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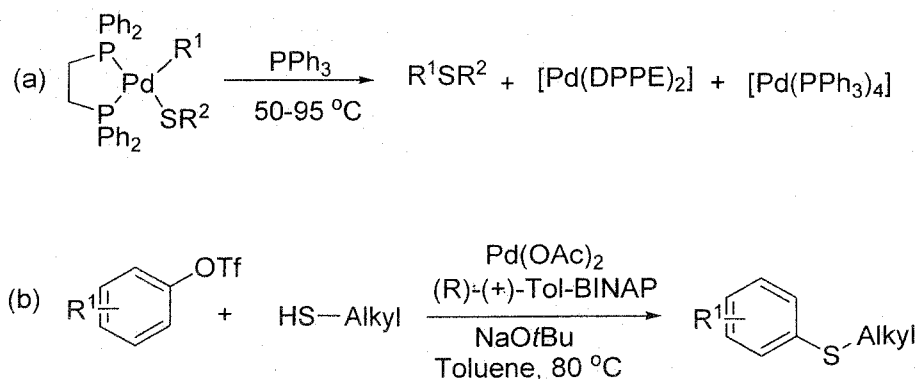
- Examples with Pd-catalyzed C-S coupling reactions:

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'Bu 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]
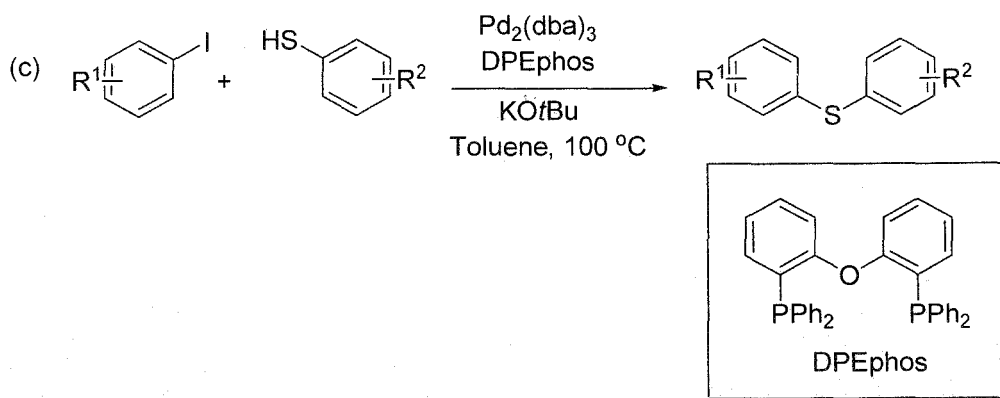
Scheme 1
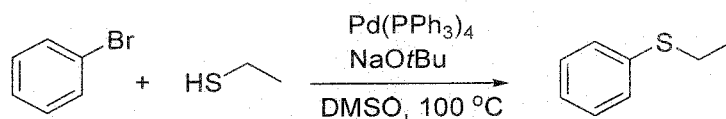
Other efficient palladium catalysts based on phosphines or diverse organophosphane derivatives have also been reported by Hartwig,[15] Zheng,[16] and more recently by Schopfer and Schlapbach (Scheme 2).[17a]

Scheme 2

(c)


(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.
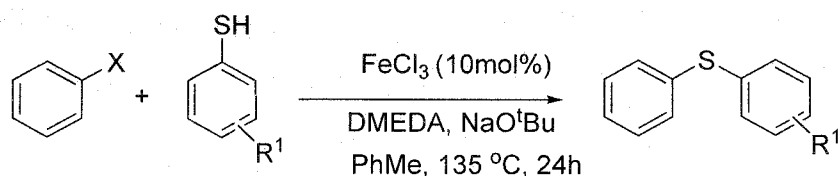
Scheme 3

(a)

(b)

X = I, Br   R' = aryl, alkyl
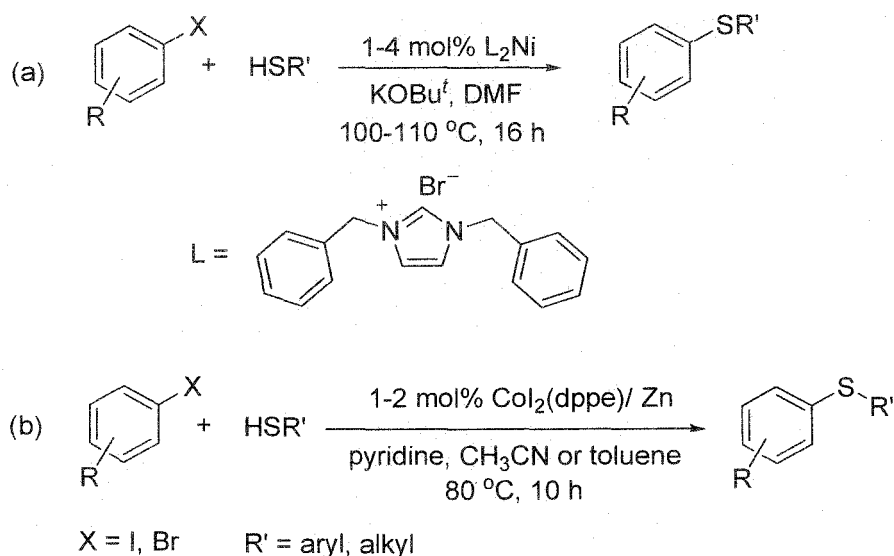
(a) Zhang's N-heterocyclic carbene-based Ni-catalyzed C-S coupling
(b) Cheng's Cobalt-catalyzed thiolation of aryl halides.

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.
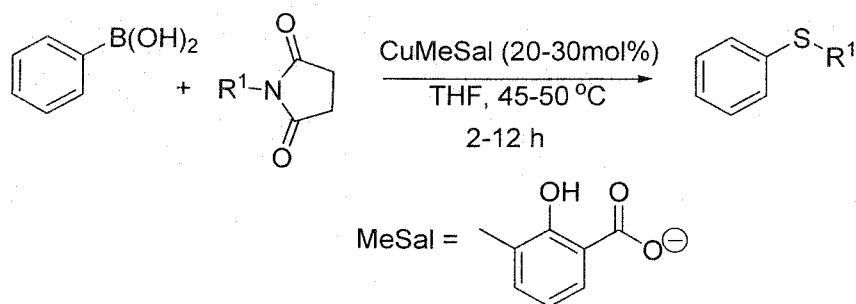
Scheme 5
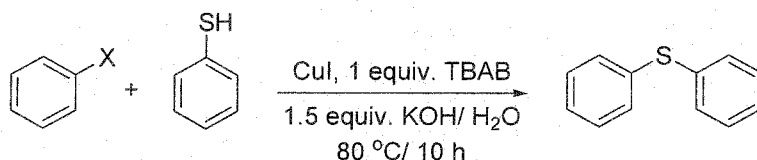
Punniyamurthy's copper catalyzed thiolation of aryl halides in water

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
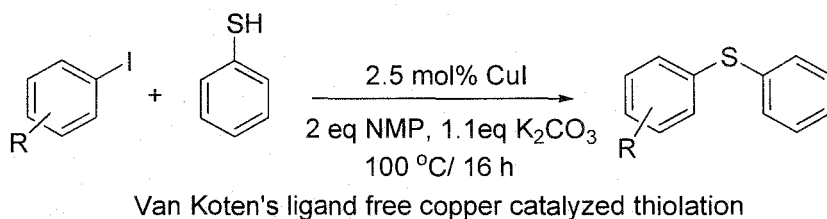
In most of the cases, the protocol is either substrate-specific or requires phosphine or phosphine-free ligands besides requirement high temperature, strong base, long reaction time, etc. Therefore, the development of more efficient, inexpensive, and mild catalytic systems involving copper and more generalized 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
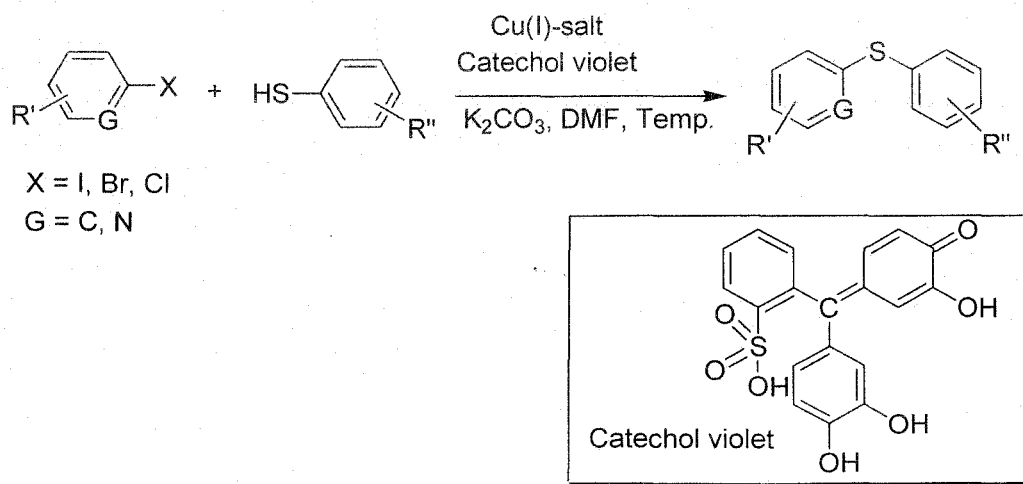
The CuI-CV-catalysed synthesis of diarylsulphides is represented

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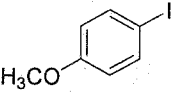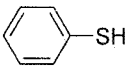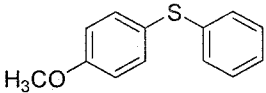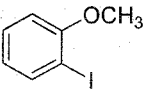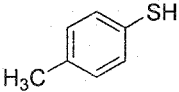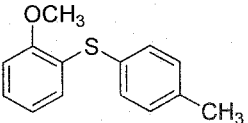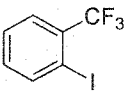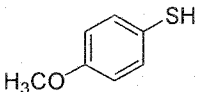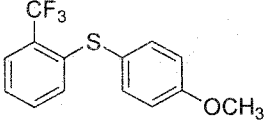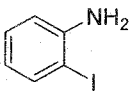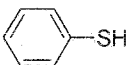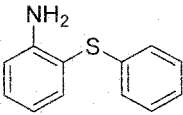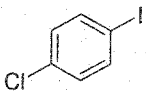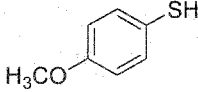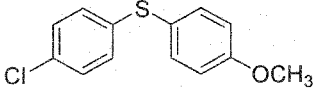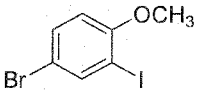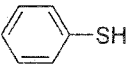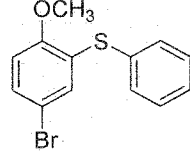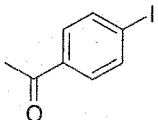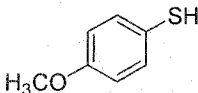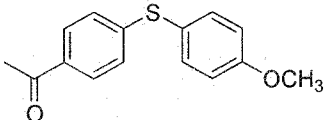
It is evident from Table 1 that the combination of CuI, CV, K_2CO_3 and DMF as solvent are apt for C-S coupling reaction. The optimized reaction conditions were then employed to the coupling of various functionalized aryliodides and aryl thiols (Scheme 9).

Scheme 9

yield 70 - 90 %
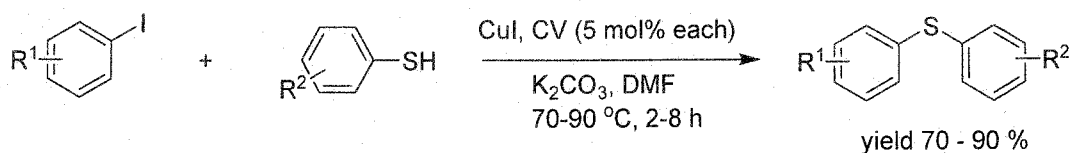
The results clearly demonstrated that the presence of electron donating or withdrawing group attached with aryl iodide did not influence the reactions. Furthermore, sterically hindered aryl iodides (entries 2, 3, 4 & 6) underwent C–S coupling smoothly to give corresponding diaryl sulfide in good to excellent 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	H₃CO—C₆H₄—I (H$_3$CO)	C₆H₅—SH	90 °/ 2 h	H₃CO—C₆H₄—S—C₆H₅	90
2	OCH₃-substituted aryl iodide	H₃C—C₆H₄—SH	70 °/ 8 h	OCH₃ / CH₃ diaryl sulfide	75
3	CF₃-substituted aryl iodide	H₃CO—C₆H₄—SH	85 °/ 6 h	CF₃ / OCH₃ diaryl sulfide	89
4	NH₂-substituted aryl iodide	C₆H₅—SH	90 °/ 4 h	NH₂ diaryl sulfide	90
5	Cl-substituted aryl iodide	H₃CO—C₆H₄—SH	80 °/ 6 h	Cl / OCH₃ diaryl sulfide	87
6	OCH₃ / Br-substituted aryl iodide	C₆H₅—SH	90 °/ 8 h	OCH₃ / Br diaryl sulfide	70
7	acetyl-substituted aryl iodide (O)	H₃CO—C₆H₄—SH	70 °/ 5 h	acetyl / OCH₃ diaryl sulfide (O)	86

Aryl iodide: thiol: CuI-CV (1 mmol: 1.1mmol: 5 mol %) and K₂CO₃ (1mmol), DMF (2ml).
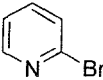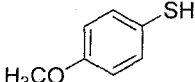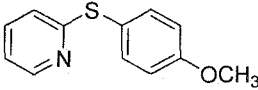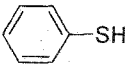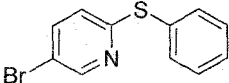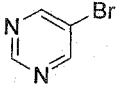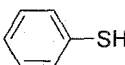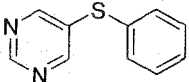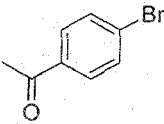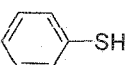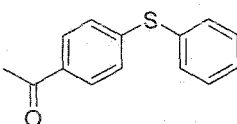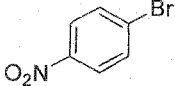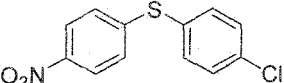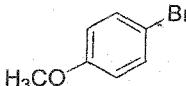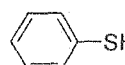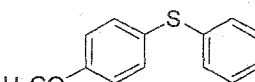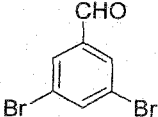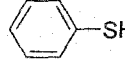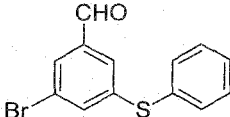
The next part of this study involved the application of our protocol to the CuI-CV-catalyzed S-arylation of thiols with aryl bromides. It was noted that in case of bromoiodoarene, S-arylation selectively occurred with iodide keeping the bromide unchanged. Electron-deficient pyridine ring bearing bromo 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 K₂CO₃ as the base (Scheme 10).

Scheme 10

$$Ar^1\!-\!Br \;+\; Ar^2\!-\!SH \xrightarrow[\text{K}_2\text{CO}_3,\ \text{DMF},\ 70\ ^\circ\text{C}]{\text{CuI, CV (5 mol\% each)}} Ar^1\!-\!S\!-\!Ar^2$$
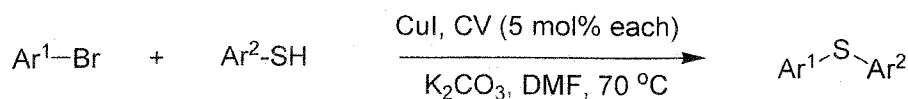
A reaction between *p*-bromoanisole & thiophenol under this condition leaves the *p*-bromoanisole intact even after 21 h (Table 3, entry 6).

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

yield 83- 90 %
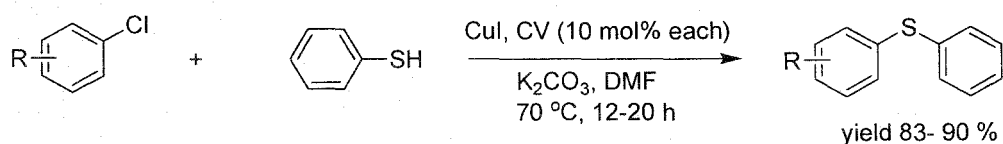
Table 4

Entry	Aryl Chloride	Thiol	Temp/Time	Product	Yield(%)
1	O_2N ... Cl, NO_2	SH	70 °C/ 18 h	NO_2 ... S ... O	83
2	O_2N ... Cl	SH	70 °C/ 20 h	O_2N ... S	85
3	... Cl, O	SH	70 °C/ 12 h	... S, O	90
4	HO ... Cl	SH	70 °C/ 20 h	HO ... S	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) (PPh₃)₂] NO₃ 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

Yield 80-85 °C

94
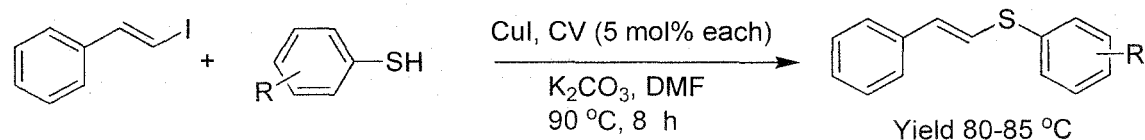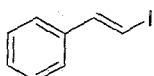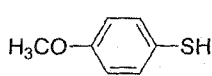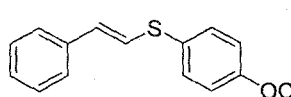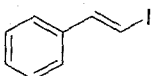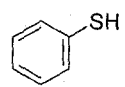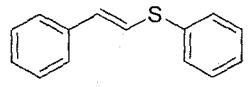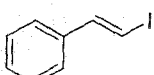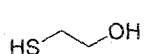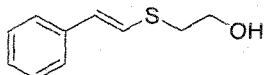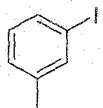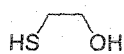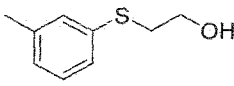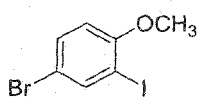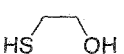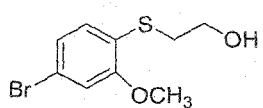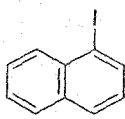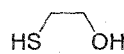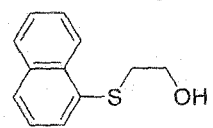
Table 5

Entry	Iodide	Thiol	Temp/Time	Product	Yield(%)
1		H₃CO—⟨⟩—SH	90 °C / 9 h		83
2		⟨⟩—SH	90 °C / 9 h		83
3		HS⌐⌐OH	90 °C/ 9 h		93

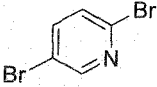Styryl iodide: thiol: CuI-CV (1 mmol: 1.1mmol: 5 mol %) and K₂CO₃ (1mmol), DMF(2ml).

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		HS⌐OH	90 ° / 4 h		83
2		HS⌐OH	90 ° / 4 h		87
3		HS⌐OH	90 ° / 4 h		78

Aryl iodide: thiol: CuI-CV (1 mmol: 1.1mmol: 5 mol %) and K₂CO₃ (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 %), K₂CO₃ (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): v_{max} 2934, 2837, 1460, 1299 cm^{-1}; ^{1}H 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): v_{max} 2923, 1682, 1462 cm^{-1}; ^{1}H 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): v_{max} 2924, 2855, 1461 cm^{-1}; ^{1}H 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): v_{max} 3058, 1556, 1450, 1010 cm^{-1}; ^{1}H 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): v_{max} 3048, 1546, 1440 cm^{-1}; ^{1}H 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): v_{max} 3412, 2924, 1044 cm^{-1}; ^{1}H 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): v_{max} 3062, 2829, 2720, 1704, 1557, 1194 cm^{-1}; ^{1}H 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): v_{max} 2924, 2857, 1461 cm^{-1}; ^{1}H 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): v_{max} 3097, 3063, 1336, 1083 cm^{-1}; ^{1}H 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): v_{max} 2923, 2855, 1462 cm^{-1}; ^{1}H 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): v_{max} 2924, 2876, 1597, 1042 cm^{-1}; ^{1}H 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): v_{max} 2924, 2872, 1462, 1377 cm^{-1}; ^{1}H 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): v_{max} 3400, 2924, 2876, 1597, 1042 cm^{-1}; ^{1}H 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): v_{max} 3424, 2924, 1475, 1044 cm^{-1}; ^{1}H 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$_9$H$_{12}$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): v_{max} 3390, 2935, 2838, 1400, 1070 cm^{-1}; ^{1}H 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$_9$H$_{11}$BrO$_2$SNa: [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): v_{max} 3401, 3054, 2924, 1504, 1046 cm^{-1}; ^{1}H 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: ¹H NMR

(5-Bromo-2-methoxyphenyl)(phenyl)sulfane
Solvent : CDCl₃, Instrument Frequency: 300 MHz

Table 1: Entry 6: ¹³C NMR

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

7.331
7.304
7.256
7.166
7.153
7.146
7.139
6.949
6.943
6.923
6.918
6.888
6.860
6.853
6.828

3.888

2.354
2.278
2.171

1.587

0.000

OMe
S
Me

(2-Methoxyphenyl)(p-tolyl)sulfane
Solvent: CDCl$_3$, Instrument Frequency: 300 MHz

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

OMe
S
Me

(2-Methoxyphenyl)(p-tolyl)sulfane
Solvent: CDCl$_3$, Instrument Frequency: 75 MHz

156.47

137.75
132.99
130.09
129.83
127.39
125.70
121.19
110.56

77.45
77.02
76.60

55.86

21.18

0.00

101

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

Solvent: CDCl$_3$, Instrument Frequency: 300 MHz

7.555
7.529
7.388
7.360
7.200
7.172
7.120
7.094
6.900
6.870
6.840

3.785
3.755

3.785
3.755

2.068

0.065
0.056
0.033
0.000

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

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

Solvent: CDCl$_3$, Instrument Frequency: 75 MHz

159.47
138.12
135.76
130.84
128.49
125.52
125.44
124.01
121.31
114.28

76.42
76.00
75.57

54.35

0.00
-1.04

7.4068
7.3852
7.2501
7.1952
7.1739
7.0795
7.0583
6.9079
6.8863

3.8176

1.5453

0.0702
-0.0032

7.4068
7.3852

7.2501

7.1952
7.1739

7.0795
7.0583

6.9079
6.8863

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

(4-Chlorophenyl)(4-methoxyphenyl)sulfane
Solvent: CDCl$_3$, Instrument Frequency: 400 MHz

1.85 1.82 1.80 2.00

7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 ppm

1.85 1.82 1.80 2.00

3.46

10   9   8   7   6   5   4   3   2   1   0   ppm

160.0570

137.3471
135.4487
131.6102
129.3339
128.9841
123.8001

115.1178

77.3145
76.9972
76.6797

55.3539

1.0016

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

(4-Chlorophenyl)(4-methoxyphenyl)sulfane
Solvent: CDCl$_3$, Instrument Frequency: 100 MHz

137.3471
135.4487

131.6102

129.3339
128.9841

123.8001

135   130   ppm

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

103

¹H NMR spectrum

Peak labels (left to right): 7.7851, 7.7639, 7.4760, 7.4543, 7.2496, 7.0947, 7.0737, 6.9611, 6.9394

Expansion peak labels: 7.7851, 7.7639 / 7.4760, 7.4543 / 7.2496 / 7.0947, 7.0737 / 6.9611, 6.994

Upfield singlets: 3.8455, 2.5235, 1.5602, -0.0110

Integrations (expansion): 1.77, 1.61, 1.66, 1.76

Integrations (full): 1.77, 1.61, 1.66, 1.75, 3.00, 2.93

Table 2: Entry 7: ¹H NMR

1-(4-(4-Methoxyphenylthio)phenyl)ethanone
Solvent: CDCl₃, Instrument Frequency: 400 MHz

¹³C NMR spectrum

Peak labels: 196.9401, 160.5957, 146.7466, 136.6927, 133.8381, 128.6995, 125.7616, 121.3537, 115.3007, 77.3154, 76.9976, 76.6796, 55.3225, 26.3007

Expansion peak labels: 160.5957, 146.7466, 136.6927, 133.8381, 128.6995, 125.7616, 121.3537, 115.3007

Table 2: Entry 7: ¹³C NMR

1-(4-(4-Methoxyphenylthio)phenyl)ethanone
Solvent: CDCl₃, Instrument Frequency: 100 MHz

9.0849
9.0792
8.1259
8.1200
8.1032
8.0973
7.5011
7.4794
7.2496
7.0596
7.0379
6.9927
6.9701
3.8834
1.5364
0.0584
-0.0122

(4-Methoxyphenyl)(2,4-dinitrophenyl)sulfane
Solvent: CDCl₃, Instrument Frequency: 400 MHz

0.56
0.83
1.80
1.85
0.99

9.0   8.5   8.0   7.5   7.0   ppm

0.66
0.83
1.80
1.85
0.99
3.00

10   9   8   7   6   5   4   3   2   1   0   ppm

161.8914
149.4531
144.1291
143.6448
137.5138
128.6471
126.7265
121.3738
119.1986
116.2489
77.3115
76.9939
76.6763
55.5327

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

(4-Methoxyphenyl)(2,4-dinitrophenyl)sulfane
Solvent: CDCl₃, Instrument Frequency: 100 MHz

161.8914
149.4531
144.1291
143.6448
137.5138
128.6471
126.7265
121.3738
119.1986
116.2489

160   150   140   130   120   ppm

200   190   180   170   160   150   140   130   120   110   100   90   80   70   60   50   40   30   20   10   0   ppm

105

13C NMR

Table 3: Entry 2: 13C NMR

1-(4-(Phenylthio)phenyl)ethanone
Solvent: CDCl₃, Instrument Frequency: 75 MHz

196.9221

144.7612
134.9359
134.4342
133.7326
132.0523
131.9428
130.4372
129.5609
128.7935
128.6774
127.4127
124.3317

134.9359
134.4342
133.7326

132.0523
131.9428

130.4372

129.5609
128.7935
128.6774

127.4127

77.3128
76.9950
76.6770

26.3375

0.9418

134   132   130   128   ppm

¹H NMR

Table 3: Entry 2: ¹H NMR

1-(4-(Phenylthio)phenyl)ethanone
Solvent: CDCl₃, Instrument Frequency: 400 MHz

7.8197
7.7988

7.4996
7.4899
7.4810
7.4774
7.3962
7.3849
7.3814
7.2496
7.2128
7.1918

7.8197
7.7988
7.4996
7.4899
7.4810
7.4774
7.3962
7.3849
7.3814
7.2496
7.2128
7.1918

2.6534
2.5408

1.5811

-0.0100

8.0   7.8   7.6   7.4   7.2   ppm

2.00
1.65
2.70
1.82

2.00
1.65
2.70
1.82

3.10

10   9   8   7   6   5   4   3   2   1   0   ppm

220   200   180   160   140   120   100   80   60   40   20   0   ppm

1H NMR (peak list)

9.0177
8.5763
7.4451
7.4370
7.4331
7.4256
7.4214
7.4011
7.3901
7.3791
7.3737
7.3660
7.3616
7.2495

1.5658
1.5369

-0.0122

Table 4. Entry 3: 1H NMR
Solvent: CDCl3, Instrument Frequency: 400 MHz

5-(Phenylthio)pyrimidine

Integration: 1.00, 1.99, 2.06, 3.30

9.0177
8.5763
7.4451
7.4370
7.4331
7.4256
7.4214
7.4011
7.3901
7.3791
7.3737
7.3660
7.3616
7.2495

0.00

13C NMR

157.00
156.23

132.73
131.59
129.90
128.84

77.46
77.04
76.61

Table 4. Entry 3: 13C NMR
Solvent: CDCl3, Instrument Frequency: 75 MHz

5-(Phenylthio)pyrimidine

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

Phenyl(styryl)sulfane
Solvent: CDCl$_3$, Instrument Frequency: 300 MHz

Table 5: Entry 1: ^{13}C NMR

Phenyl(styryl)sulfane
Solvent: CDCl$_3$, Instrument Frequency: 75 MHz

108

Table 5: Entry 3: ^{1}H NMR

2-(Styrylthio)ethanol
Solvent: CDCl$_3$, Instrument Frequency: 300 MHz

7.408 7.393 7.382 7.344 7.326 7.295 7.281 7.248 7.243 7.226 7.215 7.199 7.163 6.700 6.680 6.648 6.629 6.598 6.579 6.567

6.680 6.648 6.629 6.598

3.853 3.833 3.813 3.777

3.853 3.833 3.813 3.777

2.999 2.979 2.959 2.923

2.159 2.120

0.000 -0.011

2.999 2.979 2.959 2.923

3.0 ppm

ppm

ppm

2.930 1.155 0.997 1.000 0.665
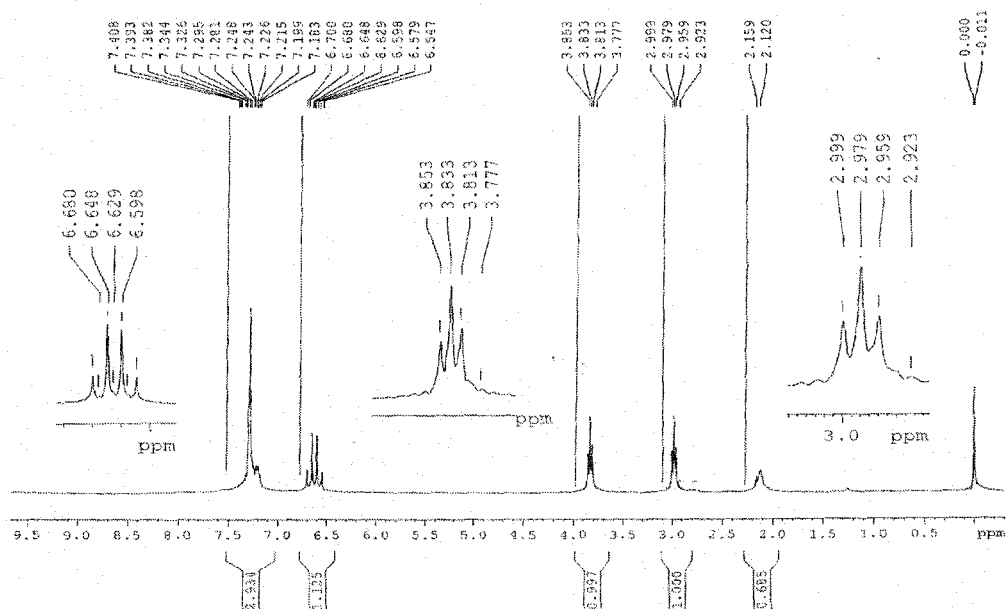
Table 5: Entry 3: ^{13}C NMR

2-(styrylthio)ethanol
Solvent: CDCl$_3$, Instrument Frequency: 75 MHz

136.64 128.92 128.67 127.21 125.63 123.73

77.49 77.06 76.64

61.02

35.93

0.00

109

QtofMicro

Qtof Micro YA263

BB-312 (0.010) Cu (0.50); Is (1.00,1.00) C9H12OSK
TOF MS ES+
7.99e12

207.0246

Table 6: Entry 1: HRMS

2-(*m*-Tolylthio)ethanol

208.0246 209.0246

BB-312 (0.010) Is (1.00,1.00) C9H12OSK
TOF MS ES+
7.99e12

207.0246

208.0277 209.0223 210.0253

BB-312 13 (0.127) Sm (Mn, 20x4.00); Cm (11:27)
TOF MS ES+
229

207.0244

208.0297 209.0220

204   205   206   207   208   209   210   211   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

Table 6: Entry 2: HRMS

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

285.9561   287.9561   288.9483

BB-311 (0.010) Is (1.00,1.00) C9H11BrO2SNa
TOF MS ES+
4.45e12

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

283   284   285   286   287   288   289   290   m/z

110

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

OMe

S

OH

Br

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

Solvent: CDCl₃, Instrument Frequency: 300 MHz

7.345
7.337
7.316
7.309
7.270
6.757
6.728

3.876
3.729
3.710
3.691
3.066
3.042

2.175
1.002

3.034
1.856
1.916
1.518

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

OMe

S

OH

Br

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

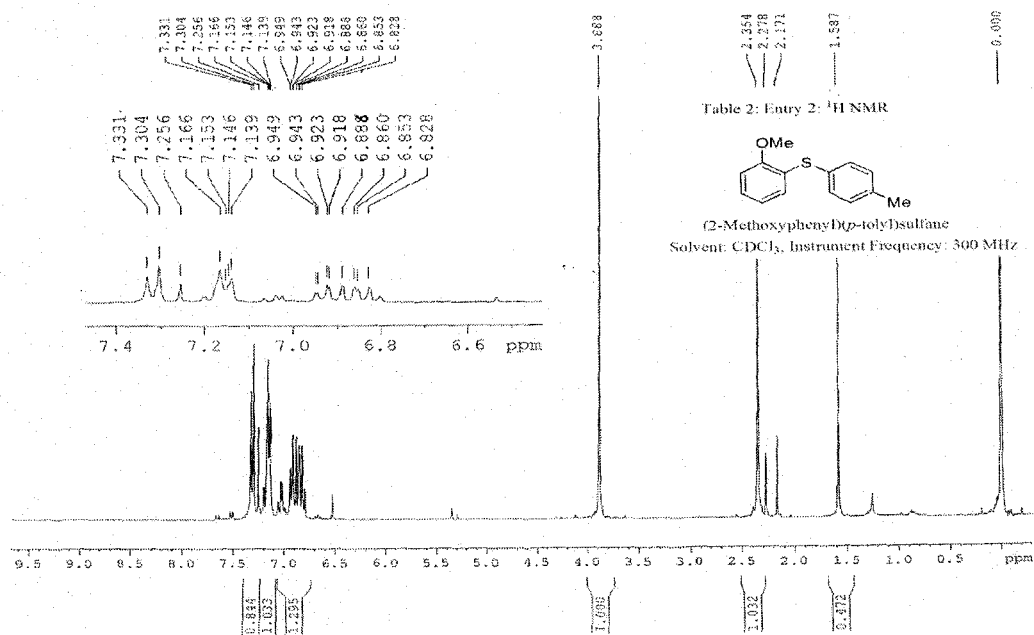Solvent: CDCl₃, Instrument Frequency: 75 MHz

157.39

133.80
130.90
125.06
113.07
112.23

77.47
77.05
76.63

60.15
56.14

36.43

0.00

Table 6: Entry 3: ¹H NMR

2-(Naphthalen-5-ylthio)ethanol

Solvent: CDCl₃, Instrument Frequency: 400 MHz

2-(Naphthalen-5-ylthio)ethanol

Solvent: CDCl₃, Instrument Frequency: 75 MHz

¹³C peaks: 134.06, 133.31, 131.81, 129.79, 128.67, 128.08, 127.80, 127.70, 127.11, 126.67, 126.32, 125.95, 125.50, 125.16, 125.07, 77.48, 77.06, 76.64, 60.41, 37.58, 37.03, 35.20, 34.69, 0.00

Inset peaks: 134.059, 133.310, 131.812, 129.792, 128.674, 128.080, 127.798, 127.696, 127.108, 126.675, 126.323

¹H peaks: 8.4648, 8.4440, 7.8644, 7.8447, 7.7849, 7.7645, 7.6614, 7.6434, 7.5950, 7.5777, 7.5599, 7.5571, 7.5392, 7.5376, 7.5194, 7.5021, 7.4837, 7.4419, 7.4213, 7.4023, 7.3829, 7.2503, 3.6998, 3.2021, 3.1870, 3.1593, 3.1444, 3.1295, 2.6808, 2.1511, 1.6550, 0.0034
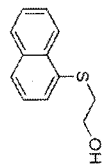
Integrations: 0.93, 1.00, 1.14, 0.94, 1.04, 0.94, 1.03, 2.35, 2.38, 0.94
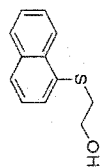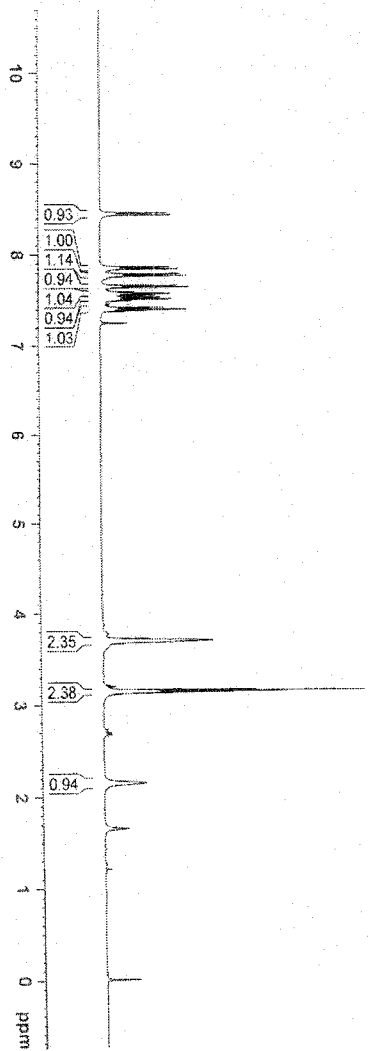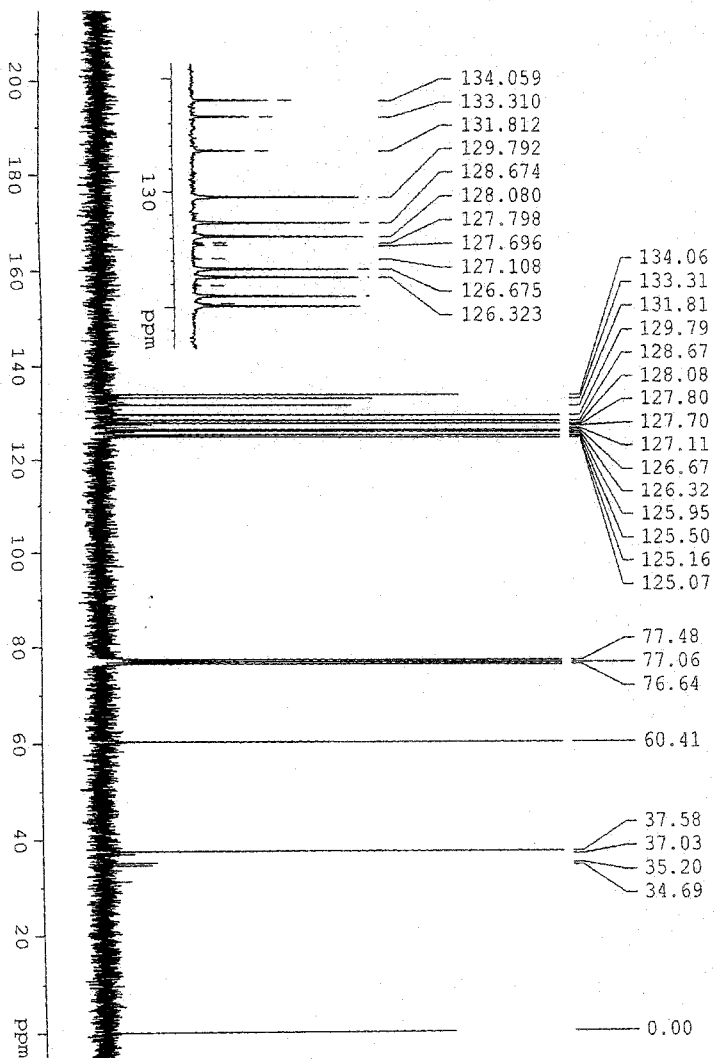
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Polyionic Heterogeneous Phenylating Agent for Base-Free Suzuki–Miyaura Coupling Reaction

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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
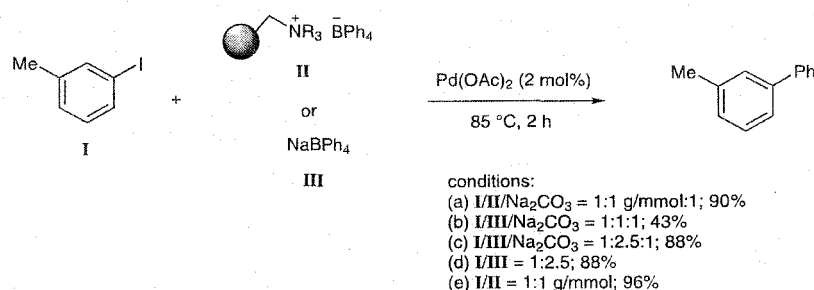
The palladium-catalyzed Suzuki–Miyaura (SM) coupling reaction of aryl halides with arylboronic acids and esters has been established as a robust synthetic protocol for the preparation of biaryl compounds.[1] The reaction has been applied to many areas, including natural product synthesis.[1c,2] Besides 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-

Scheme 1

conditions:
(a) I/II/Na$_2$CO$_3$ = 1:1 g/mmol:1; 90%
(b) I/III/Na$_2$CO$_3$ = 1:1:1; 43%
(c) I/III/Na$_2$CO$_3$ = 1:2.5:1; 88%
(d) I/III = 1:2.5; 88%
(e) I/II = 1:1 g/mmol; 96%
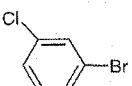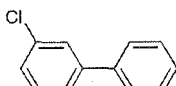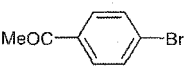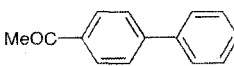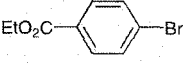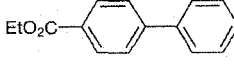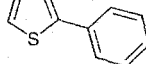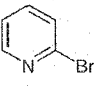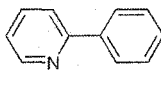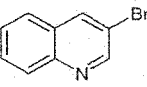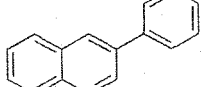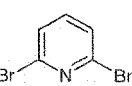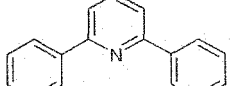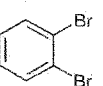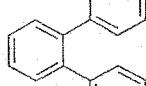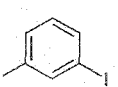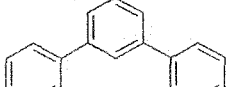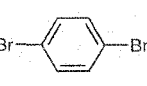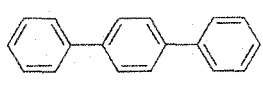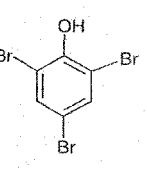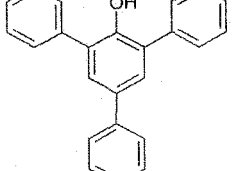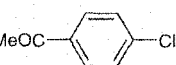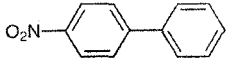
anionic character of the organic moiety attached to boron in triorganoboranes requires base to assist in the transmetalation process, the corresponding 'ate' species is capable of accelerating the transmetalation.[1e,15–19] The transmetalation process releases triphenylborane, which is water-sensitive 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$_2$Et) 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.

Acknowledgment

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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}. ^{1}H 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,
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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.

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(PPh₃)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 Pd₂(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 P₂-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] nanopar-

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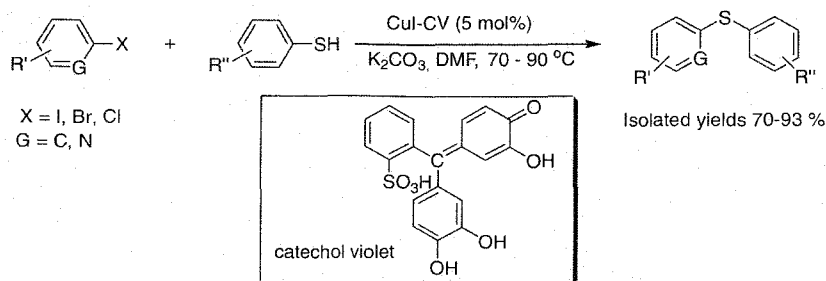
Scheme 1. The CuI-CV-catalyzed synthesis of diarylsulfides is represented.

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$_3$N	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 KOt-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 using 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 by-product 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
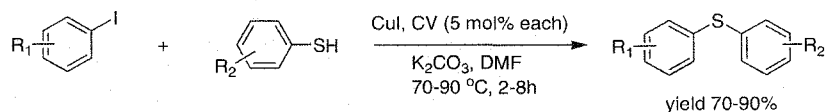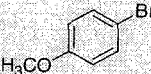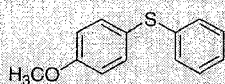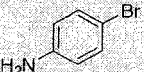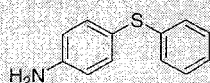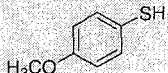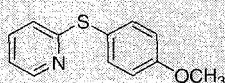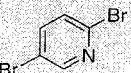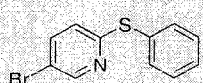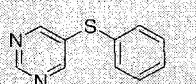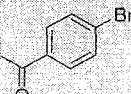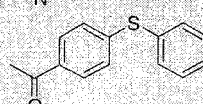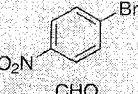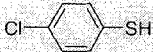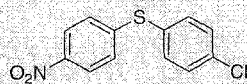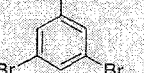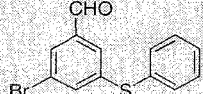
Entry	Aryl iodide	Thiol	Conditions[a] temp/time	Product	Yield[c] (%)
1			90 °C/2 h		90
2			70 °C/8 h		75
3			85 °C/6 h		89
4			90 °C/4 h		90
5			80 °C/6 h		87
6			90 °C/8 h		70
7			70 °C/5 h		86
8[b]			80 °C/4 h		71
9[b]			80 °C/4 h		69

[a] Aryl iodide: thiol: CuI-CV (1 mmol: 1.1 mmol: 5 mol %) and K₂CO₃ (1 mmol) was taken in DMF (2 mL).
[b] Aryl iodide: thiol: CuI-CV (0.5 mmol: 1.1 mmol: 10 mol %) and K₂CO₃ (1 mmol) was taken in DMF (2 mL).
[c] Yield refers to pure isolated products characterized by spectroscopic (¹H, ¹³C NMR, and IR) data.

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

$$Ar_1{-}Br \;+\; Ar_2{-}SH \xrightarrow[\text{K}_2\text{CO}_3, \text{DMF, 70-90 °C}]{\text{CuI, CV (10 mol\% each)}} Ar_1{-}S{-}Ar_2$$

yield 83-93%
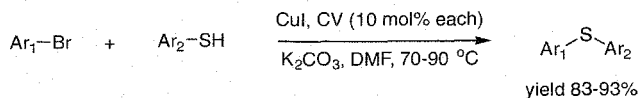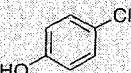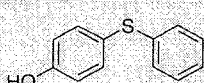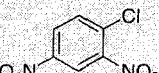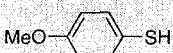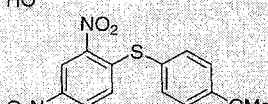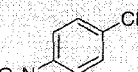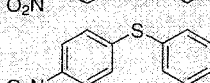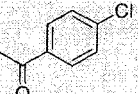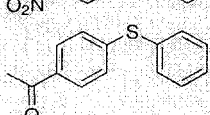
Entry	Bromoarene	Thiol	Conditions[a] temp/time	Product	Yield[b] (%)
1	H₃CO–C₆H₄–Br	C₆H₅–SH	90 °C/12 h	H₃CO–C₆H₄–S–C₆H₅	00
2	H₂N–C₆H₄–Br	C₆H₅–SH	90 °C/14 h	H₂N–C₆H₄–S–C₆H₅	00
3	2-Br-pyridine	H₃CO–C₆H₄–SH	70 °C/6 h	pyridin-2-yl–S–C₆H₄–OCH₃	88
4	2-Br-5-Br-pyridine	C₆H₅–SH	70 °C/2 h	Br–pyridinyl–S–C₆H₅	93
5	5-Br-pyrimidine	C₆H₅–SH	70 °C/7 h	pyrimidinyl–S–C₆H₅	84
6	4-Br-acetophenone	C₆H₅–SH	70 °C/18 h	acetophenyl–S–C₆H₅	87
7	O₂N–C₆H₄–Br	Cl–C₆H₄–SH	70 °C/20 h	O₂N–C₆H₄–S–C₆H₄–Cl	90
8	3,5-diBr-benzaldehyde	C₆H₅–SH	70 °C/8 h	Br–(CHO)C₆H₃–S–C₆H₅	83

[a] Bromoarene: thiol: Cul-CV (1 mmol: 1.1 mmol: 10 mol %) and K₂CO₃ (1 mmol) was taken in DMF (2 mL).
[b] Yield refers to the pure isolated products characterized by spectroscopic (¹H, ¹³C NMR, and IR) data.

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

$$R{-}C_6H_4{-}Cl \;+\; C_6H_5{-}SH \xrightarrow[\substack{\text{K}_2\text{CO}_3, \text{DMF} \\ 70\ °C, 18h}]{\text{CuI, CV (10 mol\% each)}} R{-}C_6H_4{-}S{-}C_6H_5$$

yield 86-92%
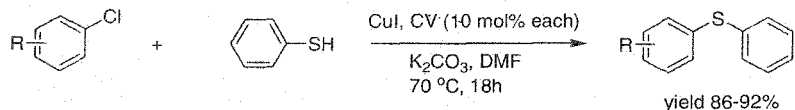
Entry	Aryl chloride	Thiol	Conditions[a] temp/time	Product	Yield[b] (%)
1	HO–C₆H₄–Cl	C₆H₅–SH	70 °C/20 h	HO–C₆H₄–S–C₆H₅	00
2	2,4-(O₂N)₂–C₆H₃–Cl	MeO–C₆H₄–SH	70 °C/18 h	(NO₂)₂C₆H₃–S–C₆H₄–OMe	86
3	O₂N–C₆H₄–Cl	C₆H₅–SH	70 °C/20 h	O₂N–C₆H₄–S–C₆H₅	88
4	4-Cl-acetophenone	C₆H₅–SH	70 °C/12 h	acetophenyl–S–C₆H₅	92

[a] Aryl chloride: thiol: Cul-CV (1 mmol: 1.1 mmol: 10 mol %) and K₂CO₃ (1 mmol) was taken in DMF (2 mL).
[b] Yield refers to the pure isolated products characterized by spectroscopic (¹H, ¹³C NMR, and IR) data.

Table 5
CuI-CV-catalyzed C–S coupling of styryl iodides with thiols
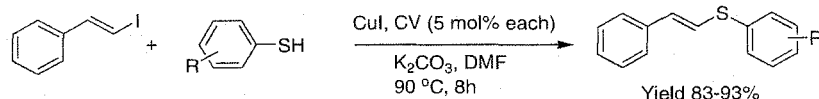
Entry	Styryl iodide	Thiol	Conditions[a] temp/time	Product	Yield[b] (%)
1		H$_3$CO—⬡—SH	90 °C/8 h		83
2		⬡(Cl)—SH	90 °C/8 h		83
3		HS⌒OH	90 °C/8 h		93

[a] Styryl iodide: thiol: CuI-CV (1 mmol: 1.1 mmol: 5 mol %) and K$_2$CO$_3$ (1 mmol) was taken in DMF (2 mL).
[b] Yield refers to the pure isolated products characterized by spectroscopic (^{1}H, ^{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		HS⌒⌒OH	90 °C/4 h		83
2		HS⌒⌒OH	90 °C/4 h		87
3		HS⌒⌒OH	90 °C/4 h		78

[a] Aryl iodide: thiol: CuI-CV (1 mmol: 1.1 mmol: 5 mol %) and K$_2$CO$_3$ (1 mmol) was taken in DMF (2 mL).
[b] Yield refers to the pure isolated products characterized by spectroscopic (^{1}H, ^{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

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}; ^{1}H 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.

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 CB₁ 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]

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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.

G = C, N, S
R¹ = Me, OMe, Br, F, NO₂, COMe, NH₂, OH
X = I, Br, Cl
R² = H, Me, OMe

Pd Catalyst = Pd(OAc)₂ or ARF-Pd
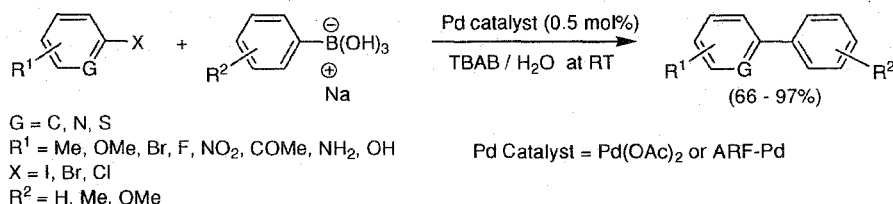
Scheme 1

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, NH₂, 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 (CDCl₃, δ ppm⁻¹ relative to TMS): 3.75 (3H, s, –OCH₃); 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). ¹³C NMR (CDCl₃, δ ppm⁻¹): 55.2 (OCH₃); 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 (CDCl₃, δ ppm⁻¹ relative to TMS): 3.79 (3H, s, –OCH₃); 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). ¹³C NMR (CDCl₃, δ ppm⁻¹): 55.54 (OCH₃); 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 (CDCl₃, δ ppm⁻¹ relative to TMS) 2.390 (6H, s, CH₃); 7.13–7.50 (8H, m, 8, all aromatic protons). ¹³C NMR (CDCl₃, δ ppm⁻¹): 21.3 (CH₃); 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 (CDCl₃, δ ppm⁻¹ relative to TMS): 2.41 (3H, s, CH₃); 3.86 (3H, s, –OCH₃); 7.11–7.39 (8H, m, all aromatic protons).¹³C NMR (CDCl₃, δ ppm⁻¹): 21.5 (CH₃); 55.3 (OCH₃); 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 (CDCl₃, δ ppm⁻¹ relative to TMS): 1.59 (3H, s, CH₃); 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). ¹³C NMR (CDCl₃, δ ppm⁻¹): 21.6 (CH₃); 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 (CDCl₃, δ ppm⁻¹ relative to TMS): 3.81 (3H, s, –OCH₃); 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). ¹³C NMR (CDCl₃, δ ppm⁻¹): 55.3 (OCH₃); 114.3; 122.1; 123.8; 127.2; 127.3; 127.9; 144.3; 159.2 (aromatic carbons).

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	(MeO-)	Ph–B(OH)$_3$Na	RT	4	(MeO-Ph)	92
2	(MeO-)	Ph–B(OH)$_3$Na	RT	4	(MeO-Ph)	88
3	(OMe)	Ph–B(OH)$_3$Na	RT	2.5	(OMe-Ph)	84
4	(Me-)	Ph–B(OH)$_3$Na	RT	4	(Me-Ph)	87
5	(F)	Ph–B(OH)$_3$Na	RT	4	(F-Ph)	92
6		Ph–B(OH)$_3$Na	RT	16		87
7	(NH$_2$)	Ph–B(OH)$_3$Na	RT	6	(NH$_2$-Ph)	85
8	(MeO, Me)	Ph–B(OH)$_3$Na	RT	8		72
9	(Me)	Ph–B(OH)$_3$Na	RT	2	(Ph)	95
10	Br–Br	Ph–B(OH)$_3$Na	RT	4	Br–Ph / Ph–Ph	22 / 66
11		Ph–B(OH)$_3$Na	RT	8		89
12		Ph–B(OH)$_3$Na	RT	6		67
13	(OH)	Ph–B(OH)$_3$Na	RT	24	(OH)	82
14	HO–Cl	Ph–B(OH)$_3$Na	100 °C	24	No Reaction	
15	H$_2$N–Cl	Ph–B(OH)$_3$Na	100 °C	24	No Reaction	
16	O$_2$N–Cl	Ph–B(OH)$_3$Na	100 °C	5	O$_2$N–Ph	90
17	(Me, O)	Ph–B(OH)$_3$Na	100 °C	4		85
18	MeO–I	Me–B(OH)$_3$Na	RT	8		79
19	Me–I	Me–B(OH)$_3$Na	RT	9		86
20	MeO–	Me–B(OH)$_3$Na	RT	8.5		74
21	Me–I	MeO–B(OH)$_3$Na	RT	7	Me–OMe	97
22		Me–B(OH)$_3$Na	RT	3.5		66
23	(Br,N,Br)	Ph–B(OH)$_3$Na	RT	8	Ph–N–Ph	83
24	(S)	MeO–B(OH)$_3$Na	RT	5	(S–OMe)	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$_2$O (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$_2$SO$_4$), 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)-1H-benzo[d]imidazole (334 mg, 1 mmol) or 1-(4-iodobenzyl)-1H-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

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	MeO—⟨ ⟩—I	PhB(OH)₃Na	RT	5	MeO—⟨ ⟩—Ph	85
2	MeO⟨ ⟩I	PhB(OH)₃Na	RT	5	MeO⟨ ⟩Ph	88
3	Me(O)C—⟨ ⟩—Br	PhB(OH)₃Na	100 °C	4	Me(O)C—⟨ ⟩—Ph	92
4	Me—⟨ ⟩—I	PhB(OH)₃Na	100 °C	3	Me—⟨ ⟩—Ph	93
5	MeO⟨ ⟩I	Me⟨ ⟩B(OH)₃Na	100 °C	5	MeO⟨ ⟩⟨ ⟩Me	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–H₂O (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 Na₂SO₄, 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. ¹H NMR (CDCl₃): δ 5.41 (2H, s, (CH₂); 7.25–7.83 (13H, m, all aromatic protons); 8.07 (1H, s, aromatic proton). ¹³C NMR (CDCl₃): δ 48.7 (CH₂ 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 C₂₀H₁₆N₂H: [M+H]⁺, 285.1392; found: 285.1387.

Spectral data for 3. ¹H NMR (CDCl₃): δ 5.88 (2H, s, (CH₂); 7.25–8.09 (13H, m, all aromatic protons). ¹³C NMR NMR (CDCl₃): δ 51.9 (CH₂ 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 C₁₉H₁₅N₃Na: [M+Na]⁺ 308.1164; found: 308.1163.

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