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 CB_1 antagonist for the treatment of obesity[8c] or apoptolidin A, a potent antitumor agent[8d] have been synthesised on a large scale employing the SM coupling as a key step. Similarly, benzimidazole derivatives bearing substituted biphenyl moieties, potential inhibitors of hepatitis C virus, have been prepared using the SM coupling reaction.[9] Review articles by Danishefsky *et al.*[10] and Nicolaou *et al.*[11] amply demonstrate various applications of the SM coupling reaction in the synthesis of natural products.

In recent years, amelioration of the SM coupling reaction has been directed towards the more efficient, economic and greener techniques, especially in respect of Pd-catalyst, requirement of base and carrying out the reaction in water or in the absence of any solvent.[12] Recent trends in organic synthesis involve reactions under solvent-free or on-water conditions to obtain the target molecule in a cleaner and environmentally benign way.[13] Although many organic reactions are facilitated in aqueous media, some reactions proceed very slowly because of poor solubility of the substrate/reagents in water. In the case of SM couplings, hydrophobic aryl boronic acids often show very slow and/or incomplete conversions along with the difficulty to isolate the products from the reaction mixture.[14]

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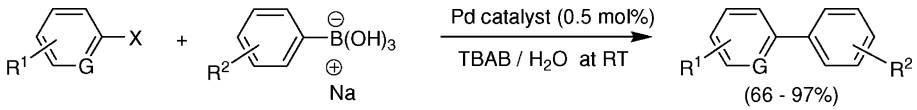
Efforts have been made to overcome the problem by introducing phase transfer catalysts,[15] water soluble salts of reagents[16] or catalysts[17] or carrying out the reaction in aqueous buffer.[18] Two types of water-soluble organoborate salts *viz*. potassium aryl trifluoroborates[16a–d] and sodium aryl 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.

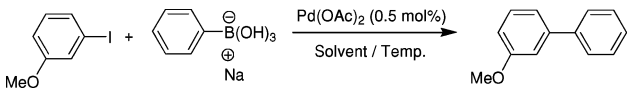


G = C, N, S
R^1 = Me, OMe, Br, F, NO_2, COMe, NH_2, OH
X = I, Br, Cl
R^2 = H, Me, OMe

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% $Pd(OAc)_2$.

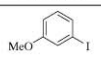
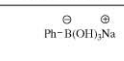
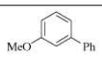
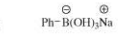
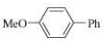
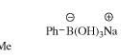
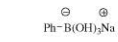
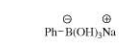
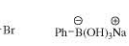
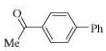
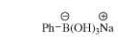
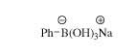
This led to the formation of the desired unsymmetrical biphenyl within 4 h at room temperature in 92% yield (Table 1, entry 6). An experiment with 0.5 equivalents of TBAB, however, afforded the desired product only in 50% yield, even after 8 h (Table 1, entry 7). It was revealed that polar protic or 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, NH_2, F and I underwent smooth SM coupling affording the corresponding unsymmetrical biphenyls in 84–94% yields (Table 2, entries 1–7). Mechanistically, the oxidative addition of aryl halides to palladium(0) depends on the nature of halogens and occurs in the descending order of I > Br > Cl.[20] We therefore examined the couplings of other aryl electrophiles bearing bromide and chloride. Several aryl bromides including di- and tribromoarenes were found to give the corresponding unsymmetrical biaryls in good to excellent yields (Table 2, entries 8–13). While *p*-bromoacetophenone showed a faster rate of reaction (2 h) (Table 2, entry 9), 2,4,6-tribromophenol required a longer time (24 h) (Table 2, entry 13) for the coupling reaction, which may be due to the presence of the electron-withdrawing acetyl group in the former example. Thus, aryl iodides and bromides underwent easy coupling with phenyl trihydroxyborate. A similar reaction with aryl chloride was not successful even after heating the reaction mixture at 100 °C for 24 h (Table 2, entries 14–15). Leadbeater *et al.*[18a] reported the microwave-assisted SM coupling of aryl chlorides at 150–175 °C in aqueous media indicating that aryl chlorides are very sluggish towards the SM coupling reaction and require relatively higher temperature, longer reaction time and/or the presence of electron-withdrawing groups. We examined aryl chlorides bearing nitro or acetyl groups, which however afforded the desired coupled products in excellent yields at refluxing temperatures (100 °C) (Table 2, entries 16–17). Changing the coupling partner phenyltrihydroxyborate with *m*-tolyltrihydroxyborate and *p*-anisyltrihydroxyborate did work efficiently with bromo and iodoarenes (Table 2, entries 18–22 and 24). The SM coupling reaction with heteroaryl halides was also successful. For example, 3-bromoquinoline or 2,6-dibromopyridine gave the desired coupled products in 66% and 83% yields respectively (entries 22–23), while similar coupling of 2-iodothiophene with *p*-anisyltrihydroxyborate afforded the corresponding unsymmetrical biphenyl in 92% yield within 3 h (Table 2, entry 24).

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

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

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

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

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

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

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

Conclusions

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

Experimental

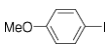
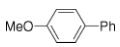
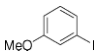
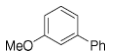
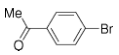
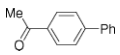
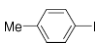
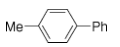
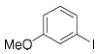
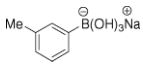
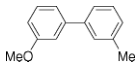
General procedure for Suzuki–Miyaura coupling

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

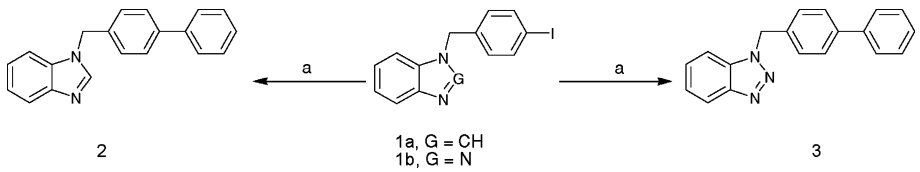
Synthesis of compounds 2 and 3

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

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

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

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



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

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

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

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

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