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Regioselective Aromatic Borylation in an Inert Solvent†

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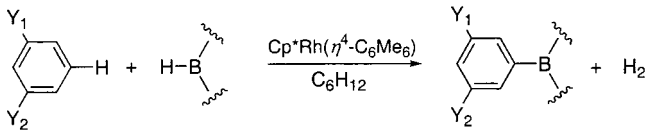
ABSTRACT



A protocol for performing Rh catalyzed aromatic borylations in cyclohexane has been devised. Borylation at the 5-position of several 1,3-substituted aromatic species ranging from electron-rich (1,3-$(NMe_2)_2C_6H_4$) to electron-deficient (1,3-$(CF_3)_2C_6H_4$) yields the corresponding aryl boronate esters. Veratrole was selectively borylated at the 4-position, thus extending regioselectivity to 1,2-substituted benzenes. Selective borylation at the 3-position of an *N*-protected pyrrole has also been demonstrated, providing a valuable reagent for cross-coupling reactions in a single step.

Boronic esters and acids are versatile synthons in organic chemistry. In addition to their role in cross-coupling reactions,[1] they also exhibit potent protease inhibition[2] and have been incorporated in chemical sensing schemes.[3] Aryl boronic acids are most economically prepared by reacting aryl Grignard or aryllithium reagents with trialkyl borates, followed by hydrolytic workup. Miyaura[4] and Masuda[5] have described some clever arylboronate ester syntheses where the generation of Grignard and lithium reagents is avoided by using metal catalysts to effect the desired transformation from borane reagents and halogenated arenes. Since the halogenated arenes required for these approaches must be synthesized from hydrocarbon feedstocks, direct routes to the arylboron reagents from hydrocarbons are attractive.

From calculated BDE's for B−H, C−H, and B−C bonds, we realized that synthesis of aryl boronic esters from boranes and arenes should be feasible, and in 1999 we reported the first metal-catalyzed reaction of a borane and an arene to effect the transformation in eq 1.[6] It is interesting to note

$$\mathrm{Ar{-}H + (RO)_2B{-}H \rightarrow Ar{-}B(OR)_2 + H_2} \qquad (1)$$

that Knochel and co-workers reported uncatalyzed C−H activations involving alkyl boranes shortly thereafter.[7] We quickly learned that both the Ir precatalysts from our initial report and the Rh precatalyst that was subsequently utilized by Hartwig and co-workers[8] gave approximately statistical distributions of meta and para isomers in the borylation of monosubstituted arenes.[6b] This apparent steric directing effect

† Preliminary results have been presented: Smith, M. R., III; Cho, J.-Y. *Abstracts of Papers*, Pacifichem 2000, Honolulu, HI, December 14-19, 2000; American Chemical Society: Washington, DC, 2000; INOR 600.

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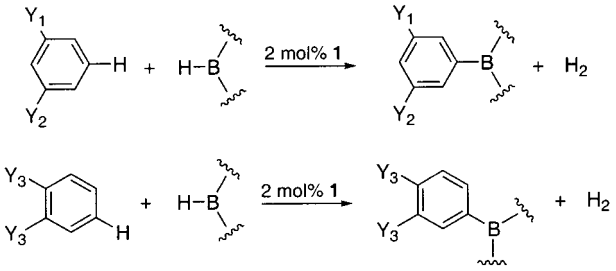
Scheme 1



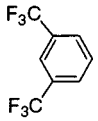
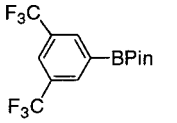
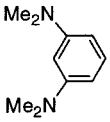
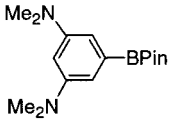
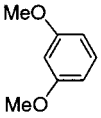
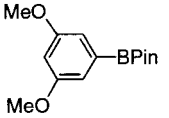
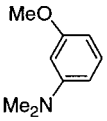
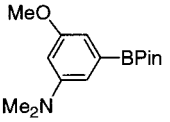
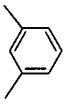
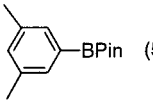
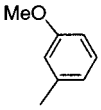
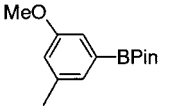
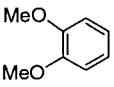
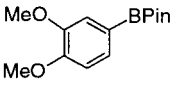
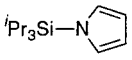
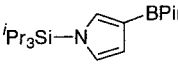
can be exploited to selectively derivatize 1,3-substituted arenes at the 5-position and 1,2-substituted arenes at the 4-position (Scheme 1). The observed selectivity for 1,3-substituted arenes is particularly important because selective functionalizations at the 5-position of *m*-xylene, and more electron-rich 1,3-substituted arenes, are generally limited to substitutions by sterically hindered electrophiles.[9,10]

In 1998, a noteworthy exception was reported by Berry and co-workers, who developed Ru- and Rh-catalyzed syntheses of arylsilanes via dehydrogenative coupling of arenes and silanes where yields were substantially improved by adding an olefin to provide a hydrogen "sink".[11] An advantage of the borylation chemistry is that sacrificial olefin acceptors are not required. Nevertheless, both borylation and silylation methodologies are important in preparing partners for coupling reactions.

Our initial reports used the substrate as solvent.[6] While this is not a significant problem for inexpensive substrates such as benzene, for nonvolatile or valuable substrates the use of an inert solvent would be preferable. Thus, we have developed a simple protocol for preparing arylboronate esters in good to moderate yields where the aromatic substrate is the limiting reagent. In addition, we have expanded the scope of selective meta borylation of 1,3-substituted benzenes and have extended the borylation chemistry to protected pyrrole.

For this study, we used Hartwig's precatalyst, Cp*Rh(η^4-C_6Me_6) (**1**),[8] whose reactivity we recently compared to Ir precatalysts that were utilized in our earlier report on the catalytic aromatic borylation of C−H bonds. Although the Ir precatalysts seem to be more selective, their effective turnover numbers are too low for practical applications. The preferential activation of the stronger aryl C−H bonds in the presence of weaker benzylic C−H bonds is significant, particularly in light of Marder and co-worker's recent report of selective benzylic borylation using the precatalyst *trans*-Rh(Cl)(P^iPr_3)$_2$(N_2).[12] Since solutions of **1** do not readily borylate secondary or tertiary C−H positions, cyclohexane was an obvious choice for an inert solvent. Indeed, catalytic borylations in cyclohexane using 2 mol % of **1** with a modest excess of pinacolborane (HBPin) gave boronate esters in reasonable yields (Table 1). Reactions were performed in sealed vessels at 150 °C until ^{11}B NMR spectra indicated that most of the borane had been consumed. Crude mixtures were analyzed by GC-MS and the reported yields are for isolated products. In cases where isomers were produced,

Table 1. Isolated Yields (Based on HBPin) of Arylboronate Esters from Catalytic Arene Borylations in Cyclohexane Using 2 mol % of Precatalyst **1**

entry	arene	[HBPin]:[Arene]	time	products (yield)
1[a]	C_6H_6	1:1	57 h	PhBPin (41), *m*- and *p*-$C_6H_4(BPin)_2$ (33, *m*:*p*=2:1)
2	C_6H_6	1:4	38 h	PhBPin (59)
3[b]	C_6H_6	4:1	61 h	*m*-$C_6H_4(BPin)_2$, *p*-$C_6H_4(BPin)_2$, 1,3,5-$C_6H_3(BPin)_3$
4		1:1	10 h	 (88)
5		3:1	28 h	 (69)
6[c]		3:1	32 h	 (62)
7		4:1	19 h	 (75)
8[d]		1:1	59 h	 (53)
9		1.2:1	25 h	 (54)
10		3:1	45 h	 (82)
11		3:1	41 h	 (81)

[a] Diborylated isomers were not separated. [b] Isomer mixture containing small amounts of PhBPin. [c] 1,3,4-$(OMe)_2C_6H_3$(BPin) was isolated in 2% yield. [d] *m*-C_6H_4(Me)(CH_2BPin) was isolated in 6% yield.

(9) (a) Voronenkov, A. V.; Aliev, A. A.; Kutrakov, A. V.; Voronenkov, V. V. *Zh. Org. Khim.* **1999**, *35*, 324−326. (b) For selective alkylation of *m*-xylene at the 5-position, please see: Fujita, K.; Oomori, H.; Yoshikazu, H. Mitsubishi Petrochemical Co. Ltd. Jpn. Kokai Tokyo Koho 91 24,021, 1991.

(10) Substitution for hydrogen at the 5-position in 1,3-substituted benzenes by electrophiles, nucleophiles, and radicals is difficult: March, J. In *Advanced Organic Chemistry: Reactions, Mechanisms, and Sructure*, 4th ed.; John Wiley and Sons: New York, 1992; pp 513−514, 666−668, 686−687.

(11) Boryl intermediates that have been recently proposed in catalytic borylations[8] are analogous to suggested silyl intermediates in Rh-catalyzed aromatic silylations: Ezbiansky, K.; Djurovich, P. I.; LaForest, M.; Sinning, D. J.; Zayes, R.; Berry, D. H. *Organometallics* **1998**, *17*, 1455−1457.

compounds were separated by chromatography, unless otherwise noted.

We have found that trace solvent impurities can inhibit catalytic borylations. Hence, the solvent purification outlined in the Supporting Information should be followed to maximize yields. With the exception of benzene, the substrates have been selected to test the generality of sterically directed borylation.

For benzene three sets of conditions were employed (Table 1, entries 1−3). In the first case, borylation was examined with equimolar quantities of benzene and HBPin. The isolated yields of products based on borane as the limiting reagent are 41% for PhBPin and 33% for $C_6H_4(BPin)_2$ both as a 2:1 mixture of meta and para isomers. Using a 4:1 ratio of benzene to borane, diborylation is minimized and PhBPin can be isolated in 59% yield. If a moderate excess of HBPin is used, the major species in the crude reaction mixture are *m*-$C_6H_4(BPin)_2$, *p*-$C_6H_4(BPin)_2$, and 1,3,5-$C_6H_3(BPin)_3$ in an approximate 1.0:1.2:1.7 ratio as determined from GC and NMR data. Further purification was not attempted; however, comparison of the weight of the crude mixture (311 mg) to the combined weights of HBPin, C_6H_6, and catalyst (340 mg) indicates efficient conversion to borylated species.

In cyclohexane solvent, 1,3-substitued arenes yield 1,3,5-substituted aryl boronate esters as major products (entries 4−9). Reactivities for arene substrates were similar except for 1,3-$(CF_3)_2C_6H_4$, which was substantially more reactive. In the previous report,[6b] significant benzylic activation was observed in neat *m*-xylene. To determine whether acceptable yields for methyl-substituted arenes could be obtained, 1 equiv of HBPin was used for the borylation of *m*-xylene in cyclohexane. The aryl and benzyl boronate esters were separated, with the aryl product being favored by a factor of ∼9:1. For 3-methylanisole, a modest excess of HBPin was used and the 1,3,5-substituted major product was readily obtained in 54% yield after chromatography. Entries 7 and 9 demonstrate that preference for borylation at the 5-position holds for unsymmetrically substituted arenes. We attempted the borylation of *m*-dichlorobenzene and found a mixture of products with unreacted arene, chlorobenzene, $ClC_6H_4(BPin)$, and $Cl_2C_6H_4(BPin)$ isomers as the major species. This is not surprising since we previously observed competitive C−H and C−F activation using the same precatalyst for borylations of fluorinated arenes.[6b] Consequently, no other halogenated arenes were examined. An attempted borylation of benzonitrile led to nitrile reduction instead of aromatic C−H activation.[13]

Entries 10 and 11 represent extensions of directed borylations to 1,2-substituted arenes and pyrrole. For veratrole, two isomers were detected by GC in a 99:1 ratio with the expected major product being 1,2,4-$C_6H_3(OMe)_2(BPin)$. After chromatographic purification, the major isomer was isolated in 82% yield. Direct borylations of pyrrole and trimethylsilyl pyrrole were ineffective. However, selective borylation at the less hindered 3-position could be achieved by increasing the steric bulk of the silyl protecting group. The regiochemistry of the borylation was verified by preparing the known phenyl-substituted pyrrole[14] via the Suzuki coupling of the pyrrolyl boronate ester with IC_6H_5.

The pyrrole result represents an important extension of the arene chemistry because selective functionalization at the 3-position is considerably more difficult than at the 2-position. For example, the best reported synthesis of 3-^{i}Pr$_3$-$SiNC_4H_3(B(OH)_2)$ involves iodination of ^{i}Pr$_3$$SiNC_4H_4$ by *N*-iodosuccinamide to afford 3-^{i}Pr$_3$$SiNC_4H_3I$, generation of the lithiated pyrrole with ^{t}BuLi, quenching with $B(OMe)_3$, and hydrolytic workup to afford the boronic acid in 27% yield from ^{i}Pr$_3$$SiNC_4H_4$.[14] In a single step, the reaction in entry 11 provides a stable source of the boronic acid in 81% yield.

In summary, we have shown that cyclohexane can serve as an inert solvent for Rh-catalyzed borylations of arenes. In addition, selective borylation at the 5-position of 1,3-substituted arenes has been demonstrated for a broader range of substrates, including dimethyl resorcinol and 1,3-$(NMe_2)_2C_6H_4$ where functionalizations at the 5-position are difficult. An example of regioselective borylation of a symmetric, 1,2-substituted arene has been demonstrated for veratrole. Last, ^{i}Pr$_3$$SiNC_4H_4$ has been selectively borylated at the less hindered 3-position in high yield.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Shimada, S.; Batsanov, A. S.; Howard, H. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168−2171.

(13) Although we have not examined the borylation of aromatic esters or amides in cyclohexane, we expect that borylations should be feasible since aromatic C−H activation is preferred over ester or amide reduction for borylations in the corresponding neat arenes.[6b]

(14) Alvarez, A.; Guzman, A.; Ruiz, A.; Velarde, E.; Muchowski, J. M. *J. Org. Chem.* **1992**, *57*, 1653−1656.