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Borenium-catalysed *para*-selective borylation of alkylarenes†

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A borenium-based catalytic system for *para*-selective borylation of mono-alkylbenzenes has been developed using 4-*tert*-butyl-catecholborane (HBcat^{tBu}) as the borylation reagent and (*p*-tol)-OBcat^{tBu} as a Brønsted base additive. This study highlights the complementary selectivity of borenium-based systems compared to transition-metal catalysts and provides a straightforward approach to accessing *para*-selective arylboron compounds.

Arylboron compounds are synthetically versatile building blocks in both organic synthesis[1,2] and materials chemistry.[3] One of the most efficient ways to access arylboron compounds is catalytic C–H borylation of arenes, an area long dominated by transition-metal catalysts.[4–8] Since the regioselectivity of transition-metal-based catalytic systems is largely determined by steric factors, mono-substituted arenes, in the absence of directing groups, typically afford a mixture of *meta*- and *para*-borylated products in statistical distribution.[9–11] To overcome this limitation, taking advantage of ligand–substrate interactions, a number of strategies have been developed,[8,12–14] in which iridium catalysts with elegantly designed ligands allow selective *meta*- or *para*-borylation of aryl C–H bonds. To ensure reasonable ligand–substrate interactions, arene substrates with steric bulky[15–21] or heteroatom-containing substituents[22–28] are generally required. For mono-alkyl arenes (such as ethylbenzene), there is only one example of catalytic regioselective C–H borylations known. Asako, Ilies, and co-workers employed a bulky spirobipyridine ligated Ir complex as a catalyst to selectively borylate *meta*-C–H bonds of toluene and ethylbenzene with *meta*/*para* ratios of 5.0 : 1 and 7.3 : 1, respectively.[17] Despite these advancements, catalytic *para*-selective C–H borylation of mono-alkyl arenes still remains an unmet challenge.[29]

Main-group-element-catalysed electrophilic C–H borylation of arenes represents an alternative approach to access arylboron compounds.[30–35] These metal-free systems typically proceed *via* a S_EAr pathway with their regioselectivity determined by electronic factors, thus complementary to metal-based systems and offering a potential solution to regioselective C–H borylations of mono-alkyl arenes. Very recently, our group reported the C–H borylation of arenes using [IBn^F-B(H)-Cb^{Me}][B(C_6F_5)$_4$] (**1**, IBn^F = 1,3-bis-(2,3,4,5,6-pentafluorobenzyl)imidazol-2-ylidene, Cb^{Me} = 2-methyl-*o*-carboran-1-yl) as a catalyst with 4-chloro-catechol borane (HBcat^{Cl}) as a borylation reagent.[36] While excellent *para*-selectivity was achieved for the arenes with strong electron-donating groups such as amino and phenoxyl groups, mono-alkyl arenes gave a roughly 1 : 1 mixture of *para*- and *meta*-borylated products. In this study, we investigated how tuning the electronic factors of the borylation reagent, a borenium catalyst, and the addition of bases can enhance the *para*-selectivity of aromatic C–H borylations. We discovered that with a new borenium catalyst [IBn^{F}Me-B(H)-Cb^{Me}][B(C_6F_5)$_4$] (**2**, IBn^{F}Me = 1-methyl-3-(2,3,4,5,6-pentafluorobenzyl)imidazol-2-ylidene), mono-alkyl arenes can be borylated with *para*/*meta* (*p*/*m*) ratios up to 10 : 1 using 4-*tert*-butyl-catechol borane (HBcat^{tBu}) as a borylation reagent and (*p*-tol)OBcat^{tBu} as an additive.

Our previous work has shown that in the borenium **1** catalysed C–H borylation system,[36] the B–H bond of HBcat^{Cl} is synergistically activated by the arene substrate and **1**, leading to the formation of a boryl-substituted Wheland intermediate (**WI**) and a neutral N-heterocyclic carbene (NHC)-stabilised hydroborane (IBn^F-B(H)$_2$-Cb^{Me}, **1-H**). Subsequently, the rate-determining deprotonation of **WI** with **1-H** affords the borylation product and H_2 accompanied by the regeneration of the borenium catalyst. Although a S_EAr process involving mono-alkyl arenes typically favours electron-rich *para*-sites over *meta*-ones, the catalytic system based on **1** and HBcat^{Cl} showed a very moderate preference of the *para*-C–H bonds for the borylation of mono-alkyl arenes. For example, toluene, ethylbenzene, and cumene, gave the corresponding arylboronates with a roughly 1 : 1 mixture of *p*/*m*-isomers. We speculated that the low regioselectivity could be due to facile 1,2-boryl migration prior to the product-determining deprotonation step (Scheme 1). A similar explanation was also invoked for

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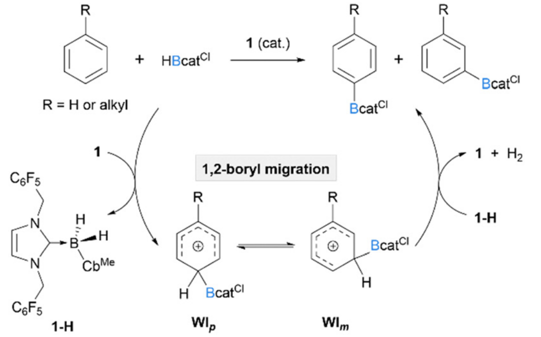
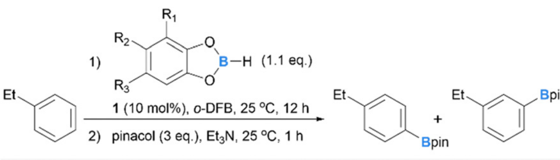


Scheme 1 Proposed reaction pathway involving a 1,2-boryl migration ($[B(C_6F_5)_4]^-$ counterion omitted for clarity).

the low *p*/*m* selectivity in the electrophilic borylation system reported by Ingleson and co-workers.[37]

Since the intramolecular 1,2-boryl migration likely involves the interactions between the π orbitals of the arene substrates and the vacant p orbital of the boron centre, we hypothesized that reducing electrophilicity of the catechol-ligated boron centre could weaken such interaction, thus mitigating the undesired 1,2-boryl migration and improving the *p*/*m* ratios. Therefore, we started our investigation by exploring how tuning the electrophilicity of the borylation reagent would affect the regioselectivity. A series of borylation reagents with variant catechol ligands ($HBcat^R$), including 3,5-di(*tert*-butyl)-catechol borane ($HBcat^{tBu2}$), $HBcat^{tBu}$, 4-methyl-catechol borane ($HBcat^{Me}$), 4-fluoro-catechol borane ($HBcat^F$), and $HBcat^{Cl}$, were synthesized from their corresponding catechol precursors (22 to 74% yield). Ethylbenzene was chosen as the model substrate with **1** (10 mol%) as the catalyst (Table 1). The moisture-sensitive $Bcat^R$ moiety was converted to a Bpin moiety by treating with pinacol and Et_3N after the reaction. The *p*/*m* ratio of $Et\text{-}C_6H_4\text{-}Bpin$ was determined by ^1H-NMR analysis. As we expected, the *para*-selectivity of ethylbenzene steadily increases with decreasing electrophilicity of the borylation reagent. Borylation reagents containing electron-withdrawing groups (EWGs), such as fluoro or chloro substituents, led to high efficiency yet poor regioselectivity (*p*/*m* = 0.8 : 1 in both cases, Table 1, entries 1 and 2). The selectivity was marginally improved (*p*/*m* = 1.0 : 1, Table 1, entry 3) with moderately electron-donating methyl groups. When better electron-donating *tert*-butyl groups were introduced to the catechol ligand, the regioselectivity was improved further with *p*/*m* ratios of 1.1 : 1 for $HBcat^{tBu}$ and 1.4 : 1 for $HBcat^{tBu2}$, respectively (Table 1, entries 4 and 5). However, the yield was low (29%) for $HBcat^{tBu2}$ which was probably due to the insufficient electrophilicity of $Bcat^{tBu2}$ in the initial S_EAr process. Therefore, $HBcat^{tBu}$ was chosen as the borylation reagent for further optimizations.

Table 1 Screening of the borylation reagents

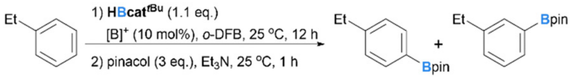


Entry	R_1	R_2	R_3	Yield (%)	*p*/*m* ratio
1 (ref. 36)	H	Cl	H	86	0.8
2	F	H	H	92	0.8
3	H	Me	H	22	1.0
4	H	*t*Bu	H	63	1.1
5	*t*Bu	H	*t*Bu	29	1.4

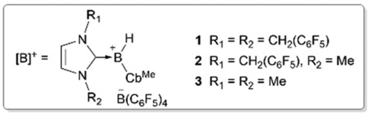
Besides the modification of the borylation reagents, another approach to enhance *para*-selectivity is to accelerate the intermolecular deprotonation of $\mathbf{WI_p}$, allowing it to outcompete the intramolecular 1,2-boryl migration. One possible way to facilitate deprotonation involves increasing the hydricity of B–H bonds in neutral hydroborane species, which would promote effective dehydrocoupling with the Brønsted acidic $\mathbf{WI_p}$. To probe the effects of the NHC ligand of borenium catalysts 4 regioselectivity, we synthesized two new borenium ions $[IBn^FMe\text{-}B(H)\text{-}Cb^{Me}][B(C_6F_5)_4]$ (**2**, IBn^FMe = 1-methyl-3-(2,3,4,5,6-pentafluorobenzyl)imidazol-2-ylidene) and $[IMe_2\text{-}B(H)\text{-}Cb^{Me}][B(C_6F_5)_4]$ (**3**, IMe_2 = 1,3-dimethylimidazol-2-ylidene) and examined their catalytic performance. For borenium **2**, a *p*/*m* ratio of 1.5 : 1 and borylation yield of 70% were observed (Table 2, entry 2). Borenium **3**, which contains a more electron-donating IMe_2 ligand, gave a higher *para*-selectivity (*p*/*m* = 4.4 : 1) yet unsatisfactory yield (24%). Although increasing the reaction temperature to 60 °C can improve the borylation efficiency to 42% yield, the selectivity dropped to 1.5 : 1 (Table 2, entries 3 and 4). **2** was thus chosen as the borenium catalyst for further optimizations.

Subsequently, we examined if addition of exogenous Brønsted bases could further improve the regioselectivity. 2,6-Dibromopyridine was evaluated first as the addition of pyridine derivatives was well-documented to promote C–H borylation catalysis *via* an FLP-type mechanism.[38–41] However, 2,6-dibromopyridine (10 mol%) completely shut down the borylation of ethylbenzene with borenium **2** as the catalyst and $HBcat^{tBu}$ as the borylation reagent (Table 3, entry 2). Using $P(C_6F_5)_3$ as an exogenous base gave borylation products with an increased *p*/*m* ratio of 2.9 : 1, and *p*-tolyl ether further improved the *p*/*m* ratio to 5.0 : 1 (Table 3, entries 3 and 4). Encouraged by the performance of this *O*-based additive, we then examined phenoxyl boronates as additives due to the following reasons: (1) phenoxyl boronates can

Table 2 Screening of the borenium catalysts

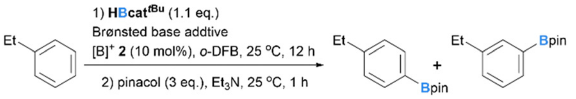


Entry	Catalyst	Yield (%)	*p*/*m* ratio
1	**1**	63	1.1
2	**2**	70	1.5
3	**3**	24	4.4
4[a]	**3**	42	1.5



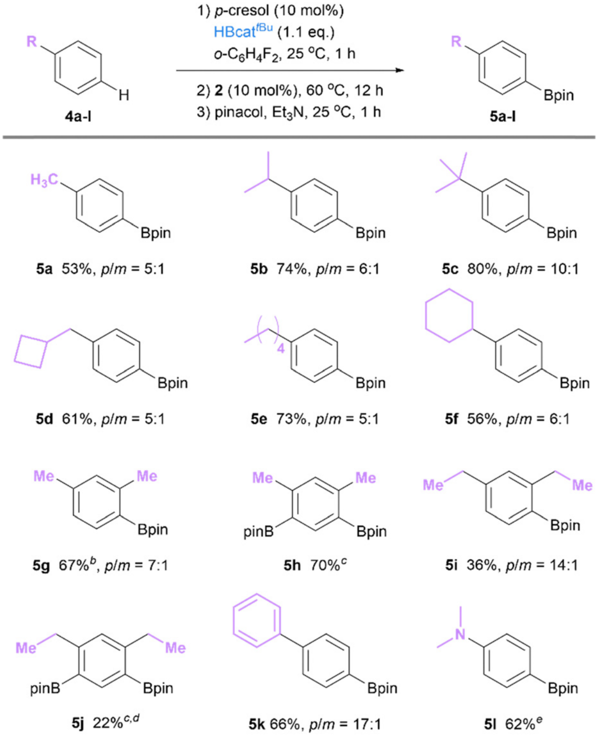
[a] 60 °C.

Table 3 Screening of the Brønsted base additive



Entry	Additive	Yield (%)	*p*/*m* ratio
1	None	70	1.5
2	2,6-Br$_2$-py	NR	—
3	P(C$_6$F$_5$)$_3$	50	2.9
4	(*p*-tol)O(*p*-tol)	32	5.0
5^{a}	C$_6$H$_5$OH	38	5.1
6^{a,b}	(*p*-Cl)C$_6$H$_4$OH	44	2.3
7^{a}	*p*-Cresol	59	7.1
8^{a,b}	*p*-Cresol	74	7.4
9^{ab}	(*p*-Et)C$_6$H$_4$OH	53	5.0
10^{a,b}	(*p*-iPr)C$_6$H$_4$OH	49	4.9
11^{b}	*t*BuOBcat^{tBu}	32	3.9
12^{b}	(*p*-tol)OBcat^{tBu}	72	6.7

[a] Phenoxyl boronates generated *in situ* by dehydrocoupling of HBcat^{tBu} and corresponding phenols. [b] 60 °C.



Scheme 2 Borylation of alkylarenes catalysed by **2**.[a] [a] **2** (10 mol%), *p*-cresol (10 mol%), arene (0.5 mmol), and HBcat^{tBu} (0.55 mmol) in 0.6 mL of *o*-C$_6$H$_4$F$_2$ with isolated yields based on arenes. [b] 9% of 4,6-diborylated product was also obtained. [c] 2.5 equivalent of HBcat^{tBu} was applied. [d] 17% of 5-monoborylated product was also obtained. [e] Without (*p*-tol)OBcat^{tBu} additive.

be readily accessed *via in situ* dehydrocoupling of phenol and the borylation reagent; (2) the electronic properties of phenoxyl boronates could be easily tuned by varying the substituents on the phenyl ring. One-pot reaction was carried out by pre-mixing 10 mol% phenol and 1.1 equiv. of HBcat^{tBu}, followed by the addition of ethylbenzene (1.0 equiv.) and catalyst **2** (10 mol%). Subsequent stirring at room temperature for 12 h afforded the borylation product in a *p*/*m* ratio of 5.1 : 1 with 38% yield after workup (Table 3, entry 5). Switching phenol to *p*-cresol gave the best *para*-selectivity obtained so far (*p*/*m* = 7.1 : 1), albeit with a relatively low borylation yield of 59% (Table 3, entry 7). Running the reactions at 60 °C can improve the borylation efficiency (74% yield, Table 3, entry 8) while maintaining the same *para*-selectivity. A similar result was observed when isolated (*p*-tol)OBcat^{tBu} was applied as an additive (Table 3, entry 12). Phenols containing a chloro group (Table 3, entry 6) or other alkyl groups (Table 3, entries 9 and 10) all showed inferior regioselectivities. The addition of alkoxyl boronates such as ^{tBu}OBcat^{tBu} also gave lower *para*-selectivity (Table 3, entry 11). When the reaction was carried in a 5 mmol scale, the borylation product was obtained with 69% yield and a *p*/*m* ratio of 7.1 : 1.

With the optimal reaction conditions in hand, we examined the substrate scope of our catalytic system. A comparable *para*-selectivity was achieved with toluene (**4a**), (cyclobutylmethyl)benzene (**4d**) and *n*-amylbenzene (**4e**), providing the corresponding borylation products in a 5 : 1 mixture of *para*- and *meta*-isomers. Mono-alkyl arenes bearing a secondary alkyl group such as isopropyl (**4b**) and cyclohexyl (**4f**) gave a higher *p*/*m* ratio of 6 : 1. Notably the *para*-selectivity reached 10 : 1 with *tert*-butylbenzene (**4c**). 1,3-Disubstituted arenes were also explored. Such substitution patterns, in iridium catalysis systems, typically give 5-borylated products as the exclusive regioisomer.[4] With our catalytic platform, *m*-xylene (**4g**) was converted to a mixture of 4- and 5-borylated isomers in a ratio of 7 : 1, showcasing complementary regioselectivity compared to transition-metal catalysis.[9] The 4,6-diborylated product was also obtained as a minor product in 9% yield. When 2.5 equiv. of HBcat^{tBu} was applied, the yield of 4,6-diborylated product **5h** can be enhanced to 70%, thus providing a straightforward route for the preparation of *meta*-diboryl benzenes, useful building blocks for covalent organic frameworks.[42] Additionally, diphenyl can be borylated with *para*-selectivity of 17 : 1, substantially higher compared to our previous system based on **1** and HBcat^{Cl} (2.5 : 1).[36] For substrates containing heteroatom substituents, exclusive *para*-borylation products can be obtained without a (*p*-tol)OBcat^{tBu} additive (Scheme 2).

Furthermore, we investigated the activity of our system in the borylation of polystyrene, as the boryl moiety can provide a valuable linchpin for the modification of the bulk and surface properties of polystyrene.[4,43] To the best of our knowledge, the state of the art polystyrene borylation was reported by Bae and co-workers, where an iridium complex was employed as a catalyst at 150 °C with a *p*/*m* selectivity of 3 : 4.[44] In our study, syndiotactic polystyrene (M_n = 9.39 × 10^4 g mol^{-1}, PDI = 2.06) was chosen as the substrate. Under standard conditions (10 mol% catalyst based on styrene unit), 19% of the phenyl ring was borylated with a *para*-selectivity of 1.6 : 1. The M_n of the resulting polymer slightly increased to 1.46 × 10^5 g mol^{-1} with an almost unchanged PDI (1.58), revealing little alteration of the polystyrene main chain. When the borylation reaction was repeated without (*p*-tol)OBcat^{tBu} additive, nearly identical polymer was obtained, implying that the additive has little effect on the regioselectivity of borylation. This could be due to the difficulty associated with diffusion[45] of the additive in the medium containing the polymer, which might hinder the deprotonation process.

In this study, we investigated the influence of borylation reagents, borenium catalysts and Brønsted base additives on the *para*-selectivity of borylation of mono-alkylbenzenes. It was found that an electron-rich catecholborane derivative HBcat$^{t\text{Bu}}$ as a borylation reagent, a moderate electrophilic borenium **2** and (*p*-tol)OBcat$^{t\text{Bu}}$ as an additive can lead to the borylation of mono-alkylbenzenes with *p*/*m* ratios up to 10 : 1. Furthermore, this catalytic system can be readily applied to the borylation of polystyrene, albeit with moderate *p*/*m* selectivity of 1.6 : 1. These results showcased the complementary selectivity of the borenium catalytic system compared to transition-metal ones. Exploring the application of the borenium catalytic system in other C–H functionalizations is currently underway in our laboratory.

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Data availability

The data supporting this article were available within the article and the ESI.†

Conflicts of interest

There are no conflicts of interest to declare.

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