Part 1

Section B

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

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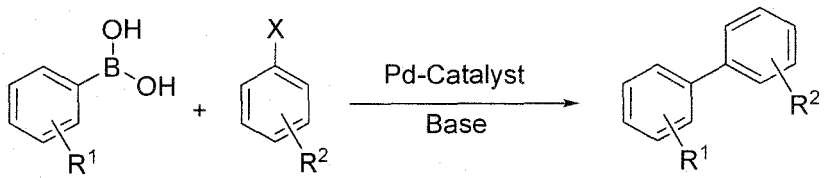
1. B.1. Introduction

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).

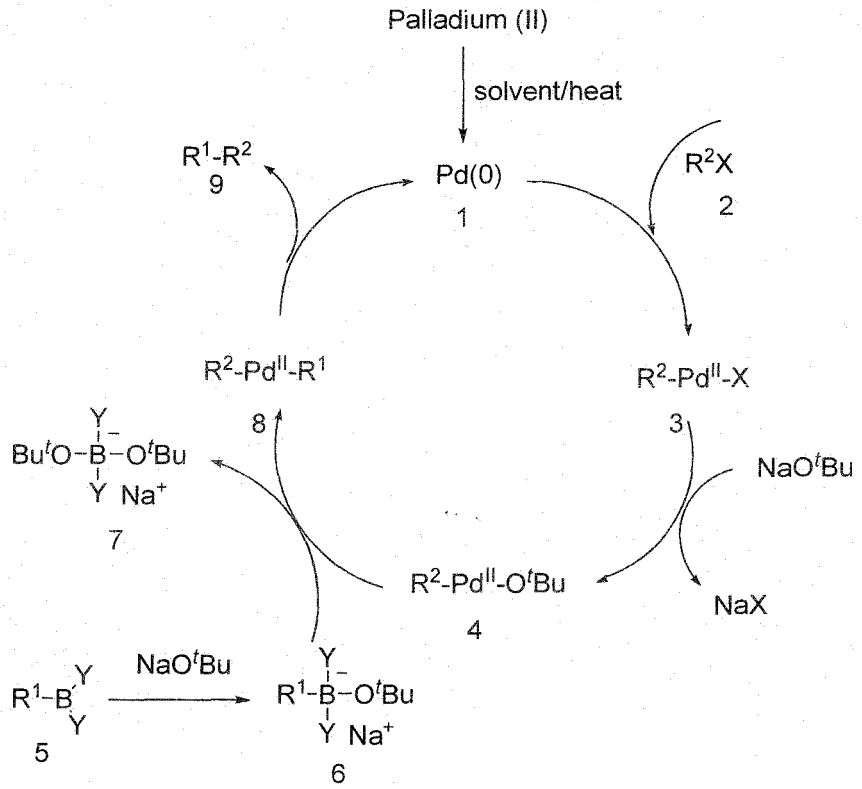


Fig. 1: Typical catalytic cycle for Suzuki-Miyaura coupling reactions

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

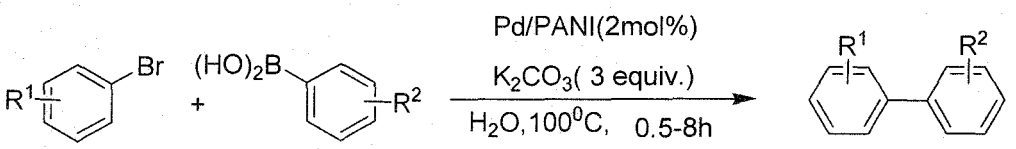
required for the development of new variants of the organoboron species, the catalyst and the base in the SM coupling reaction and the optimizing process have remained challenging areas of research. One solution emerged in the 1960s with the discovery of potassium organotrifluoroborates, boron ate complex 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:

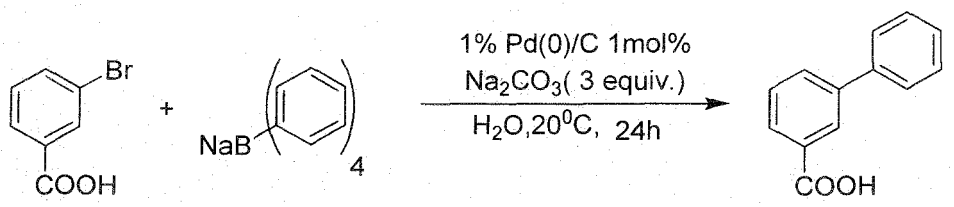
Kantam and co-workers[26]used 2 mol% of Pd/ Polyaniline (PANI) with K_2CO_3 as a base in refluxing water for Suzuki–Miyaura cross-coupling reactions. While under these conditions bromoarenes were efficiently coupled with various substituted boronic acids (Scheme 1), chloro-arenes required the use of 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.

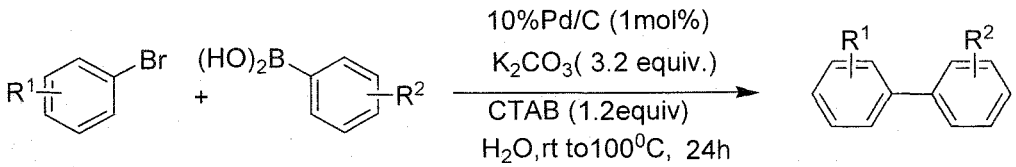
Scheme 3



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.

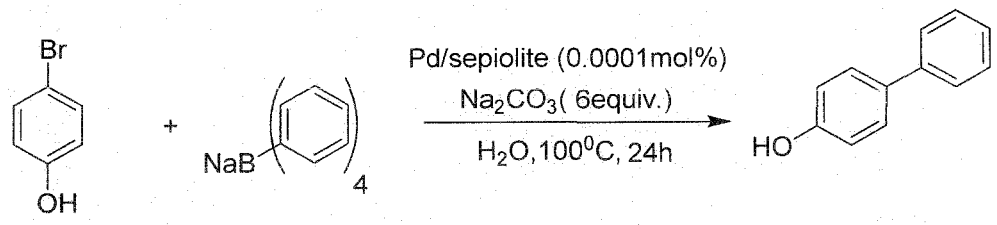
Kçhler and Lysen had shown that for non-water-soluble aryl halides were less reactive, opted for the use of surfactants as additives. The water-surfactant Pd/C system gave good catalytic activity after several recycling experiments rendering the method environmentally friendly. The activation role of 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



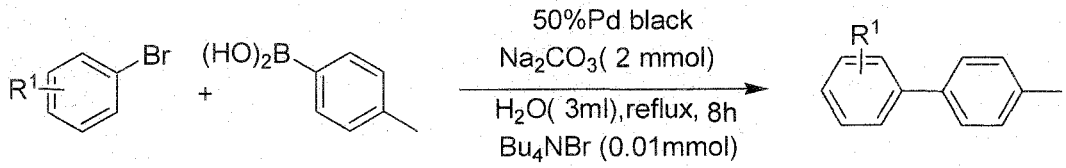
A sepiolite-supported palladium (II) catalyst has been successfully used by Kitayama et al. for the cross-coupling of 4-bromophenol with phenylboronic acid or tetraphenylborate at room temperature and get more than 94% yield. Sepiolite is a hydrated magnesium silicate with the ideal formula of $Mg_8Si_{12}O_{30}4H_2O{\cdot}nH_2O$.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

Scheme 5



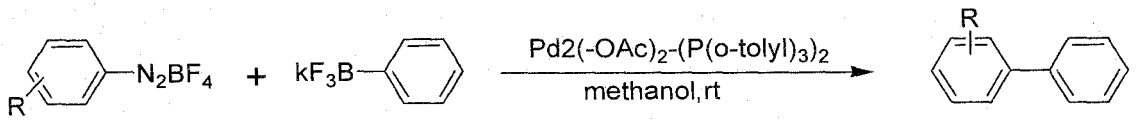
Bumagin and co-workers[29] synthesized biaryl moiety via cross coupling of *p*-tolylboronic acid with bromo arene using 50 mol% palladium black as acatalyst in water. Again they have shown catalytic system is so efficient that water-soluble aryl halides react in 5-10 min even in the presence of 1 mol.%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

Scheme 6



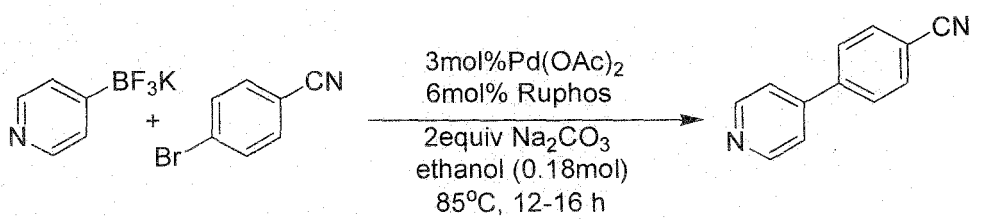
In 1997, Scientist Darses and Genet were the first to show that potassium aryltrifluoroborates were suitable substrates in palladium-catalyzed reactions.[30] Highly stable and nonexplosive arenediazonium tetrafluoroborates were chosen for the coupling pattern because of their ready availability from 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



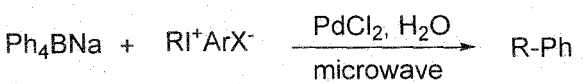
Molander *et al.*[34] synthesized variety of heteroaryltrifluoroborates (five-membered, six-membered, and benzannulated heteroaryltrifluoroborate derivatives) from commercially available boronic acids by the addition of inexpensive potassium hydrogen fluoride (KHF_2)[35] and disclose their efficient 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



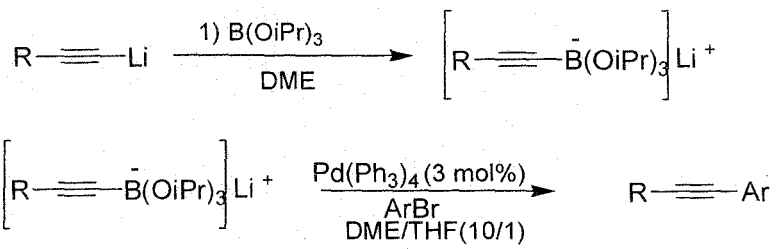
Yan and coworkers have recently reported base-free SM reaction using hypervalent iodonium aryl salts instead of aryl halides.[36]

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).

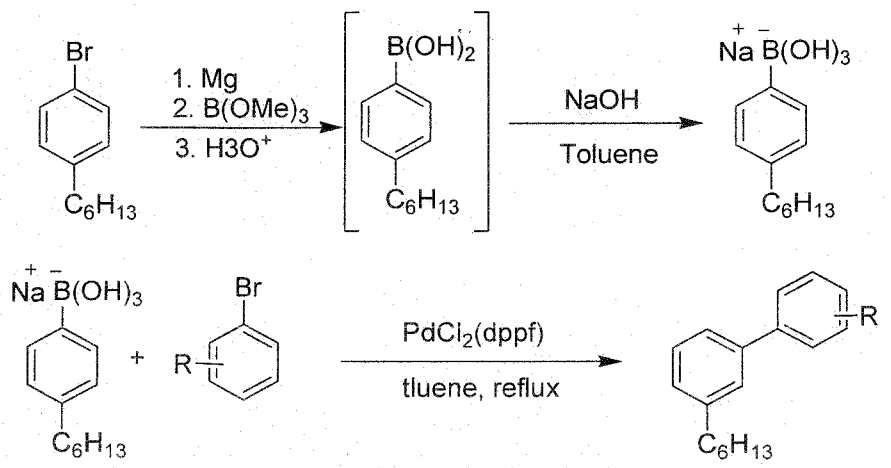
Scheme 10:



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

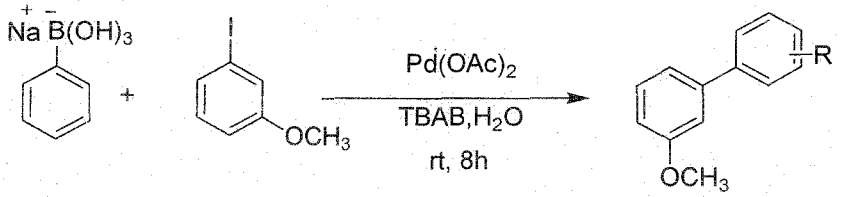


Table 1: Optimization of reaction conditions for the SM coupling using 3-Iodoanisole and phenyltrihydroxyborate

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]

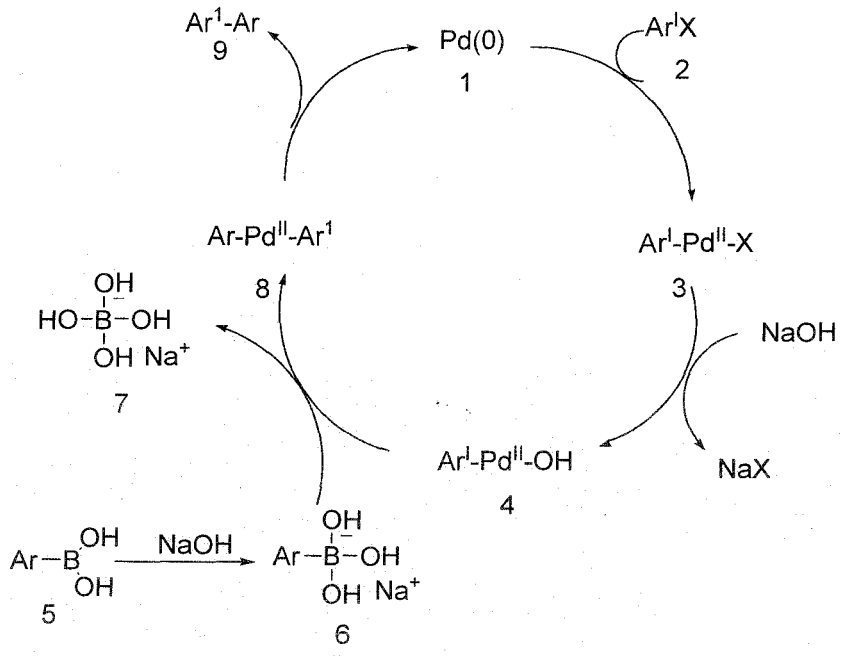


Fig. 1 A general catalytic cycle for Suzuki–Miyaura coupling reaction

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 $Pd(OAc)_2$

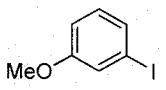
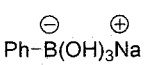
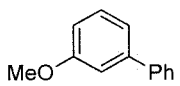
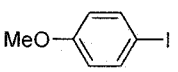
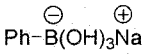
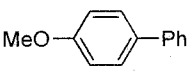
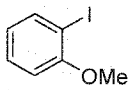
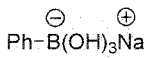
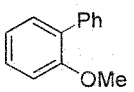
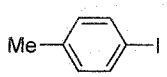
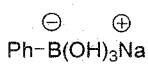
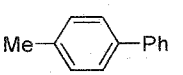
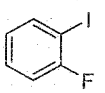
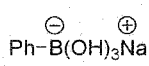
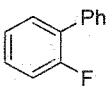
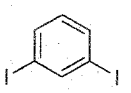
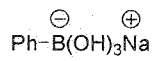
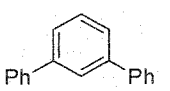
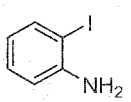
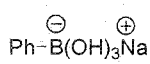
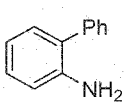
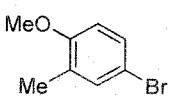
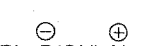
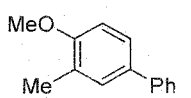
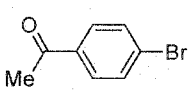
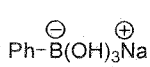
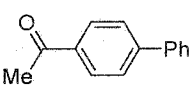
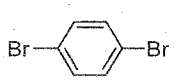
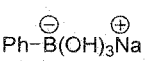
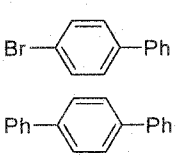
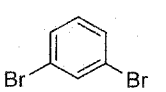
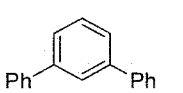
Entry	Aryl halides	Aryl boronic acid salts[a]	Temp.	Time (h)	Product	Yield (%)[b]
1			RT	4		92
2			RT	4		88
3			RT	2.5		84
4			RT	4		87
5			RT	4		94
6			RT	16		87
7			RT	6		85
8			RT	8		72
9			RT	2		95
10			RT	4		22 66
11			RT	8		89

Table 2 cotinued.....

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

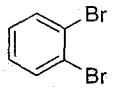
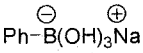
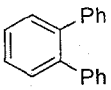
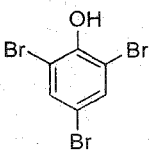
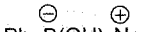
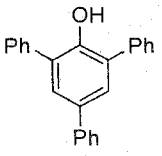
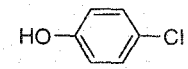
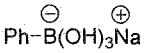
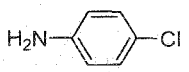
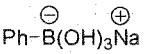
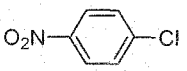
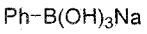
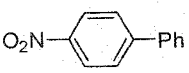
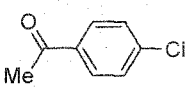
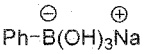
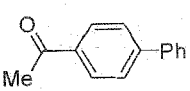
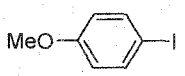
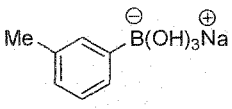
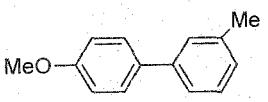
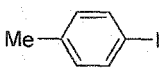
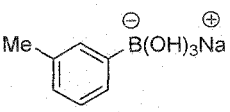
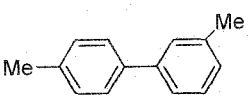
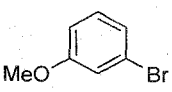
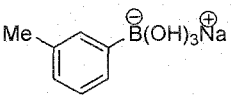
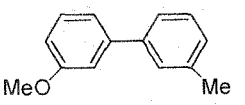
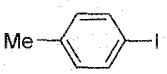
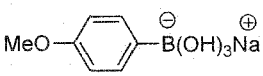
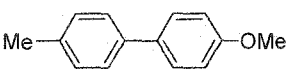
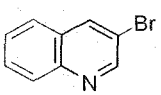
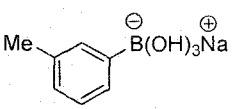
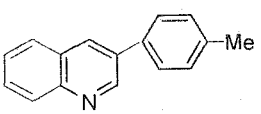
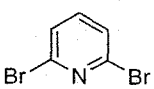
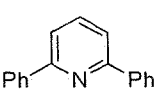
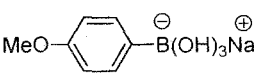
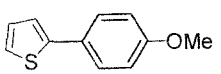
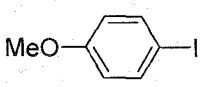
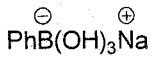
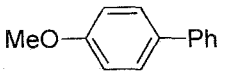
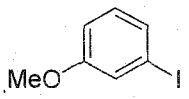
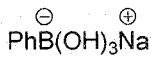
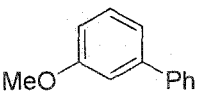
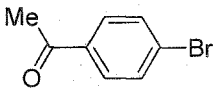
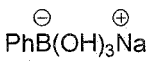
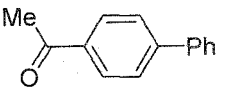
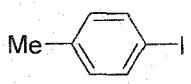
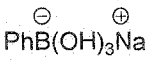
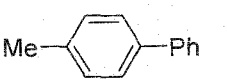
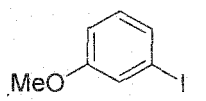
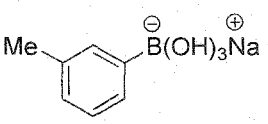
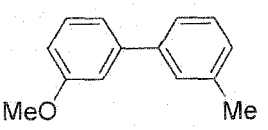
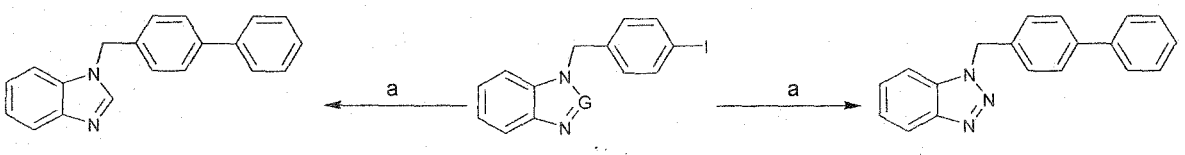
Entry	Aryl halides	Aryl boronic acid salts[a]	Temp.	Time (h)	Product	Yield (%)[b]
12			RT	6		67
13			RT	24		82
14			100° C	24		No Reaction
15			100° C	24		No Reaction
16			100° C	5		96
17			100° C	4		85
18			RT	8		79
19			RT	8		86
20			RT	3.5		74
21			RT	7		97
22			RT	3.5		66
23			RT	8		83
24			RT	3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

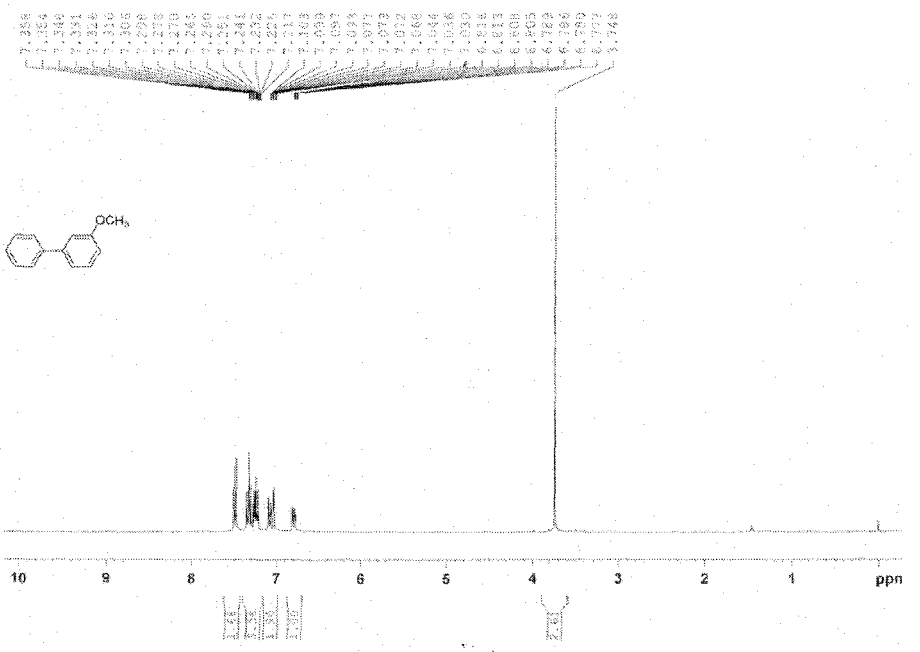
IR (KBr): υ_{max} 1610, 1653 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ = 5.41 (s, 2H), 7.25–7.83 (m, 13H), 8.07 (s, 1H), ^{13}C NMR (CDCl3): δ = 48.7, 110.2, 120.2, 122.6, 123.3, 127.1, 127.6, 127.8, 128.8, 129.1, 133.8, 134.2, 140.3, 141.4, 143.1, 143.3, HRMS: calculated for $C_{20}H_{16}N_2H$: $[M+H]^+$, 285.1392;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

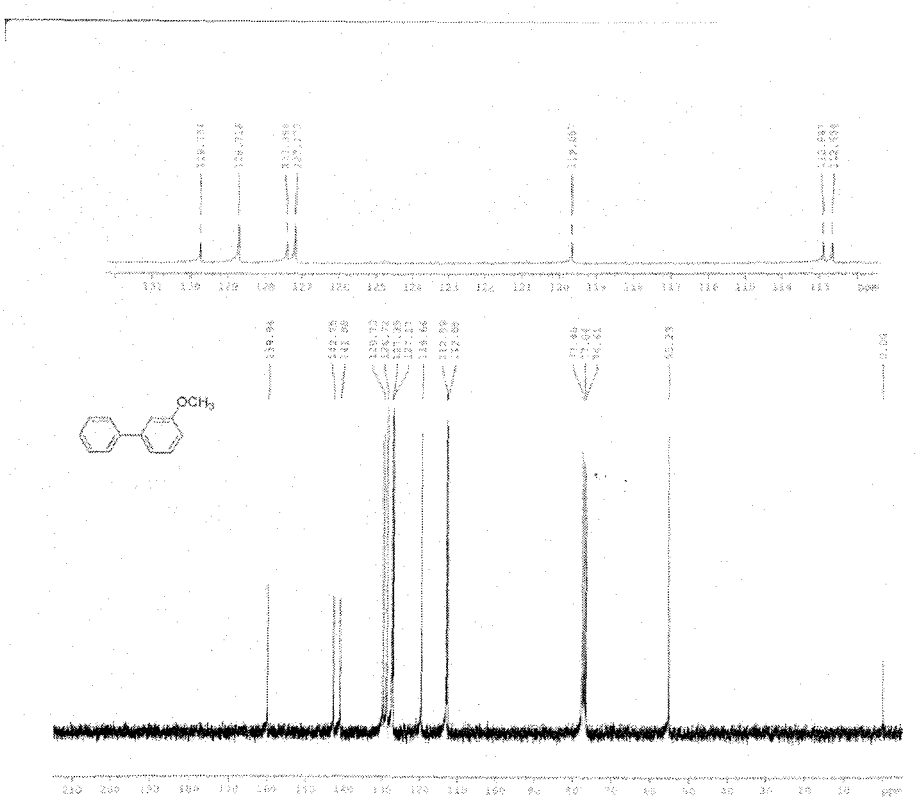
Scheme 2: N-(4-phenyl benzyl) benzotriazole (solid): Mp 163 °C

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.


OCH3
10
9
8
7
6
5
4
3
2
1
ppm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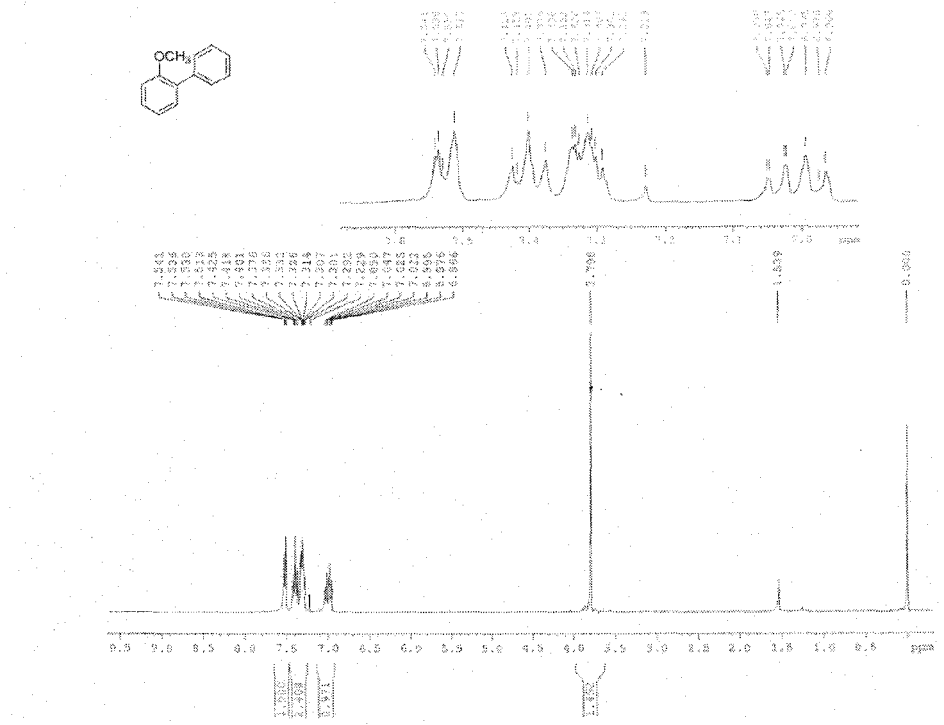
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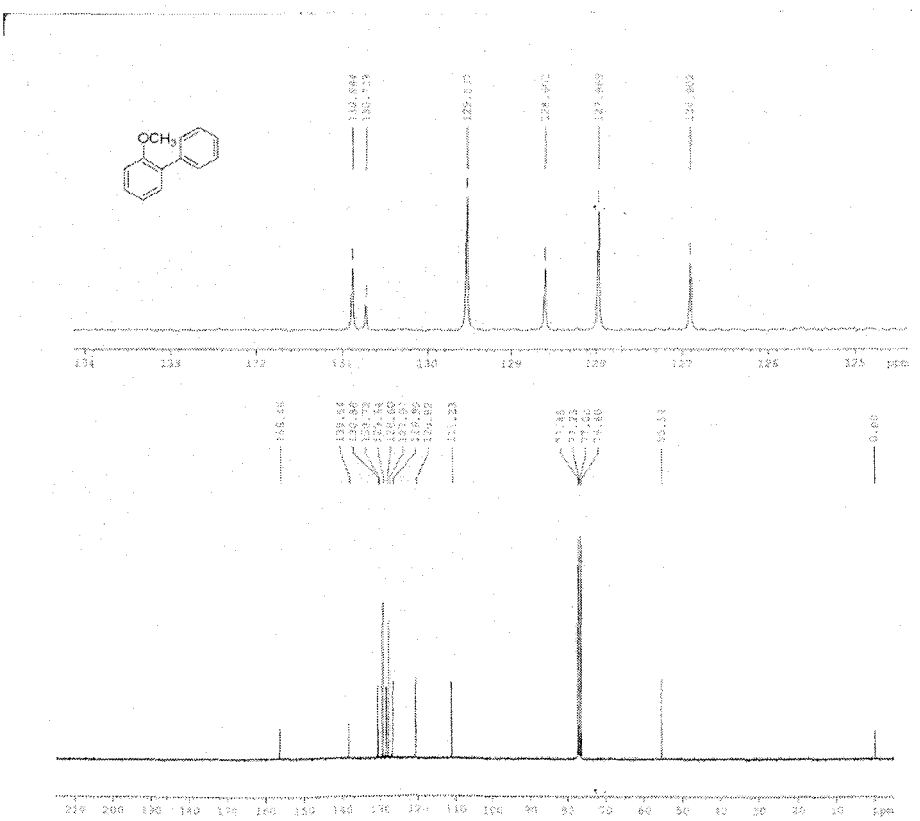
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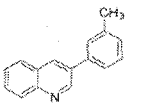
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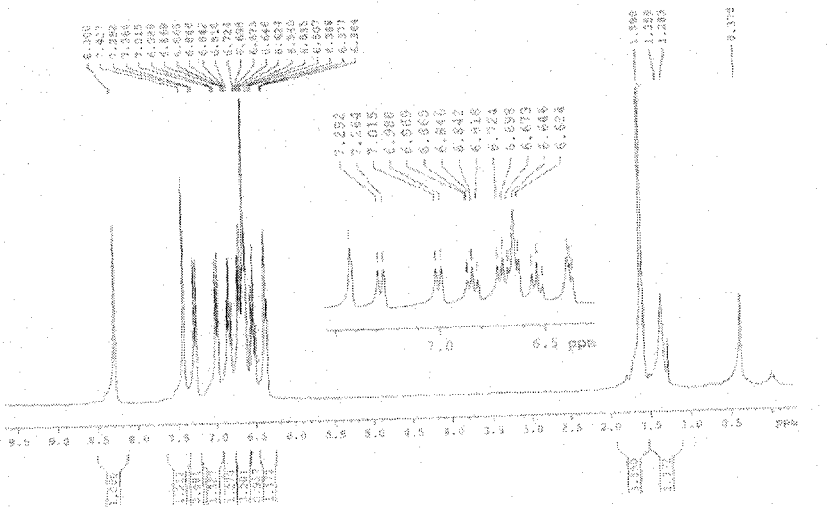
N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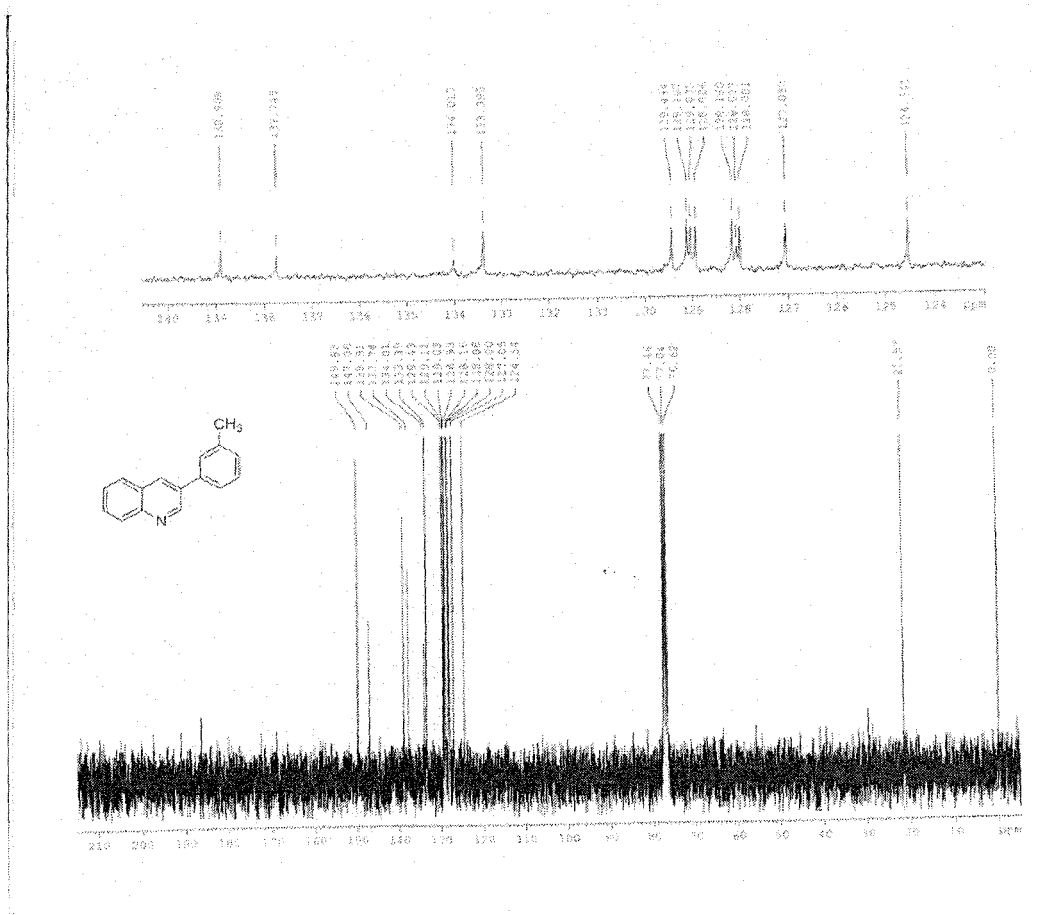
6.5 ppm
ppm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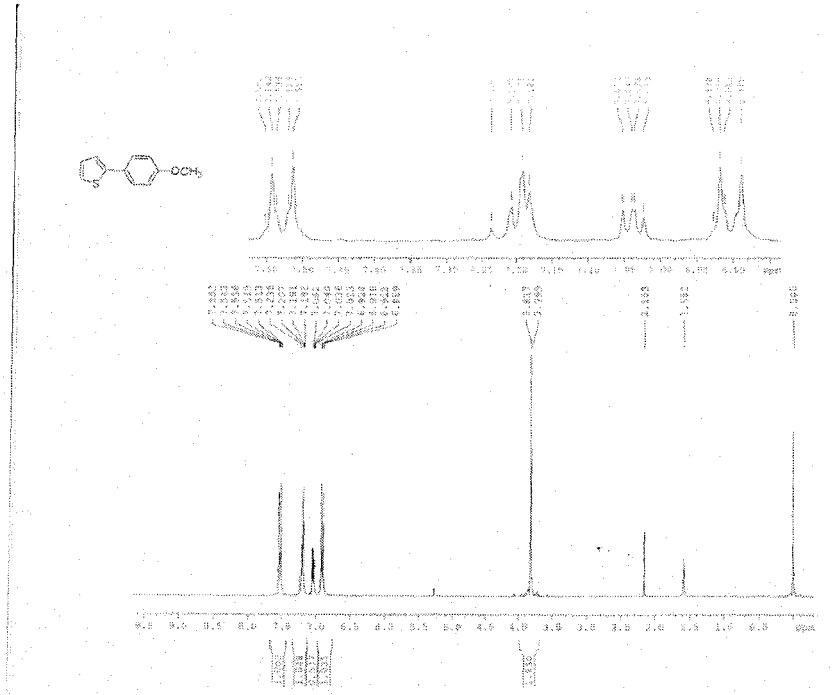
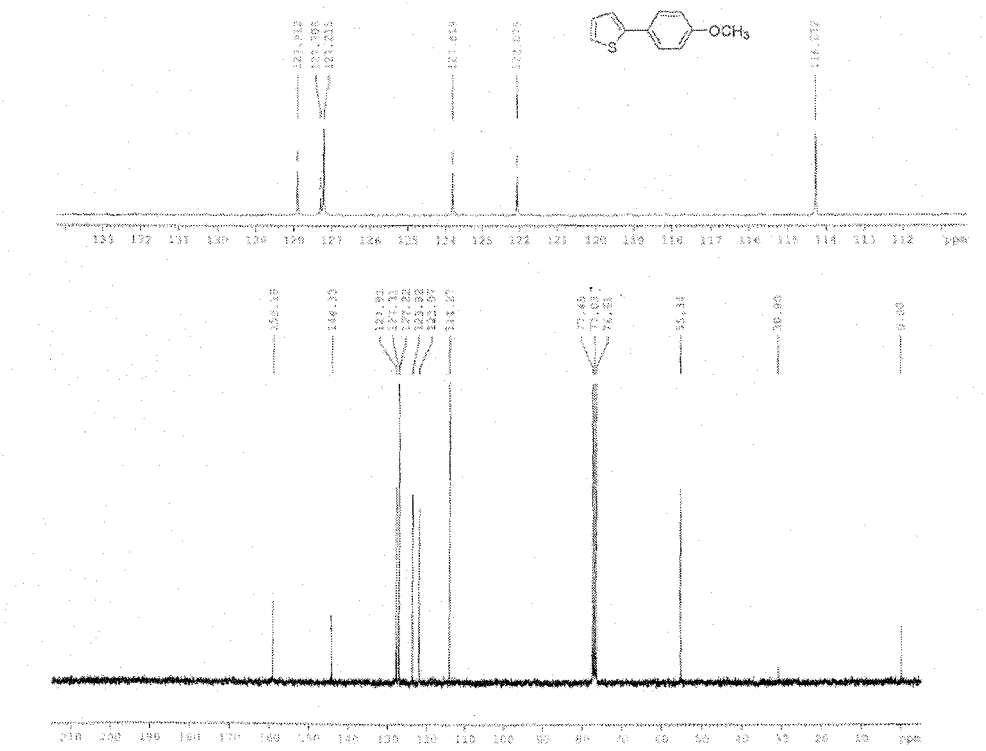
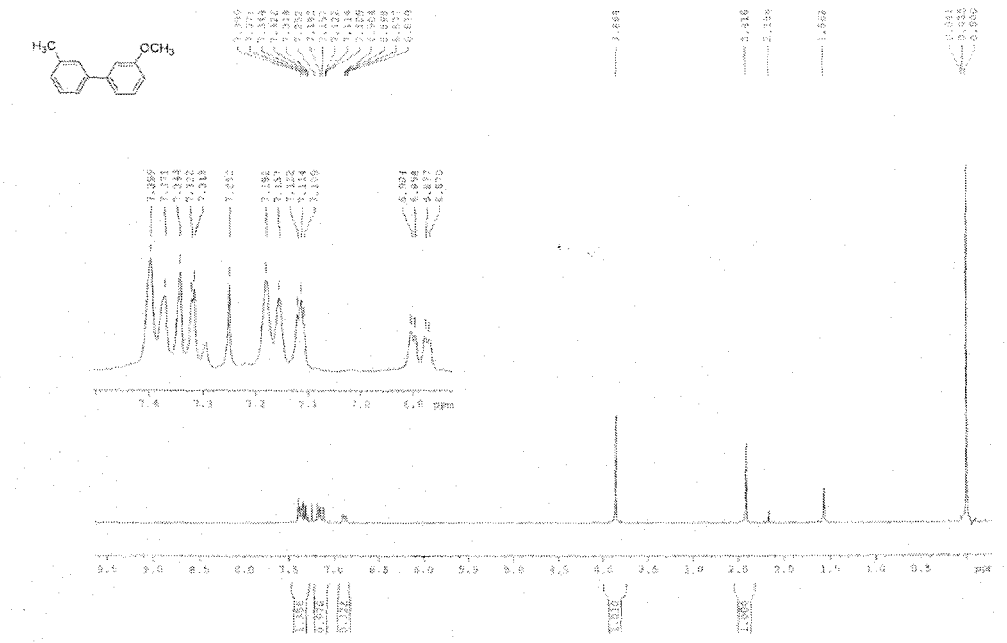
N



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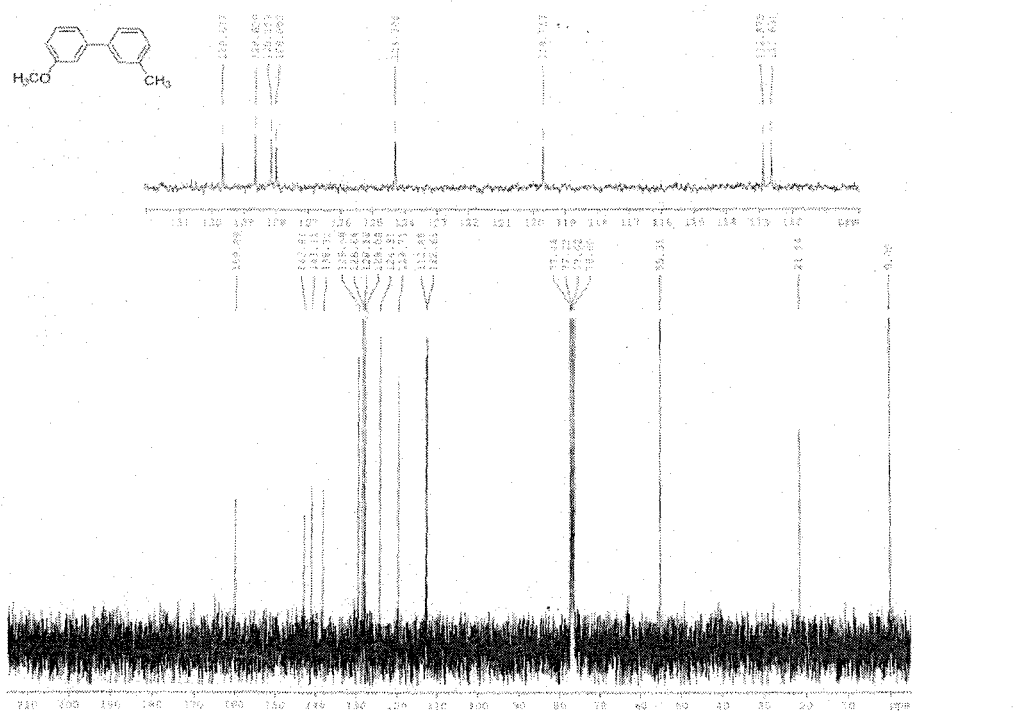
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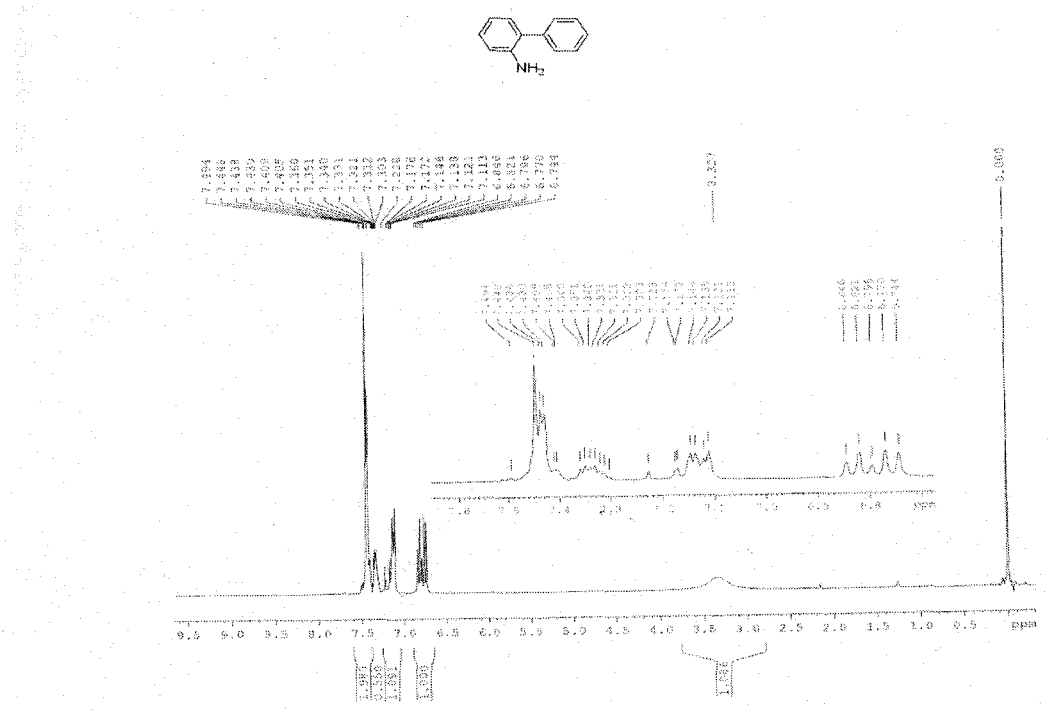

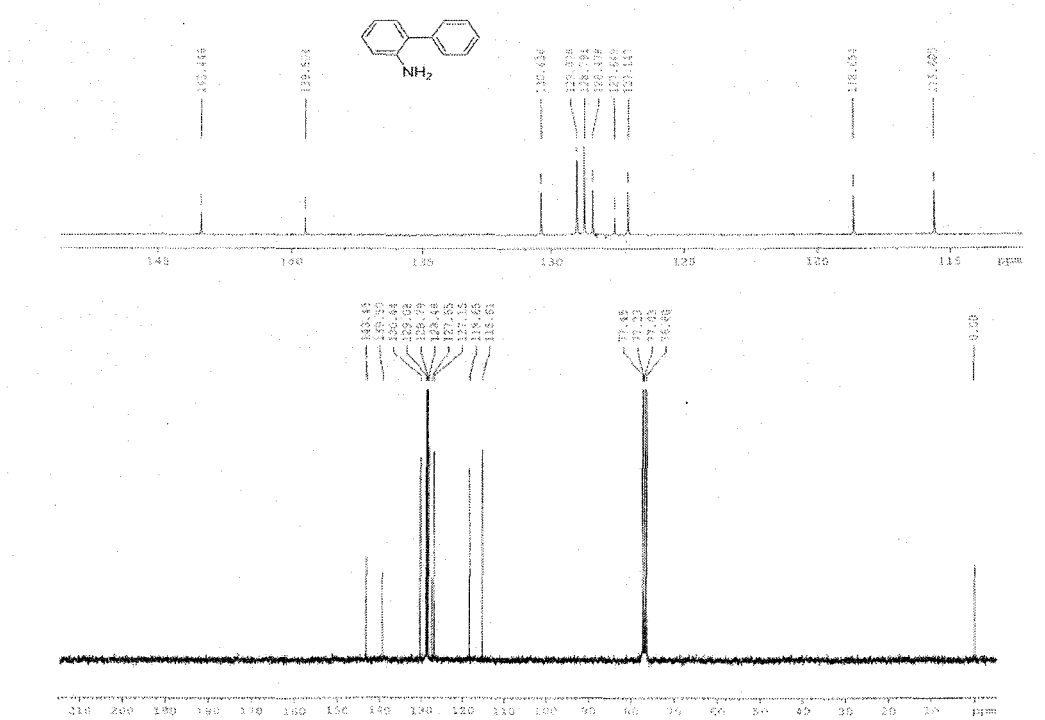

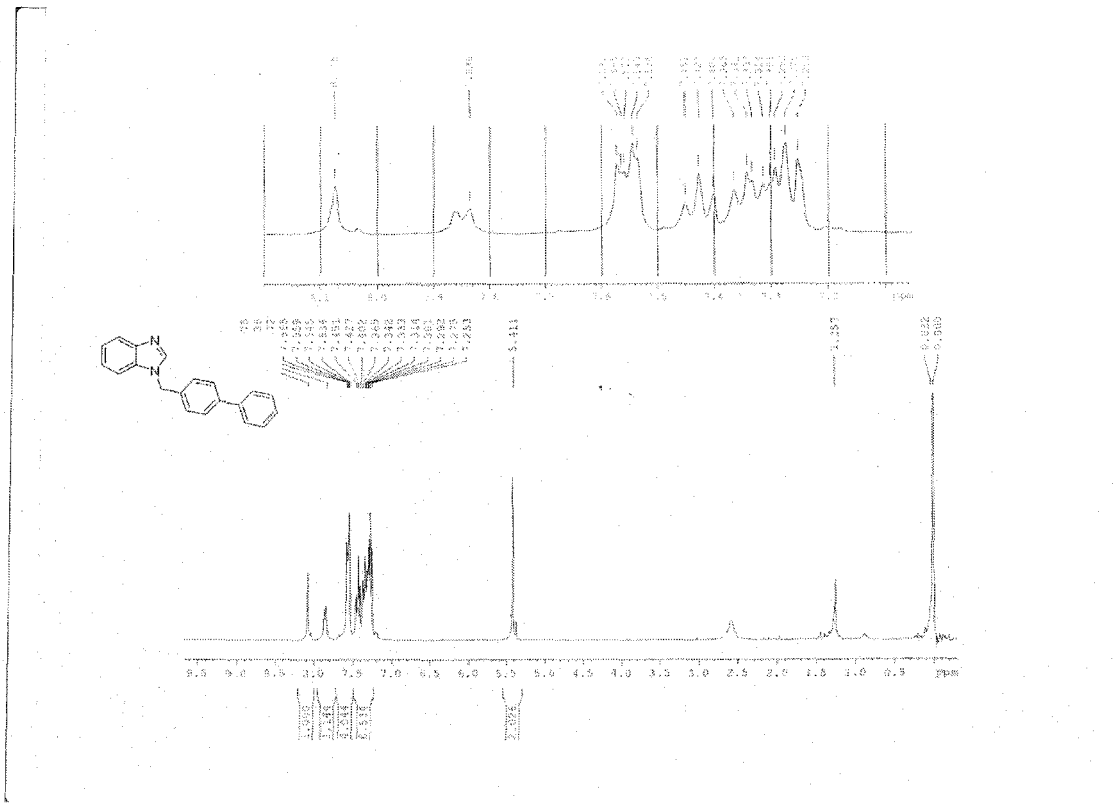

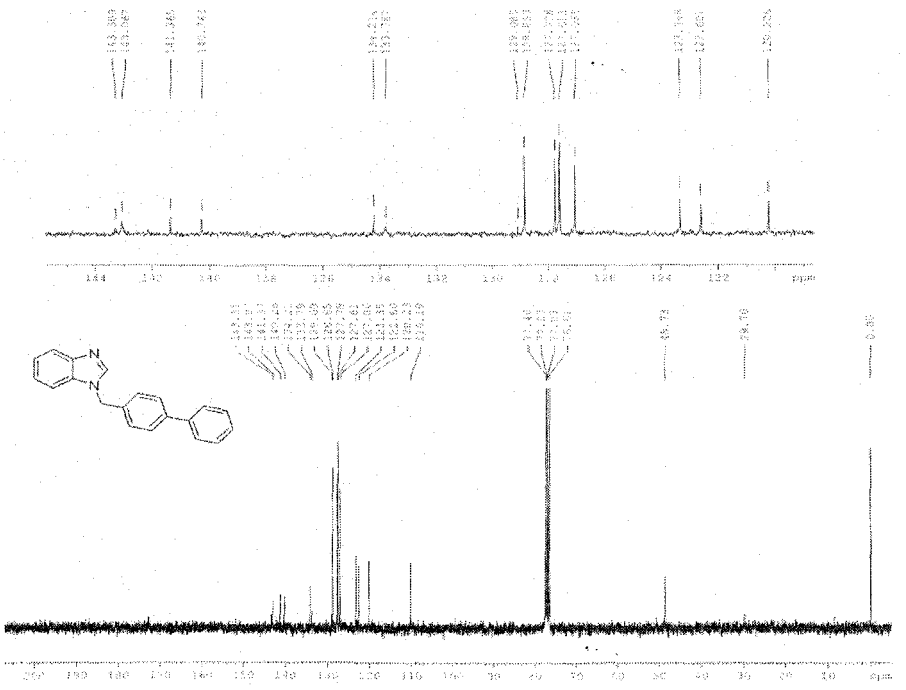

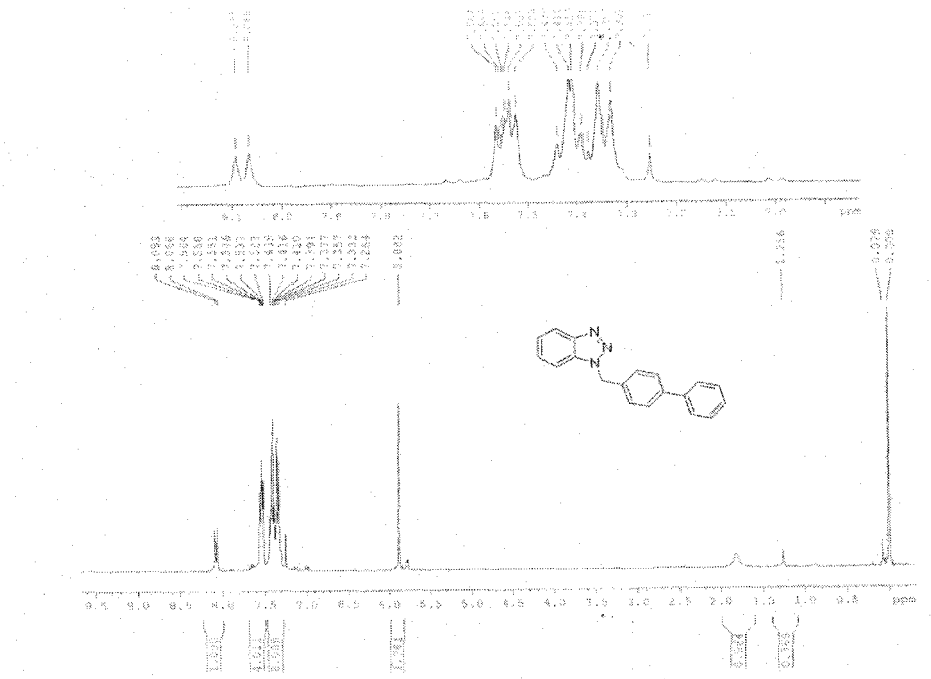

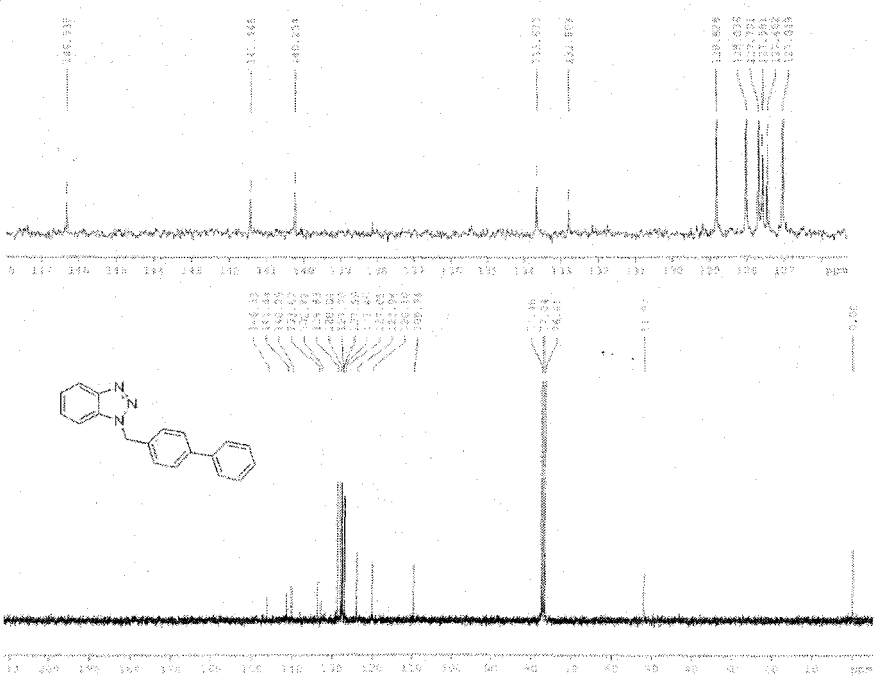

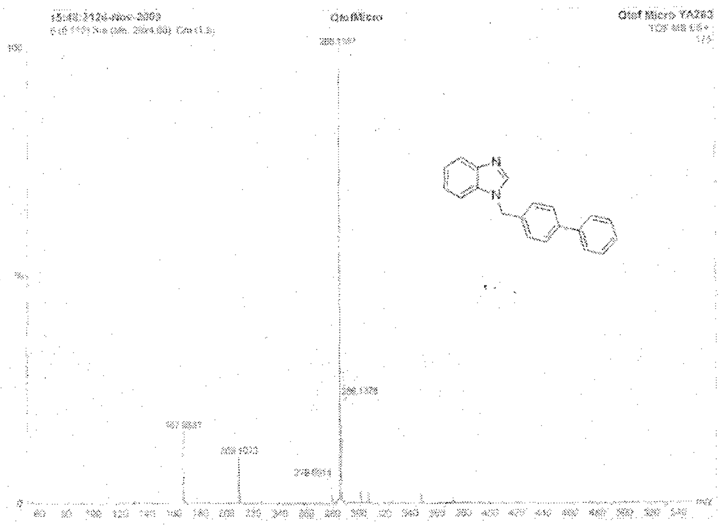
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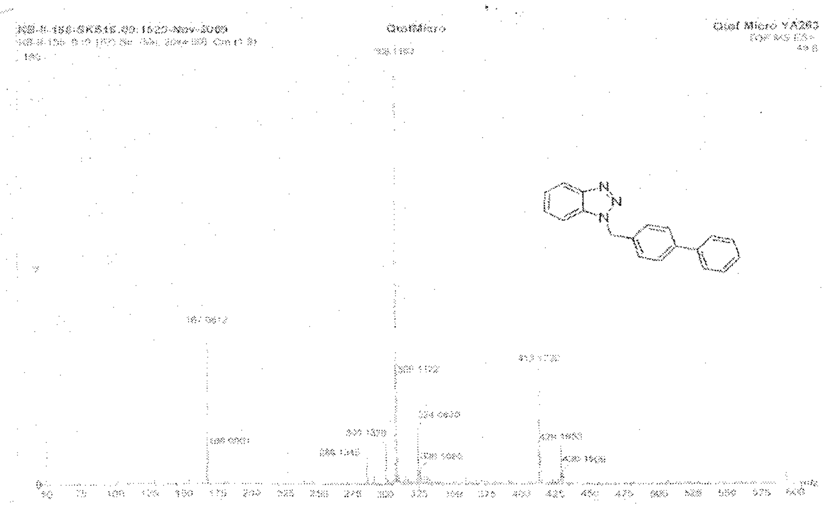
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