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Iridium-catalyzed C–H activation/borylation/oxidation for the preparation of bis-protected phloroglucinol derivatives

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ABSTRACT

The preparation of bis-protected phloroglucinol derivatives from a range of protected resorcinol substrates is presented. Functionalization was achieved via a two-step, one-pot iridium-catalyzed C–H activation/borylation/oxidation protocol. Our system gave high conversions to the arylboronic esters and good yields of the desired phenols following subsequent oxidation. A range of common protecting group categories was studied including alkyl, silyl, ether and ester.

New routes for the preparation of phenols are important in natural product synthesis as many naturally occurring compounds such as the flavonoids and the anthocyanins, contain mono-phenolic or polyphenolic moieties.[1] In 1993, Marder and co-workers[2] reported the borylation of toluene in the presence of catecholborane and an iridium catalyst—this was the beginning of iridium-catalyzed C–H activation/borylation as we know it now.[3] Maleczka et al.[4] reported the preparation of phenols from electron-poor substrates using an iridium-catalyzed C–H activation/borylation/oxidation procedure. Miyaura and co-workers[5] also utilized a similar system, and in both papers the majority of substrates studied were restricted to those containing halide substituents. This route to phenols is of great importance as it allows the introduction of a *meta*-arylboronic ester in arenes bearing *ortho/para* directing groups, followed by conversion into the *meta*-substituted phenol via oxidation. The regioselectivity observed is largely due to steric factors in both the substrate and the catalyst/ligand system.

According to the conditions reported by Maleczka,[4] transformation of the 1,3-disubstituted benzene into the arylboronic ester was achieved through treatment of the arene with pinacolborane (HBPin), an iridium catalyst (Ind)Ir(COD) and either 1,2-bis(dimethylphosphanyl)ethane (dmpe) or 1,2-bis(diphenylphosphanyl)ethane (dppe) as a ligand, at temperatures ranging from room temperature to 150 °C. Conversion of the arylboronic ester into the phenol was accomplished by treatment with a 50:50 mixture of acetone and aqueous Oxone® at room temperature (Scheme 1).

Due to the importance of polyphenolic compounds and also the desire for the use of a range of protecting groups in organic synthesis, we chose to expand the scope of the existing methodology to include the use of electron-rich diprotected resorcinol substrates to yield phloroglucinol derivatives **3a–g** (Scheme 1). Protecting groups bearing aromatic or unsaturated hydrocarbon units were not suitable for this protocol, as these moieties would also be functionalized during the borylation step. Scheme 1 outlines the substrates utilized in our studies (**1a–g**) which incorporate a range of common protecting groups.

Studies were undertaken in order to determine the optimum conditions required for the C–H activation/borylation of our substrates. We found that the reagents and conditions reported by Maleczka et al.[4] for relatively electron-poor substrates were not suitable. Under these conditions no conversion was achieved to the desired arylboronic ester intermediates **2a–g** even after prolonged heating. Due to the fact that our protected resorcinol substrates **1a–g** were comparatively electron-rich, it was concluded that an alternative system would be required. Indeed, it was found that the use of bis(pinacolato)diboron (B_2Pin_2) in *iso*-hexane, catalyzed by the iridium dimer $[Ir(OMe)(COD)]_2$ with 4,4′-di-*tert*-butyl-2,2′-bipyridine (d*t*bpy) as ligand[4,5] was successful for the majority of our substrates (Table 1).[6]

We found that a decrease in catalyst/ligand loading was beneficial (1.0 mol % catalyst, 2.0 mol % ligand, cf. 1.5 mol % and 3.0 mol %, respectively[4]). An increase in the quantity of B_2Pin_2 (0.6–1.0 equiv) was also required to reach conversions above 60%. As expected, due to the electron-rich nature of our substrates,

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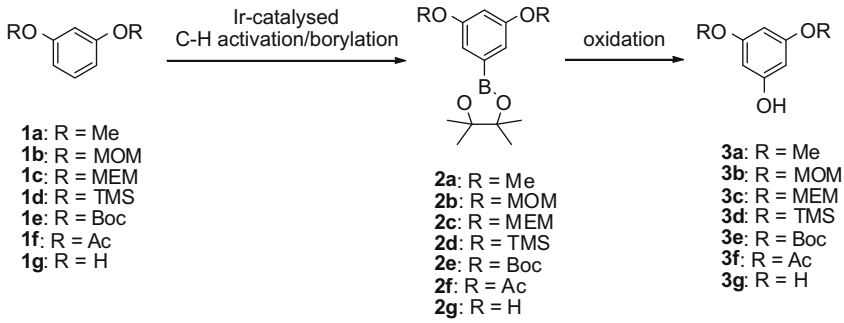

Scheme 1. Synthesis of 1,3,5-trisubstituted arenes from protected resorcinol derivatives.

Table 1
Reaction conditions and results for the C–H activation/borylation/oxidation[6]

Entry	Substrate	Product	B_2Pin_2 (equiv)	$[Ir(OMe)(COD)]_2$ (mol %)	dtbpy (mol %)	Conversion to intermediate **2a–f**[a] (%)	Yield of **3** (%)
1	**1a**	**3a**	1.0	1.0	2.0	97	59
2	**1b**	**3b**	1.0	1.0	2.0	95	61
3	**1c**	**3c**	1.0	1.0	2.0	71	62
4	**1d**	**3g**	1.0	1.0	2.0	92[b]	87[c]
5	**1e**	**3e**	1.6	1.3	2.1	99	51
6[d]	**1f**	**3f**	1.0	2.0	2.0	45	44

[a] Conversion calculated from the integration of the ^1H NMR signals of the starting material and intermediate.
[b] Desired intermediate **2d** isolated.
[c] Unprotected phloroglucinol (**3g**) obtained as the only product.
[d] HBPin (1.0 equiv) was also added to reaction mixture; dppe was used as the ligand in place of dtbpy.

we observed that the use of a higher reaction temperature (110 °C cf. 25 °C)[4,5] significantly increased the conversions. Oxidation of the arylboronic esters **2a–g** to the desired phenols **3a–c,e–g** also took longer than reported (30 min cf. 7 min).

Initially, we investigated the reaction of 1,3-dimethoxybenzene (**1a**). Efficient conversion into the arylboronic ester **2a** was achieved after heating at 110 °C for 18 h (Table 1, entry 1).[6] Subsequent oxidation of this intermediate followed by purification yielded 3,5-dimethoxyphenol (**3a**) in 59% yield.[7,8] We then undertook studies using the other five protecting groups previously outlined (Scheme 1) in order to expand the scope of the reaction. Similar results were obtained using MOM- and MEM-protected substrates **1b** and **1c**, giving 95% and 71% conversion to arylboronic esters **2b** and **2c**, respectively. Isolated yields of 61% of **3b**[9] and 62% of **3c**[10] were recorded (Table 1, entries 2 and 3).

An interesting result was obtained with the TMS-protected substrate **1d** (Table 1, entry 4). Analysis of the crude intermediate showed 92% conversion to arylboronic ester **2d**. However, during the oxidation step, deprotection of the TMS groups was observed, with phloroglucinol (**3g**) being isolated in 87% yield as the sole product.[11,12] This result is of particular importance when considering the preparation of phloroglucinol via this route, as a deprotection step would not be required. Under all conditions attempted, the reaction was not successful with resorcinol (**1g**) as a substrate.

Application of the optimized conditions to the borylation of Boc-protected resorcinol **1e** resulted in lower conversions than those observed for all other substrates studied so far. It was found that increasing the quantity of B_2Pin_2 and increasing the catalyst/ligand loading were beneficial, with 99% conversion to arylboronic ester **2e** being achieved (Table 1, entry 5). Subsequent oxidation and purification gave **3e** in 51% yield.[13]

Conversion of the acetoxy-protected resorcinol **1f** into arylboronate **2f** was poor (<10%) using our conditions (Table 1, entry 6). Use of HBPin and dppe, as previously reported for electron-poor substrates was more successful.[4] The highest conversion achieved using the conditions described in the literature[4] was 11%. However, it should be noted that HBPin alone was not the best reagent for the borylation. We found that use of a combination of both B_2Pin_2 (1 equiv) and HBPin (1 equiv) was optimal for the reaction. A higher catalyst/ligand loading was also required, as was the use of dppe as ligand in place of dtbpy. Under these conditions, conversion into **2f** was achieved, giving 3,5-diacetoxyphenol (**3f**) in 44% yield after oxidation and purification.[14] Although this substrate proved to be the most troublesome, with significantly lower conversions being observed, the yield of the **3f** was only slightly lower than those achieved for substrates **1a–1e**.

We conclude that the scope of the iridium-catalyzed C–H activation/borylation/oxidation procedure[2–4] has been extended to include the use of bis-protected resorcinols. The use of such substrates gives potential for the methodology to be applied to the synthesis of polyphenols. We report the successful regioselective functionalization of six substrates utilizing a range of protecting group classes which are common in natural product synthesis. Use of our optimized conditions resulted in high conversions into the arylboronic ester intermediates and good to excellent yields of the desired arenes bearing 1,3,5-substitution. A noteworthy result was the preparation of phloroglucinol (**3g**) from 1,3-di(trimethylsilyl)resorcinol (**1d**) with cleavage of the silyl-protecting groups being observed during the oxidation step.

Acknowledgements

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6. *General procedure for the preparation of* **3a–g** *via* **2a–g**: A degassed solution of substrate (1 equiv) in *iso*-hexane (5 mL/mmol) was transferred into an air-free flask containing B_2Pin_2, HBPin (if required), $[Ir(OMe)(COD)]_2$ and either dtbpy or dppe. The flask was sealed and the reaction mixture was stirred at 110 °C for 18 h. *Iso*-hexane was removed under reduced pressure to give the intermediate borolane **2a–g**. Acetone (3.2 mL/mmol) was added to the crude aryl boronate and aqueous Oxone® (1.2 equiv in 3.2 mL/mmol H_2O) added dropwise over 2–4 min. The reaction mixture was stirred vigorously for 30 min and then the reaction was quenched by the addition of saturated Na_2SO_3 solution. The aqueous phase was extracted with EtOAc. The organic solvents were removed under reduced pressure and the crude material was dissolved in CH_2Cl_2 and passed through a plug of silica gel. The solvents were then removed under reduced pressure to give the crude product **3a–g**. Purification was by column chromatography.
7. *3,5-Dimethoxyphenol* (**3a**): mp 41–42 °C (lit.[8] 40 °C); δ_H (400 MHz, $CDCl_3$) 3.76 (6H, s, CH_3), 6.04 (2H, d, J = 2.2 Hz, H-2,6), 6.08 (1H, t, J = 2.2 Hz, H-4); δ_C (100 MHz, $CDCl_3$) 55.3 (*C*H_3), 93.1 (*C*H-4), 94.3 (*C*H-2,6), 157.4 (*C*-OH), 161.6 (*C*-3,5).
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9. *3,5-Bis(methoxymethyl)phloroglucinol* (**3b**): ν_{max}/cm^{-1} 3365, 2958, 1601, 1498, 1467, 1214, 1149, 1031, 922, 828; δ_H (400 MHz, $CDCl_3$) 3.39 (6H, s, CH_3), 5.03 (4H, s, CH_2), 6.14–6.17 (2H, m, H-4,6), 6.20–6.23 (1H, m, H-2), 6.62 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 56.0 (*C*H_3), 94.3 (*C*H_2), 97.2 (*C*H-2), 97.6 (*C*H-4,6), 157.8 (*C*-OH), 159.0 (*C*-OMOM); HRMS (CI): MH^+, $C_{10}H_{15}O_5$ requires 215.0919, found 215.0919.
10. *3,5-Bis(2-methoxyethoxymethoxy)phenol* (**3c**): ν_{max}/cm^{-1} 3381, 2952, 2899, 1598, 1495, 1469, 1213, 1149, 1029, 918, 830; δ_H (400 MHz, $CDCl_3$) 3.31 (6H, s, CH_3O), 3.48–3.52 (4H, m, *C*H_2OCH$_3$), 3.71–3.76 (4H, m, CH_2O), 5.12 (4H, s, OCH_2O), 6.19 (2H, d, J = 2.1 Hz, H-2,6), 6.22 (1H, t, J = 2.1 Hz, H-4); δ_c (100 MHz, $CDCl_3$) 59.0 (*C*H_3O), 67.6 (*C*H_2O), 71.6 (*C*H_2OCH$_3$), 93.5 (OCH_2O), 97.4 (*C*H-4), 97.6 (*C*H-2,6), 157.7 (*C*-1), 159.0 (*C*-3,5); HRMS (ES): M+Na^+, $C_{14}H_{22}O_7Na$ requires 325.1263, found 325.1262.
11. *Phloroglucinol* (**3g**): mp 213–214 °C (lit.[12] 216 °C); δ_H (300 MHz, $CDCl_3$-DMSO-d_6) 5.82 (3H, s, H-2,4,6); δ_C (100 MHz, $CDCl_3$-DMSO-d_6) 94.8 (*C*H-2,4,6), 158.8 (*C*-1,3,5).
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13. *Di-tert-butyl 5-hydroxy-1,3-phenylene biscarbonate* (**3e**): ν_{max}/cm^{-1} 3373, 2950, 2871, 1597, 1481, 1210, 1124, 915; δ_H (400 MHz, $CDCl_3$) 1.48 (18H, s, CH_3), 6.45 (2H, d, J = 2.1 Hz, H-4,6), 6.57 (1H, t, J = 2.1 Hz, H-2); δ_c (100 MHz, $CDCl_3$) 27.7 (*C*H_3), 84.0 (*C*(CH$_3$)$_3$), 106.5 (*C*H-2), 106.9 (*C*H-4,6), 151.4 (*C* = O), 151.9 (*C*-1,3), 157.0 (*C*-5); HRMS (ES): M+Na^+, $C_{16}H_{22}O_7Na$ requires 349.1263, found 349.1263.
14. *3,5-Diacetoxyphenol* (**3f**): mp 165 °C (lit.[15] 168 °C); δ_H (400 MHz, $CDCl_3$) 2.18 (6H, s, CH_3), 6.32 (1H, t, J = 2.0 Hz, H-4), 6.40 (2H, d, J = 2.0 Hz, H-2,6), 8.40 (1H, br s, OH).
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