Steric and Chelate Directing Effects in Aromatic Borylation

Jian-Yang Cho, Carl N. Iverson, and Milton R. Smith, III*

Department of Chemistry, Michigan State University
East Lansing, Michigan 48824

Received April 14, 2000
Revised Manuscript Received October 18, 2000

Hydrocarbon activation has attracted considerable attention because hydrocarbon feedstocks are ubiquitous.[1] Since metal-catalyzed cross-couplings of aryl and alkyl boronic acids with aryl halides represent one of the most general and widely applied means for constructing C−C bonds, the generic conversion depicted in eq 1 would have broad appeal.[2] Indeed, stoichiometric, photochemical catalytic, and thermal catalytic examples of this type have been reported.[3] We recently described the first thermal, catalytic example shown in eq 1, where R−H is benzene and

$$R{-}H + H{-}BX_2 \rightarrow R{-}BX_2 + H{-}H \qquad (1)$$

HBX_2 is pinacolborane (HBPin).[4] Clearly, the synthetic utility of catalytic borylation hinges on the demonstration of functional group tolerance and regioselective activation for substituted arenes. Herein, promising results in both respects are described. Specifically, the compatibility of heteroatom substituents, as well as amide and ester groups, is demonstrated. In addition, borylation regioselectivity is sterically controlled for most substituted arenes. Thus, catalytic borylations offer unique selectivities when compared to traditional aromatic substitutions where electronic effects determine the regioselectivity.[5]

In the initial borylations of substituted arenes, 20 mol % solutions of Cp*Ir(PMe_3)(H)(BPin) (**1**, Cp* = η^5-C_5Me_5) or Cp*Ir(PMe_3)($H)_2$ (**2**) were dissolved with HBPin in neat arene solvents, and the reactions were run at 150 °C. Once borylation had commenced, ^{31}P NMR spectroscopy indicated that compound **1** was the predominant Ir species irrespective of the Ir starting material. Analogous borylations were also performed using the more active pre-catalyst Cp*Rh(η^4-C_6Me_6) (**3**), which was recently utilized by Hartwig and co-workers.[3e] After the borane was consumed, product ratios were determined by GC analysis of crude reaction mixtures. Isolated yields of isomer mixtures are reported in Table 1, and product assignments were corroborated by comparisons to authentic samples.[6]

In a simple assay of regioselectivity toluene borylation primarily gave a statistical distribution of *m*- and *p*-C_6H_4Me(BPin). To ensure that the isomer distribution was kinetically determined, the catalytic borylation of C_6D_6 by HBPin in the presence of *m*-C_6H_4Me(BPin) was examined. Under the reaction conditions *m*-C_6H_4Me(BPin) did not isomerize and toluene was not generated. Thus, borylation products are kinetically determined. It is noteworthy that arene C−H bonds are functionalized in the presence of weaker benzylic C−H bonds.

Table 1. Isolated Yields (based on HBPin) and Isomer Distributions for Catalytic Borylation of Aromatic Hydrocarbons Catalyzed by Solutions of Compounds **1** and **3**

Arene	Product(s)	Precatalyst **1**: % yield (para:meta:ortho), time[a]	Precatalyst **3**: % yield (para:meta:ortho), time[b]
		53, 120 h[c]	92, 2.5 h[d]
		91 (1.00:1.83:0.12),[e] 51 h	72 (1.00:1.93:0.15),[f] 3.5 h
		99 (1.00:2.00:0.00),[c] 17 h	84 (1.00:2.00:0.00), 1.5 h
		55 (1.00, 4.06, 0.08) 65 h	65 (1.00:2.63:0.30), 1 h
		--	65 (1.00:1.74:0.04), 3.5 h
		52 (1.00, 2.19, 0.03) 142 h	67 (1.00:1.99:0.02), 2 h
		81,[g] 18 h	41,[h] 0.5 h
		--	46,[i,j] 0.5 h
		--	(1.00, 1.74, 0.29)[k], 1 h
		--	50 (1.00, 1.98, 4.17), 0.5 h
		81,[c] 10 h	86, 3 h
		60,[l] 151 h	73,[m] 4 h
		--	41, 6 h

[a] 20 mol % **1**, generated in situ from compound **2** and HBPin at 150 °C. [b] 2 mol % **3** at 150 °C. [c] 20 mol % **1** at 150 °C. [d] GC yield reported in ref 3e. [e] <1% of the isomer mixture is $C_6H_5CH_2$BPin. [f] 3% of the isomer mixture is $C_6H_5CH_2$BPin. [g] 4% of the isolated product is isomers of C_6F_4H(BPin). [h] 16% of the isolated product is isomers of C_6F_4H(BPin). [i] Reaction was run in a 2:1 mixture of 1,3,5-$C_6H_3F_3$:*p*-xylene-d_{10}. [j] $C_6HF_3(BPin)_2$ (7%) and an isomer of $C_6H_3F_2$(BPin) (6%). [k] Products were not isolated. [l] 3% of the isolated product is *m*-C_6H_4(Me)(CH_2BPin). [m] 12% of the isolated product is *m*-C_6H_4(Me)(CH_2BPin).

A range of monosubstituted arenes was examined to determine whether reaction conditions would tolerate heteroatom substituents and to assess the generality for statistical meta/para substitution. The results in Table 1 indicate that meta/para ratios are predominantly statistical with the largest deviations occurring for $PhNMe_2$, which favors para substitution, and anisole, which favors meta substitution. For Rh-catalyzed reactions the deviations were relatively small, but meta borylation of anisole is pronounced for Ir. Since cumene gave a statistical distribution of meta and para borylation products, electronic effects are responsible for enhanced para selectivity for $PhNMe_2$. Benzylic activation of toluene increased for Rh (~3% $PhCH_2$BPin) versus Ir (~1% $PhCH_2$BPin).

Fluorinated arenes were also tested for compatibility. Ir- or Rh-catalyzed borylation of C_6HF_5 gave C_6F_5BPin as the primary product. Similarly, compound **3** catalyzed borylation in a 2:1 mixture of 1,3,5-$C_6H_3F_3$ and *p*-xylene-d_{10} to yield $C_6H_2F_3$BPin. Attempts to prepare the di- and triborated compounds, $C_6HF_3(BPin)_2$ and $C_6F_3(BPin)_3$, from stoichiometric amounts of 1,3,5-$C_6H_3F_3$ in *p*-xylene-d_{10} yielded significant quantities of $C_6H_3F_2$(BPin) (~60% of the borylated products). The selectivity for C−H activation is significant considering that Rh-catalyzed reactions of silanes with C_6F_5H give C−F activation products exclusively.[7]

* Author for correspondence. E-mail: smithmil@msu.edu.

(1) For accounts and reviews of hydrocarbon activation, please see: (a) Jones, W. D.; Feher, F. J. *Acc. Chem. Res.* **1989**, *22*, 91−100. (b) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154−162. (c) Crabtree, R. H. *Chem. Rev.* **1995**, *95*, 987−1007. (d) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180−2192.

(2) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(3) (a) Waltz, K. M.; He, X.; Muhoro, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11357−11358. (b) Waltz, K. M.; Hartwig, J. F. *Science* **1997**, *277*, 211−213. (c) Waltz, K. M.; Muhoro, C. N.; Hartwig, J. F. *Organometallics* **1999**, *18*, 3383−3393. (d) Chen, H. Y.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 3391−3393. (e) Chen, H. Y.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995−1997.

(4) Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **1999**, *121*, 7696−7697.

(5) (a) Some preliminary findings have been presented: Smith, M. R., III; Cho, J.-Y.; Iverson, C. N.: 219th ACS National Meeting, San Francisco, CA, March 26−30, 2000 (INOR 367). (b) Iverson, C. N., Ph.D. Dissertation, Michigan State University, 1999.

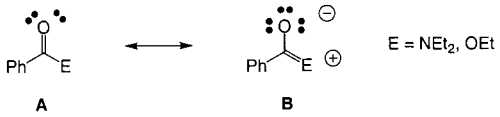
(6) Experimental details and spectroscopic data are included in the Supporting Information.

10.1021/ja0013069 CCC: $19.00
Published on Web 12/06/2000

Table 2. Relative Ratios of Arylboronic Esters for Borylations of Equimolar Mixtures of Substituted Arenes Catalyzed by Compounds **2** and **3**

	(Catalyzed by solutions of **2**)	(Catalyzed by solutions of **3**)
X = CF_3, Y = CH_3	8.09:1.00	2.70:1.00
X = OCH_3, Y = CH_3	1.63:1.00	1.04:1.00
X = $N(CH_3)_2$, Y = CH_3	--	0.69:1.00
X = $N(CH_3)_2$, Y = $CH(CH_3)_2$	0.45:1.00	0.67:1.00

For arenes bearing ester or amide functionality reduction of the carbonyl groups could potentially compete with aromatic borylation. Rh-catalyzed borylations of ethyl benzoate and diethyl benzamide gave primarily aromatic borylation. For ethyl benzoate, the extent of meta/para borylation predominates with a modest increase in ortho borylation, whereas diethyl benzamide gave *o*-$C_6H_4(C(O)NEt_2)(BPin)$ as the major isomer. The shift in substitution pattern is consistent with chelate-directed borylation at the ortho position. Since resonance structure B has a larger contribution for an amide relative to an ester, chelation of the amide oxygen to Rh or B in the catalytically active species is more favorable for the amide.[8] The statistical meta:para ratio for the minor isomers suggests that chelate and sterically directed pathways compete.



To probe the role of electronic effects, relative product ratios from catalytic borylations in equimolar mixtures of substituted arenes were determined (Table 2). Electron-deficient arenes are generally more reactive in both systems, and relative rate differences for Ir are more pronounced than those for Rh. Ir-catalyzed borylation in neat $PhNMe_2$ was extremely slow. Factors besides deactivation of the arene ring may be responsible because cumene borylation in $PhNMe_2$/cumene mixtures was suppressed relative to borylation in neat cumene. The electronic effects on relative reaction rates contrast those observed in arylboronate ester formation from Fe boryl complexes[3c] and are similar to trends in nucleophilic aromatic substitutions of arene metal complexes.[9] However, the regioselectivity for nucleophilic substitutions is very sensitive to electronic variations,[10] in contrast to the statistical product distributions in Table 1.

Statistical ratios for meta and para activation are typical for C−H activations by Cp*Rh(PMe_3). Although Jones and Perutz have shown that activation of electron-deficient arenes by Cp*Rh(PMe_3) is thermodynamically and perhaps kinetically preferred,[11] the origins of the relative rate differences in Table 2 cannot be interpreted until mechanisms for Ir- and Rh-catalyzed borylation are firmly established. The potential mechanistic complexity is exemplified by the observation of traces of Cp*BPin and Cp*H in Ir-catalyzed reactions and Cp*H in Rh-catalyzed reactions at 20 mol % catalyst loading. Consequently, the generation of active species via Cp* loss cannot be discounted.

Steric effects in aromatic substitution are uncommon, and electronic effects generally dictate substitution patterns. Furthermore, selective meta functionalization is difficult and generally requires strong electron-withdrawing or -donating groups for electrophilic or nucleophilic aromatic substitution, respectively. Since most substituents in Table 1 block ortho activation, selective borylation should be possible for 1,3-substituted arenes. Indeed, this was observed for 1,3-$C_6H_4(CF_3)_2$, *m*-xylene, and 2,6-lutidine where aromatic borylation is observed only at the common meta position (Table 1). The difference in selectivity between the Ir and Rh catalysts for benzylic versus aromatic activation of toluene is amplified for *m*-xylene. For Rh, 12% of the borylation products result from benzylic activation compared to 3% for Ir. Hence, Ir catalysts may offer advantages over Rh systems if the turnover numbers can be increased.

Two classes of arene functionalization that merit comparison to catalytic borylation are ortho lithiations[12,13] and metal-catalyzed arene olefination and carbonylation reactions.[14−16] Often, a chelating group that directs functionalization at an ortho C−H position is required. Ortho lithiation of arenes is achieved at low temperature, and the aryllithium intermediates are reacted with electrophiles, while olefination and carbonylation conditions are more similar to those for aromatic borylation. In addition to introducing a synthetically versatile B−C bond, catalytic borylations do not require activating or directing groups. Also, the chelate effects are weaker than in the aforementioned methods, which may allow for differentiation between amides and weaker chelating groups. The most unique feature of the borylation reaction is the steric influence of aromatic substituents on the regiochemistry of borylation. The extension of steric directing effects to selective functionalization of 1,3-substituted aromatics is nicely demonstrated in the case of *m*-xylene where aromatic borylation occurs exclusively at the 5-position. The only other examples where *m*-xylene is selectively functionalized at this site are stoichiometric C−H activations by transition metal complexes[11,17] and alkylations with sterically hindered carbon electrophiles.[18]

In conclusion, this preliminary study demonstrates generality and selectivities that bode favorably for synthetic applications of aromatic borylations in arene functionalization.

Acknowledgment. We appreciate support from the National Science Foundation (CHE-9817230). C.N.I. gratefully acknowledges support from Carl H. Brubaker and Dow Fellowships. We thank Aaron Odom for helpful discussions and the reviewers for their constructive comments.

Supporting Information Available: Synthetic and spectroscopic (^1H, ^{19}F, and ^{11}B NMR data) details for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0013069

(7) Aizenberg, M.; Milstein, D. *Science* **1994**, *265*, 359−361.
(8) Related amide direction in regioselective olefin hydroboration has been reported: Evans, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1991**, *113*, 4042−4043.
(9) Kane-Maguire, L. A. P.; Sweigart, D. A. *Inorg. Chem.* **1979**, *18*, 700−706.
(10) Semmelhack, M. F.; Clark, G. *J. Am. Chem. Soc.* **1977**, *99*, 9, 1675−1676.
(11) Selmeczy, A. D.; Jones, W. D.; Osman, R.; Perutz, R. N. *Organometallics* **1995**, *14*, 5677−5685.
(12) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.
(13) Buchwald has demonstrated that the benzyne complexes derived from C−H activation of group 4 aryl complexes are versatile reagents for ortho functionalization: Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047−1058.
(14) (a) Pd-catalyzed addition of CO_2 to benzene proceeds under mild conditions, and regioselectivities for substituted arenes follow electrophilic substitution patterns. Please see: Lu, W. J.; Yamaoka, Y.; Taniguchi, Y.; Kitamura, T.; Takaki, K.; Fujiwara, Y. *J. Organomet. Chem.* **1999**, *580*, 290−294. (b) For Pd-catalyzed alkyne insertions into ortho aromatic C−H bonds and references to related olefinations, see: Jia, C. G.; Piao, D. G.; Oyamada, J. Z.; Lu, W. J.; Kitamara, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992−1995.
(15) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529−531. (b) Murai, S.; Chatani, N.; Kakiuchi, F. *Pure Appl. Chem.* **1997**, *69*, 589−594.
(16) For related Rh-catalyzed ortho olefination of aromatic ketones, please see: Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616−6623.
(17) Green, M. L. H.; Joyner, D. S.; Wallis, J. M. *J. Chem. Soc., Dalton Trans.* **1987**, 2823−2830.
(18) (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, see: Fujita, K.; Oomori, H.; Yoshikazu, H. (Mitsubishi Petrochemical Co. Ltd.). Jpn. Kokai Tokyo Koho 91 24,021, 1991.