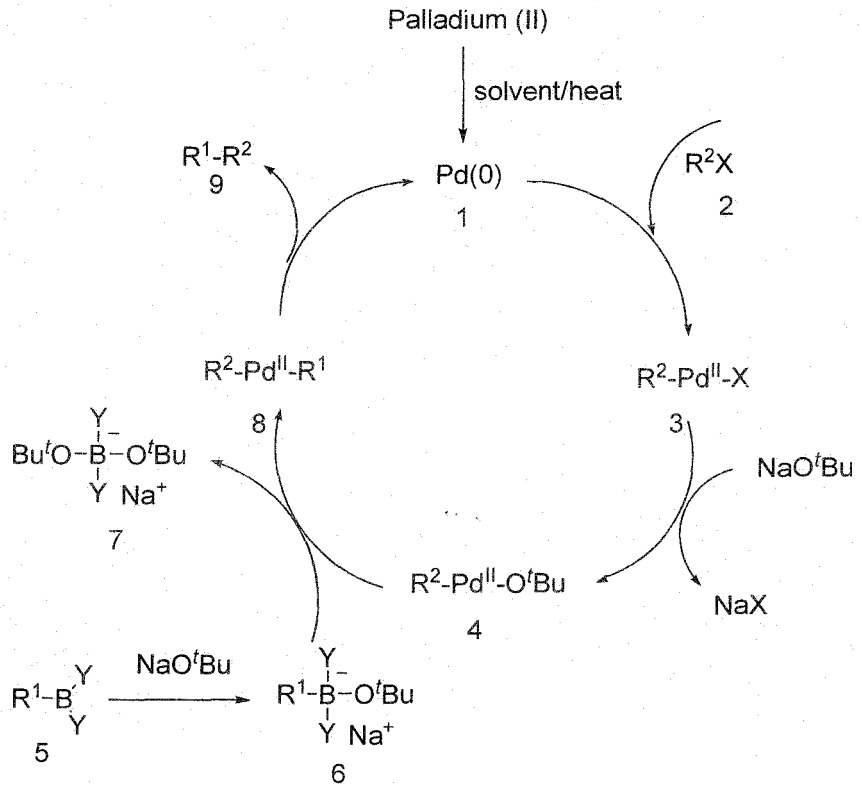


Fig. 1: Typical catalytic cycle for Suzuki-Miyaura coupling reactions

The first step is the oxidative addition of Pd (0) to the aryl halide (2) to form organo-palladium species (3). This on reacting with base gives intermediate (4) which via transmetalation with the boron-ate complex and then reductive elimination of the desire product (9) restores the original palladium catalyst.

However, for planning an organic reaction, one of the major concerns to chemists is the choice of solvent and this is not without a reason. Solvents play essential roles in chemical processes not only serving to put reactants into contact by dissolution but also affecting rates, chemo-, regio- and stereoselectivities of the reactions. Again, solvents used in the later stages of a reaction, which means extraction and purification of the products. The most used organic

solvents comprise hydrocarbons (including halogenated and aromatic hydrocarbons), ethers, ketone and alcohols. Despite the usefulness and importance of these compounds in organic reactions they undoubtfully have a detrimental impact on the environment. Some intrinsic characteristics of most organic solvents are their high flammability and volatility, their hazardness and toxicity. Each year millions tons of solvents are discharged into the atmosphere by industries worldwide. As a result, there has been an increase in air pollution and the global climate is continuously changing. This scenario has substantially changed during the last decade or so due to the intensive research towards environmentally benign substitutes for volatile and toxic organic solvents. Now chemists have to deal with the challenge of reducing the environmental impact of the processes without losing their efficiency by using the so-called green solvents under the concepts of green chemistry, which has emerged as an important area of chemistry and has achieved outstanding progresses towards the development of green reaction processes.[4] Green chemistry is a set of principles dedicated to creating efficient industrial chemicals, drugs and products, driven by a mixture of political, economic and cultural factors. The economic drive is to reduce waste. The political drive comes from regulations, such as the US Pollution Protection Act, that are forcing companies to develop cleaner processes. In addition, consumers and scientists who are becoming more aware of the need for cleaner processes provide the cultural drive.

A green solvent must ideally have a high boiling point, a low vapour pressure, be non-toxic, dissolve a great range of organic compounds, be inexpensive and of course be recyclable. All these things put together tend to narrow the possibilities of finding a compound or a class of compounds that can be effectively called a green solvent. However, many efforts from research groups all around the world have enabled the appearance of some good alternatives for organic solvents, which include supercritical fluids, ionic liquids, low melting polymers, perfluorinated solvents and water. Water is perhaps one of the greener solvents one can imagine in terms of costs, availability, on toxic safety and environmental impact. But because of the low solubility of most organic compounds in it and its great reactivity towards some organic compounds (e.g., organometallics), the use of water as solvent was limited to hydrolysis reactions until the pioneering works of Breslow[5] and Grieco[6] in the early 1980s. For instance, the rates and stereoselectivities of many organic reactions that can dramatically enhanced in water due to solvo-phobic effects. The use of organic co-solvents water-soluble or surfactants helps to increase the solubility of nonpolar reactants in water by disrupting the strong hydrogen-bond network of pure water.[7] With its high dielectric constant, water is also potentially a very useful solvent for microwave-mediated organic synthesis.[8] Additionally, organic products can be separated by simple decantation (especially on the large scale) or via an extraction step.

Therefore, the development of new technologies that allow a complete pollution control of the aqueous phase remains one of the biggest challenges in working with water as solvent. Aqueous-phase, palladium-catalyzed cross coupling reactions are of interest as environmentally benign synthetic methods that would decrease the use of volatile organic solvents and simplify catalyst recovery.[9] Like Kharasch coupling,[10] Negishi coupling,[11]Stille coupling,[12] Hiyama coupling,[13] and Kumada coupling,[14] the Suzuki-Miyaura (SM) coupling reaction has arguably received much more popularity. The Suzuki–Miyaura reaction allows the cross-coupling of electrophiles with boron compounds in the presence of a base. This reaction has proved over the years to be one of the most popular reactions for carbon-carbon bond formation through palladium catalysis[15] since its discovery in 1979.[16] The impressive development of boron-based protocols in both academic and industrial laboratories can be explained for several reasons:

- A wide range of functional groups are tolerated due to the mild reaction conditions,
- Boron compounds (and especially boronic acids) are readily available, bench stable and have low toxicity,
- Dry solvents are generally not required,
- The reaction is workable with a wide range of substrates.

Usual catalytic systems rely on homogeneous palladium catalysts associated with an appropriate ligand in conventional organic or biphasic media. In this respect, a number of remarkable results have been reported concerning the cross-coupling of boronic compounds with aryl or vinyl iodide, bromide and even demanding chloride substrates under mild conditions.[17] Nevertheless, the development of heterogeneous catalysis in pure water seems particularly suitable for the Suzuki–Miyaura reaction due to the excellent stability of boronic acids in aqueous media.[18] Although boronic acids have several advantages in the Suzuki–Miyaura coupling but far from being ideal, they exhibit several limitations that make them unattractive nucleophilic coupling partners. Boronic acids are not monomeric materials, but rather exist in equilibrium with dimers and cyclic trimers (boroxines).[19] Consequently, many boronic acids are waxy solids that are difficult to purify. Most importantly, many boronic acids, and especially electron-deficient heteroarylboronic acids, have a short shelf life owing to their tendency to undergo facile protodeboronation. This instability often requires their storage at low temperatures. The tendency to protodeboronate quite often manifests itself during cross-coupling reactions carried out in polar protic solvents.[20] The protodeboronation influences the stoichiometry of the reaction, requiring practitioners to use excess boronic acids to ensure that an adequate amount of this nucleophilic partner is available in cross-coupling reactions. The lack of stability of organoboranes is due to the vacant orbital on boron, which can be attacked by oxygen[21] or water, resulting in decomposition of the reagent. In view of the several aspects

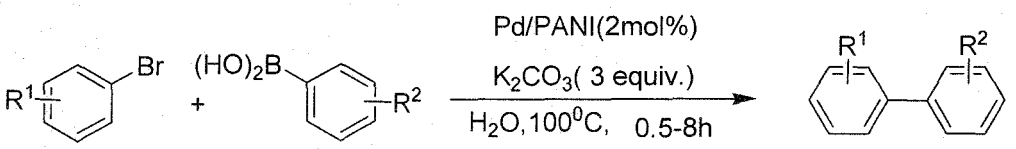
required for the development of new variants of the organoboron species, the catalyst and the base in the SM coupling reaction and the optimizing process have remained challenging areas of research. One solution emerged in the 1960s with the discovery of potassium organotrifluoroborates, boron ate complex derivatives. In contrast to trivalent organoboranes, these reagents showed exceptional stabilities toward nucleophilic compounds as well as air and moisture. The vast majority can be stored indefinitely at room temperature without any precaution. A variety of supports appropriately functionalized for a high affinity with a palladium catalyst have been proposed. Potassium organotrifluoroborates have been used in several transition-metal-catalyzed reactions such as Suzuki-Miyaura cross-coupling reactions, addition to α, β- unsaturated substrates or aldehydes (Miyaura-Hayashi-type reactions),[22] and formation of ethers or amines.

The Suzuki–Miyaura coupling has found widespread applications in academic laboratories, fine chemical industries, and synthesis of biologically active pharmaceuticals, as well as in the burgeoning area of nanotechnology, as reflected from contributions from myriad research groups. For example, Losartan, an antihypertensive drug, CI-1034, a potent endothelian receptor antagonist, CE-178253 benzenesulfonate, a CB_1 antagonist for the treatment of obesity or apoptolidin A, a potent antitumor agent Flurbiprofen,[23] a commercially available nonsteroidal antiinflammatory and analgesic drug,[24] have been synthesised on a large scale employing the SM coupling as a key step. Similarly, benzimidazole derivatives bearing substituted biphenyl moieties, potential inhibitors of hepatitis C virus, have been prepared using the SM coupling reaction. Review articles by Danishefsky *et al.*[25a] and Nicolaou *et al.*[25b] amply demonstrate various applications of the SM coupling reaction in the synthesis of natural products.

1. B.2. Background and Objectives:

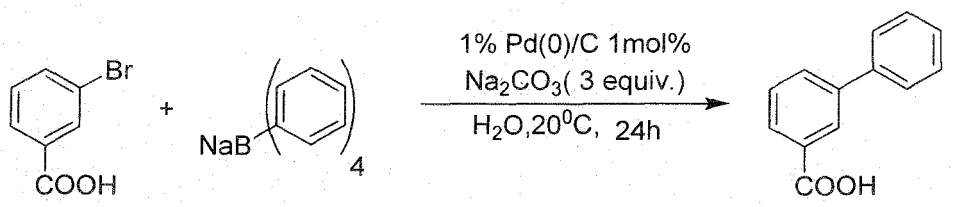
Kantam and co-workers[26]used 2 mol% of Pd/ Polyaniline (PANI) with K_2CO_3 as a base in refluxing water for Suzuki–Miyaura cross-coupling reactions. While under these conditions bromoarenes were efficiently coupled with various substituted boronic acids (Scheme 1), chloro-arenes required the use of 50 mol% of tetrabutylammonium salt (TBAB) as an additive. The rate enhancing effect of TBAB is sufficient to drive the reaction to completion even when using deactivated chloroarenes, and only hindered chloroarenes remained reluctant to the cross-coupling. Moreover, the influence of PANI on the palladium catalytic activity is clear since the same reactions, conducted with $PdCl_2$ under analogous conditions, gave only low conversions along with the formation of palladium black. Recycling studies showed that the Pd/PANI catalyst `could be reused at least five times with consistent activity.

Scheme 2



Bumagin and Bykov[27] have reported that water-soluble 3-bromobenzoic acid could be efficiently crosscoupled with tetraphenylborate in neat water using Pd (0)/C (Scheme 3). Tetraphenylborate is a very stable and inexpensive substitute for boronic acid.

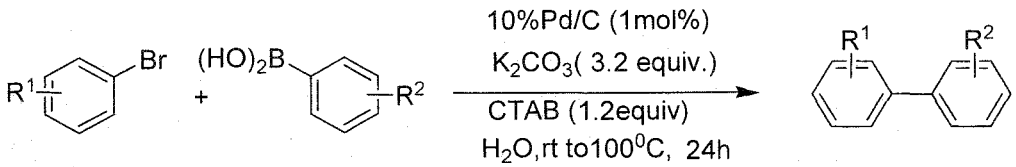
Scheme 3



More recently, Xu and co-workers[28] reinvestigated the results from Bumagin and Bykov with ample details. They confirmed that water-soluble aryl bromides could react efficiently with $NaB(Ph)_4$ and $NaB(tol)_4$ in refluxing water under very low catalyst loading (0.1 to 0.0025 mol%).With turnover numbers (TON) as high as 37600, the protocol proved to be remarkably reactive for a heterogeneously catalyzed reaction. The reusability of the catalyst showed some capabilities over five cycles but suffered from gradual diminished reactivity.

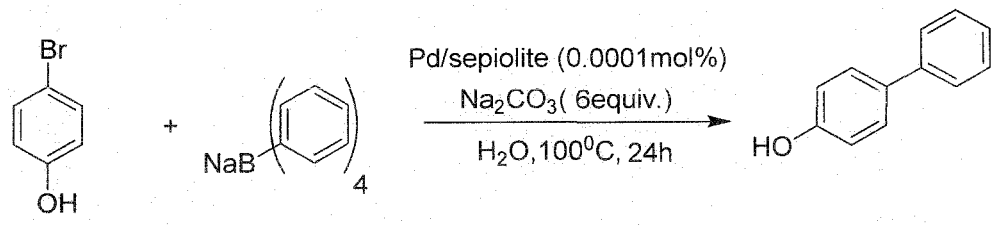
Kçhler and Lysen had shown that for non-water-soluble aryl halides were less reactive, opted for the use of surfactants as additives. The water-surfactant Pd/C system gave good catalytic activity after several recycling experiments rendering the method environmentally friendly. The activation role of CTAB or TBAB is thought to be two-fold. The presence of positive R_4N^+ ions could favour the transmetalation step by the formation of a highly reactive boronate complex $[ArB(OH)_3^-R_4N]^+$ In addition, the ammonium salt could facilitate the solvation of organic molecules in aqueous media.

Scheme 4



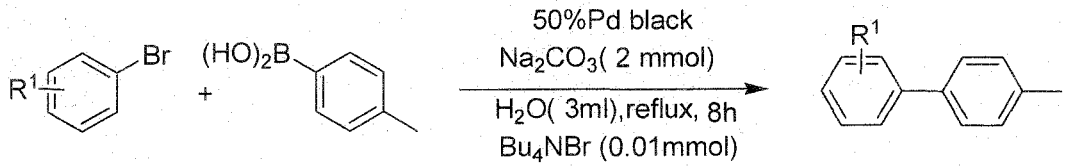
A sepiolite-supported palladium (II) catalyst has been successfully used by Kitayama et al. for the cross-coupling of 4-bromophenol with phenylboronic acid or tetraphenylborate at room temperature and get more than 94% yield. Sepiolite is a hydrated magnesium silicate with the ideal formula of $Mg_8Si_{12}O_{30}4H_2O{\cdot}nH_2O$. Palladium loading of 0.1 mol%, the Pd (II)/sepiolite catalyst could be reused three times with no apparent deactivation.

Scheme 5



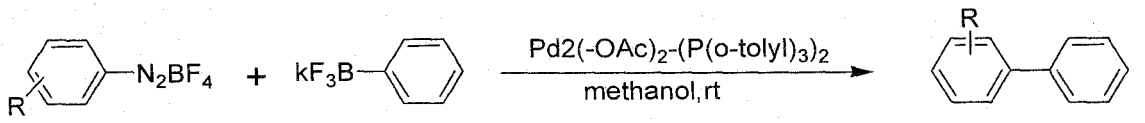
Bumagin and co-workers[29] synthesized biaryl moiety via cross coupling of *p*-tolylboronic acid with bromo arene using 50 mol% palladium black as acatalyst in water. Again they have shown catalytic system is so efficient that water-soluble aryl halides react in 5-10 min even in the presence of 1 mol.% of the catalyst.

Scheme 6



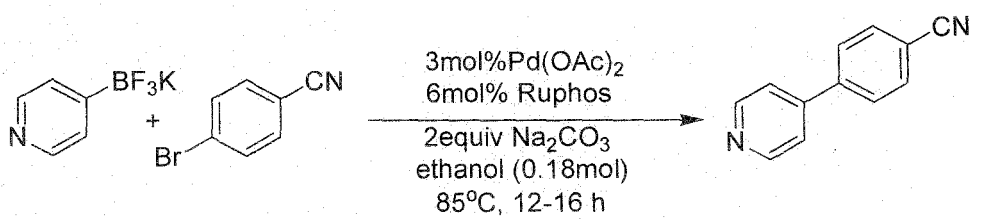
In 1997, Scientist Darses and Genet were the first to show that potassium aryltrifluoroborates were suitable substrates in palladium-catalyzed reactions.[30] Highly stable and nonexplosive arenediazonium tetrafluoroborates were chosen for the coupling pattern because of their ready availability from inexpensive aromatic amines.[31] They are synthesized biaryl via cross-coupling of arenediazonium with potassium aryltrifluoroborates occurred at room temperature in the presence of a catalytic amount of palladium and in the absence of any base. Two sets of catalyst/solvent systems worked efficiently, $Pd(OAc)_2$[32] in 1,4-dioxane and the palladacycle $Pd_2(i\text{-}OAc)_2\text{-}(P(o\text{-}tolyl)_3)_2$ in methanol. The reactivity of aryltrifluoroborates was far superior to that of the corresponding boronic acids,[33] giving higher yields of biaryls, particularly when hindered substrates were involved.

Scheme 7



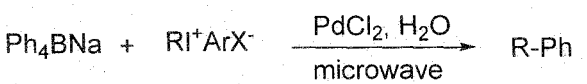
Molander *et al.*[34] synthesized variety of heteroaryltrifluoroborates (five-membered, six-membered, and benzannulated heteroaryltrifluoroborate derivatives) from commercially available boronic acids by the addition of inexpensive potassium hydrogen fluoride (KHF_2)[35] and disclose their efficient cross-couplings to a broad range of aryl and heteroaryl halides in presence of catalytic amount $Pd(OAc)_2$ and RuPhos. By combining the electron-rich, monodentate ligand, RuPhos, with heteroaryltrifluoroborates as the nucleophilic coupling partners, general, mild, and efficient reaction conditions for cross-coupling were developed.

Scheme 8



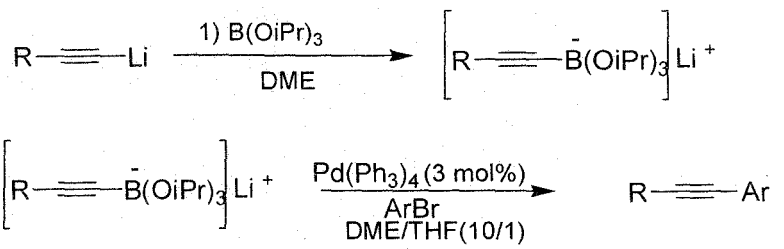
Yan and coworkers have recently reported base-free SM reaction using hypervalent iodonium aryl salts instead of aryl halides.[36]

Scheme 9



Schlama *et.al.*[37] first prepared boronate complex by the treatment of octynyllithium with triisopropoxyborane in DME at -78°C and subsequently employed it Suzuki cross-coupling reactions and isolate 75% yield, at the reflux condition using mixed solvent DME/THF (10:1).

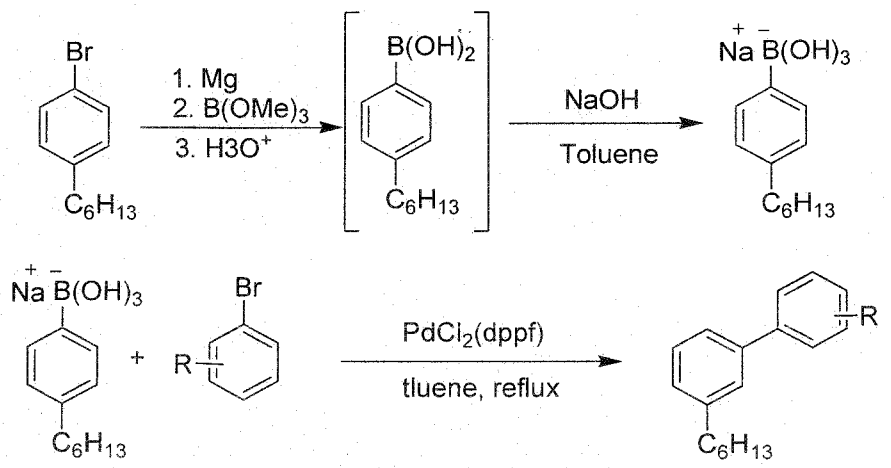
Scheme 10:



Cammidge and coworkers[38] synthesized biaryl by an alternative method instead of phenyl boronic acid. They first synthesized a water soluble activated complex, sodium trihydroxyarylborate salt, from 4-bromo-1-hexylbenzene via formation of the Grignard reagent followed by quenching with trimethylborate, the residue is dissolved in toluene which on

treating with a concentrated solution of sodium hydroxide forms the activated sodium trihydroxyarylborate salt immediately and can be isolated by filtration as a free-flowing, pure colourless powder. This activated complex have been employed base-free SM coupling reaction using catalytic amount of palladium with aryl halide and also for other cross-couplings reaction and get more than 80% yield.

Scheme 11



1. B.3. Present Work: Result and Discussion:

In recent years, amelioration of the SM coupling reaction has been directed towards the more efficient, economic and greener techniques, especially in respect of Pd-catalyst, requirement of base and carrying out the reaction in water or in the absence of any solvent.[39] Recent trends in organic synthesis involve reactions under solvent-free or on-water conditions to obtain the target molecule in a cleaner and environmentally benign way.[40] Although many organic reactions are facilitated in aqueous media, some reactions proceed very slowly because of poor solubility of the substrate/reagents in water. In the case of SM couplings, hydrophobic aryl boronic acids often show very slow and/or incomplete conversions along with the difficulty to isolate the products from the reaction mixture. In connection with our interest in the development of carbon-carbon cross coupling reaction specially for Suzuki Miyaura,[41] we have prepared phenyl trihydroxyborate salt and successfully used directly without further purification for Suzuki–Miyaura coupling reaction. Preliminary optimization of the SM coupling reactions was carried out using 3-iodoanisole and phenyltrihydroxyborate with the aid of 0.5 mol% $Pd(OAc)_2$ (Table 1). The phenyl trihydroxyborate salt was prepared following the reported procedure,[42] and used directly without further purification. Investigations using different solvents revealed that the coupling is unsuccessful in toluene (Table 1 entry 1), partly successful in dioxane (Table 1, entry 2) but worked efficiently in DMF (Table 1, entry 3). On switching over to aqueous media, it was found that a mixture of acetone–water also worked

efficiently within 8 h under mild conditions (Table 1, entry 4). However, carrying out the reaction in only water resulted in the formation of the biphenyl derivative in 38% yield (Table 1, entry 5), which may be attributed to the poor solubility of aryl iodide in water. To overcome this shortcoming, we decided to use tetrabutylammonium bromide (TBAB), a phase transfer reagent, in an equimolar amount. This led to the formation of the desired unsymmetrical biphenyl within 4 h at room temperature in 92% yield (Table 1, entry 6). An experiment with 0.5 equivalents of TBAB, however, afforded the desired product only in 50% yield, even after 8 h (Table 1, entry 7). It was revealed that polar protic or aprotic solvents are good enough to affect the SM coupling at room temperature. A further interesting observation was that the yield of the coupled product was not influenced by the absence of base. Thus, the optimized reaction conditions are: 0.5 mol% of $Pd(OAc)_2$ and 1 equivalent of TBAB in water at room temperature.

Scheme 12

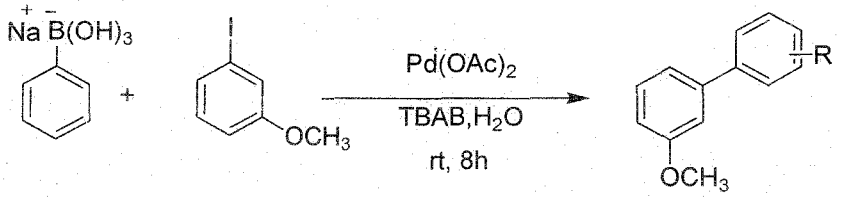


Table 1: Optimization of reaction conditions for the SM coupling using 3-Iodoanisole and phenyltrihydroxyborate

Entry	Solvent	Temperature	Time	% of Yield[a]
1	Toluene	100 °C	8 hrs	00
2	Dioxane	RT	24 hrs	45
3	DMF	RT	4 hrs	96
4	Acetone:Water	RT	8 hrs	93
5	Water	RT	4 hrs	38
6	Water[b]	RT	4 hrs	92
7	Water[c]	RT	8 hrs	50

The common mechanism of SM coupling reactions (i.e., sequential oxidative addition, transmetalation, and reductive elimination[43] includes a base, which is believed to be involved in several steps of the catalytic cycle, most notably the transmetalation process.[44]

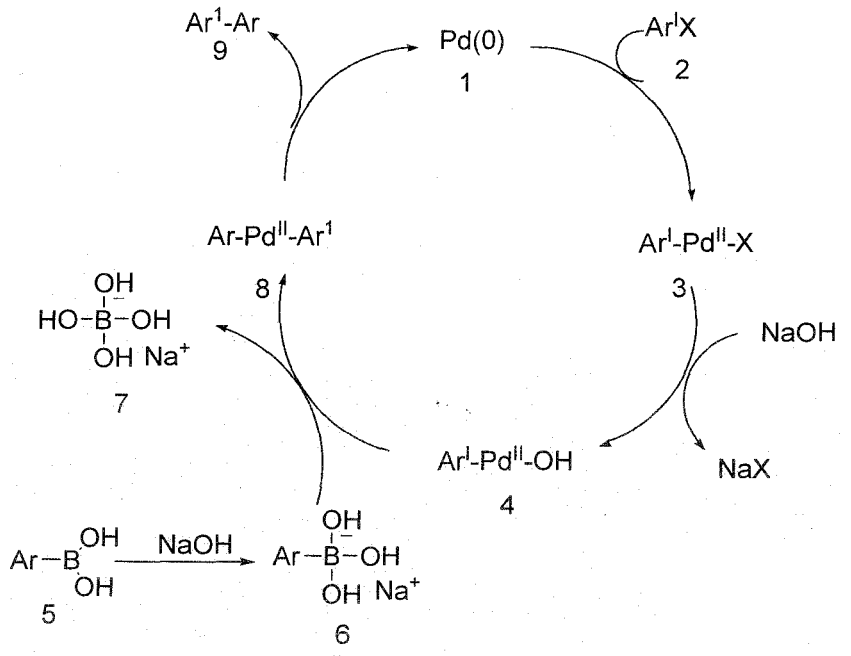


Fig. 1 A general catalytic cycle for Suzuki–Miyaura coupling reaction

The efficiency of palladium originates from its ability, when it is zerovalent, to activate C-X bonds (X=I, Br, Cl) by an oxidative addition which provides an organopalladium (II) complex prone to react with nucleophiles.[45]This is followed by the transmetallation step between the organopalladium (II) complex and the organoboron compound in the presence of a base. The transmetalation between organopalladium(II) halides and organoboron compounds does not occur readily due to the low nucleophilicity of organic group on boron atom.[46] However, the nucleophilicity of organic group on boron atom can be enhanced by quaternization of the boron with negatively charged bases giving the corresponding "ate" complexes.[47] It is reported that such "ate" complexes undergo a clean coupling reaction with organic halide,[48] therefore it may be proposed that the sodium trihydroxy phenyl salt not only serves as an efficient phenylating agent but also acts as a suitable nucleophile requisite in the transmetalation process. A variety of aryl bromides and iodides bearing electron donating or withdrawing groups as well as heteroaryl halides underwent SM coupling in this condition. There are many examples have been illustrated in Table 1. Mechanistically, the oxidative addition of aryl halides to palladium(0) depends on the nature of halogens and occurs in the descending order of I > Br > Cl.[49] Several aryl bromides including di- and tribromoarenes were found to give the corresponding unsymmetrical biaryls in good to excellent yields (Table 2, entries 8–13). While p-bromoacetophenone showed a faster rate of reaction (2 h) (Table 2, entry 9), 2,4,6-tribromophenol required a longer time (24 h) (Table 2, entry 13) for the coupling reaction, which may be due to the presence of the electron-withdrawing acetyl group in the former example. A similar reaction with aryl chloride was not successful even after heating the

reaction mixture at 100^0C for 24 h (Table 2, entries 14–15). Leadbeater *et al.*[50] reported the microwave-assisted SM coupling of aryl chlorides at 150–175^0C in aqueous media indicating that aryl chlorides are very sluggish towards the SM coupling reaction and require relatively higher temperature, longer reaction time and/or the presence of electron-withdrawing groups. We examined aryl chlorides bearing nitro or acetyl groups, which however afforded the desired coupled products in excellent yields at refluxing temperatures (100°C) (Table 2, entries 16–17).Changing the coupling partner phenyltrihydroxyborate with *m*- tolyltrihydroxyborate and *p*-anisyltrihydroxyborate did work efficiently with bromo and iodoarenes (Table 2, entries 18–22 and 24). The SM coupling reaction with heteroaryl halides was also successful. For example, 3-bromoquinoline or 2, 6-dibromopyridine gave the desired coupled products (Table 2, entry 22-24). We developed a new Pd-catalyst (where Pd was immobilized onto ion-exchange resins), designated as ARF– Pd, which was successfully applied to Heck, Suzuki–Miyaura and Sonogashira coupling reactions.[51] To extend further, we employed the heterogeneous Pd-catalyst (ARF–Pd) replacing $Pd(OAc)_2$. Indeed, trihydroxyborate salts were found to be equally active in SM coupling reactions in the presence of a catalytic amount of ARF–Pd. In all the cases, the ARF–Pd was separated by filtration and the desired products were obtained after chromatographic purification in excellent yields (85–93%) (Table 3, entries 1–5).

Table 2: On-water SM coupling reactions with sodium aryl trihydroxyborates using 0.5 mol% of $Pd(OAc)_2$

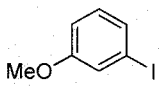
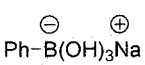
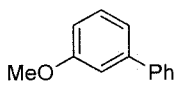
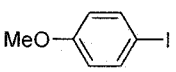
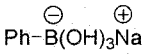
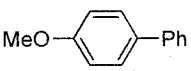
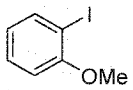
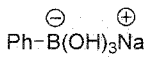
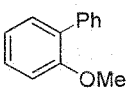
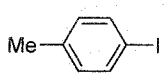
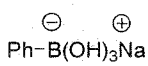
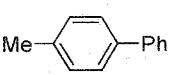
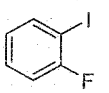
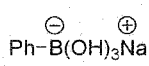
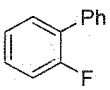
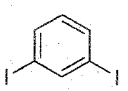
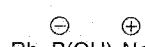
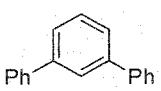
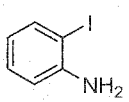
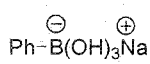
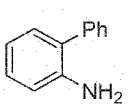
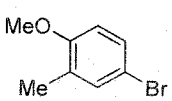
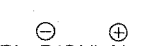
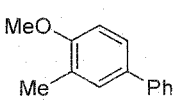
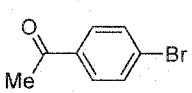
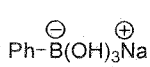
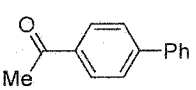
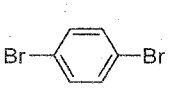
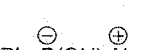
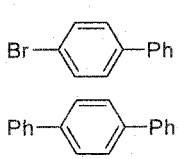
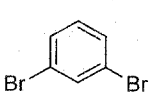
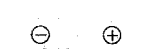
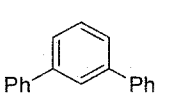
Entry	Aryl halides	Aryl boronic acid salts[a]	Temp.	Time (h)	Product	Yield (%)[b]
1			RT	4		92
2			RT	4		88
3			RT	2.5		84
4			RT	4		87
5			RT	4		94
6			RT	16		87
7			RT	6		85
8			RT	8		72
9			RT	2		95
10			RT	4		22 66
11			RT	8		89

Table 2 cotinued.....

Table 2: On-water SM coupling reactions with sodium aryl trihydroxyborates using 0.5 mol% of $Pd(OAc)_2$

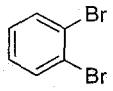
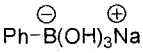
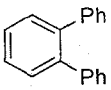
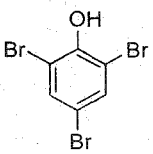
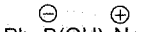
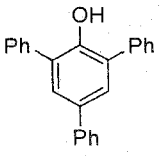
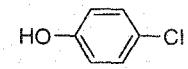
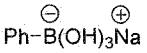
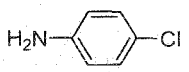
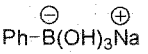
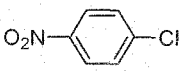
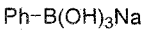
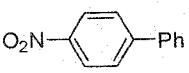
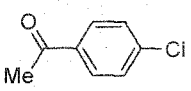
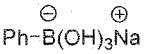
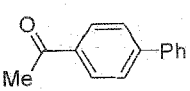
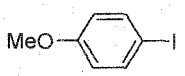
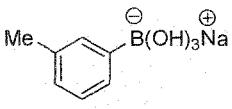
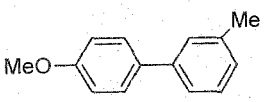
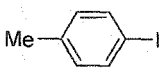
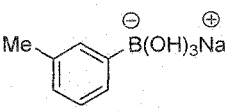
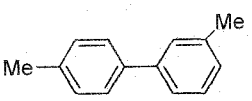
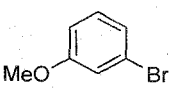
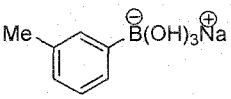
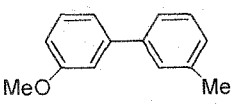
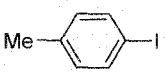
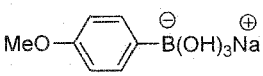
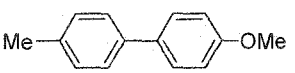
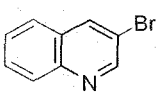
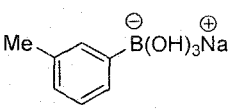
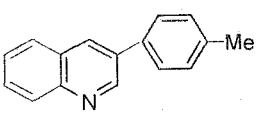
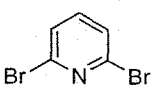
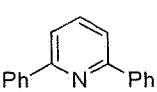
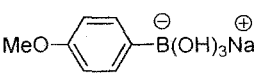
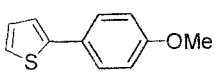
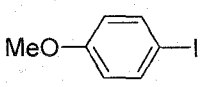
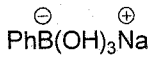
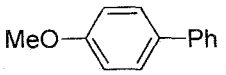
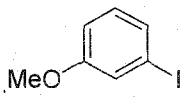
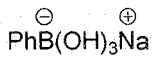
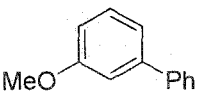
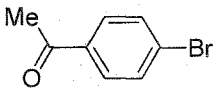
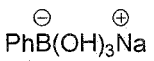
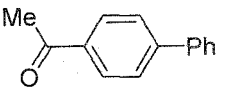
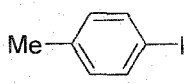
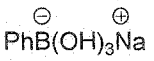
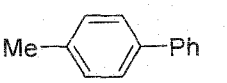
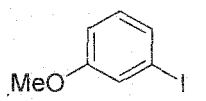
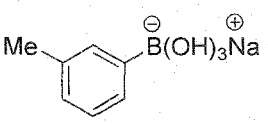
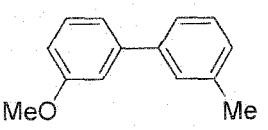
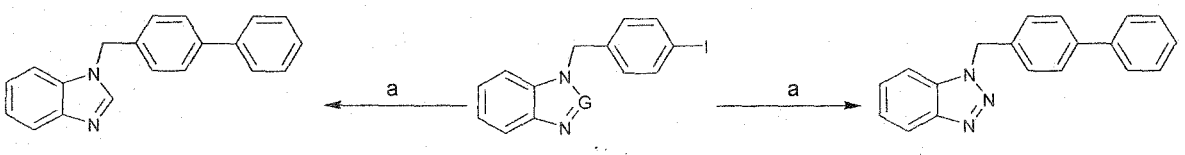
Entry	Aryl halides	Aryl boronic acid salts[a]	Temp.	Time (h)	Product	Yield (%)[b]
12			RT	6		67
13			RT	24		82
14			100° C	24		No Reaction
15			100° C	24		No Reaction
16			100° C	5		96
17			100° C	4		85
18			RT	8		79
19			RT	8		86
20			RT	3.5		74
21			RT	7		97
22			RT	3.5		66
23			RT	8		83
24			RT	3		92

Table 3: SM coupling reactions with aryltrihydroxy borates in water using heterogeneous Pd-catalyst (ARF-Pd)

Entry	Aryl halides[a]	Sodium trihydroxyborate	Temp.	Time (h)	Product	Yield[b] (%)
1			RT	5		85
2			RT	5		88
3			100°C	4		92
4			100°C	3		93
5			100°C	5		87

[a]300 mg ARF-Pd (0.94 mol%Pd) was used. [b]Isolated yields after purification by column chromatography on silica.

Scheme 2



conditions: 1a or 1b (1mmol), $PhB(OH)_3^-Na$ (1.1 mmol) in DMF-H_2O(2:1: 3ml), $Pd(OAC)_2$(1.1mg, 0.5 mol%), 100 °C for 24h.

1. B.4. Experimental Section:

General procedure for the preparation of aryl trihydroxyboronate salts from boronicids.

The corresponding arylboronic acid was dissolved in a minimum amount of warm toluene with stirring and the solution was allowed cool to room temperature. Once saturated, aqueous sodium hydroxide solution was added dropwise until no further precipitate formed. The mixture was allowed to stir for 30 min and the colourless precipitate was filtered off and washed with toluene to give the corresponding salt.

Representative procedure for Suzuki–Miyaura coupling

A mixture of 3-iodoanisole (468 mg, 2 mmol), sodium phenyltrihydroxyborate (354 mg, 2.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.5 mol%) and TBAB (644 mg, 2 mmol; 1 equiv) was taken in distilled water (5mL) The mixture was magnetically stirred at room temperature for several hours (see Table 2). After the reaction was complete (monitored by tlc), the mixture was extracted with ether (3 x 20 mL). The combined organic layer was then washed with brine (10 mL), dried (anhydrous Na_2SO_4), and evaporated. The residue was purified on a short column of silica using light petroleum as the eluent to afford the desired unsymmetrical biphenyl (338 mg, 92%); liquid.

1. B.5. Conclusions:

Easily accessible, air-stable and water soluble sodium aryl trihydroxyborates can be effectively used as an alternative source of organoboron species in SM cross-coupling reactions in water under an aerobic atmosphere and at room temperature. Low loading of the Pd-catalyst (direct use of $Pd(OAc)_2$ or polymer-bound Pd) and absence of any phosphine ligands are notable features for the reaction . The protocol has been found to be broadly applicable to a variety of aryl halides (X = Br, I) and also to aryl chlorides bearing electron withdrawing groups. It is further shown to be effective with heterogeneous Pd-catalysts and also extended to the modular synthesis of some pharmaceutically important benzimidazole and benzotriazole-based biphenyl scaffolds.

1. B.6. Spectral data analysis:

Table-2, Entry-1: 3-Methoxy biphenyl (liquid);

IR (film): υ_{max} 1574, 1610 cm-1. ^{1}H NMR ($CDCl_3$): δ = 3.75 (s, 3H,); 6.77–6.81 (m, 1H), 7.03–7.10 (m, 2H), 7.21–7.36 (m, 4H), 7.47–7.51 (m, 2H); ^{13}C NMR ($CDCl_3$, δ = 55.2, 112.6, 112.8, 119.6, 127.1, 127.4, 128.7, 129.7, 141.0, 142.7, 159.9.

Table-2, entry-2: 4-Methoxy biphenyl; Mp 88-90 °C. (Lit.[52] 91-92 °C)

IR (KBr): υ_{max} 1458, 1519, 1608, 2923, 2854, 1034, 833, 687 cm^{-1} . ^{1}H NMR ($CDCl_3$): δ = 3.83 (s, 3H), 6.96 (d, J = 8.7Hz, 2H), 7.22-7.55 (7H, m). ^{13}C NMR ($CDCl_3$): δ = 55.3, 114.2, 126.6, 126.7, 128.2, 128.7, 133.8, 140.8, 159.2.

Table-2, Entry-3: 2-Methoxybiphenyl (liquid);

IR (film): υ_{max} 1504, 1597 cm-1. ^{1}H NMR ($CDCl_3$: δ = 3.79 (s, 3H), 6.96–7.05 (m, 2H,), 7.29–7.42 (m, 5H), 7.51–7.54 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 55.54, 111.2, 120.8, 126.9, 127.9, 128.6, 129.5, 130.7, 130.8, 138.5, 156.5.

Table-2, entry-7: 2-Amino biphenyl; Mp. 51°C

IR (KBr): υ_{max} 1481,1500,1579,1614, 3030, 3480, 3390, 1284, 1313 cm^{-1}.^{1}H NMR ($CDCl_3$,): δ = 3.33 (s, br., 2H,), 6.75-6.85 (m, 2 H), 7.11-7.23 (m, 2H), 7.30-7.36 (m, 1H), 7.40-7.49 (m,

4H). ^{13}CNMR ($CDCl_3$): δ = 115.6, 118.6, 127.1, 127.6, 128.4, 128.8, 129.8, 130.44, 139.5, 143.4.

Table-2, Entry 8: 4-Phenyl-2-methyl anisole (solid) Mp 74–75 °C;

IR (Nujol): ν_{max} 1605, 1515, 1246 cm^{-1}; ^{1}H 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 = 16.4, 55.4, 110.2, 125.4, 126.5, 126.8, 126.9, 128.7, 129.5, 133.4, 141.1, 157.4.

Table-2, Entry-9: 4-Acetyl biphenyl (solid): Mp 120-121 °C (Lit.[52] 120-121 °C)

IR (KBr): ν_{max} 1458, 1610, 2923, 1681, 825, 690 cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ = 2.63 (s, 3H), 7.40-7.47 (m, 3H), 7.62-7.70 (m, 4H), 8.03 (d, J = 8.4, 2H). ^{13}C NMR ($CDCl_3$): δ = 26.9, 127.2, 128.2, 128.9, 129.8, 131.8, 135.8, 139.8, 145.8, 197.7.

Table-2, Entry-10: 1, 4-Diphenyl benzene; Mp. 214-216 °C (Lit.[53] 215-217 °C)

IR (KBr): υ_{max} 1454, 1477, 1574, 1597, 2935, 2970, 3035, 837, 744, 686 cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ = 7.23-7.67 (m, 14H).^{13}C NMR ($CDCl_3$): δ = 127.0, 127.3, 127.4, 128.8, 140.1, 140.6.

Table-2, Entry-11: 1, 3-Di phenyl benzene (solid) Mp. 87-88 °C (Lit.[54] 89 °C)

IR (KBr): υ_{max} 1470, 1493, 1570, 1593, 3028, 3062, 806,891, 698,748 cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ = 7.28-7.62 (m, 13H); 7.78 (s, 1H). ^{13}C NMR ($CDCl_3$): δ = 126.1; 127.2; 127.3; 128.7; 129.1; 141.1; 141.7.

Table-2, Entry-16: 4-Nitro biphenyl, Mp. 114-115 °C (Lit.[55] 114-115 °C)

IR (KBr): υ_{max} 1458, 1512, 1597, 2854, 2923, 1512, 1346, 852, 740 cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ = 7.46-7.53 (m, 3H), 7.61-7.64 (m, 2H), 7.73 (d, J = 8.7 Hz, 2H), 8.29 (d, J = 9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ = 124.1, 127.3, 127.8, 128.9, 129.1, 138.7, 147.0, 147.6.

Table-2, Entry-18: 3-Methyl 4′-methoxy biphenyl, Mp. 55 °C

IR (KBr): υ_{max} 1574, 1589, 1604, 1652, 2970, 3030 2910, 2837, 1028, 837, 860 cm $^{-1}$

^{1}H NMR ($CDCl_3$): δ = 2.40 (s, 3H), 3.84 (s, 3H); 6.95 (d, J = 9 Hz, 2H), 7.11-7.36 (m, 4H), 7.52 (d, J = 8.7, 2H). ^{13}C NMR ($CDCl_3$): δ = 21.5, 55.4, 114.1, 123.8, 127.4, 128.1, 128.7, 133.9, 138.3, 140.8, 159.1.

Table-2, Entry-19: 3, 4′-Dimethyl biphenyl (liquid)

IR (film): 1606, 1588, 1569, 1558, 1516, 1500, 3023, 2919, 779 802,821 cm $^{-1}$; ^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 6H) 7.13-7.50 (m, 8H). ^{13}C NMR (CDCl3): δ = 21.3, 124.1, 127.0, 127.7, 127.8, 128.6, 129.4, 136.9, 138.2, 138.5, 141.1.

Table-2, Entry-20: 3- Methoxy-3'-methyl biphenyl (liquid);

IR (neat): υ_{max} 1593 cm-1. ^{1}H NMR ($CDCl_3$): δ = 2.41 (3H, s, CH_3); 3.86 (s, 3H), 7.11–7.39 (m, 8H,); ^{13}C NMR ($CDCl_3$): δ = 21.5, 55.3, 112.6, 112.9, 119.7, 124.3, 128.0, 128.1, 128.6, 129.6, 138.3, 141.1, 142.9, 159.9.

Table-2, Entry-22: 3-(3-Methyl phenyl) quinoline (liquid).

IR (film): υ_{max} 1580, 1606 cm-1. ^{1}HNMR ($CDCl_3$,): δ = 1.59 (s, 3H), 6.36–6.87 (m, 6H), 7.00 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 8.4 Hz 1H,), 7.43 (s, 1H), 8.3 (1H, s). ^{13}CNMR ($CDCl_3$): δ = 21.6, 124.5, 127.1, 128.0, 128.1, 128.2, 128.9, 129,0, 129.1, 129.4, 133.4, 134.0, 137.7, 138.9, 147.1, 149.8.

Table-2, Entry-23: 2, 6-Di phenyl pyridine (solid) Mp 80-81 °C (Lit. 81 °C)

IR (KBr): υ_{max} 1458, 1489, 1566, 1586, 2923, 3035, 3055, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ =7.39-7.51 (m, 6H), 7.65-7.80 (m, 3H), 8.15 (d, J = 7.5 Hz, 4H), ^{13}C NMR ($CDCl_3$): δ = 118.7, 126.9, 128.7, 128.9, 137.5, 139.4, 156.3.

Table-2, Entry-24: 2-(4-Methoxy phenyl) thiophene; mp 106 °C. (Lit.[56] 107-108 °C)

IR (KBr): υ_{max} 1500, 1533, 1606 cm-^{1}. ^{1}H NMR ($CDCl_3$): δ = 3.81 (s, 3H), 6.91(d, J = 9 Hz, 2H), 7.03–7.25 (m, 3H), 7.53 (d, J = 8.7Hz, 2H). ^{13}CNMR ($CDCl_3$): δ = 55.3, 114.3, 122.1, 123.8, 127.2, 127.3, 127.9, 144.3, 159.2.

Scheme 2: N-(4-phenyl benzyl) benzimidazole (solid): Mp 163 °C

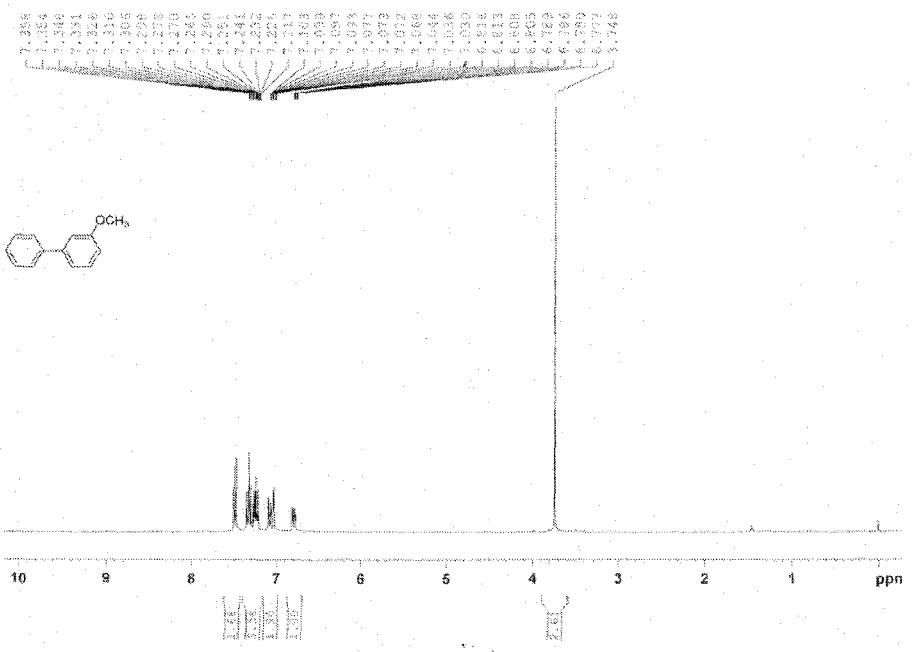
IR (KBr): υ_{max} 1610, 1653 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ = 5.41 (s, 2H), 7.25–7.83 (m, 13H), 8.07 (s, 1H), ^{13}C NMR (CDCl3): δ = 48.7, 110.2, 120.2, 122.6, 123.3, 127.1, 127.6, 127.8, 128.8, 129.1, 133.8, 134.2, 140.3, 141.4, 143.1, 143.3, HRMS: calculated for $C_{20}H_{16}N_2H$: $[M+H]^+$, 285.1392; found 285.1387.

Scheme 2: N-(4-phenyl benzyl) benzotriazole (solid): Mp 163 °C

IR (KBr): υ_{max} 1590, 1616 cm-^{1}.^{1}H NMR (CDCl3): δ= 5.88 (s, 2H), 7.25–8.09 (m, 13H).^{13}C NMR (CDCl3): δ = 51.9, 109.7, 120.1, 124.0, 127.0, 127.5, 127.6, 127.7, 128, 128.8, 132.8, 133.6, 140.2, 141.4, 146.3. HRMS: Calculated for $C_{19}H_{15}N_3Na$: $[M+Na]^+$ 308.1164; found 308.1163.

Table-3, entry-1: 4-Methoxy biphenyl; Mp 88-90 °C. (Lit.[52] 91-92 °C)

IR (KBr): υ_{max} 1458, 1519, 1608, 2923, 2854, 1034, 833, 687 cm^{-1} . ^{1}H NMR ($CDCl_3$): δ = 3.83 (s, 3H), 6.96 (d, J = 8.7Hz, 2H), 7.22-7.55 (7H, m). ^{13}C NMR ($CDCl_3$): δ = 55.3, 114.2, 126.6, 126.7, 128.2, 128.7, 133.8, 140.8, 159.2.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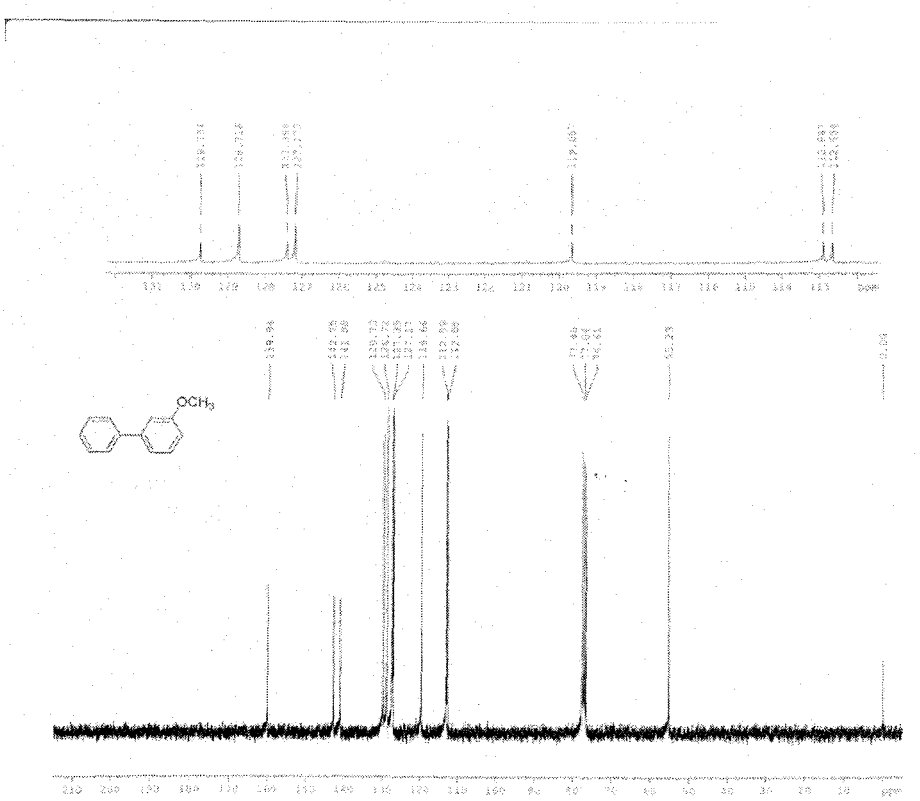
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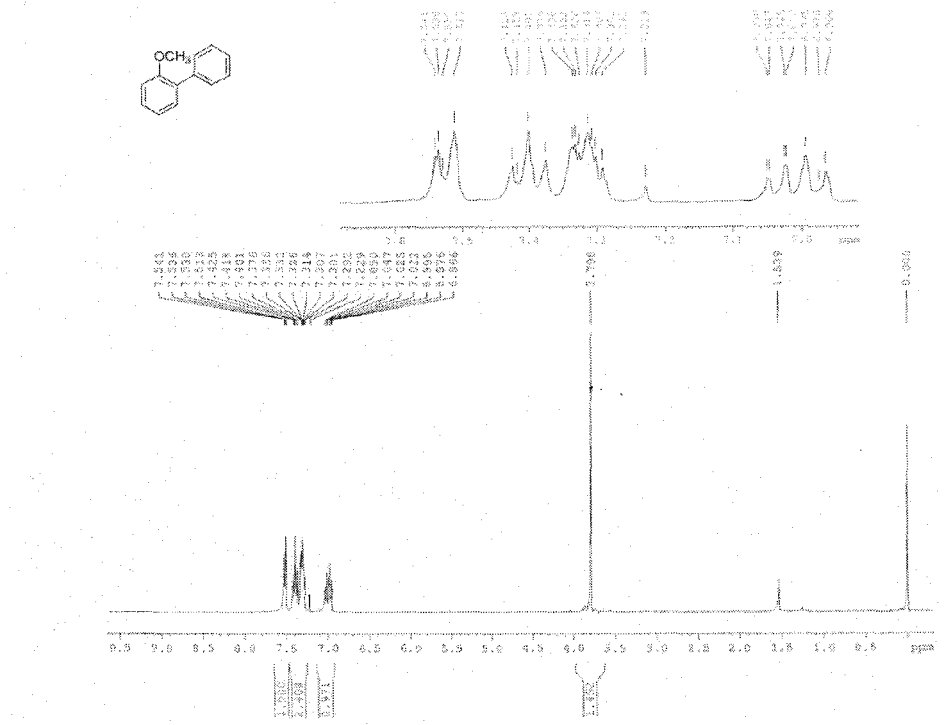
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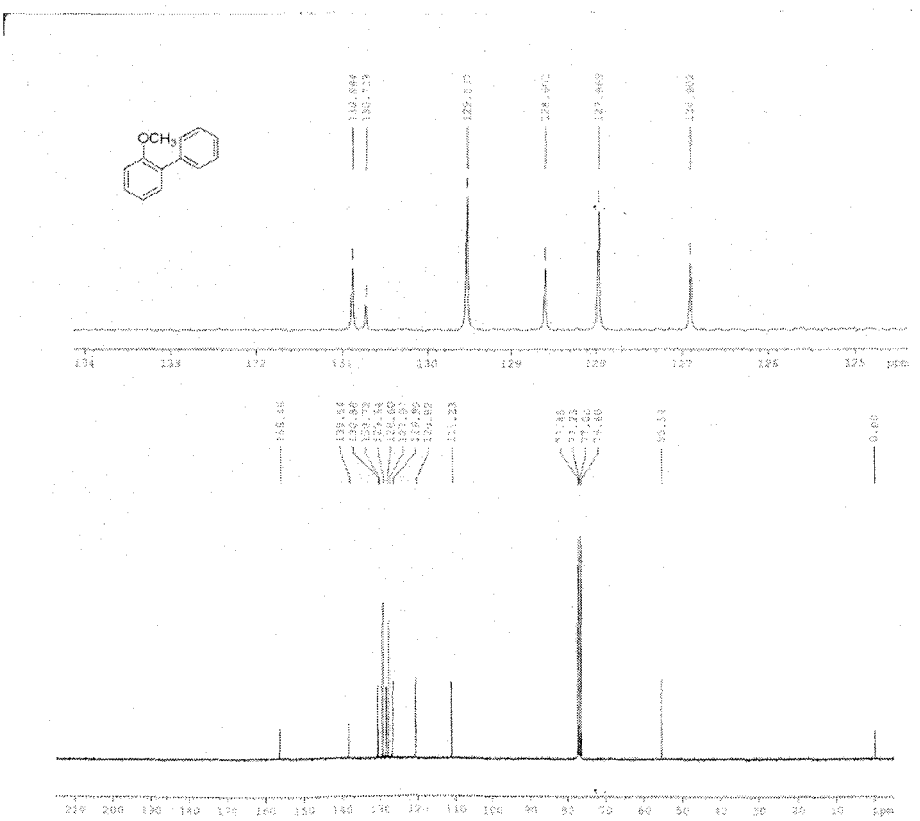
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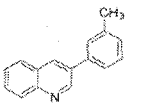
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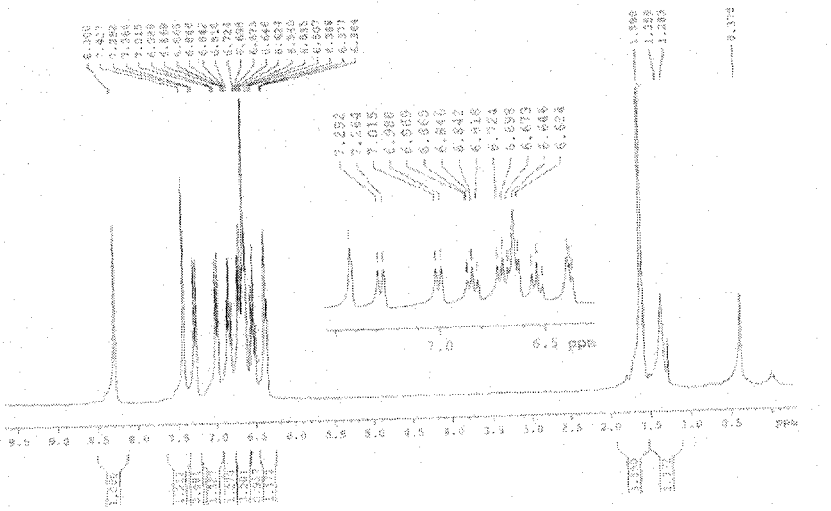
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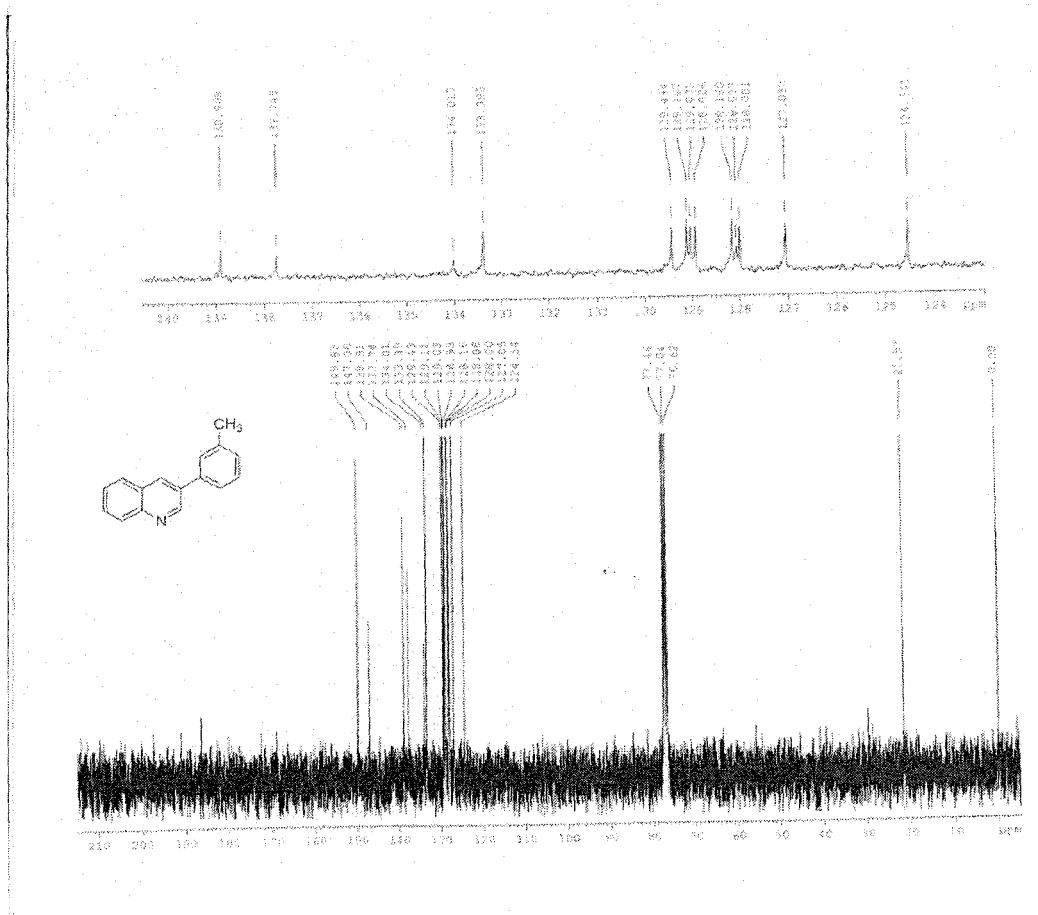
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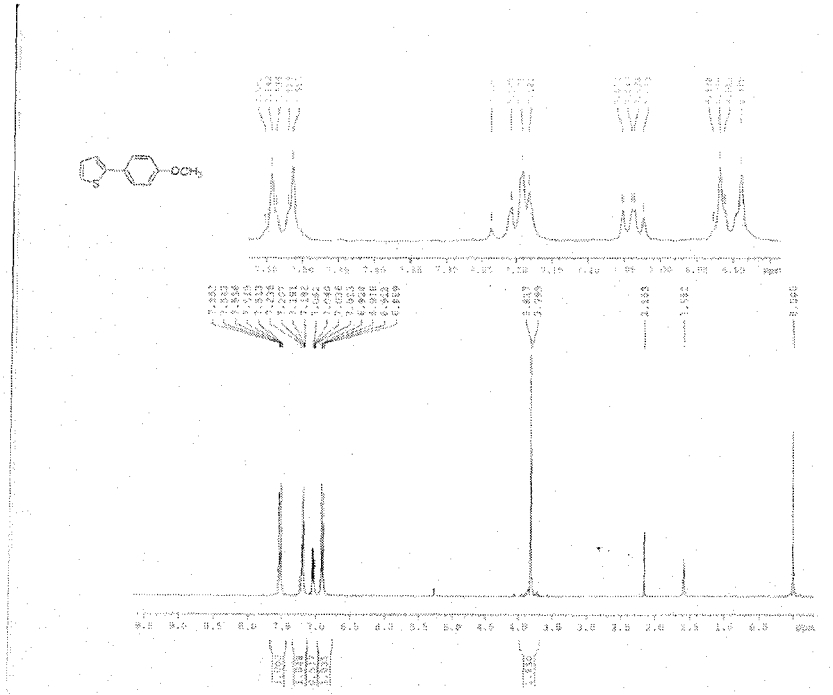

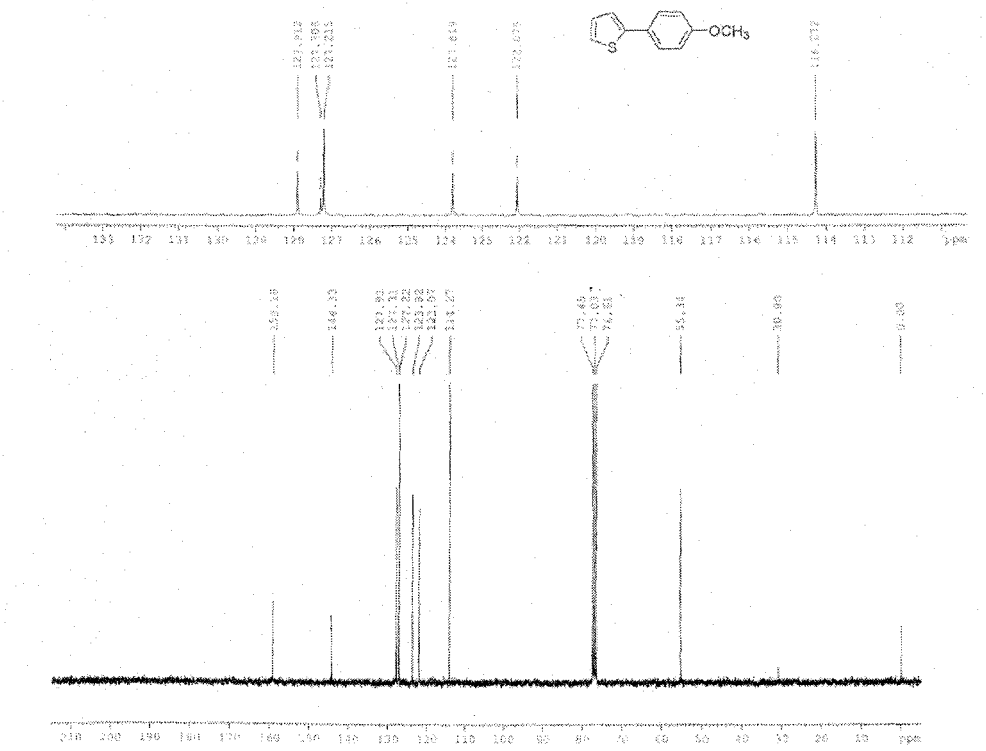

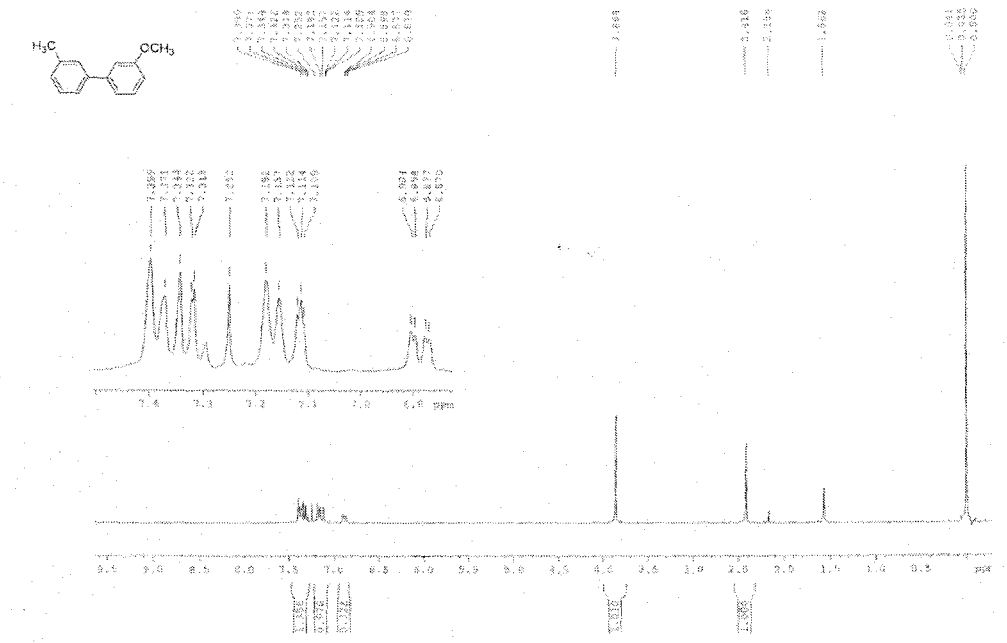
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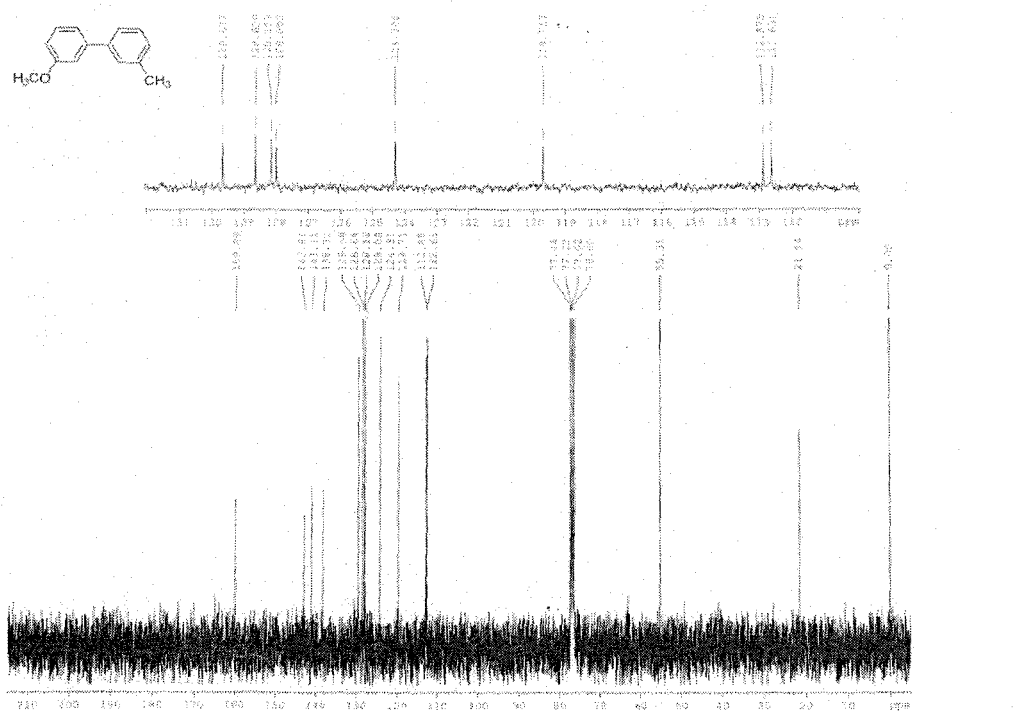
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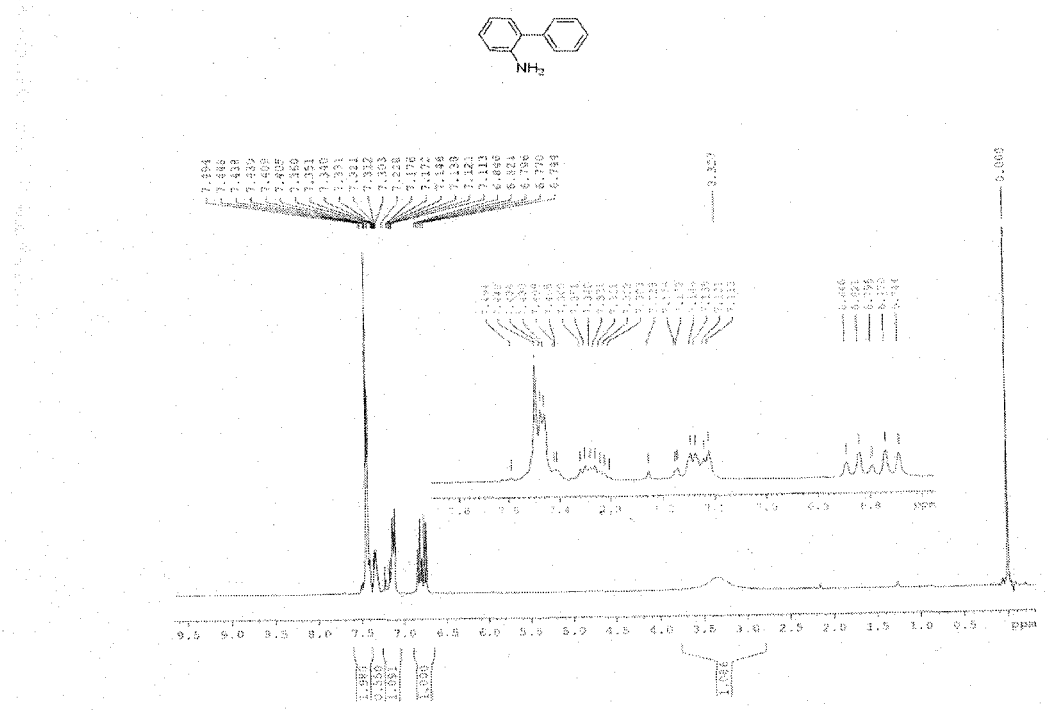

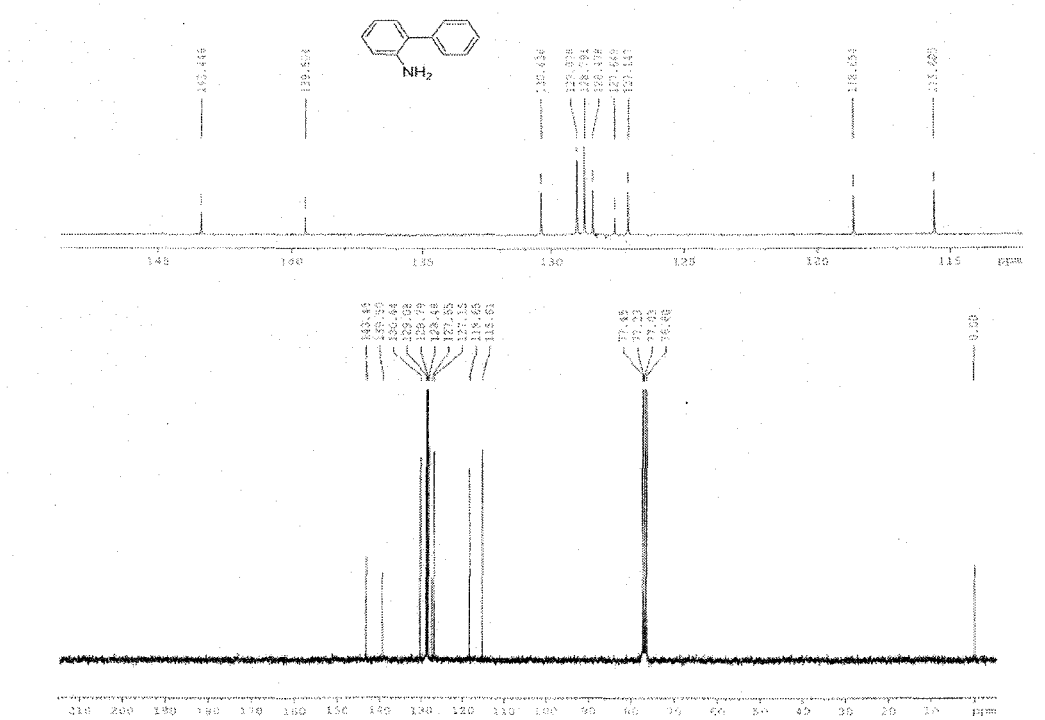

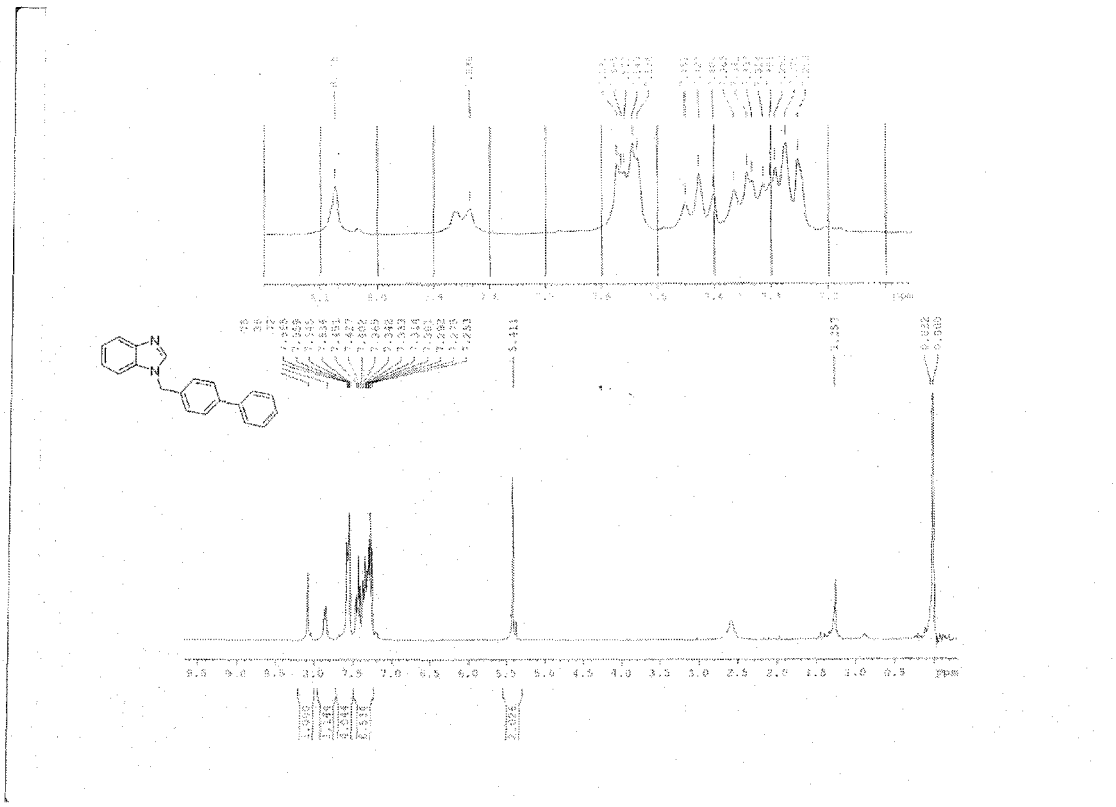

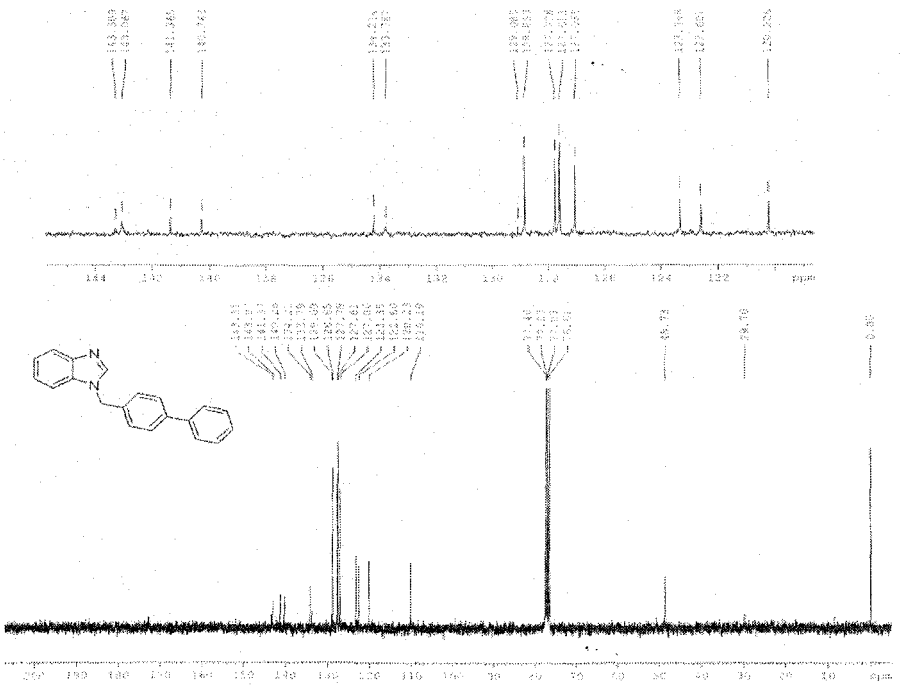

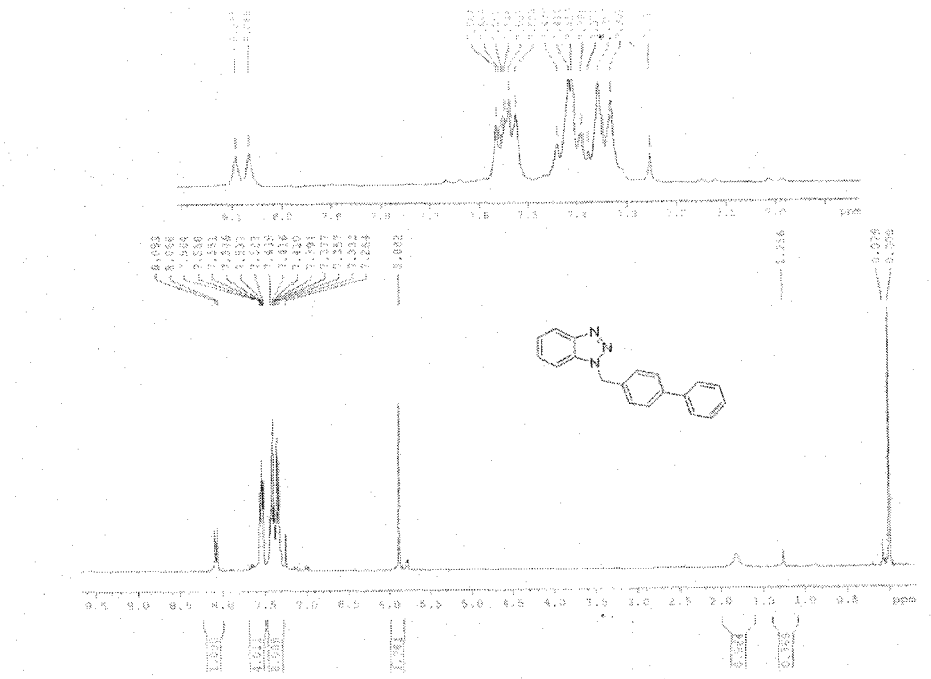

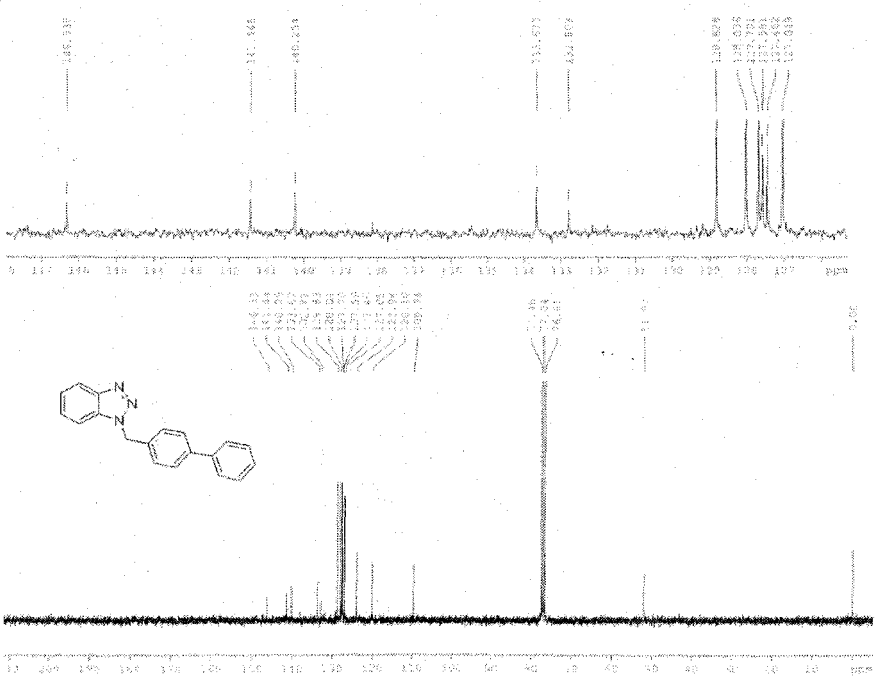

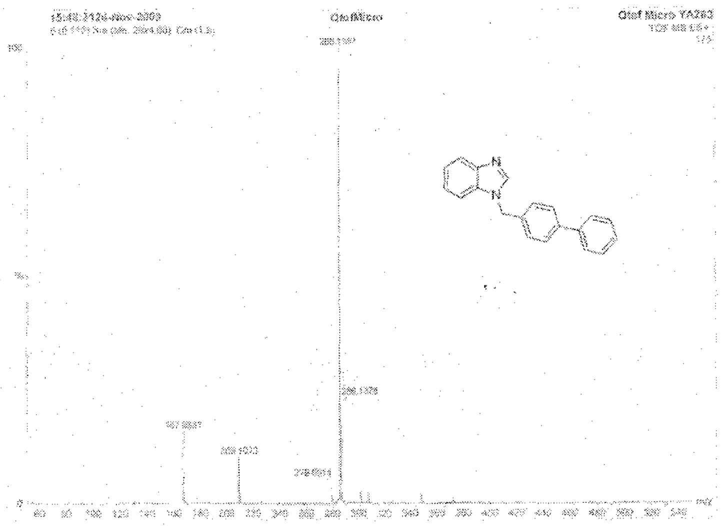
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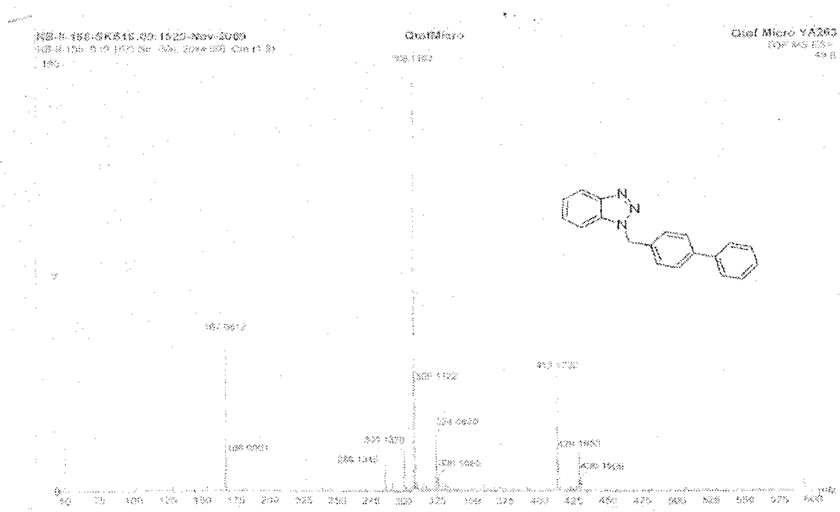
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Part II

"Catechol Violet as Novel and Efficient Ligand for Cu (I)-Catalyzed C-S Coupling Reactions"

II.1 Introduction

The formation of carbon-heteroatom bonds using metal catalysis is emerging as one of the most significant classes of cross-coupling reactions. In recognition of their widespread importance, over the years, transition-metal-catalyzed cross-coupling reactions of aryl halides with nitrogen, oxygen, and sulfur nucleophiles are powerful tools for the formation of C-N, C-O, and C-S bonds, respectively.[1] These cross-coupling reactions currently fall into two broad categories: the anaerobic, metal-catalyzed cross-coupling of N, O, S, and P nucleophiles with organic halides or their equivalents[2] and complementary "oxidative" aminations, amidations, alkoxylations, aryloxylations, and thiolations of boronic acids mediated by Cu(II) salt or catalyst. Aryl sulfides are of great significance to the pharmaceutical industry.[3] and are common functionality found innumerous drugs in therapeutic areas, such as diabetes, anti-inflammatory, Alzheimer's, Parkinson's diseases,[4] treatment of cancer,[5] and treatment of human immunodeficiency virus diseases.[6] The traditional method for C–S coupling is a substitution reaction via an addition–elimination mechanism,[7] that usually requires harsh reaction conditions, means high reaction temperature and long reaction times.[8]Migita and his co-workers first reported the C-S coupling of iodo and bromo arenes with thiols using $Pd(PPh_3)_4$ as catalyst under mild conditions, and subsequently many ligands have been tested for this reaction.[9] However, the high cost of palladium catalyst, high oxophilicity associated with phosphine ligands and tedious multistep processes involved in the synthesis of these ligands have rendered Pd unpopular, particularly for large scale reactions. Recently, the application of other metals in the catalytic carbon-sulfur bond formation resulted in synthetic protocols based on nickel[10]and cobalt,[11] but these were fraught with common problems such as metal toxicity, low turnover numbers, and reagents needed in excess. Use of copper salt, mainly copper halides, together with a suitable ligand is the best alternative for expensive palladium or other metal catalyst for the C-S bond formation reaction starting from aryl halides and thiols. From industrial view point, the low cost of copper and the readily accessible stable ligands provide an indisputable advantage over the other catalytic systems. The synthesis of diaryl sulfides under classical Ullmann reaction condition is well known. This copper catalysed coupling reactions generally employ organic solvents such as DMF, NMP, DMSO, HMPA etc, in the presence of base, and a nitrogen or phosphorus containing ligand. However, transition-metal-mediated C-S bond formation is much less studied than similar C-N and C-O bond formations. The synthetic reaction involving sulfur-containing compounds poses special requirements because the sulfur functionality is known to be reactive and may act as a poison for metal-based catalysts because of its strong coordinative properties, often making the catalytic reaction ineffective.[12] Traditional methods for the formation of C-S bonds often

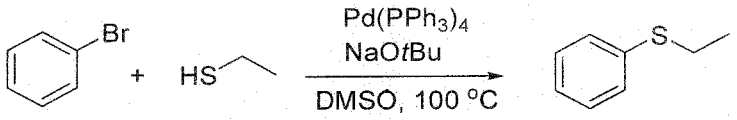
require harsh reaction conditions. For example, the coupling of copper thiolates with aryl halides takes place in polar solvents, such as HMPA, and high temperatures around 200 °C. Reduction of aryl sulfones or aryl sulfoxides is the alternative method for the synthesis of sulfides and it requires strong reducing agents such as DIBAL-H or LiAlH4.[13] To overcome these difficulties, considerable attention has been focused on the development of new catalytic systems for the C-S cross-coupling reaction.

II.2. Background & Objectives

- Examples with Pd-catalyzed C-S coupling reactions:

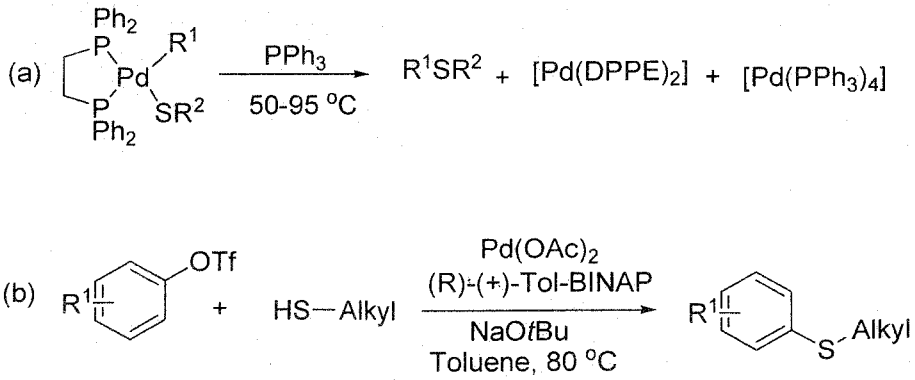
One of the first reports involving the cross-coupling between aryl halides and thiols refers to Migita's system, using $Pd(PPh_3)_4$ as the catalyst, NaO^tBu as the base, in polar solvents such as refluxing ethanol or DMSO at 90 °C (Scheme 1).[14a] Although Migita's condition was successful for the synthesis of thio-ether, it has some limitations such as the high cost and air sensitivity of Pd catalysts and often tedious procedure for the preparation of ligands. This restricts their applications in large-scale processes and also the problems associated with the removal of palladium-residues from polar reaction products during the late stages of compound synthesis. Moreover, sulphur-containing compounds have long been known to act as catalyst poisons because of their strong coordinating and adsorptive properties and often rendered the catalytic reactions totally ineffective.[14b, c]

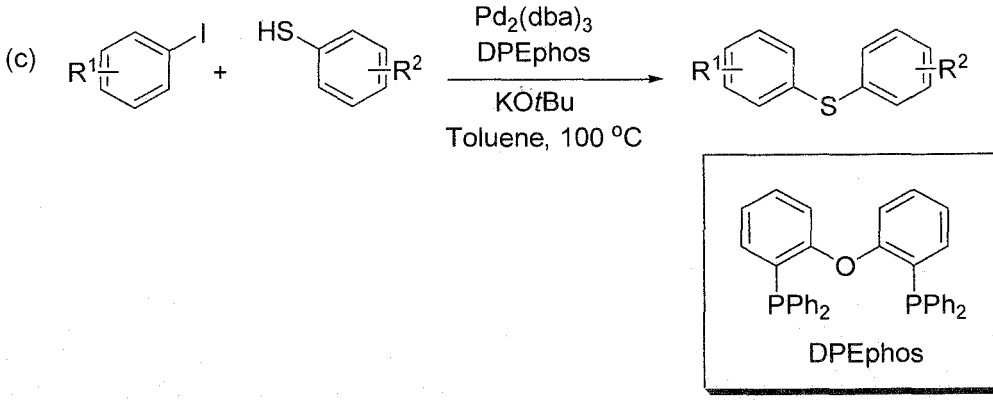
Scheme 1



Other efficient palladium catalysts based on phosphines or diverse organophosphane derivatives have also been reported by Hartwig,[15] Zheng,[16] and more recently by Schopfer and Schlapbach (Scheme 2).[17a]

Scheme 2



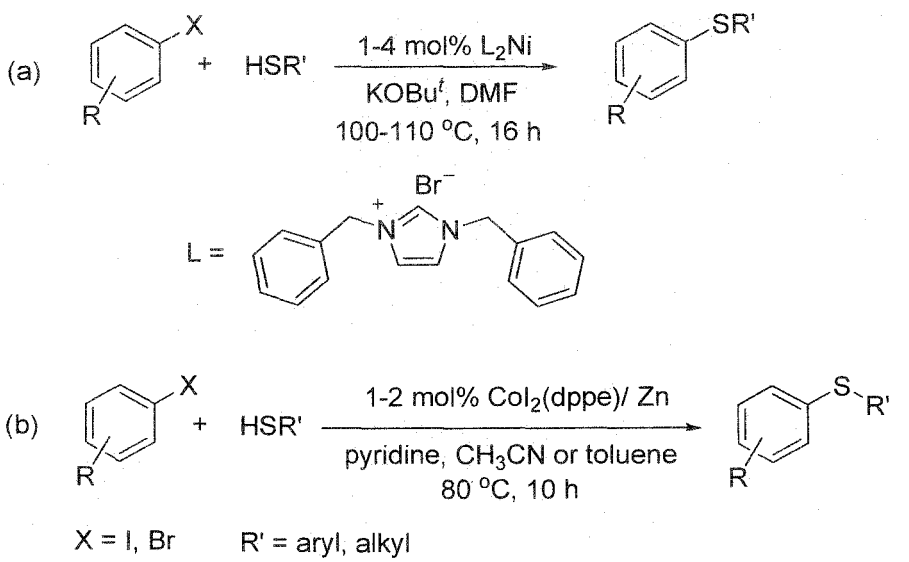


(a) Hartwig's palladium(II) arylthiolate complexes with chelating phosphines,
(b) Zheng's protocol
(c) Conditions developed by Schopfer and Schlapbach

- Examples with other transition metal-catalyzed C-S coupling reactions:

Nickel and Cobalt salts are also used as the catalysts in carbon-sulfur coupling reactions, but these were fraught with common problems such as metal toxicity, low turnover numbers, and reagents needed in excess.

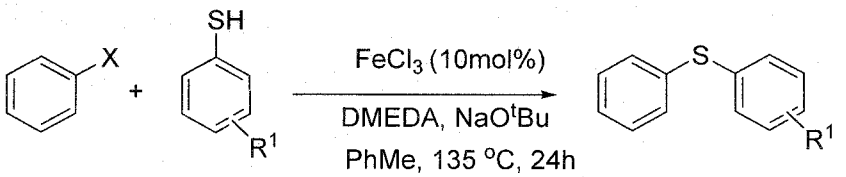
Scheme 3



(a) Zhang's N-heterocyclic carbene-based Ni-catalyzed C-S coupling
(b) Cheng's Cobalt-catalyzed thiolation of aryl halides.

Bolm *et al.* reported the use of catalytic iron (III) chloride in the *S*-arylation of thiols (Scheme 4)[17b]. The reaction was only compatible with aryl iodides and aryl thiols to construct biaryl sulfides.

Scheme 4

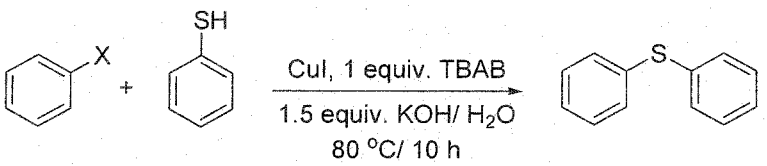


Shortly after this report, experiments performed in the Buchwald laboratory determined that copper, as little as 10 parts per million, was essential for catalytic activity.[17c] Although the presence of copper may play a role in the iron-catalyze process, the efficacy of a C-S bond formation requiring only 10 mol % $FeCl_3$ makes for an attractive, cost-friendly process.

- Examples with Cu-catalyzed C-S coupling reactions:

Therefore, several approaches are in progress to develop more general and efficient system for the preparation of diaryl thioethers. Examples of attractive and cheap copper-catalyzed processes have recently been reported by Palomo,[18] Buchwald[19] Venkataraman, [20] and others.[21] Very recently, Domínquez[22] and Verma,[23] Punniyamurthy's,[24] have reported Cu(I) catalyzed C-S coupling reaction in water medium.

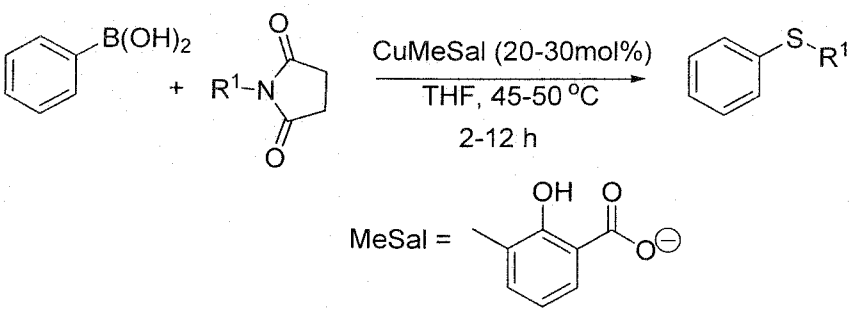
Scheme 5



Punniyamurthy's copper catalyzed thiolation of aryl halides in water

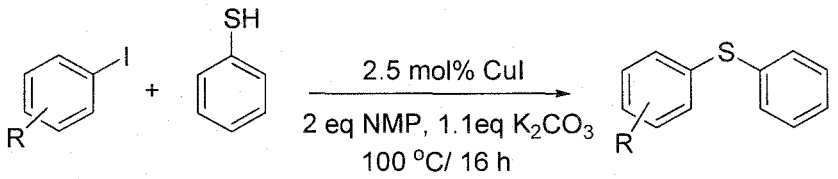
Liebeskind *et al.*[25] synthesized biaryl-sulphide with moderate efficacy where Copper (I)-carboxylate complex catalyzes the cross-coupling of aryl boronic acids with thioimides in the absence of a base under mild condition (Scheme 6).

Scheme 6



Koten and his co-workers[26] synthesized a variety of diaryl thioethers under relatively mild reaction conditions with good chemoselectivity and functional group tolerance in organic solvent such as NMP.

Scheme 7



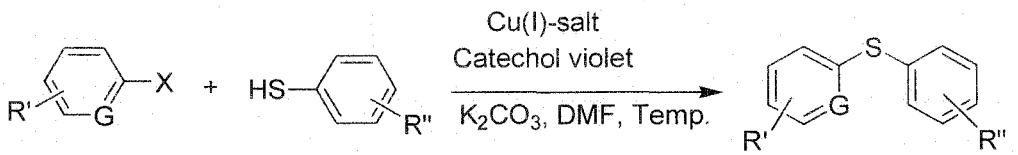
Van Koten's ligand free copper catalyzed thiolation

In most of the cases, the protocol is either substrate-specific or requires phosphine or phosphine-free ligands besides requirement high temperature, strong base, long reaction time, etc. Therefore, the development of more efficient, inexpensive, and mild catalytic systems involving copper and more generalized mild reaction conditions for the C–S coupling reactions has been the major target of contemporary research. In search of more efficient and mild conditions for C-S coupling, we conducted some studies using Cu(I) catalysts and water soluble ligand – Catechol Violet (CV). Our studies eventually established that the catalytic system Cu(I)–CV is highly effective for C–S coupling between haloarenes or vinyl iodide and thiols affording corresponding thioethers in good to excellent yields. Broad range of functional group tolerance present in both the coupling partners has also been observed in this reaction protocol.

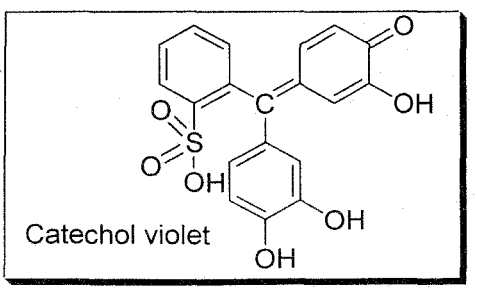
II.3. **Results and Discussion**

Preliminary optimization of the C–S coupling reactions between aryl halide and aryl thiol with the aid of catalytic Cu (I) salt and catechol violet was tested with *p*-iodoanisole and thiophenol (Table 1). As expected, in the absence of copper no aryl sulfide was detected (Table 1, entry 1). Using CuI (5 mol %) and carrying out the reaction at 90 °C for 21 h in DMF yielded the desired diaryl sulfide in 78% (entry 2).

Scheme 8



X = I, Br, Cl
G = C, N



The CuI-CV-catalysed synthesis of diarylsulphides is represented

On the other hand, similar reaction in presence of CuI and catechol violet (5 mol% each), the coupling reaction afforded the desired diaryl sulfide in 93% yield in only 2 h (entry 3). Disulfide is often obtained as a by-product, which is dependent of the medium (*i.e.* the solvent) of reaction. Screening of a number of solvents, bases, and temperatures revealed that the use of polar aprotic solvent resulted in the formation of the disulfide in substantial amount (entries 7-13). Conducting the reaction at room temperature for long time (9 days) afforded the desired diaryl sulfide in 15% yield only (entry 6). Use of K_2CO_3 as the base was found to be superior to KO*t*-Bu, KF or trialkyl amine (entries 14-16). Thus, the optimized reaction conditions utilized 5 mol % of Cu(I), 5 mol % of catechol violet (CV), and K_2CO_3 (1 equiv) in DMF as a solvent at 70–90 °C under nitrogen.

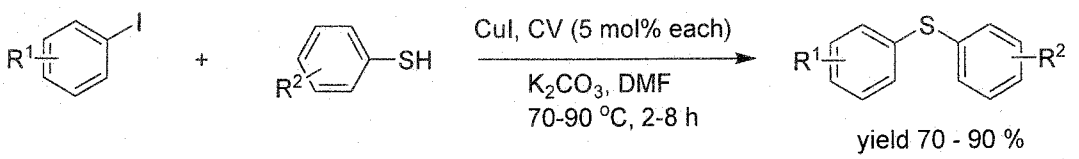
Table 1

Entry[a]	Solvent	Base	Temperature(°C)	Time (h)	Yield[b] (%)
1[c]	DMF	K_2CO_3	90	24	00
2[d]	DMF	K_2CO_3	90	21	78
3	DMF	K_2CO_3	90	2	93
4	DMF	K_2CO_3	70	4	80
5	DMF	K_2CO_3	55	17	20
6	DMF	K_2CO_3	rt	9 days	15
7	Dioxane	K_2CO_3	70	8.5	72
8	THF	K_2CO_3	90	6	80
9	CH_3CN	K_2CO_3	90	6	75
10	Toluene	K_2CO_3	70	10	00
11	Cyclohexane	K_2CO_3	90	8	08
12	Water	K_2CO_3	70	10	00
13	Methanol	K_2CO_3	70	10	10
14	DMF	$KOBu^t$	70	9	61
15	DMF	KF	70	9	49
16	DMF	Et_3N	70	9	55

[a] The reactions are carried in with 5 mol% CuI and 5 mol% CV. [b] Yields are based on HPLC analysis. [c]Reactions were carried out in absence of CuI and CV. [d] Reactions carried out using 5 mol% CuI.

It is evident from Table 1 that the combination of CuI, CV, K_2CO_3 and DMF as solvent are apt for C-S coupling reaction. The optimized reaction conditions were then employed to the coupling of various functionalized aryliodides and aryl thiols (Scheme 9).

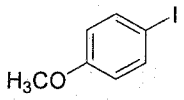
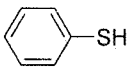
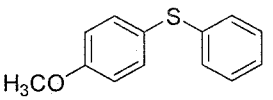
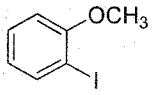
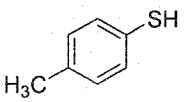
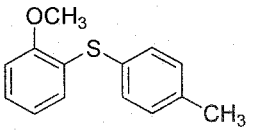
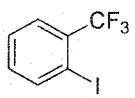
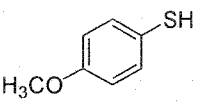
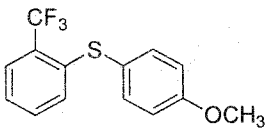
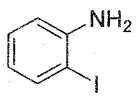
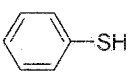
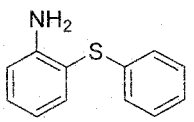
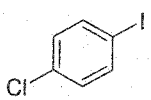
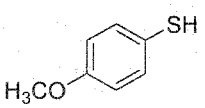
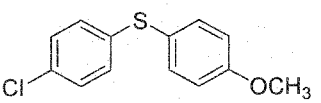
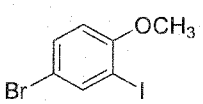
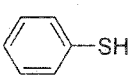
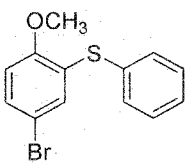
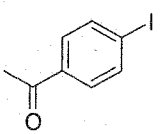
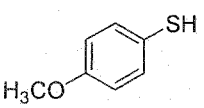
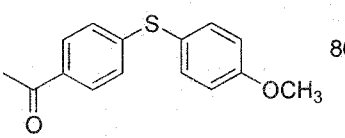
Scheme 9



yield 70 - 90 %

The results clearly demonstrated that the presence of electron donating or withdrawing group attached with aryl iodide did not influence the reactions. Furthermore, sterically hindered aryl iodides (entries 2, 3, 4 & 6) underwent C–S coupling smoothly to give corresponding diaryl sulfide in good to excellent yield. On the other hand, selectivity has also been observed in this case due to the fact that though bromo & iodo present in the same moiety (entry 6) only iodo participated in C-S coupling reaction under this condition whereas bromo remains intact after the reaction.

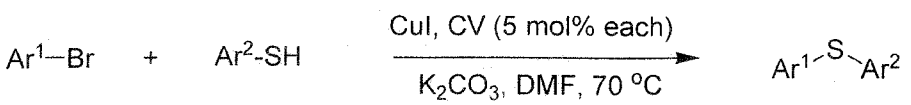
Table 2

Entry	Aryl Iodide	Thiol	Temp/Time	Product	Yield(%)
1			90 °/ 2 h		90
2			70 °/ 8 h		75
3			85 °/ 6 h		89
4			90 °/ 4 h		90
5			80 °/ 6 h		87
6			90 °/ 8 h		70
7			70 °/ 5 h		86

Aryl iodide: thiol: CuI-CV (1 mmol: 1.1mmol: 5 mol %) and K_2CO_3 (1mmol), DMF (2ml).

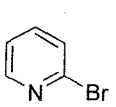
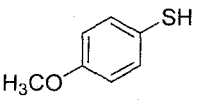
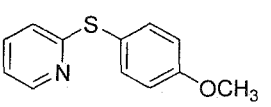
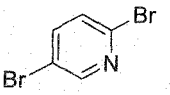
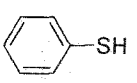
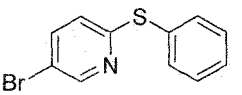
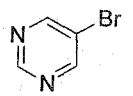
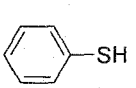
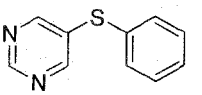
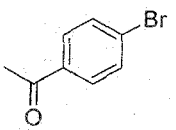
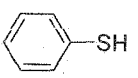
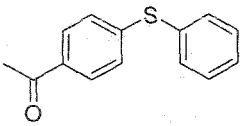
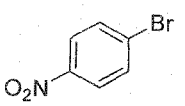
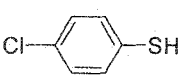
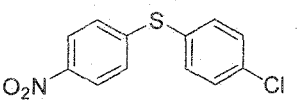
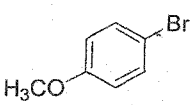
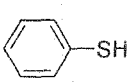
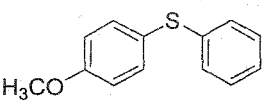
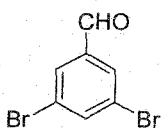
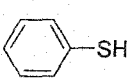
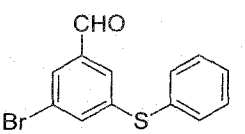
The next part of this study involved the application of our protocol to the CuI-CV-catalyzed S-arylation of thiols with aryl bromides. It was noted that in case of bromoiodoarene, S-arylation selectively occurred with iodide keeping the bromide unchanged. Electron-deficient pyridine ring bearing bromo substituent's (Table 3, entries 1–3) or bromoarenes bearing electron-withdrawing groups such as nitro, acyl, or aldehyde function (Table 3, entries 4,5,7) underwent C–S coupling smoothly yielding unsymmetrical diaryl sulfides in excellent yield using CuI-CV (10 mol % each) and K_2CO_3 as the base (Scheme 10).

Scheme 10



A reaction between *p*-bromoanisole & thiophenol under this condition leaves the *p*-bromoanisole intact even after 21 h (Table 3, entry 6).

Table 3

Entry	Bromoarene	Thiol	Temp/Time	Product	Yield(%)
1			70 °/ 6 h		83
2			70 °/ 2 h		90
3			70 °/ 7 h		78
4			70 °/ 18 h		83
5			70 °/ 20 h		85
6			90 °/ 21 h		00
7			70 °/ 8 h		80

Aryl bromide: thiol: CuI-CV (1 mmol: 1.1mmol: 10 mol %) and K_2CO_3 (1mmol), DMF (2ml).

Itoh *et al.* reported palladium catalyzed C–S coupling reactions of activated aryl chlorides.[27] Here we applied our optimized reaction conditions with slight modification (Scheme 11). In these cases we need to take 10 mol% of CuI instead of 5 mol%. Only activated aryl chlorides undergo C–S coupling in our method to give the corresponding aryl sulfide in high yield (83-90%) whereas the unactivated did not give the corresponding sulfide even after prolonging the reaction time(Table 4, entry 4) . C–S couplingreactions of activated aryl chloride have been considered to follow the nucleophilic substitution mechanism and thus do not ordinarily need a catalyst. However, the competition between nucleophilic substitution and metal-catalyzed oxidative addition followed by reductive elimination pathways still remains unclear. We did observe a clear advantage between the presence and absence of metal-ligand catalyst, the former combination being much more efficient even for activated aryl chloride.

Scheme 11

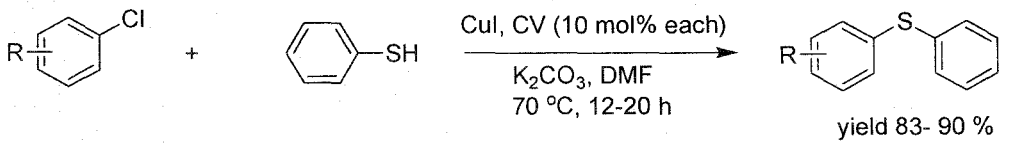
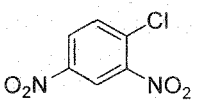
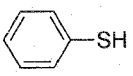
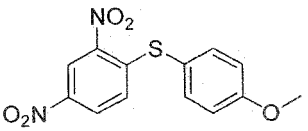
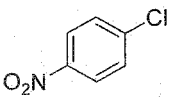
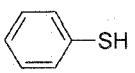
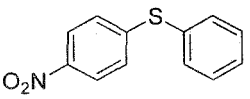
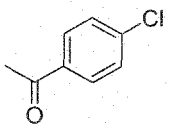
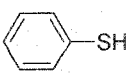
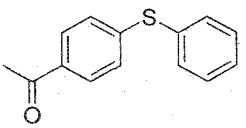
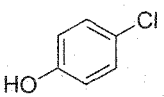
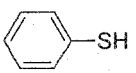
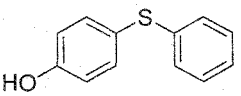


Table 4

Entry	Aryl Chloride	Thiol	Temp/Time	Product	Yield(%)
1			70 °C / 18 h		83
2			70 °C / 20 h		85
3			70 °C/ 12 h		90
4			70 °C / 20 h		00

Aryl chloride: thiol: CuI-CV (1 mmol: 1.1mmol: 10 mol %) and K_2CO_3 (1mmol), DMF (2ml).

Vinyl sulfides are very important intermediates in organic chemistry. They are used as enolate ion equivalents,[28] michael acceptors,[29] as intermediates in the synthesis of oxetanes,[30] cyclopentanones[31] and cyclopentanes.[32] Due to the importance of these compounds a number of methods have been reported. Most noteworthy among them involves the addition of thiol to an alkyne.[33] More recently, Venkataraman *et al.*[34] reported a synthesis of vinyl sulfides by the thiolation of vinyl iodides using [Cu (phen) $(PPh_3)_2$] NO_3 as the catalyst. So, we applied our reaction conditions for the coupling of thiols with vinyl iodides and indeed obtained very good yields of the corresponding vinyl sulfides (Scheme 12).

Scheme 12

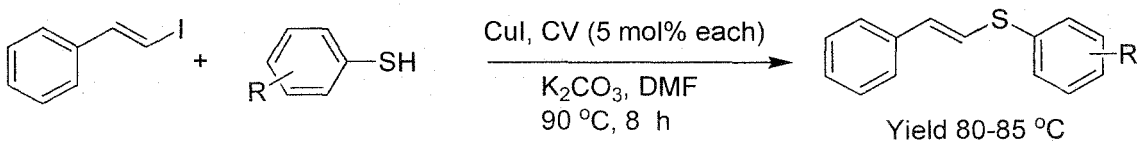
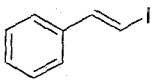
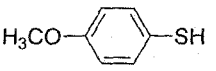
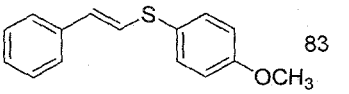
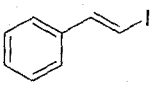
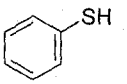
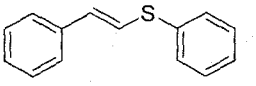
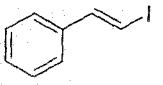
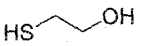
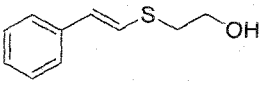


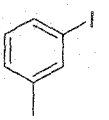
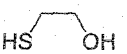
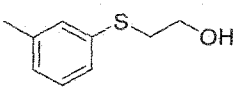
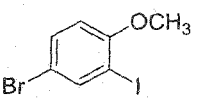
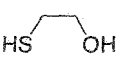
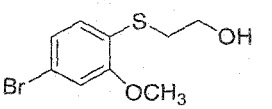
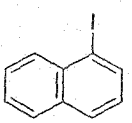
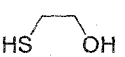
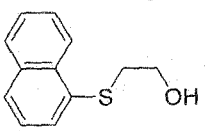
Table 5

Entry	Iodide	Thiol	Temp/Time	Product	Yield(%)
1			90 °C / 9 h		83
2			90 °C / 9 h		83
3			90 °C/ 9 h		93

Styryl iodide: thiol: CuI-CV (1 mmol: 1.1mmol: 5 mol %) and K_2CO_3 (1mmol), DMF(2ml).

Finally, we applied the protocol to aliphatic thiol, 2-mercaptoethanol couples with various aryl iodides under the conditions giving the aryl sulfides in excellent yields (Table 6).

Table 6

Entry	Aryl Iodides	Thiol	Temp/Time	Product	Yield(%)
1			90 ° / 4 h		83
2			90 ° / 4 h		87
3			90 ° / 4 h		78

Aryl iodide: thiol: CuI-CV (1 mmol: 1.1mmol: 5 mol %) and K_2CO_3 (1mmol), DMF (2ml)

II.4. Conclusion

In conclusion we have tried to explore all the avenues of Cu(I) catalyzed mild and efficient method for cross coupling reaction between carbon and sulfur using a wide variety of aromatic halides such as aryl iodides, bromo-pyridines, activated aryl chlorides and vinyliodide to afford the corresponding thioether in good to excellent yields with aromatic and aliphatic thiols. Presence of economical catechol violet greatly accelerates the course of the reaction. A wide variety of functional group tolerance has also been observed in this recation methodology.

II.5. Representative Experimental Procedure

A mixture of 4-iodoanisole (234 mg, 1 mmol), CuI (9.5 mg, 5 mol %), catechol violet (19 mg, 5 mol %), K_2CO_3 (138 mg, 1 mmol) and thiophenol (121 mg, 1.1 mmol) was taken in a screw capped vial. DMF (2 mL) was added to it and it was placed on a preheated oil-bath at 90 °C for 2 h. The mixture was then cooled to room temperature followed by dilution with water (6 mL).

It was then extracted with ether (3x10 mL) and the combined organic layer was washed with brine and dried over anhydrous sodium sulphate. Removal of the solvent left an oily residue which was passed through a short column of silica gel (60-120 mesh). Elution with light petroleum afforded the desired product as a colourless liquid[35] (194 mg, yield 90 %). IR (neat): ν_{max} 2959, 2835, 1529, 1478, 1172 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) δ=7.41 (2H, d, *J* = 8.2Hz); 7.23 (2H, m); 7.15 (3H, m); 6.90 (2H, d, *J* = 8.2Hz), 3.82 (3H, s). ^{13}CNMR ($CDCl_3$, 100MHz) δ=159.8, 138.6, 135.3, 128.9, 128.2, 125.7, 124.3, 115.0, 55.3.

II.6. Spectral Data:

Table 2: Entry 2: (2-Methoxyphenyl) (*p*-tolyl) sulfane

Reaction Temp: 70 °C, Time: 8 h, Yield: 75% (obtained as liquid).

IR (neat): ν_{max} 2922, 2836, 1576, 1474, 1274 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300MHz) δ=7.32 (d, 2H, *J* = 8.1 Hz), 7.15 (d, 2H, *J* = 8.1 Hz), 6.94 (dd, 1H, *J* = 7.8 & 1.8 Hz), 6.93 (dd, 1H, *J* = 7.5 & 1.5 Hz), 6.87 (dd, 1H, *J* = 9.9 & 7.8 Hz), 6.84 (dd, 1H, *J* = 9.6 & 7.5 Hz), 3.89 (s, 3H), 2.35 (s, 3H). ^{13}CNMR ($CDCl_3$, 75 MHz) δ=156.5, 137.8, 133.0, 130.1, 129.8, 127.4, 125.7, 121.2, 110.6, 55.9, 21.2.

Table 2: Entry 3: (2-(Trifluromethyl) phenyl) (4-methoxyphenyl) sulfane

Reaction Temp: 85 °C, Time: 6 h, Yield: 89%, mp. 55 °C (recrystallised from ether).

IR (nujol): ν_{max} 2986, 2854, 1462 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.54 (d, 1H, *J* = 7.8 Hz), 7.37 (d, 2H, *J* = 8.4 Hz), 7.15 (dd, 2H, *J* = 8.4 & 7.8 Hz), 6.87 (t, 3H, *J* = 9.0 Hz), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=160.5, 139.1, 136.8, 131.8, 129.5, 126.5, 126.4, 125.0, 122.2, 115.3, 55.4.

Table 2: Entry 4: 2-(Phenylthio) benzenamine[36]

Reaction Temp: 90 °C, Time: 4 h, Yield: 90% (obtained as liquid).

IR (neat): ν_{max} 3061, 3048, 1542, 1480 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ=7.45 (d, 1H, *J* = 7.6Hz); 7.22 (dd, 3H, *J* = 14.8 & 7.5Hz); 7.08 (m, 3H); 6.76 (m, 2H); 4.28 (br s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ=148.8, 137.4, 136.8, 131.1, 128.9, 126.4, 125.4, 118.7, 115.3, 114.3.

Table 2: Entry 5: (4-Chlorophenyl)(4-methoxyphenyl)sulfane[37]

Reaction Temp: 80 °C, Time: 6 h, Yield: 87% (obtained as liquid).

IR (neat): ν_{max} 2934, 2836, 1299 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ=7.40 (d, 2H, *J* = 8.6Hz); 7.18 (d, 2H, *J* = 8.5Hz); 7.07 (d, 2H, *J* = 8.5Hz); 6.89 (d, 2H, *J* = 8.6Hz); 3.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ=160.1, 137.3, 135.4, 131.6, 129.3, 128.9, 123.8, 115.1, 55.6.

Table 2: Entry 6: (5-Bromo-2-methoxyphenyl)(phenyl)sulfane

Reaction Temp: 90 °C, Time: 8 h, Yield: 70% (obtained as liquid).

IR (neat): ν_{max} 2934, 2837, 1460, 1299 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ=7.40-7.29 (m, 5H), 7.27 (dd, 1H, J = 9 & 2.4 Hz), 7.03 (d, 1H, J = 2.4 Hz), 6.76 (d, 1H, J = 9 Hz), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=159.5, 132.8, 132.1, 130.2, 129.5, 128.1, 116.0, 112.1, 56.1.

Table 2: Entry 7: 1-(4-(4-Methoxyphenylthio)(phenyl)ethanone

Reaction Temp: 70 °C, Time: 5 h, Yield: 86%; mp. 48 °C (recrystallised from ether).

IR (nujol): ν_{max} 2923, 1682, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=7.77 (d, 2H, J = 8.4 Hz), 7.47 (d, 2H, J = 8.7 Hz); 7.08 (d, 2H, J = 8.4 Hz); 6.95 (d, 2H, J = 8.7Hz), 3.85 (s, 3H); 2.52 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ=196.9, 160.6, 146.7, 136.7, 133.8, 128.7, 125.8, 121.4115.3, 55.3, 26.3.

Table 3: Entry 1: 2-(4-Methoxyphenylthio) pyridine

Reaction Temp: 70 °C, Time: 6 h, Yield: 83%; mp. 50 °C (recrystallised from ether).

IR (nujol): ν_{max} 2924, 2855, 1461 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=8.38 (d, 1H, J = 3.9 Hz); 7.51 (d, 2H, J = 8.7 Hz); 7.39 (m, 1H), 6.93 (m, 3H); 6.76 (d, 1H, J = 8.2 Hz); 3.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=162.8, 160.7, 149.4, 137.3, 136.6, 121.1, 120.4, 119.5, 115.3, 55.4.

Table 3: Entry 2: 5-Bromo-2-(phenylthio) pyridine

Reaction Temp: 70 °C, Time: 2 h, Yield: 90% (obtained as liquid).

IR (neat): ν_{max} 3058, 1556, 1450, 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=8.46 (s, 1H); 7.55 (m, 3H); 7.42 (m, 3H); 6.79 (d, 1H, J = 7.6Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=160.2, 150.3, 139.1, 134.9, 130.4, 129.7, 129.3, 122.5, 116.5.

Table 3: Entry 3: 5-(Phenylthio) pyrimidine[38]

Reaction Temp: 70 °C, Time: 7 h, Yield: 78% (obtained as liquid).

IR (neat): ν_{max} 3048, 1546, 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=9.02 (s, 1H); 8.58 (s, 2H); 7.43 (m, 2H); 7.38 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=157.0, 156.2, 132.7, 131.6, 129.9, 128.8.

Table 3: Entry 4: 1-(4-Phenylthio) phenyl ethanone

Reaction Temp: 70 °C, Time: 18 h, Yield: 83%

Same as Table 3, Entry 3.

Table 3: Entry 5: (4-Chlorophenyl)(4-nitrophenyl)sulfane

Reaction Temp: 70 °C, Time: 20 h, Yield: 85%, mp. 92 °C (recrystallised from ether).

IR (nujol): ν_{max} 3412, 2924, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.09 (2H, d, J = 9 Hz), 7.49 (d, 2H, J = 9 Hz), 7.21-7.04 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ= 146.8, 141.8, 135.9, 133.8, 132.6, 130.3, 126.9, 124.2.

Table 3: Entry 6: (4-Methoxyphenyl) (phenyl) sulfane

Reaction Temp: 90 °C, Time: 12 h, Yield: 0%

Table 3: Entry 7: 3-Bromo-5-(phenylthio) benzaldehyde

Reaction Temp: 70 °C, Time: 8 h, Yield: 80% (obtained as liquid).

IR (neat): ν_{max} 3062, 2829, 2720, 1704, 1557, 1194 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ=7.78 (s, 2H), 7.58 (dd, 4H, *J* = 13.8 & 1.8 Hz), 7.49-7.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=189.1, 140.7, 137.1, 135.3, 132.4, 130.9, 128.8, 128.7, 127.9, 127.2, 122.7.

Table 4: Entry 1: (4-Methoxyphenyl)(2,4-dinitrophenyl)sulfane

Reaction Temp: 70 °C, Time: 18 h, Yield: 83%; mp. 128 °C (recrystallised from ether).

IR (nujol): ν_{max} 2924, 2857, 1461 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=9.08 (d, 1H, *J* = 2.3 Hz); 8.11 (1H, dd, *J* = 9.1 & 2.4Hz); 7.49 (2H, d, *J* = 8.7 Hz); 7.05 (2H, d, *J* = 8.7Hz); 6.98 (1H, d, *J* = 9.0Hz), 3.89 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ=161.9, 149.5, 144.1, 143.6, 137.5, 128.6, 126.7, 121.4, 119.2, 116.2, 55.5.

Table 4: Entry 2: (4-Nitrophenyl)(phenyl)sulfane

Reaction Temp: 70 °C, Time: 20 h, Yield: 85% mp. 54 °C (lit.[39] 55 °C) (recrystallised from ether).

IR (nujol): ν_{max} 3097, 3063, 1336, 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=8.06 (d, 2H, J = 8.8Hz), 7.54 (m, 2H), 7.45 (m, 3H), 7.17 (d, 2H, J = 8.8Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 148.5, 145.3, 134.8, 130.4, 130.0, 129.7, 126.6, 124.0.

Table 4: Entry 3: 1-(4-Phenylthio) phenyl) ethanone[15a]

Reaction Temp: 70 °C, Time: 12 h, Yield: 90%, mp. 56 °C (recrystallised from ether).

IR (nujol): ν_{max} 2923, 2855, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=7.81 (d, 2H, *J* = 8.4Hz); 7.49 (m, 2H); 7.39 (m, 3H); 7.20 (d, 2H, *J* = 8.4 Hz); 2.54 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ=196.9, 144.8, 134.4, 133.7, 132.1, 129.6, 128.8, 128.7, 127.4, 26.3.

Table 4: Entry 4: 4-(Phenylthio) phenol

Reaction Temp: 70 °C, Time: 20 h, Yield: 0%

Table 5: Entry 1: (4-Methoxyphenyl)(styryl)sulfane

Reaction Temp: 90 °C, Time: 9 h, Yield: 83%, mp. 54 °C (recrystallised from ether).

IR (nujol): ν_{max} 2924, 2876, 1597, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ=7.40 (d, 2H, *J* = 8.7 Hz), 7.29-7.24 (m, 5H), 6.90 (d, 2H, *J* = 8.7 Hz), 6.82 (d, 1H, *J* = 15.6 Hz), 6.51 (d, 1H, *J* = 15.6 Hz), 3.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 159.6, 136.7, 133.5, 128.9, 128.6, 127.2, 125.8, 125.7, 124.5, 114.9, 55.4. ^{13}C NMR DEPT 135 ($CDCl_3$, 75MHz) δ = 133.5, 128.9, 128.6, 128.3, 127.2, 125.8, 125.7, 114.9, 114.8, 55.4.

Table 5: Entry 2: Phenyl (styryl) sulfane[40]

Reaction Temp: 90 °C, Time: 9 h, Yield: 83% (obtained as liquid).

IR (neat): ν_{max} 2924, 2872, 1462, 1377 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 6.09-5.99 (m, 10H), 5.57 (d, 1H, *J* = 15.6 Hz), 5.49 (d, 1H, *J* = 15.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=

136.3, 133.8, 132.9, 132.8, 130.9, 129.3, 128.7, 127.8, 126.1, 122.5. ^{13}C NMR DEPT 135 ($CDCl_3$, 75MHz) δ=132.8, 130.9, 129.3, 128.7, 127.8, 126.1, 122.5.

Table 5: Entry 3: 2-(styrylthio) ethanol

Reaction Temp: 90 °C, Time: 9 h, Yield: 93% (obtained as liquid).

IR (neat): ν_{max} 3400, 2924, 2876, 1597, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ=7.41-7.18 (m, 5H), 6.67 (d, 1H, *J* = 15.6 Hz), 6.57 (d, 1H, *J* = 15.6 Hz), 3.83 (t, 2H, *J* = 6Hz), 2.98 (t, 2H, *J* = 6Hz), 2.12 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=136.6, 128.9, 128.7, 127.2, 125.6, 123.7, 61.0, 35.9.

Table 6: Entry 1: 2-(*m*-tolylthio) ethanol

Reaction Temp: 90 °C, Time: 4 h, Yield: 83% (obtained as liquid).

IR (neat): ν_{max} 3424, 2924, 1475, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ=7.21-7.18 (m, 3H), 7.09 (m, 1H), 3.65 (br s, 1H), 3.11 (d, 2H, *J* = 6 Hz), 2.33 (s, 3H), 1.62 (d, 2H, *J* = 6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=138.9, 130.9, 128.9, 127.6, 127.3, 60.3, 37.4, 21.3. HRMS: Calcd for $C_9H_{12}OSK$: $[M+K]^+$, 207.0246; found: 207.0246.

Table 6: Entry 2: 2-(4-bromo-2-methoxyphenylthio) ethanol

Reaction Temp: 90 °C, Time: 4 h, Yield: 87% (obtained as liquid).

IR (neat): ν_{max} 3390, 2935, 2838, 1400, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=7.45 (d, 1H, *J* = 2.4 Hz), 7.33 (dd, 1H, *J* = 8.7 & 2.4 Hz), 6.74 (d, 1H, *J* = 8.7 Hz), 3.88 (s, 3H), 3.71 (t, 2H, *J* = 5.7 Hz), 3.06 (t, 2H, *J* = 5.7 Hz), 2.16 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=157.4, 133.8, 130.9, 125.1, 113.1, 112.2, 60.2, 56.1, 36.4. ^{13}C NMR DEPT 135 ($CDCl_3$, 75 MHz) δ = 133.8, 130.9, 112.2, 60.2, 56.1, 36.4. HRMS: Calcd for $C_9H_{11}BrO_2SNa$: $[M+Na]^+$, 284.9561, 286.9540; found: 284.9567, 286.9541.

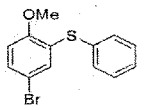
Table 6: Entry 3: 2-(naphthalen-5-ylthio) ethanol

Reaction Temp: 90 °C, Time: 4 h, Yield: 78% (obtained as liquid).

IR (neat): ν_{max} 3401, 3054, 2924, 1504, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ = 8.45 (d, 1H, J = 8.3Hz), 7.85 (d, 1H, J = 7.9Hz), 7.77 (d, 1H, J = 8.2Hz), 7.65 (d, 1H, J = 7.2Hz), 7.58 (m, 1H), 7.52 (m, 1H), 7.40 (t, 1H, J = 7.7Hz), 3.69 (br s, 2H), 3.14 (t, 2H, J = 5.9Hz), 2.15 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ= 134.1, 133.3, 131.8, 129.8, 128.7, 128.1, 126.7, 126.3, 125.5, 125.1, 60.4, 37.6.

NMR Spectra and HRMS of Some Selected Compounds

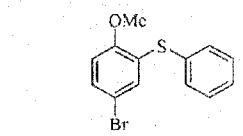
Table 1: Entry 6: ^{1}H NMR



(5-Bromo-2-methoxyphenyl)(phenyl)sulfane

Solvent : $CDCl_3$, Instrument Frequency: 300 MHz

Table 1: Entry 6: ^{13}C NMR



(5-bromo-2-methoxyphenyl)(phenyl)sulfane

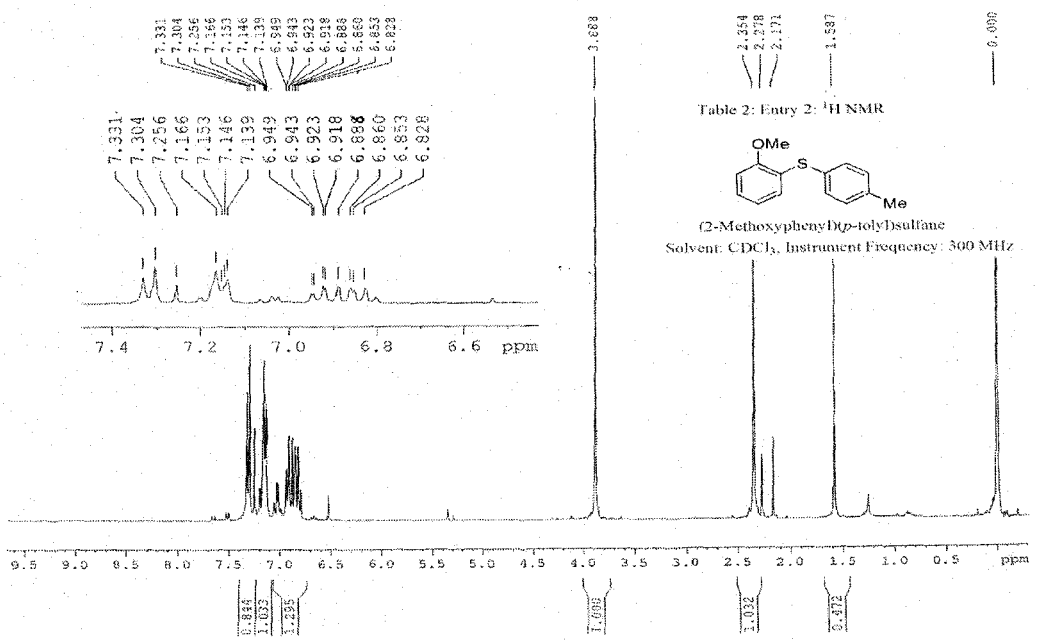
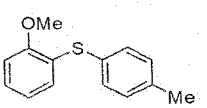


Table 2: Entry 2: ^{1}H NMR

(2-Methoxyphenyl)(*p*-tolyl)sulfane

Solvent: $CDCl_3$, Instrument Freqeuncy: 300 MHz

Table 2: Entry 2: ^{13}C NMR



(2-Methoxyphenyl)(*p*-tolyl)sulfane

Solvent: $CDCl_3$, Instrument Frequency: 75 MHz

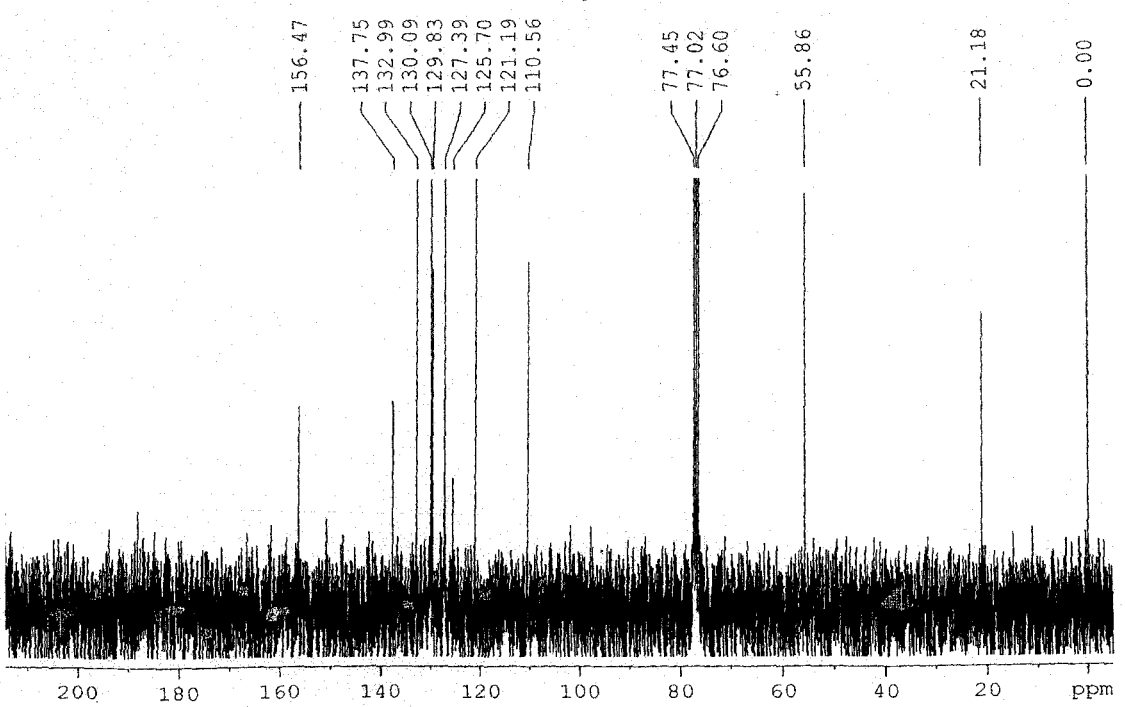
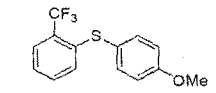


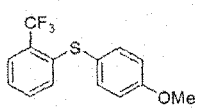
Table 2: Entry 3: ^{1}H NMR



(2-(Trifluoromethyl)phenyl)(4-methoxyphenyl)sulfane

Solvent: $CDCl_3$, Instrument Frequency: 300 MHz

Table 2: Entry 3: ^{13}C NMR



(2-(Trifluoromethyl)phenyl)(4-methoxyphenyl)sulfane

Solvent: $CDCl_3$, Instrument Frequency: 75 MHz

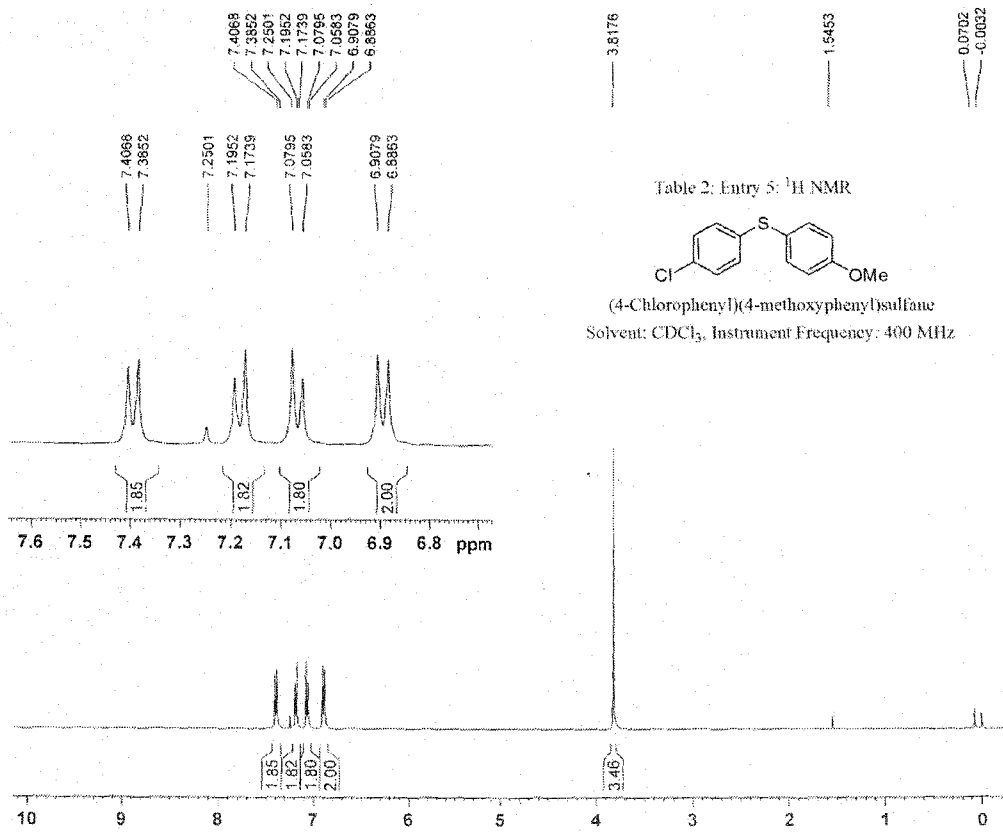


Table 2: Entry 5: ^{1}H NMR

(4-Chlorophenyl)(4-methoxyphenyl)sulfane

Solvent: $CDCl_3$, Instrument Frequency: 400 MHz

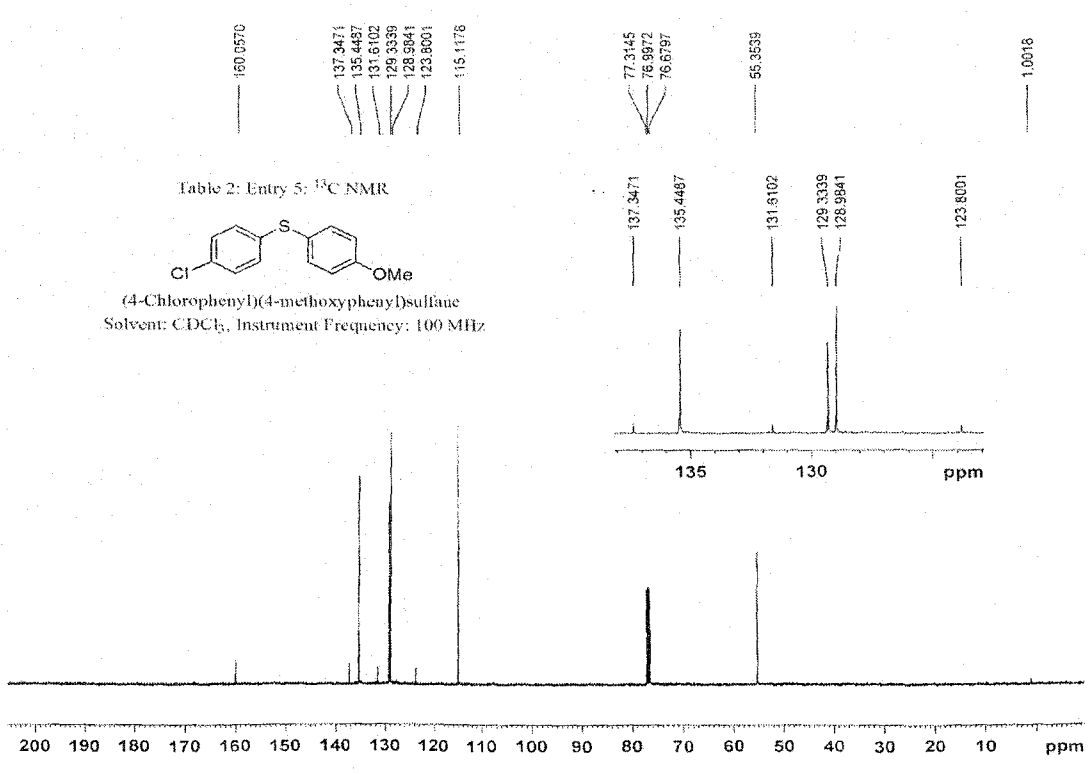


Table 2: Entry 5: ^{13}C NMR

(4-Chlorophenyl)(4-methoxyphenyl)sulfane

Solvent: $CDCl_3$, Instrument Frequency: 100 MHz

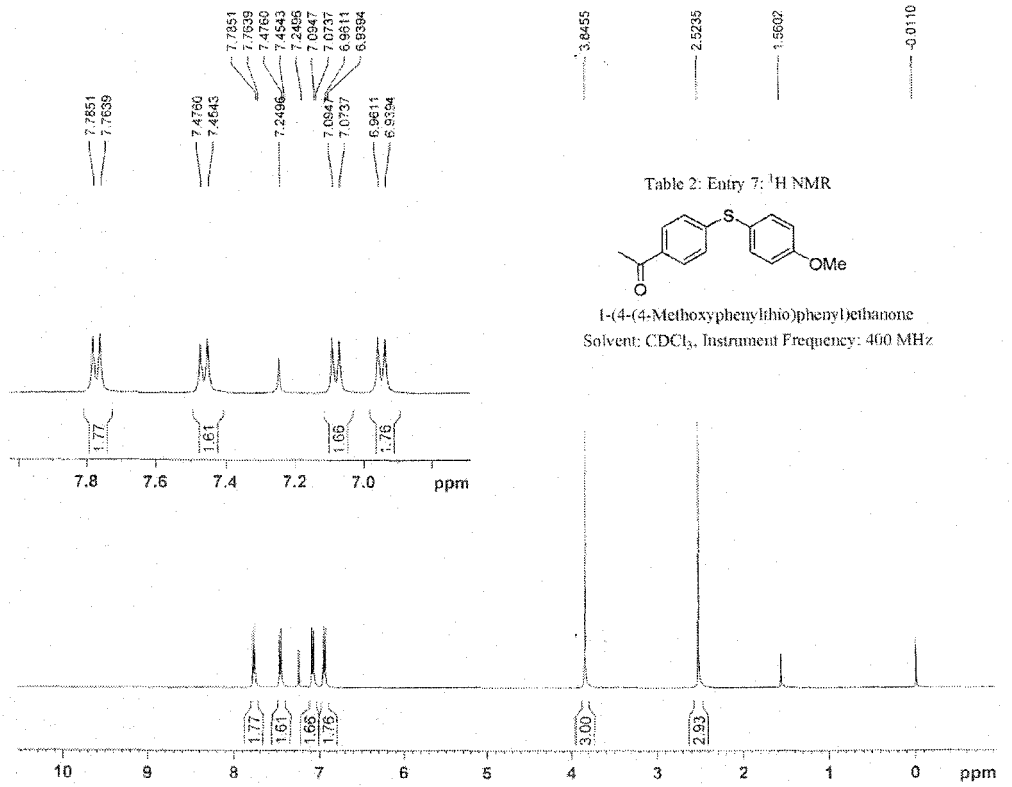


Table 2: Entry 7: ^{1}H NMR

1-(4-(4-Methoxyphenylthio)phenyl)ethanone
Solvent: $CDCl_3$, Instrument Frequency: 400 MHz

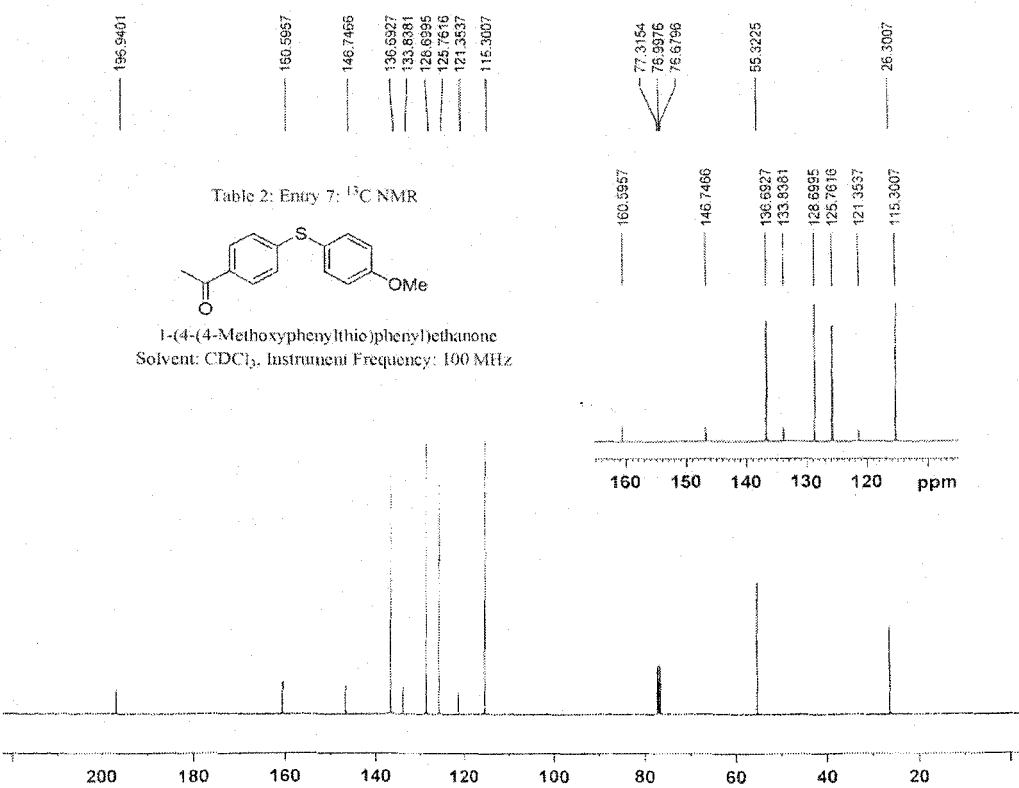


Table 2: Entry 7: ^{13}C NMR

1-(4-(4-Methoxyphenylthio)phenyl)ethanone
Solvent: $CDCl_3$, Instrument Frequency: 100 MHz

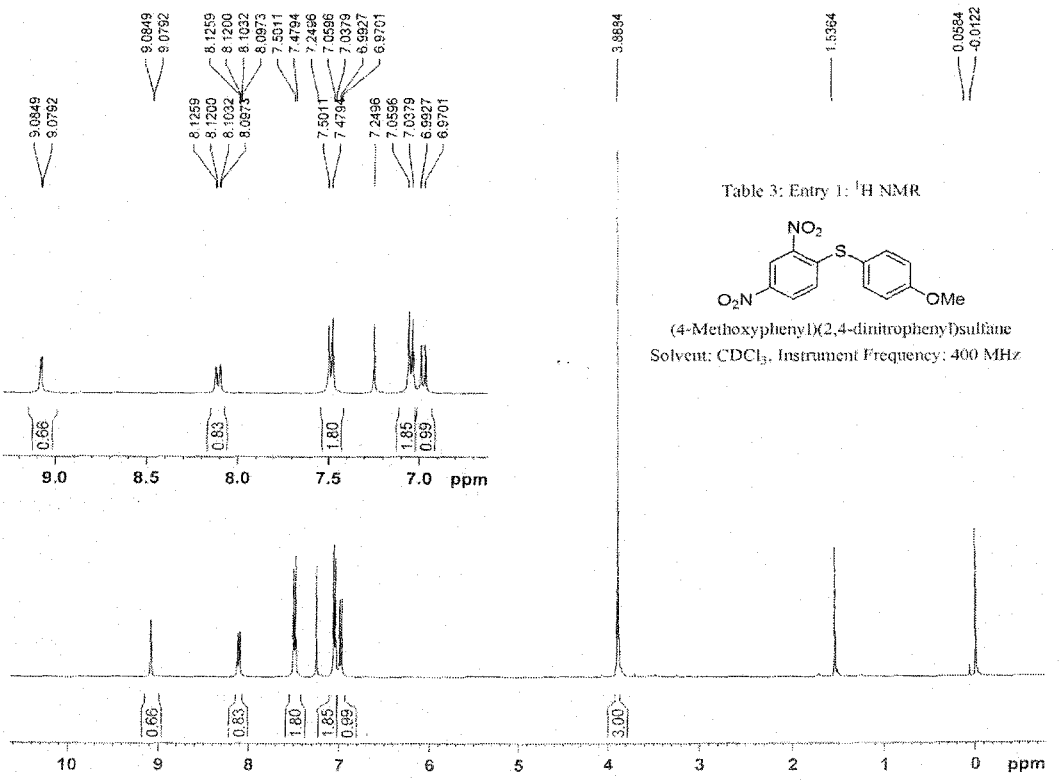


Table 3: Entry 1: ^{1}H NMR

(4-Methoxyphenyl)(2,4-dinitrophenyl)sulfane
Solvent: $CDCl_3$, Instrument Frequency: 400 MHz

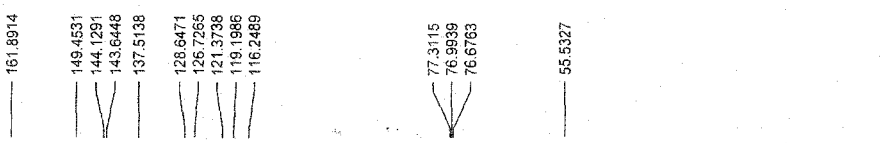
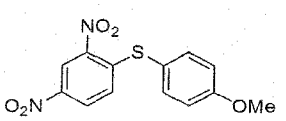
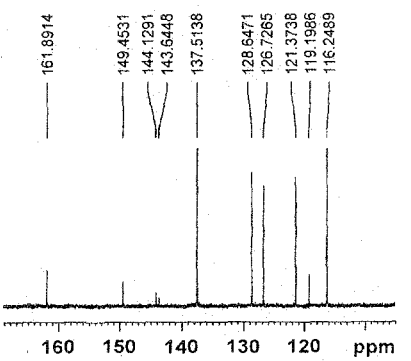


Table 3: Entry 1: ^{13}C NMR



(4-Methoxyphenyl)(2,4-dinitrophenyl)sulfane
Solvent: $CDCl_3$, Instrument Frequency: 100 MHz



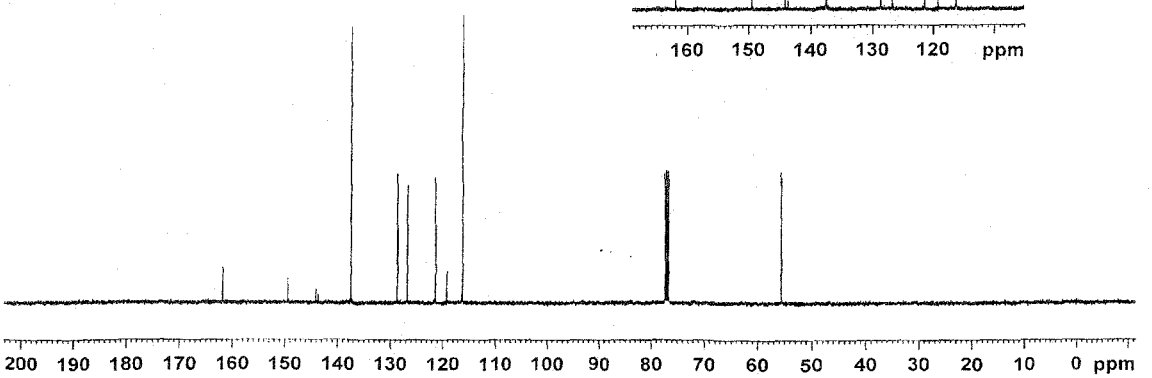
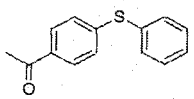


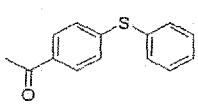
Table 3: Entry 2: ^{1}H NMR



1-(4-(Phenylthio)phenyl)ethanone

Solvent: $CDCl_3$, Instrument Frequency: 400 MHz

Table 3: Entry 2: ^{13}C NMR



1-(4-(Phenylthio)phenyl)ethanone

Solvent: $CDCl_3$, Instrument Frequency: 75 MHz

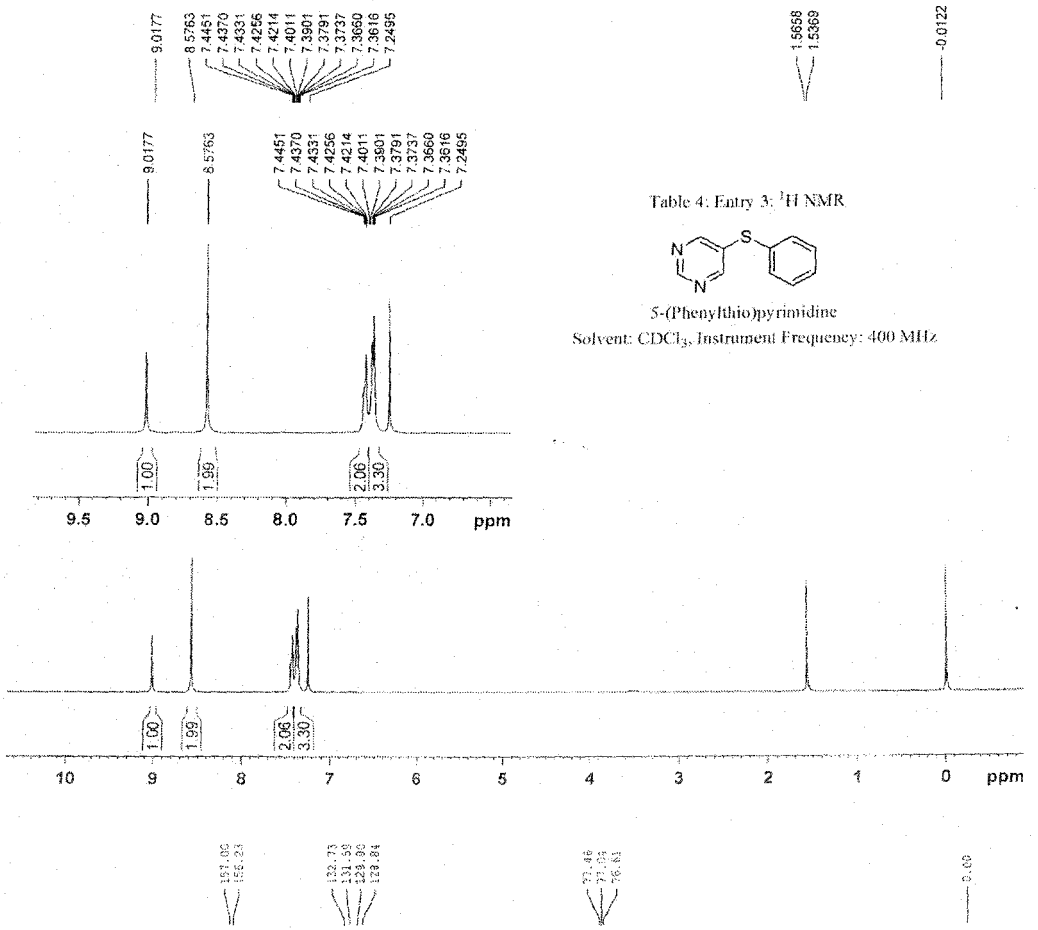
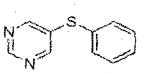


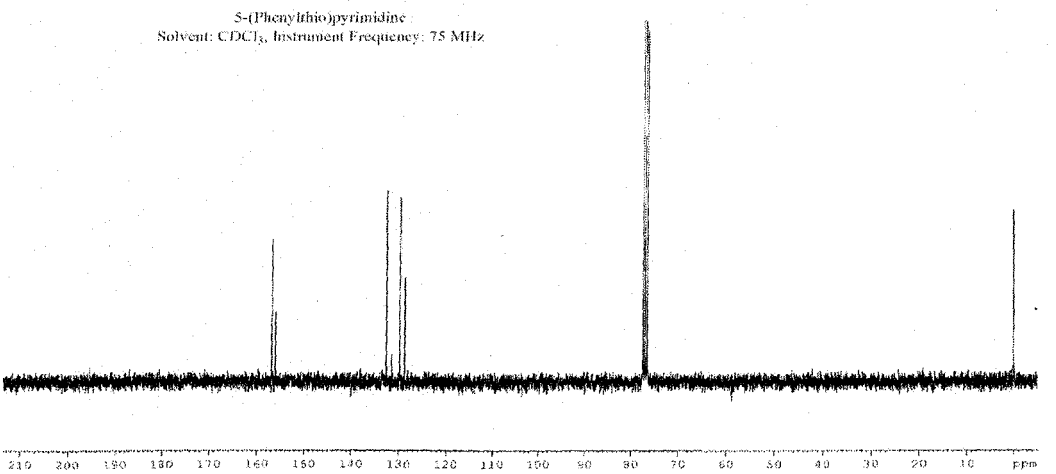
Table 4: Entry 3: ^{1}H NMR

5-(Phenylthio)pyrimidine
Solvent: $CDCl_3$, Instrument Frequency: 400 MHz

Table 4: Entry 3: ^{13}C NMR



5-(Phenylthio)pyrimidine
Solvent: $CDCl_3$, Instrument Frequency: 75 MHz



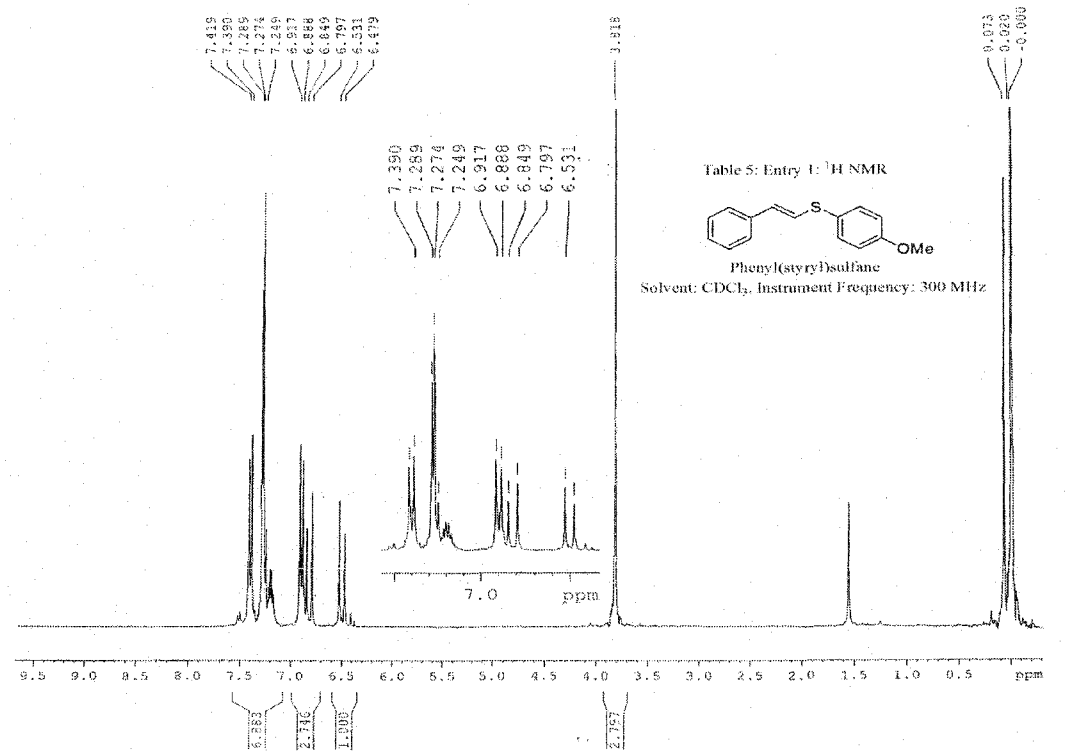
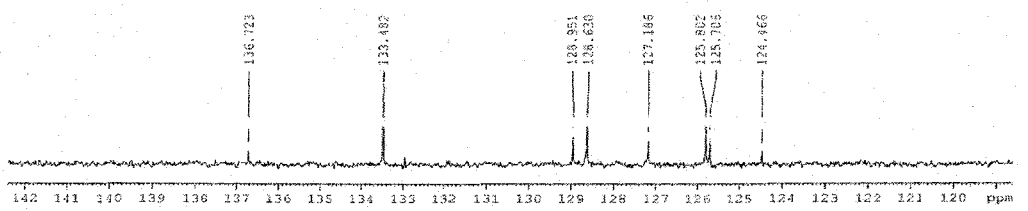


Table 5: Entry 1: ^{1}H NMR
Phenyl(styryl)sulfane
Solvent: $CDCl_3$, Instrument Frequency: 300 MHz
OMe
7.0
ppm



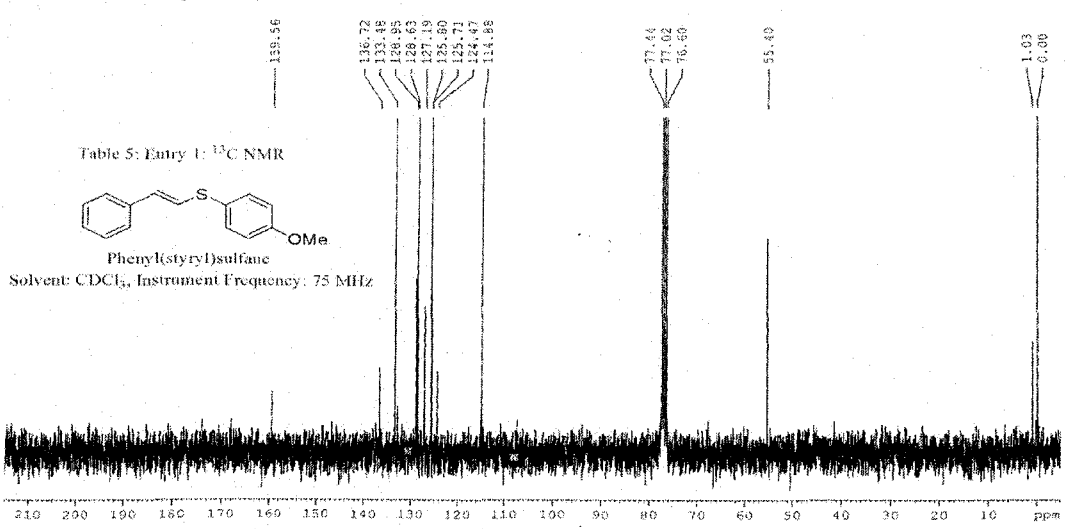
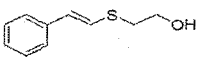


Table 5: Entry 1: ^{13}C NMR
Phenyl(styryl)sulfane
Solvent: $CDCl_3$, Instrument Frequency: 75 MHz
OMe
ppm

Table 5: Entry 3: ^1H NMR



2-(Styrylthio)ethanol

Solvent: $CDCl_3$, Instrument Frequency: 300 MHz

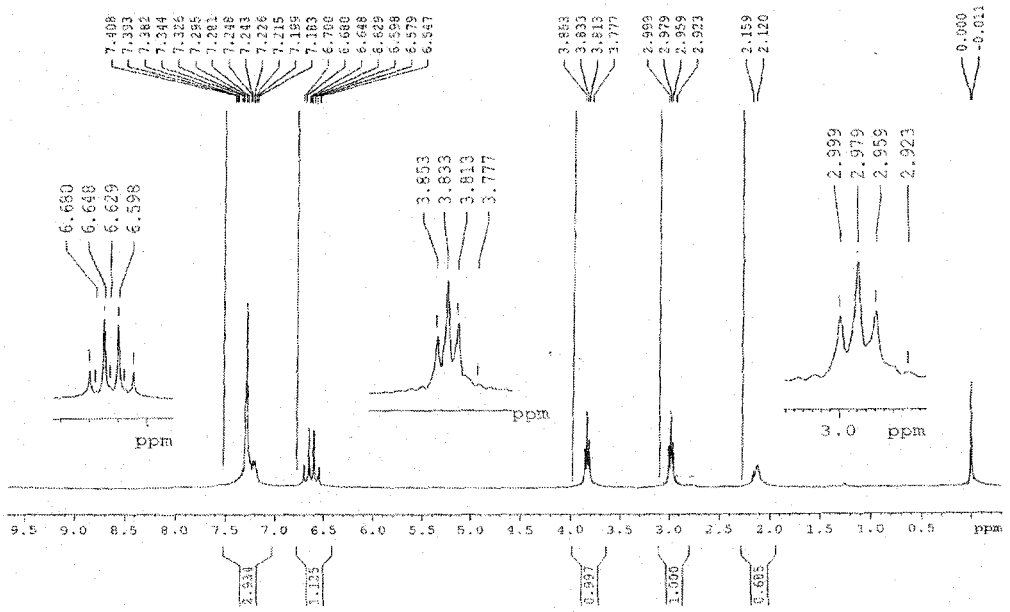
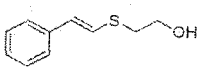
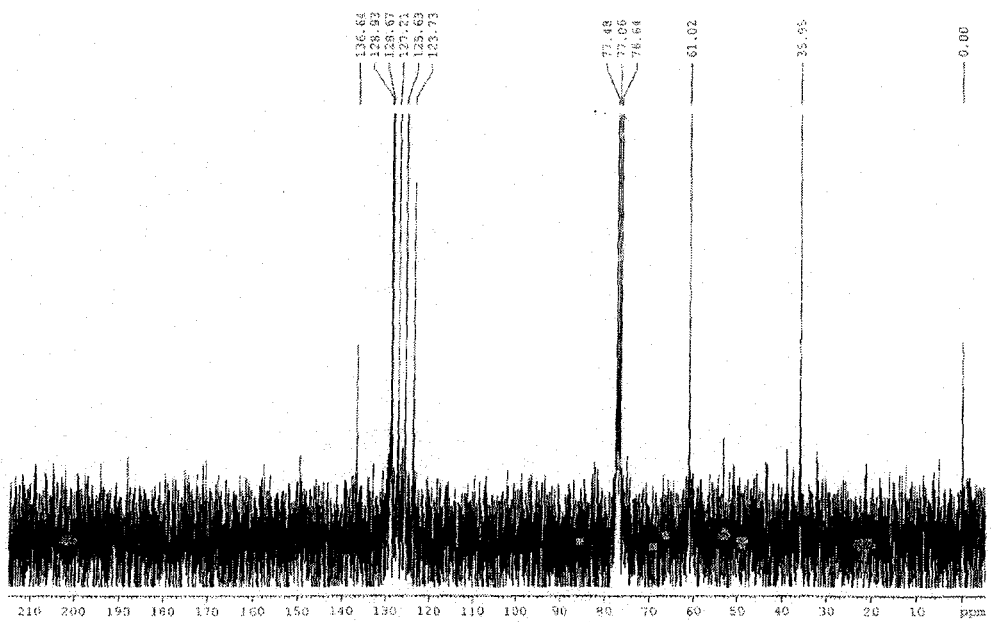


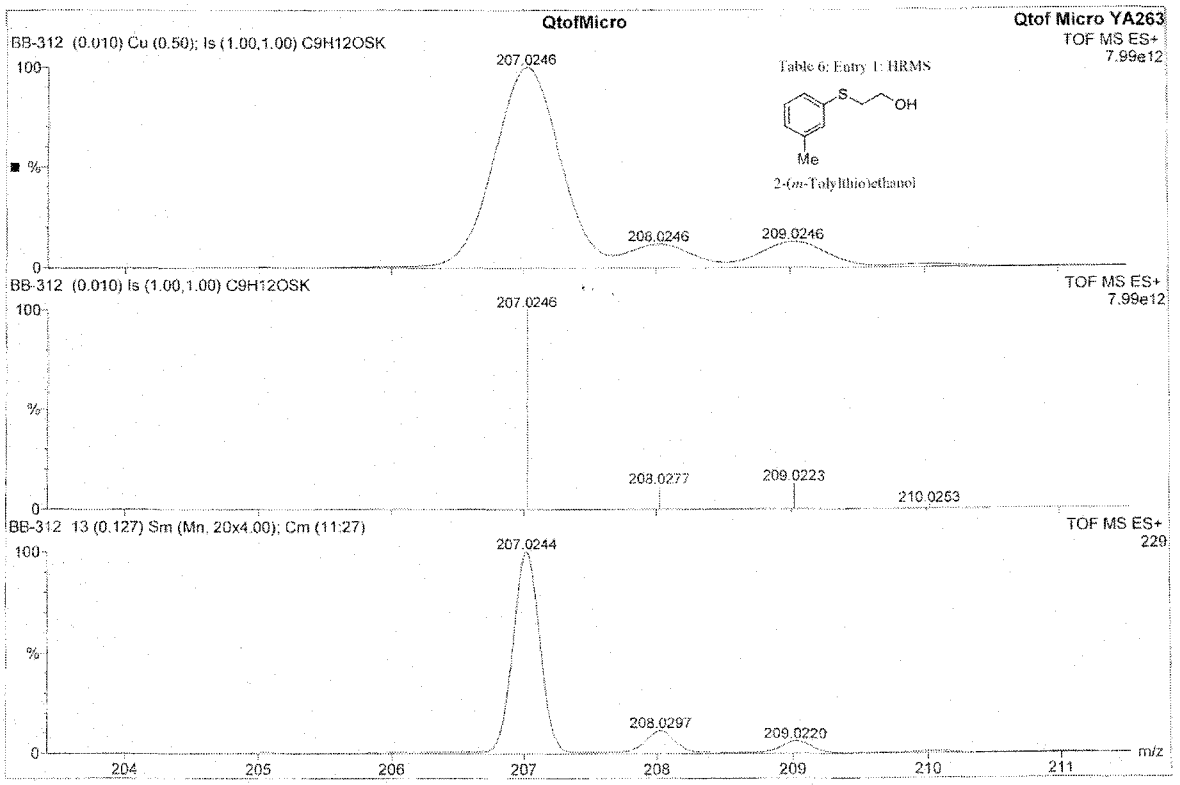
Table 5: Entry 3: ^{13}C NMR

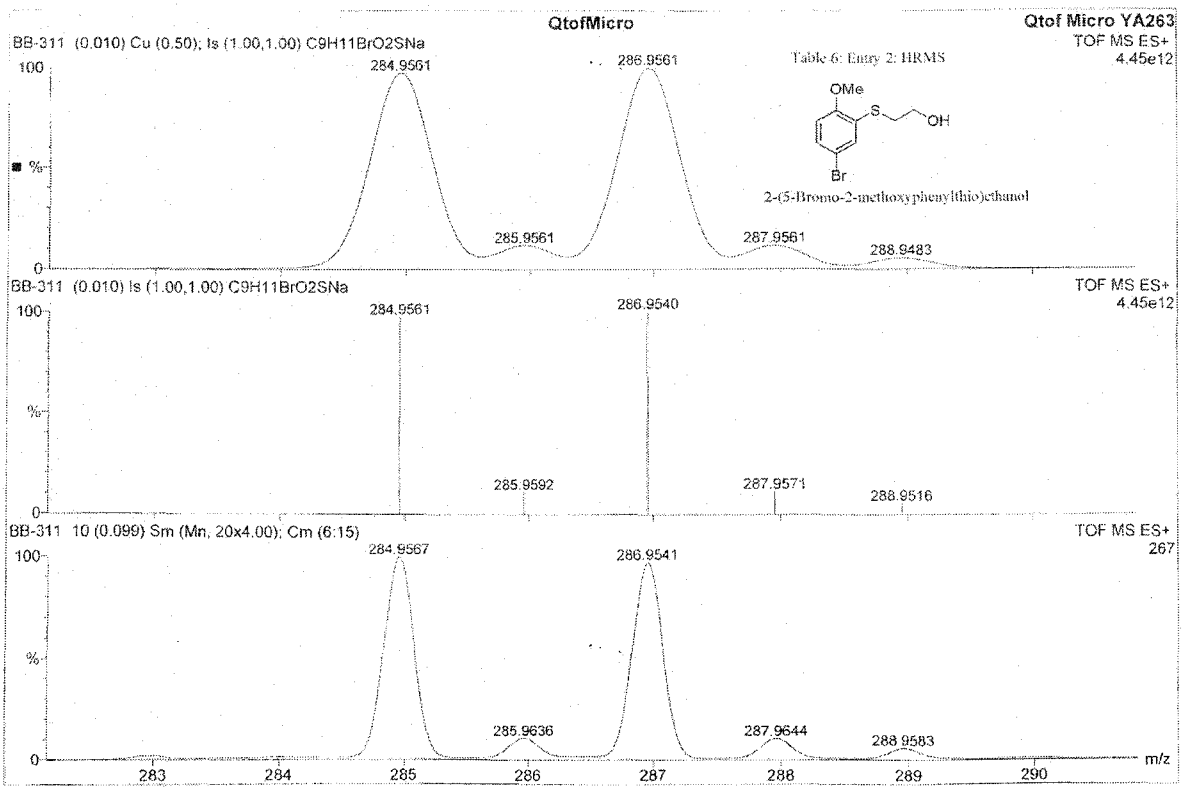


2-(styrylthio)ethanol

Solvent: $CDCl_3$, Instrument Frequency: 75 MHz




QtofMicro
Qtof Micro YA263
BB-312 (0.010) Cu (0.50); Is (1.00,1.00) C9H12OSK
TOF MS ES+
7.99e12
207.0246
208.0246
209.0246
Table 6: Entry 1: HRMS
OH
Me
2-(m-Tolylthio)ethanol
BB-312 (0.010) Is (1.00,1.00) C9H12OSK
207.0246
208.0277
209.0223
210.0253
BB-312 13 (0.127) Sm (Mn, 20x4.00); Cm (11:27)
TOF MS ES+
220
207.0244
208.0297
209.0220
m/z


QtofMicro
Qtof Micro YA263
BB-311 (0.010) Cu (0.50); Is (1.00,1.00) C9H11BrO2SNa
TOF MS ES+
4.45e12
284.9561
286.9561
285.9561
287.9561
288.9483
Table 6: Entry 2: HRMS
OMe
OH
Br
2-(5-Bromo-2-methoxyphenylthio)ethanol
BB-311 (0.010) Is (1.00,1.00) C9H11BrO2SNa
284.9561
286.9540
285.9592
287.9571
288.9516
BB-311 10 (0.099) Sm (Mn, 20x4.00); Cm (6:15)
TOF MS ES+
267
284.9567
286.9541
285.9636
287.9644
288.9583
m/z

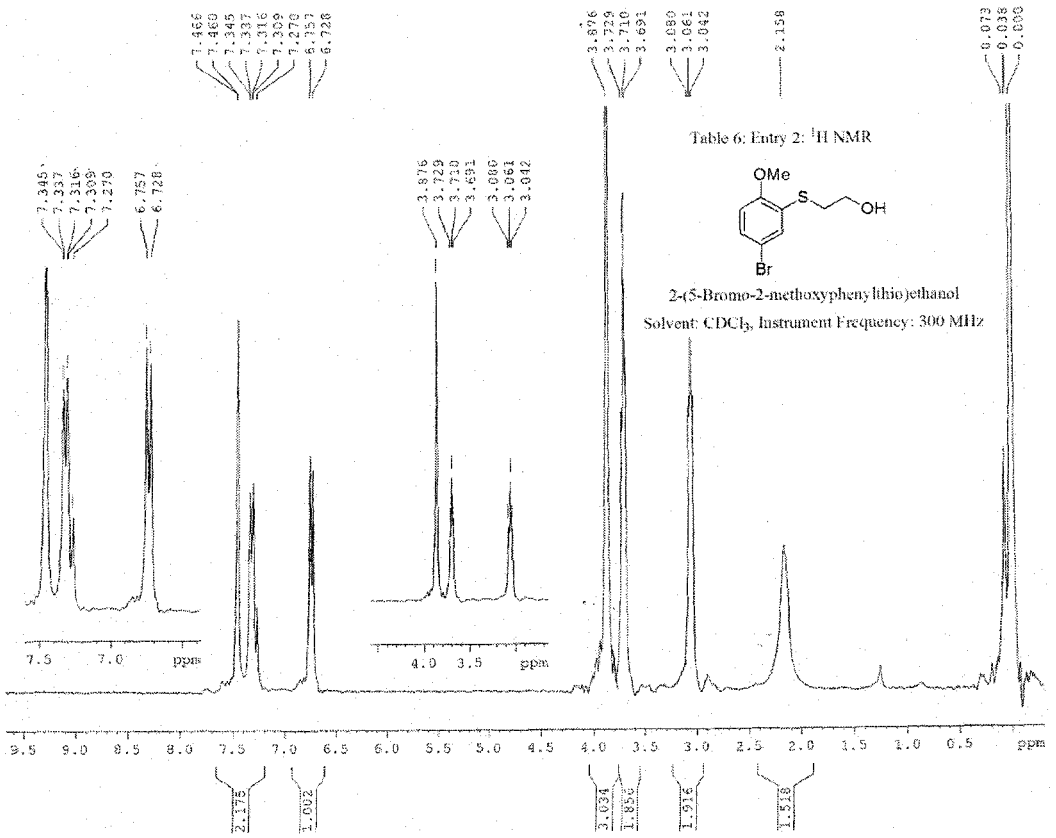


Table 6: Entry 2: ^{1}H NMR

2-(5-Bromo-2-methoxyphenylthio)ethanol

Solvent: $CDCl_3$, Instrument Frequency: 300 MHz

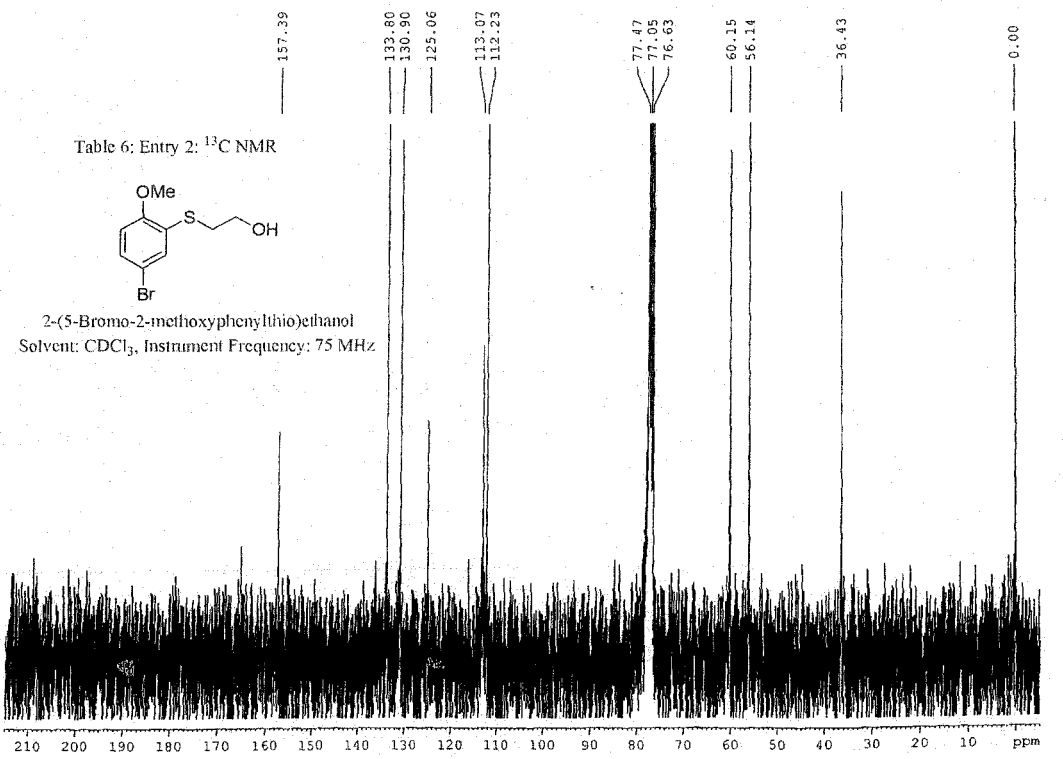
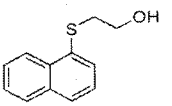


Table 6: Entry 2: ^{13}C NMR

2-(5-Bromo-2-methoxyphenylthio)ethanol

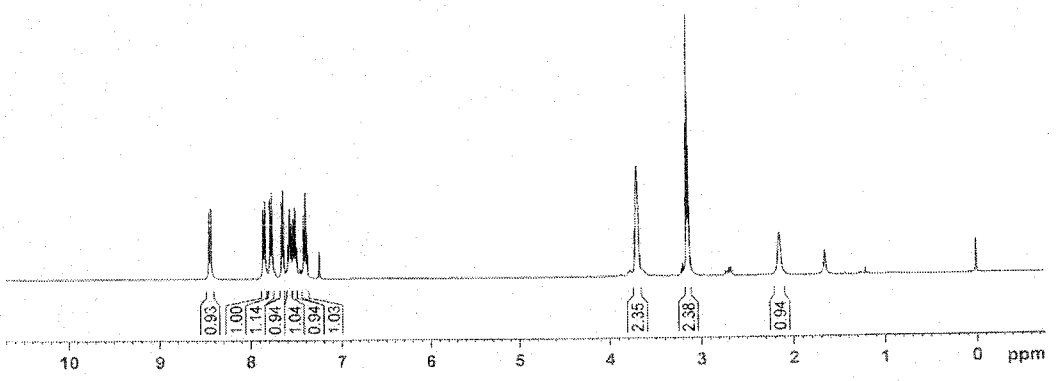
Solvent: $CDCl_3$, Instrument Frequency: 75 MHz

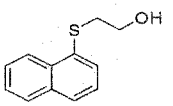
Table 6: Entry 3: ^{1}H NMR



2-(Naphthalen-5-ylthio)ethanol

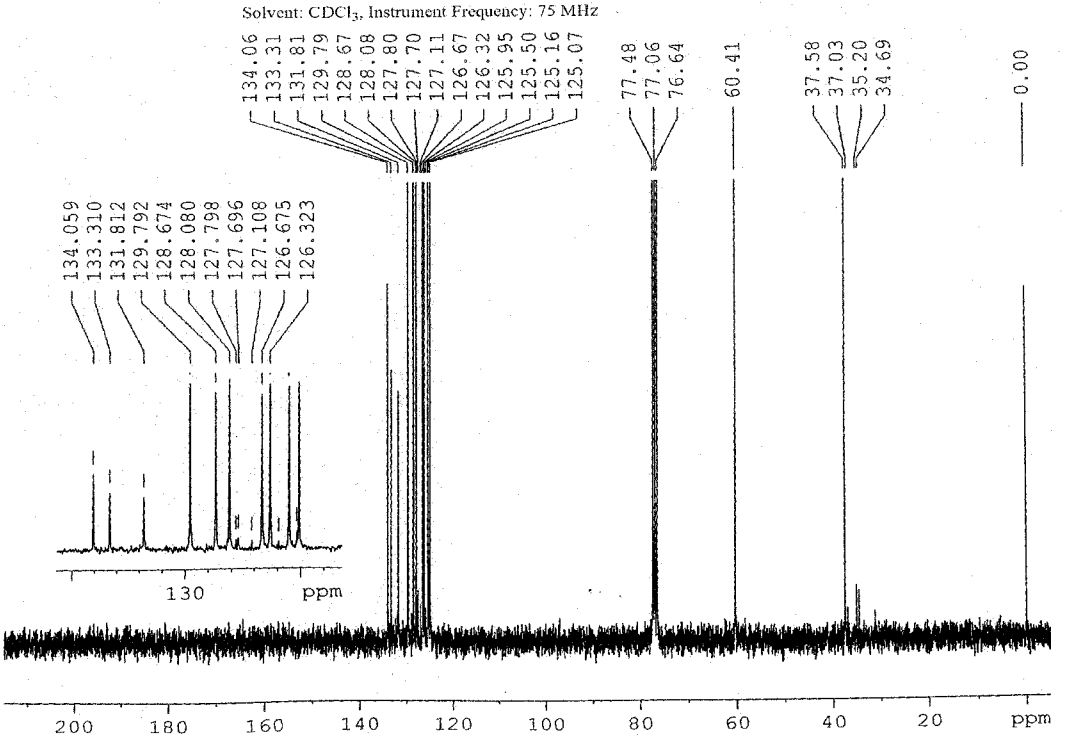
Solvent: $CDCl_3$, Instrument Frequency: 400 MHz





2-(Naphthalen-5-ylthio)ethanol

Solvent: $CDCl_3$, Instrument Frequency: 75 MHz



II.7. References:

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Polyionic Heterogeneous Phenylating Agent for Base-Free Suzuki–Miyaura Coupling Reaction

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Abstract: A new polyionic resin-bound tetraphenylborate has been prepared, which can serve as efficient phenylating agent in Pd-catalyzed Suzuki–Miyaura (SM) coupling with aryl halides in the absence of any base. The conditions are mild, operationally simple and the polyionic resin can be recharged and reused for several runs.

Key words: polyionic resins, tetraphenylborate, Suzuki–Miyaura coupling, base-free conditions, biphenyls

The palladium-catalyzed Suzuki–Miyaura (SM) coupling reaction of aryl halides with arylboronic acids and esters has been established as a robust synthetic protocol for the preparation of biaryl compounds.[1] The reaction has been applied to many areas, including natural product synthesis.[1c,2] Besides the coupling partners, the reaction typically requires Pd catalysts, preferably as complexes with suitable ligands and a base. In the past few years, great advances have been made in developing active and efficient catalysts by modifying traditional ligands and discovering new ones. Among the variations of the catalyst and the base, Leadbeater et al.[3] reported SM coupling reactions using very low levels of Pd (50 ppb),[3c] believed to be delivered within the sodium carbonate base, while Yan and co-workers have recently reported base-free SM reaction using hypervalent iodonium aryl salts instead of aryl halides.[4] Besides arylboronic acids and boronate esters, tetraphenylborates and related borates species being more stable and water resistant, have also been used as arylating agents in SM cross-coupling reactions.[5] In view of its versatility, the development of new variants of the organoboron species, the catalyst and the base in the SM coupling reaction and the optimization of the process have remained challenging areas of research.

The concept of a resin-capture-release technique generating the polymer-bound reactive species has been established as a potential method for several organic transformations.[6] Although polymer-bound boronic acids were reported as early as 1976,[7] Frenette and Friesen,[8] in 1994, investigated the utility of the SM coupling reaction on a solid support for combinatorial chemistry. A variety of techniques to immobilize different components of SM reactions on macroporous solids clearly revealed the lack of application of polyionic resins soaked with organoboron species.[9,10] Lobrégat et al. showed that arylboronic acid may be trapped by an ammonium hydroxide form Dowex® ion-exchange resin and the resulting species can be used for macroheterocyclization under SM conditions.[11] In connection with our interest in the development of ionic resin-bound reagents and/or catalysts,[12] we sought to develop an ion-exchange resin-supported borate species as a heterogeneous phenylating agent. In this article, we report the preparation of polyionic resin-bound tetraphenylborate from commercially available anion-exchange resins and its preliminary evaluation in SM coupling reactions.

Our initial studies began with Amberlite® (chloride form) ion-exchange resins, which were exchanged with tetraphenylborate anion (Ph_4B^-) by continuous rinsing with an aqueous solution of $NaBPh_4$ until the washings gave negative response to chloride anion (monitored with $AgNO_3$ solution followed by addition of aqueous ammonia). The resin beads were then washed successively with water (to make it free from sodium ions), acetone and finally dried under vacuum for several hours to afford the Amberlite resin (Ph_4B^- form). Loading of the borate anion was determined by differential weighing between the quantities of the resin (chloride form) initially taken and recovered after several washings with aqueous solution of $NaBPh_4$, water and drying.[13] This was used directly for the SM coupling with 3-iodotoluene in the presence of $Pd(OAc)_2$ (2 mol%) and Na_2CO_3 (1 equiv) and the corresponding unsymmetrical biphenyl was isolated in 90% yield (Scheme 1, conditions a). Similar coupling of 3-iodotoluene and $NaBPh_4$ in the presence of Na_2CO_3 afforded only 43% yield of the coupled product (Scheme 1, conditions b). However, on increasing the quantity of $NaBPh_4$ in 3-iodotoluene–$NaBPh_4$ (1:2.5), the resulting coupled product could be isolated in 88% yield (Scheme 1, conditions c). A further interesting observation was that the yield of the coupled product was not influenced by the absence of base (Scheme 1, conditions d and e). Such base-free conditions for SM reactions offer significant practical advantages and have not previously been reported with the organoborate ion immobilized onto polymers.

The common mechanism of SM coupling reactions (i.e., sequential oxidative addition, transmetalation, and reductive elimination) includes a base, which is believed to be involved in several steps of the catalytic cycle, most notably the transmetalation process.[1c,14] While the weak carb-

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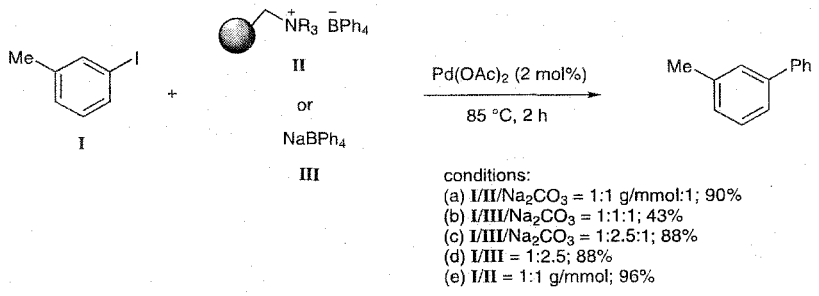


Scheme 1

anionic character of the organic moiety attached to boron in triorganoboranes requires base to assist in the transmetalation process, the corresponding 'ate' species is capable of accelerating the transmetalation.[1e,15–19] The transmetalation process releases triphenylborane, which is water-sensitive and may be hydrolyzed during the workup, producing phenyl boronic acid. Indeed, we were able to isolate and characterize phenylboronic acid from the reaction mixture. It may therefore be proposed that the resin-supported tetraphenylborate not only serves as an efficient phenylating agent but also acts as a suitable nucleophile requisite in the transmetalation process.

Efficient coupling between 3-iodotoluene and the immobilized tetraphenylborate under base-free conditions prompted us to develop a general method for the SM reaction.[20] A variety of aryl iodides or bromides bearing electron-donating or electron-withdrawing groups as well as heteroaryl halides underwent SM couplings in either DMF or water at 80–90 °C, resulting in the formation of the desired products in excellent yields (Table 1). In order to broaden the scope of the base-free reaction conditions, we also examined bis- or trisaryl halides (Table 1, entries 16–20). In all cases, the desired adducts were isolated in good to excellent yields.

Table 1 Suzuki–Miyaura Couplings Using Amberlite Resins (Tetraphenylborate Form)

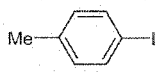
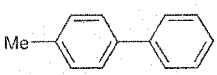
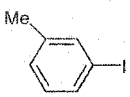
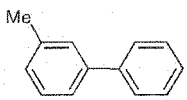
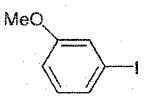
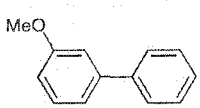
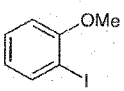
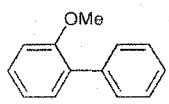
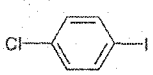
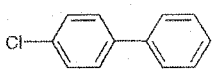
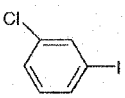
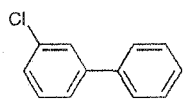
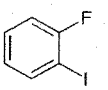
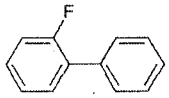
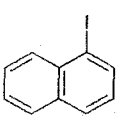
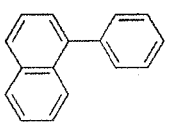
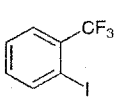
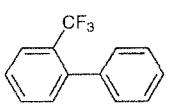
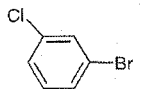
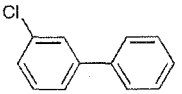
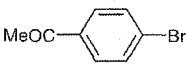
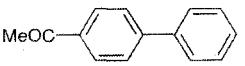
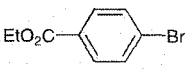
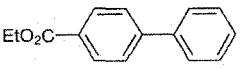
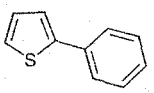
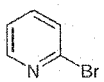
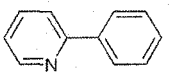
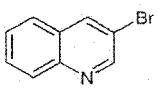
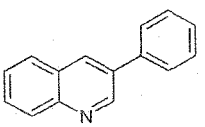
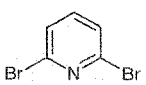
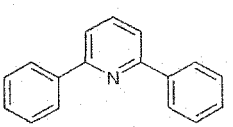
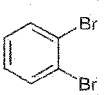
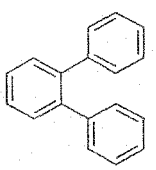
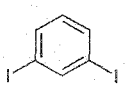
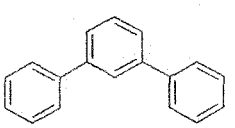
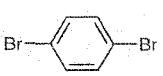
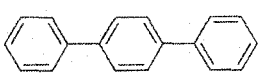
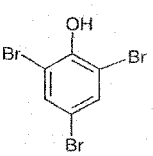
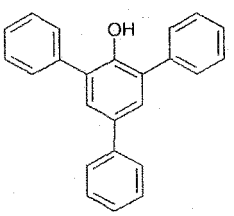
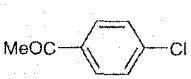
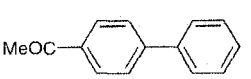
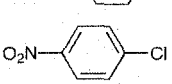
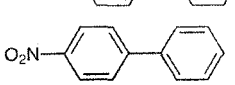
Entry	Aromatic halide[a]	Temp (°C)	Time (h)	Product[b]	Yield (%)[c]
1		80	2		91 (91)
2		85	2		96 (95)
3		85	3		89
4		90	4		76
5		80	2.5		95 (92)
6		80	2		95
7		90	3		88
8		85	4		91
9		80	6		71

Table 1 Suzuki–Miyaura Couplings Using Amberlite Resins (Tetraphenylborate Form) (continued)

Entry	Aromatic halide[a]	Temp (°C)	Time (h)	Product[b]	Yield (%)[c]
10		80	2		86 (88)
11		80	3		92
12		80	3		83
13		80	3		90
14[d]		85	6		80 (75)
15[d]		80	4		97
16[d]		90	3		84
17		90	4		77
18		80	3		78 (85)
19		85	3		87
20		90	8		58
21[e]		90	5		(88)
22[e]		85	5		(95)

[a] Reaction conditions: aryl halide (1 mmol), resin-TPB (1 g), and $Pd(OAc)_2$ (2 mol%) in DMF or H_2O.
[b] All compounds were characterized by known mp, IR, ^1H NMR and ^{13}C NMR spectral data.
[c] Yields in parentheses represent reactions carried out in H_2O.
[d] $Pd_2(dba)_3$ (1.5 mol%) was used instead of $Pd(OAc)_2$.
[e] TBAB (1 equiv) and Na_2CO_3 (1 equiv) were required.

Typical problems encountered during SM coupling reactions using the base, such as saponification of esters or aldol-type condensations of carbonyl compounds limit the functionality that can be present in the aryl moiety. To extend the scope of this reaction condition, couplings of aryl bromides bearing ketone (COMe), ester (CO_2Et) and OH groups were studied (Table 1, entries 11, 12, 20 and 21). The results from these reactions are listed in Table 1.

Activated aryl chlorides are known to undergo SM coupling reactions.[21] Using the immobilized borate we performed base-free couplings with activated aryl chlorides successfully (Table 1, entries 21 and 22) in presence of one equivalent of tetrabutylammonium salts (TBAB).[22]

Finally, we considered recycling the recovered resin in SM coupling reactions. The formation of the desired adduct was obtained in lower yield than in the first run, which might be due to poor availability of the tetraphenylborate counter anions. However, recharging the resin and recycling the reaction was successfully achieved for five runs.[23] Conducting reactions in aqueous medium can be advantageous, particularly for large-scale industrial applications, as a result of ease of purification as well as the environmental friendliness of water. The newly developed polyionic resins are equally effective in the aqueous-medium SM reaction thereby offering greater scope for its applications.

In summary, we have shown that polyionic resins may be used for immobilizing tetraphenylborate as well as for fulfilling the function of a base and the resulting species are potential phenylating agents in the SM cross-coupling. The reaction conditions offer an efficient and general method for base-free SM cross-coupling reactions leading to the formation of biaryls. Easy isolation of the desired coupled products in high yields along with base- and ligand-free conditions offer distinct advantages over the direct use of corresponding alkali metal salts or phenylboronic acid. Further exploration of the methodology is underway in this laboratory.

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(13) Amberlite® IRA-900 resin (chloride form; 2.50 g) was stirred with aq $NaBPh_4$ (1.73 g) until complete exchange as judged by Cl^- loss ($AgNO_3$). The exchanged resin was washed with H_2O, acetone and dried to give the tetraphenylborate-form resin (3.92 g). The mass difference between product and starting materials (ca. 310 mg) was comparable with the calculated difference (296 mg). The resulting borate-bound resin thus contained a 1.14 mmol g^{-1} loading of the borate ions and was used directly in the SM coupling reactions.

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(20) **Representative Procedure for Suzuki–Miyaura Reaction**: A mixture of 3-iodotoluene (218 mg, 1 mmol), Amberlite resin (Ph_4B^- form) (1 g, 1.14 mmol) and $Pd(OAc)_2$ (4.5 mg, 2 mol%) was taken in DMF (2 mL) and heated in an oil bath at 85 °C for 2 h. After cooling, the reaction mixture was diluted with H_2O (5 mL) and the resin was filtered off. The filtrate was extracted with Et_2O (3 × 15 mL) and the combined organic layers were dried over anhyd Na_2SO_4. Removal of the solvent left an oily residue, which was passed through a short column of silica gel (60–120 mesh) eluting with light petroleum to afford 3-phenyltoluene as a colorless liquid (161 mg, yield 96%). IR (neat): 3031, 2900, 1604 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.87 (m, 2 H), 7.56–7.71 (m, 6 H), 7.42 (d, *J* = 7.2 Hz, 1 H), 2.67 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.3, 141.2, 138.2, 128.7, 128.6, 127.94, 127.89, 127.2, 127.1, 124.2, 21.5.

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(23) After the first run, the resin beads were filtered off, washed with MeOH, then with H_2O and finally rinsed again with aq $NaBPh_4$ solution. The resulting borate-bound resin could be reused for the SM reaction. Employing the recovered and recharged resin (tetraphenylborate form) for SM coupling with 3-iodotoluene (1 mmol scale), provided the desired biaryl in 95% yield. The three subsequent runs gave the biaryl in 92%, 92% and 88% yields.

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Catechol violet as new, efficient, and versatile ligand for Cu(I)-catalyzed C–S coupling reactions

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ABSTRACT

Combination of CuI and Catechol violet (CuI-CV) was employed as catalyst for the first time in the C–S coupling reaction of a wide variety of aromatic halides, such as aryl iodides, bromo pyridines, activated aryl chlorides, and vinyl iodide with thiols to afford the corresponding thioethers in good to excellent yields. Broad range of functional group tolerance present in both the coupling partners has been observed in this reaction protocol.

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After the seminal discovery of copper-promoted Ullmann reaction[1] for the construction of carbon-hetero atom bonds, several protocols have been reported over the years to perform C–N, C–O, and C–S linkages. The carbon-sulfur bonds are prevalent in numerous pharmaceutically and biologically active compounds.[2] Traditional copper-mediated C–S couplings between thiols and aryl halides require use of copper salts in greater than stoichiometric amounts, polar solvents, and high temperatures of around 200 °C.[3] Current interests for C–S bond construction have been mostly directed toward transition metal-catalysts (mainly Fe, Cu, Ni, and Pd) complexed with suitable ligands.[4] Migita and co-workers first reported the Pd-catalyzed cross-coupling of aryl bromides with thiols using $[Pd(PPh_3)_4]$.[5] Recently, Itoh et al. screened a number of phosphine ligands for Pd-catalyzed C–S coupling of aryl bromides (or triflate) with aryl thiols using a combination of $Pd_2(dba)_3$ and xantphos.[6] Other Pd-catalyzed C–S couplings were found to be selective for alkane thiols.[7] Since copper is an inexpensive metal as compared to palladium and other late-transition metals, several studies have been directed toward copper-catalyzed C–S cross-coupling reactions. Over the last decade, Venkataraman,[8] Buchwald,[9] and Palomo[10] have investigated the combination of aryl iodides with thiols using copper catalyst. In the process of development, various Cu–ligand complexes based on Schwesinger's phosphazene P_2-Et base,[10] neo-cuproine,[8] 1,2-diol,[9] 1,2-diamines,[11] amino acids,[12] 1,1,1-tris(hydroxymethyl)ethane—a tripod,[13] as well as ligand-free CuO[4c] and Indium oxide[4g] nanoparticles have been studied with varying success. In most cases, the protocol either is substrate-specific or requires specially designed phosphine or phosphine-free ligands besides requirement of high temperature, strong base, long reaction time, etc. Therefore, the development of more efficient, inexpensive, and mild catalytic systems involving copper and more generalized mild reaction conditions for the C–S coupling reactions has been the major target of contemporary research.

Over the last few years, we have been working on the development of several Pd- and Cu-catalyzed C–C and C–N coupling reactions.[14] In conjunction with our interest, we wish to report herein a general and efficient C–S coupling reaction between aryl halides and thiols using catalytic amounts of CuI and catechol violet (CV), as shown in Scheme 1.

Preliminary optimization of the C–S coupling reactions between aryl halide and aryl thiol with the aid of catalytic CuI and catechol violet was tested with *p*-iodoanisole and thiophenol (Table 1). As expected, in the absence of copper no aryl sulfide was detected (entry 1). Using only CuI (5 mol %) and carrying out the reaction at 90 °C for 21 h in DMF yielded the desired diaryl sulfide in 78% (Table 1, entry 2). On the other hand, similar reaction in presence of CuI and catechol violet (5 mol % each) afforded the desired diaryl sulfide in 93% yield in only 2 h (entry 3). Since formation of disulfide as a by-product is dependent on the reaction medium (i.e., the solvent), screening of a number of solvents and base was done at various temperatures. It was revealed that use of polar aprotic solvents resulted in the formation of the desired diaryl sulfide in substantial amount, whereas a polar protic or a non-polar solvent gave the disulfide as the main product (Table 1, entries 3, 7–13).

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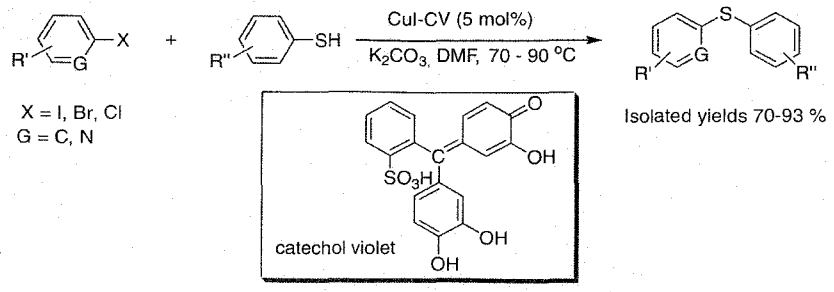


Scheme 1. The CuI-CV-catalyzed synthesis of diarylsulfides is represented.

Table 1
Optimization of conditions for the CuI-CV-catalyzed coupling of *p*-iodoanisole and thiophenol

Entry[a]	Solvent	Base	Temperature (°C)	Time (h)	Yield[b] (%)
1[c]	DMF	K_2CO_3	90	24	00
2[d]	DMF	K_2CO_3	90	21	78
3	DMF	K_2CO_3	90	2	93
4	DMF	K_2CO_3	70	4	80
5	DMF	K_2CO_3	50	17	20
6	DMF	K_2CO_3	rt	9 days	15
7	Dioxane	K_2CO_3	80	8	72
8	THF	K_2CO_3	65	8	76
9	CH3CN	K_2CO_3	80	6	70
10	Toluene	K_2CO_3	70	10	00
11	Cyclohexane	K_2CO_3	80	8	08
12	Water	K_2CO_3	70	10	00
13	Methanol	K_2CO_3	65	10	10
14	DMF	KO^{t}Bu	70	9	61
15	DMF	KF	70	9	49
16	DMF	Et_3N	70	9	55

[a] Reactions carried out with 5 mol % each of CuI and CV.
[b] Yield based on HPLC analysis.
[c] Reactions carried out in absence of CuI and CV.
[d] Reactions carried out using 5 mol % CuI only.

Performing the reaction at room temperature for a long time (9 days) afforded the desired diaryl sulfide in only 15% yield (entry 6). Use of K_2CO_3 as the base was found to be superior to KO*t*-Bu, KF, or trialkyl amine (entries 14–16). Thus, the optimized reaction conditions utilized 5 mol % of Cu(I), 5 mol % of catechol violet, and K_2CO_3 (1 equiv) in DMF as a solvent at 70–90 °C under nitrogen.

In the first part of this study, these reaction conditions[15] were applied to the coupling of various functionalized aryl iodides and aryl thiols (Table 2). No significant electronic effects were observed. Sterically hindered (*ortho*-substituted) aryl iodides underwent C–S coupling smoothly to furnish corresponding diaryl sulfide in good to excellent yield (Table 2, entries 2–4, 6). However, selectivity has been noted when the aryl iodides bearing chloro- or bromo- substituent afforded C–S coupling substituting only the iodo group (Table 2, entries 5 and 6). Furthermore, polythioethers, which are commercially important and widely used as thermosensitive recording materials,[16] were also prepared employing the same protocol and thus *bis*(phenylthio)benzene derivatives were obtained in fairly good yields (Table 2, entries 8 and 9).

The next part of this study involved the application of our protocol to the CuI-CV-catalyzed S-arylation of thiols with aryl bromides and aryl chlorides. It was noted that in case of bromoiodoarene, S-arylation selectively occurred with iodide keeping the bromide unchanged. While attempting with only aryl bromides, similar observations were obtained. The results are presented in Table 3 (entries 1 and 2). However, electron-deficient pyridine ring bearing bromo substituents (Table 3, entries 3–5) or bromoarenes bearing electron-withdrawing groups such as nitro, acyl, or aldehyde function (Table 3, entries 6–8) underwent C–S coupling smoothly yielding unsymmetrical diaryl sulfides in excellent yield using CuI-CV (10 mol % each) and K_2CO_3 as the base. Although Zhang et al.[4d] reported C–S coupling of aryl bromides bearing electron-donating groups in presence of NHC-based Ni catalyst, our conditions were effective only for activated aryl bromides.

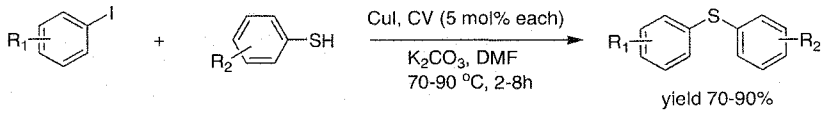
Itoh et al. reported palladium-catalyzed C–S coupling reactions of activated aryl chlorides.[6] Here, we employed our optimized reaction conditions with minor modifications (Table 4). Changing the catalytic amount of CuI-CV from 5 to 10 mol % resulted in the formation of desired diaryl sulfides from activated aryl chlorides in high yields (86–92%) (Table 4, entries 2–4), though unactivated aryl chloride did not give the corresponding sulfide even after prolonging the reaction time (20 h) (Table 4, entry 1). C–S coupling reactions of activated aryl chloride have been considered to follow the nucleophilic substitution mechanism and thus do not ordinarily need a catalyst. However, the competition between nucleophilic substitution and metal-catalyzed oxidative addition followed by reductive elimination pathways still remains unclear. We did observe a clear advantage between the presence and absence of metal-ligand catalyst, the former combination being much more efficient even for activated aryl chloride.

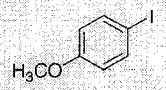
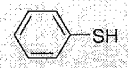
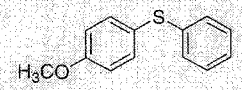
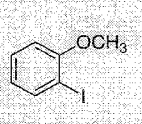
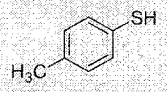
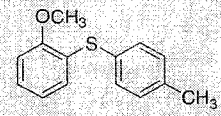
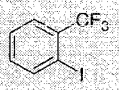
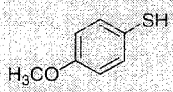
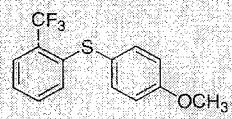
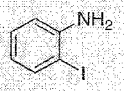
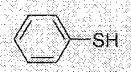
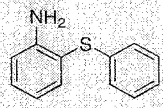
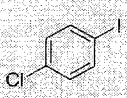
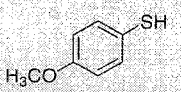
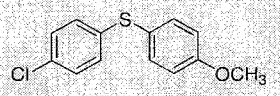
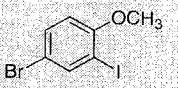
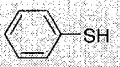
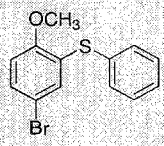
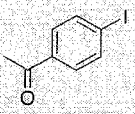
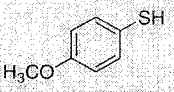
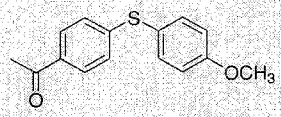
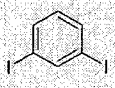
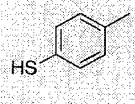
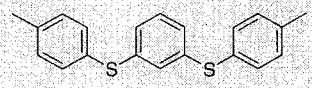
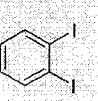
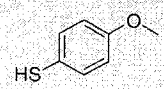
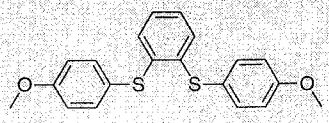
Vinyl sulfides are very important intermediates in organic chemistry. They are used as enolate ion equivalents,[17] Michael acceptors,[18] as intermediates in the synthesis of oxetanes,[19] cyclopentanones,[20] and cyclopentanes.[21] Due to the importance of these compounds a number of methods have been reported. Most noteworthy among them involves the addition of thiol to an alkyne.[22] More recently, Venkataraman et al.[23] reported the synthesis of vinyl sulfides by the thiolation of vinyl iodides using $[Cu(phen)(PPh_3)_2]NO_3$ as catalyst. To broaden the scope of our reaction protocol, we performed C–S coupling of vinyl iodides with aryl thiols using 5 mol % of CuI-CV. Gratifyingly, coupling occurred selectively and smoothly yielding the corresponding aryl vinyl sulfides in 83–93% isolated yields. Both aromatic and aliphatic thiols worked efficiently and the results are shown in Table 5.

Finally, we extended our protocol to aliphatic thiols bearing free hydroxyl group. Thus, 2-mercaptoethanol was used as the aliphatic thiol for coupling with various aryl iodides. The cross-coupling reactions were carried out under optimal catalytic conditions: aryl iodide (1 mmol), CuI (5 mol %), CV (5 mol %), 2-mercaptoethanol (1.1 mmol), and K_2CO_3 (1 mmol) in DMF at 90 °C for 8 h. The results are presented in Table 6, which showed excellent conversion to the aryl alkyl sulfides with free terminal hydroxyl group. No byproduct was isolated or observed while monitoring by TLC.

In summary, we found that inexpensive and commercially available catechol violet is a new, efficient, and versatile ligand, which could promote CuI-catalyzed C–S cross-coupling reactions between aryl or vinyl halides and various thiophenols. Generally,

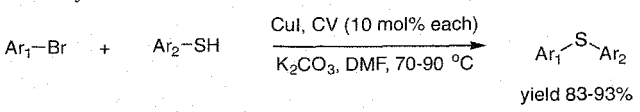
Table 2
CuI-CV-catalyzed C–S coupling of aryl iodides with aryl thiols

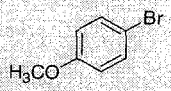
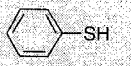
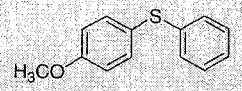
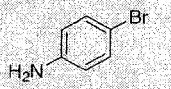
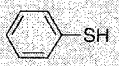
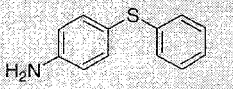
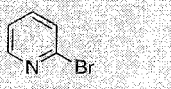
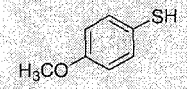
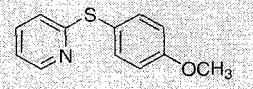
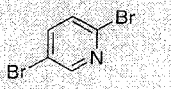
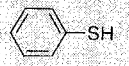
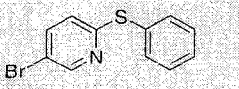
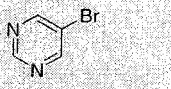
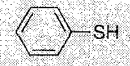
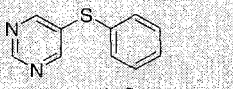
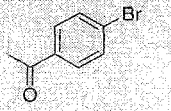
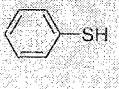
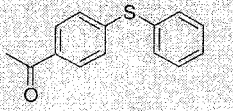
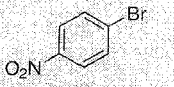
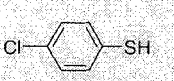
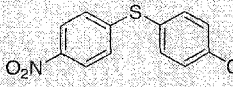
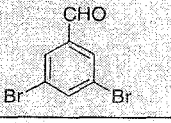
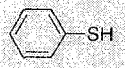
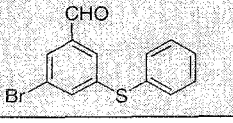


Entry	Aryl iodide	Thiol	Conditions[a] temp/time	Product	Yield[c] (%)
1			90 °C/2 h		90
2			70 °C/8 h		75
3			85 °C/6 h		89
4			90 °C/4 h		90
5			80 °C/6 h		87
6			90 °C/8 h		70
7			70 °C/5 h		86
8[b]			80 °C/4 h		71
9[b]			80 °C/4 h		69

[a] Aryl iodide: thiol: CuI-CV (1 mmol: 1.1 mmol: 5 mol %) and K_2CO_3 (1 mmol) was taken in DMF (2 mL).
[b] Aryl iodide: thiol: CuI-CV (0.5 mmol: 1.1 mmol: 10 mol %) and K_2CO_3 (1 mmol) was taken in DMF (2 mL).
[c] Yield refers to pure isolated products characterized by spectroscopic (^1H, ^{13}C NMR, and IR) data.

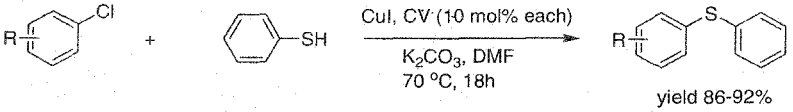
Table 3
CuI-CV-catalyzed C–S coupling of aryl bromides with aryl thiols

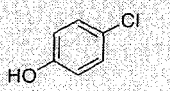
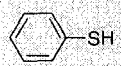
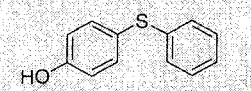
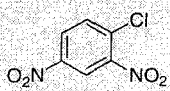
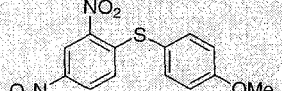
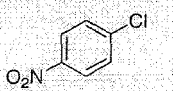
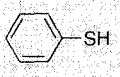
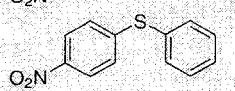
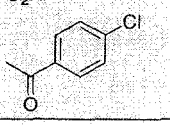
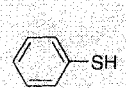
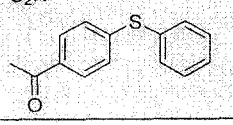


Entry	Bromoarene	Thiol	Conditions[a] temp/time	Product	Yield[b] (%)
1			90 °C/12 h		00
2			90 °C/14 h		00
3			70 °C/6 h		88
4			70 °C/2 h		93
5			70 °C/7 h		84
6			70 °C/18 h		87
7			70 °C/20 h		90
8			70 °C/8 h		83

[a] Bromoarene: thiol: CuI-CV (1 mmol: 1.1 mmol: 10 mol %) and K_2CO_3 (1 mmol) was taken in DMF (2 mL).
[b] Yield refers to the pure isolated products characterized by spectroscopic (^1H, ^{13}C NMR, and IR) data.

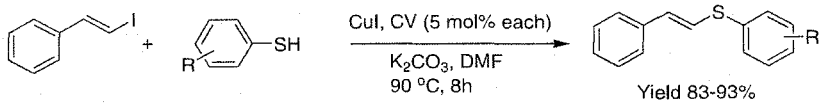
Table 4
CuI-CV-catalyzed C–S coupling of aryl chlorides with aryl thiols

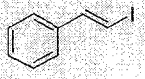
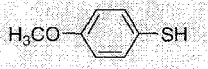
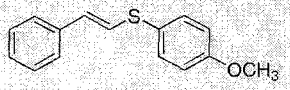
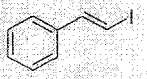
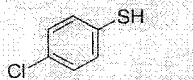
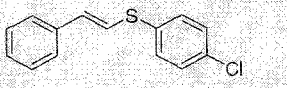
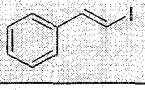
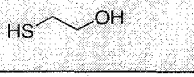
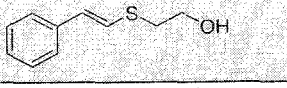


Entry	Aryl chloride	Thiol	Conditions[a] temp/time	Product	Yield[b] (%)
1			70 °C/20 h		00
2			70 °C/18 h		86
3			70 °C/20 h		88
4			70 °C/12 h		92

[a] Aryl chloride: thiol: CuI-CV (1 mmol: 1.1 mmol: 10 mol %) and K_2CO_3 (1 mmol) was taken in DMF (2 mL).
[b] Yield refers to the pure isolated products characterized by spectroscopic (^1H, ^{13}C NMR, and IR) data.

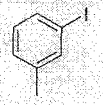
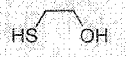
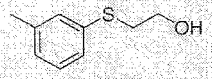
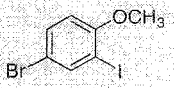
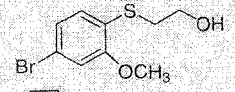
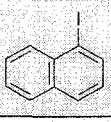
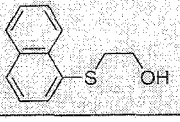
Table 5
CuI-CV-catalyzed C–S coupling of styryl iodides with thiols



Entry	Styryl iodide	Thiol	Conditions[a] temp/time	Product	Yield[b] (%)
1			90 °C/8 h		83
2			90 °C/8 h		83
3			90 °C/8 h		93

[a] Styryl iodide: thiol: CuI-CV (1 mmol: 1.1 mmol: 5 mol %) and K_2CO_3 (1 mmol) was taken in DMF (2 mL).
[b] Yield refers to the pure isolated products characterized by spectroscopic (^1H, ^{13}C NMR, and IR) data.

Table 6
CuI-CV-catalyzed C–S coupling of aryl iodides with aliphatic thiol

Entry	Aryl iodide	Thiol	Conditions[a] temp/time	Product	Yield[b] (%)
1			90 °C/4 h		83
2			90 °C/4 h		87
3			90 °C/ 4 h		78

[a] Aryl iodide: thiol: CuI-CV (1 mmol: 1.1 mmol: 5 mol %) and K_2CO_3 (1 mmol) was taken in DMF (2 mL).
[b] Yield refers to the pure isolated products characterized by spectroscopic (^1H, ^{13}C NMR, IR, and HRMS) data.

very good to excellent yields of the desired diaryl or aryl alkyl sulfides could be obtained successfully under mild reaction conditions. The catalytic combination CuI-CV offers general applicability and avoids use of expensive phosphines or other specially designed ligands. Further applications of this catalytic combination are currently under investigation.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.076.

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15. *Typical experimental procedure for the thiolation reaction of aryl iodides* (Table 2, entry 1): A mixture of 4-iodoanisole (234 mg, 1 mmol), CuI (9.5 mg, 5 mol %), catechol violet (19 mg, 5 mol %), K_2CO_3 (138 mg, 1 mmol), and thiophenol (121 mg, 1.1 mmol) was taken in a screw-capped vial. DMF (2 mL) was added to it and it was placed on a preheated oil-bath at 90 °C for 2 h. The mixture was then cooled to room temperature followed by dilution with water (6 mL). It was then extracted with ether (3 × 10 mL) and the combined organic layer was washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent left an oily residue which was passed through a short column of silica gel (60–120 mesh). Elution with light petroleum afforded the desired product as a colorless liquid (194 mg, yield 90%). IR (neat): ν_{max} 2959, 2835, 1529, 1478, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.41 (2H, d, J = 8.2 Hz); 7.23 (2H, m); 7.15 (3H, m); 6.90 (2H, d, J = 8.2 Hz), 3.82 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.8, 138.6, 135.3, 128.9, 128.2, 125.7, 124.3, 115.0, 55.3.
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Highly effective alternative aryl trihydroxyborate salts for a ligand-free, on-water Suzuki–Miyaura coupling reaction

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Aryl trihydroxyborate salts of sodium, an easily accessible and stable alternative source of organoboron species, can efficiently promote Pd-catalyzed ligand-free, on-water Suzuki–Miyaura (SM) coupling reactions at ambient temperature.

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Introduction

The seminal paper of Miyaura, Yamada and Suzuki[1] laid the foundation of one of the most important and useful methods for the construction of carbon–carbon bonds, in particular for the formation of unsymmetrical biaryls. Despite other alternative approaches for C–C bond formation such as Kharash coupling,[2] Negishi coupling,[3] Stille coupling,[4] Hiyama coupling,[5] and Kumuda coupling,[6] the Suzuki–Miyaura (SM) coupling reaction has arguably received much more popularity due to stability, commercial availability and ease of handling of the organoboron compounds. The Suzuki–Miyaura coupling has found widespread applications in academic laboratories, fine chemical industries, synthesis of biologically active pharmaceuticals, as well as in the burgeoning area of nanotechnology, as reflected from contributions from myriad research groups.[7] For example, Losartan, an antihypertensive drug,[8a] CI-1034, a potent endothelian receptor antagonist,[8b] CE-178,253 benzenesulfonate, a CB_1 antagonist for the treatment of obesity[8c] or apoptolidin A, a potent antitumor agent[8d] have been synthesised on a large scale employing the SM coupling as a key step. Similarly, benzimidazole derivatives bearing substituted biphenyl moieties, potential inhibitors of hepatitis C virus, have been prepared using the SM coupling reaction.[9] Review articles by Danishefsky *et al.*[10] and Nicolaou *et al.*[11] amply demonstrate various applications of the SM coupling reaction in the synthesis of natural products.

In recent years, amelioration of the SM coupling reaction has been directed towards the more efficient, economic and greener techniques, especially in respect of Pd-catalyst, requirement of base and carrying out the reaction in water or in the absence of any solvent.[12] Recent trends in organic synthesis involve reactions under solvent-free or on-water conditions to obtain the target molecule in a cleaner and environmentally benign way.[13] Although many organic reactions are facilitated in aqueous media, some reactions proceed very slowly because of poor solubility of the substrate/reagents in water. In the case of SM couplings, hydrophobic aryl boronic acids often show very slow and/or incomplete conversions along with the difficulty to isolate the products from the reaction mixture.[14] Efforts have been made to overcome the problem by introducing phase transfer catalysts,[15] water soluble salts of reagents[16] or catalysts[17] or carrying out the reaction in aqueous buffer.[18] Two types of water-soluble organoborate salts *viz.* potassium aryl trifluoroborates[16a–d] and sodium aryl trihydroxyborates,[16e,f] which are easy to prepare, store and handle, have been employed in Pd-catalyzed cross-couplings with aryl halides. Yet, despite some positive features of using aryl trihydroxyborate salts, aqueous SM coupling usually requires elevated temperatures, organic co-solvents, ligand-based Pd-catalysts, high catalyst loadings and/or tedious work-up. In this paper we present an ambient on-water protocol for the SM coupling reaction of a wide range of aryl halides (I, Br or Cl) including heteroaryl halides with different sodium aryl trihydroxyborates. Our observations practically constitute an efficient, mild, ligand-free method for the SM coupling reactions in water at ambient temperature by using aryl trihydroxyborate salt as one of the coupling partners (Scheme 1). This paper also reports successful extension of the procedure through the use of polymer-supported Pd-catalyst (ARF–Pd), a heterogeneous Pd-catalyst developed by our group,[19] covering the essential aspects of green chemistry. Furthermore, we have demonstrated modular synthesis of pharmaceutically important benzimidazole- and benzotriazole-based biphenyl scaffolds using an alternative water-soluble sodium organoborate salt.

Results and discussion

Preliminary optimization of the SM coupling reactions was carried out using 3-iodoanisole and phenyltrihydroxyborate with the aid of 0.5 mol% $Pd(OAc)_2$ (Table 1). The phenyl trihydroxyborate salt was prepared following the reported procedure,[16e] and used directly without further purification. Investigations using different solvents revealed that the coupling is unsuccessful in toluene (Table 1 entry 1), partly successful in dioxane (Table 1, entry 2) but worked efficiently in DMF (Table 1, entry 3). On switching over to aqueous media, it was found that a mixture of acetone–water also worked efficiently within 8 h under mild conditions (Table 1, entry 4). However, carrying out the reaction in only water resulted in the formation of the biphenyl derivative in 38% yield (Table 1, entry 5), which may be attributed to the poor solubility of aryl iodide in water. To overcome this shortcoming, we decided to use tetrabutylammonium bromide (TBAB), a phase transfer reagent, in an equimolar amount.

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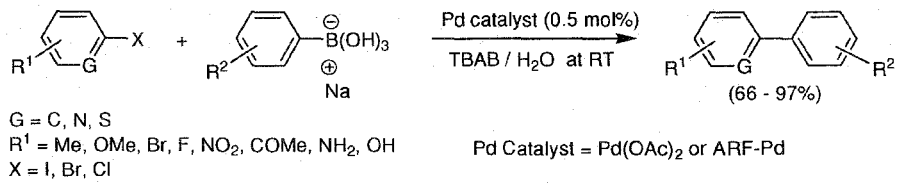
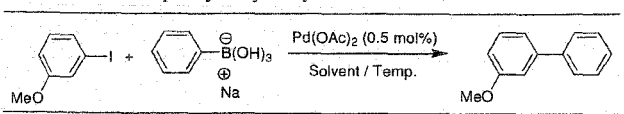


Scheme 1

Table 1 Optimization of reaction conditions for the SM coupling using 3-iodoanisole and phenyltrihydroxyborate



Entry	Solvent	Temperature	Time	% of Yield[a]
1	Toluene	100 °C	8 h	00
2	Dioxane	RT	24 h	45
3	DMF	RT	4 h	96
4	Acetone : water	RT	8 h	93
5	Water	RT	4 h	38
6	Water[b]	RT	4 h	92
7	Water[c]	RT	8 h	50

[a] Isolated yields after purification by column chromatography on silica. [b] 1 equiv. of TBAB was added. [c] 0.5 equiv. of TBAB was added. All reactions were carried out using 0.5 mol% $Pd(OAc)_2$.

This led to the formation of the desired unsymmetrical biphenyl within 4 h at room temperature in 92% yield (Table 1, entry 6). An experiment with 0.5 equivalents of TBAB, however, afforded the desired product only in 50% yield, even after 8 h (Table 1, entry 7). It was revealed that polar protic or aprotic solvents are good enough to effect the SM coupling at room temperature. Thus, the optimized reaction conditions are: 0.5 mol% of $Pd(OAc)_2$ and 1 equivalent of TBAB in water at room temperature.

After identification of the optimal conditions, the scope and limitations of the reaction were examined. Initially, we applied these reaction conditions to the coupling of various functionalized aryl iodides with the sodium salt of phenyltrihydroxyborate in water. The results are presented in Table 1. Aryl iodides bearing different substituents such as OMe, Me, NH_2, F and I underwent smooth SM coupling affording the corresponding unsymmetrical biphenyls in 84–94% yields (Table 2, entries 1–7). Mechanistically, the oxidative addition of aryl halides to palladium(0) depends on the nature of halogens and occurs in the descending order of I > Br > Cl.[20] We therefore examined the couplings of other aryl electrophiles bearing bromide and chloride. Several aryl bromides including di- and tribromoarenes were found to give the corresponding unsymmetrical biaryls in good to excellent yields (Table 2, entries 8–13). While *p*-bromoacetophenone showed a faster rate of reaction (2 h) (Table 2, entry 9), 2,4,6-tribromophenol required a longer time (24 h) (Table 2, entry 13) for the coupling reaction, which may be due to the presence of the electron-withdrawing acetyl group in the former example. Thus, aryl iodides and bromides underwent easy coupling with phenyl trihydroxyborate. A similar reaction with aryl chloride was not successful even after heating the reaction mixture at 100 °C for 24 h (Table 2, entries 14–15). Leadbeater *et al.*[18a] reported the microwave-assisted SM coupling of aryl chlorides at 150–175 °C in aqueous media indicating that aryl chlorides are very sluggish towards the SM coupling reaction and require relatively higher temperature, longer reaction time and/or the presence of electron-withdrawing groups. We examined aryl chlorides bearing nitro or acetyl groups, which however afforded the desired coupled products in excellent yields at refluxing temperatures (100 °C) (Table 2, entries 16–17). Changing the coupling partner phenyltrihydroxyborate with *m*-tolyltrihydroxyborate and *p*-anisyltrihydroxyborate did work efficiently with bromo and iodoarenes (Table 2, entries 18–22 and 24). The SM coupling reaction with heteroaryl halides was also successful. For example, 3-bromoquinoline or 2,6-dibromopyridine gave the desired coupled products in 66% and 83% yields respectively (entries 22–23), while similar coupling of 2-iodothiophene with *p*-anisyltrihydroxyborate afforded the corresponding unsymmetrical biphenyl in 92% yield within 3 h (Table 2, entry 24).

Recently, we developed a new Pd-catalyst (where Pd was immobilized onto ion-exchange resins), designated as ARF–Pd, which was successfully applied to Heck, Suzuki–Miyaura

† Spectral data of selected biphenyls: 3-Methoxy biphenyl (liquid); Table-2, Entry-1: IR (film): ν_{max} 1574, 1610 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm^{-1} relative to TMS): 3.75 (3H, s, $-OCH_3$); 6.77–6.81 (1H, m, aromatic proton); 7.03–7.10 (2H, m, 2 aromatic protons); 7.21–7.36 (4H, m, all aromatic protons); 7.47–7.51 (2H, m, 2 aromatic protons). ^{13}C NMR ($CDCl_3$, δ ppm^{-1}): 55.2 (OCH_3); 112.6; 112.8; 119.6; 127.1; 127.4; 128.7; 129.7; 141.0; 142.7; 159.9 (aromatic carbons). 2-Methoxy biphenyl (liquid); Table-2, Entry-3: IR (film): ν_{max} 1504, 1597 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm^{-1} relative to TMS): 3.79 (3H, s, $-OCH_3$); 6.96–7.05 (2H, m, 2 aromatic protons); 7.29–7.42 (5H, m, all aromatic protons); 7.51–7.54 (2H, m, 2 aromatic protons). ^{13}C NMR ($CDCl_3$, δ_P ppm^{-1}): 55.54 (OCH_3); 111.2; 120.8; 126.9; 127.9; 128.6; 129.5; 130.7; 130.8; 138.5; 156.5 (aromatic carbons). 3,4′-Dimethyl biphenyl (liquid); Table-2, Entry-19: IR (film): ν_{max} 1588, 1606 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm^{-1} relative to TMS) 2.390 (6H, s, CH_3); 7.13–7.50 (8H, m, 8, all aromatic protons). ^{13}C NMR ($CDCl_3$, δ ppm^{-1}): 21.3 (CH_3); 124.1; 127.0; 127.7; 127.8; 128.6; 129.4; 136.9; 138.2; 138.5; 141.1 (aromatic carbons). 3-Methoxy 3′-methyl biphenyl (liquid); Table-2, Entry-20: IR (neat): ν_{max} 1593 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm^{-1} relative to TMS): 2.41 (3H, s, CH_3); 3.86 (3H, s, $-OCH_3$); 7.11–7.39 (8H, m, all aromatic protons). ^{13}C NMR ($CDCl_3$, δ ppm^{-1}): 21.5 (CH_3); 55.3 (OCH_3); 112.6; 112.9; 119.7; 124.3; 128.0; 128.1; 128.6; 129.6; 138.3; 141.1; 142.9; 159.9 (aromatic carbons). 3-(3-Methyl phenyl) quinoline (liquid); Table-2, Entry-22: IR (film): ν_{max} 1580, 1606 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm^{-1} relative to TMS): 1.59 (3H, s, CH_3); 6.36–6.87 (6H, m, 6 aromatic protons); 7.00 (1H, d, J = 8.1 Hz, aromatic proton); 7.28 (1H, d, J = 8.4 Hz, aromatic proton); 7.43 (1H, s); 8.3 (1H, s). ^{13}C NMR ($CDCl_3$, δ ppm^{-1}): 21.6 (CH_3); 124.5; 127.1; 128.0; 128.1; 128.2; 128.9; 129.0; 129.1; 129.4; 133.4; 134.0; 137.7; 138.9; 147.1; 149.8 (aromatic carbons). 2-(4-Methoxy phenyl) thiophene; Table-2, Entry-24: mp 106 °C; IR (KBr): ν_{max} 1500, 1533, 1606 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm^{-1} relative to TMS): 3.81 (3H, s, $-OCH_3$); 6.91 (2H, d, J = 9 Hz, 2 aromatic protons); 7.03–7.25 (3H, m, all aromatic protons); 7.53 (2H, d, J = 8.7 Hz, 2 aromatic protons). ^{13}C NMR ($CDCl_3$, δ ppm^{-1}): 55.3 (OCH_3); 114.3; 122.1; 123.8; 127.2; 127.3; 127.9; 144.3; 159.2 (aromatic carbons).

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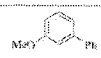
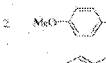
Table 2 On-water SM coupling reactions with sodium aryl trihydroxyborates using 0.5 mol% of $Pd(OAc)_2$

Entry	Aryl halides	Aryl boronic acid salts[a]	Temp	Time (h)	Product	Yield (%)[b]
1			RT	4		92
2			RT	4		88[19]
3			RT	2.5		84
4			RT	4		87[21]
5			RT	4		94[21]
6			RT	16		87[22]
7			RT	6		85[23]
8			RT	8		72[20]
9			RT	2		95[21]
10			RT	4		22 66[21]
11			RT	8		89[22]
12			RT	6		67[21]
13			RT	24		82[20]
14			150°C	24	No Reaction	
15			100°C	24	No Reaction	
16			100°C	5		96[24]
17			100°C	4		85
18			RT	8		79
19			RT	8		86
20			RT	3.5		74
21			RT	7		97
22			RT	3.5		66
23			RT	8		83
24			RT	5		92

[a] Aryl halide and arylboronic acid salt used in 1 : 1.1 ratios for mono-coupling. [b] Isolated yields after purification by column chromatography on silica.†

and Sonogashira coupling reactions.[19] To extend further, we employed the heterogeneous Pd-catalyst (ARF–Pd) replacing $Pd(OAc)_2$. Indeed, trihydroxyborate salts were found to be equally active in SM coupling reactions in the presence of a catalytic amount of ARF–Pd. The results are presented in Table 3. In all the cases, the ARF–Pd was separated by filtration and the desired products were obtained after chromatographic purification in excellent yields (85–93%) (Table 3, entries 1–5).

As shown above, water-soluble sodium salts of aryl trihydroxyborates have proven to be highly effective in SM coupling reactions in water at ambient temperatures. Low loading of the Pd-catalyst (direct use of $Pd(OAc)_2$ or polymer-bound Pd) and absence of any phosphine ligands are notable features to mention. Having established a general, mild, aerobic and on-water protocol for the SM coupling reactions using aryl trihydroxyborate salts, we probed the utility of this protocol in modular synthesis of pharmaceutically important benzimidazole- and benzotriazole-based biphenyl scaffolds. Thus, compounds **2** and **3** were synthesized from compounds **1a** and **1b** respectively (Scheme 2), where the SM couplings were efficiently performed using sodium phenyltrihydroxyborate in a mixture of DMF–H_2O (2 : 1).

Conclusions

In summary, our studies have established that easily accessible and air-stable sodium aryl trihydroxyborates can be effectively used as an alternative source of organoboron species in ligand-free Pd-catalyzed SM cross-coupling reactions in water under an aerobic atmosphere and at room temperature. The protocol has been found to be broadly applicable to a variety of aryl halides (X = Br, I) and also to aryl chlorides bearing electron-withdrawing groups. It is further shown to be effective with heterogeneous Pd-catalysts and also extended to the modular synthesis of some pharmaceutically important benzimidazole- and benzotriazole-based biphenyl scaffolds.

Experimental

General procedure for Suzuki–Miyaura coupling

A mixture of 3-iodoanisole (468 mg, 2 mmol), sodium phenyltrihydroxyborate (354 mg, 2.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.5 mol%) and TBAB (644 mg, 2 mmol; 1 equiv) was taken in water (5 mL). The mixture was magnetically stirred at room temperature for several hours (see Table 2). After the reaction was complete (monitored by tlc), the mixture was extracted with ether (3 × 20 mL). The combined organic layer was then washed with brine (10 mL), dried (anhydrous Na_2SO_4), and evaporated. The residue was purified on a short column of silica using light petroleum as the eluent to afford the desired unsymmetrical biphenyl (338 mg, 92%); liquid.

Synthesis of compounds 2 and 3

A mixture of 1-(4-iodobenzyl)-1*H*-benzo[*d*]imidazole (334 mg, 1 mmol) or 1-(4-iodobenzyl)-1*H*-benzo[*d*][1,2,3]triazole (335 mg, 1 mmol) and sodium salt of phenyltrihydroxyborate (177 mg, 1.1 mmol), ARF–Pd (300 mg, 0.94 mol% of Pd) and TBAB (322 mg, 1 mmol) was taken in a DMF–water

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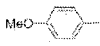
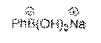
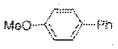
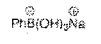
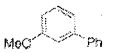
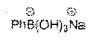
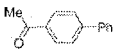
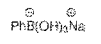
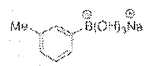
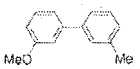
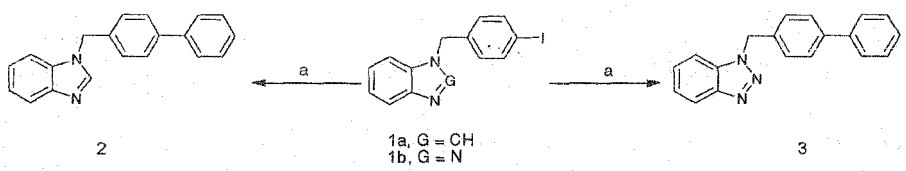
Table 3 SM coupling reactions with aryl trihydroxyborates in water using heterogeneous Pd-catalyst (ARF–Pd)

Entry	Aryl halides[a]	Sodium trihydroxyborate	Temp.	Time/h	Product	Yield[b] (%)
1			RT	5		85
2			RT	5		88
3			100 °C	4		92
4			100 °C	3		93
5			100 °C	5		87

[a] 300 mg ARF-Pd (0.94 mol% Pd) was used. [b] Isolated yields after purification by column chromatography on silica.



Scheme 2 Conditions: [a] **1a** or **1b** (1 mmol), $PhB(OH)_3Na$ (1.1 mmol) in DMF–H_2O (2 : 1; 3 mL), $Pd(OAc)_2$ (1.1 mg, 0.5 mol%), 100 °C for 24 h.

mixture (2 : 1; 3 mL). The mixture was heated at 100 °C for 24 h. After completion of the reaction (monitored by tlc), the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layer was then washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated. Finally the residue was purified over a short column of silica and elution with 1 : 9 (EA : light petroleum) afforded *N*-(4-phenyl benzyl) benzimidazole **2** (236 mg, 83%); m.p. 163 °C or *N*-(4-phenyl benzyl) benzotriazole **3** (227 mg, 80%); m.p. 180 °C.

Spectral data for 2. ^{1}H NMR ($CDCl_3$): δ 5.41 (2H, s, (CH_2); 7.25–7.83 (13H, m, all aromatic protons); 8.07 (1H, s, aromatic proton). ^{13}C NMR ($CDCl_3$): δ 48.7 (CH_2 aliphatic carbon); 110.2; 120.2; 122.6; 123.3; 127.1; 127.6; 127.8; 128.8; 129.1; 133.8; 134.2; 140.3; 141.4; 143.1; 143.3 (aromatic carbons). IR (KBr): ν_{max} 1610, 1653 cm^{-1}. HRMS: Calculated for $C_{20}H_{16}N_2H$: $[M+H]^+$, 285.1392; found: 285.1387.

Spectral data for 3. ^{1}H NMR ($CDCl_3$): δ 5.88 (2H, s, (CH_2); 7.25–8.09 (13H, m, all aromatic protons). ^{13}C NMR NMR ($CDCl_3$): δ 51.9 (CH_2 aliphatic carbon); 109.7; 120.1; 124.0; 127.0; 127.5; 127.6; 127.7; 128; 128.8; 132.8; 133.6; 140.2; 141.4; 146.3 (aromatic carbons). IR (KBr): ν_{max} 1590, 1616 cm^{-1}. HRMS: Calculated for $C_{19}H_{15}N_3Na$: $[M+Na]^+$ 308.1164; found: 308.1163.

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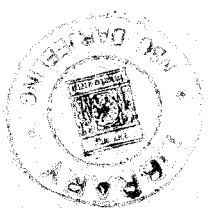

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