J|A|C|S
COMMUNICATIONS

Published on Web 11/06/2004

Regiospecific Functionalization of Methyl C−H Bonds of Alkyl Groups in Reagents with Heteroatom Functionality

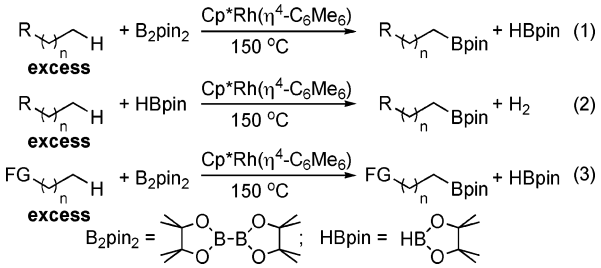
Joshua D. Lawrence, Makoto Takahashi, Chulsung Bae, and John F. Hartwig*

Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107

Received August 22, 2004; E-mail: john.hartwig@yale.edu

Most of the current regioselective, catalytic functionalizations of saturated C−H bonds occur by directed processes.[1] In these processes, the catalyst or reagent docks at a functional group or reacts at C−H bonds that are located α to a heteroatom because these bonds are weaker than more distal ones.[1c,d,h,2] If a reaction could be developed that occurs regioselectively with primary C−H bonds[3] while tolerating heteroatom functionality, then a new type of process could result. This process would complement the directed chemistry because it would occur at unactivated C−H bonds with selectivities for primary vs secondary C−H bonds that are independent of the position of the functional group in the reagent.[4]

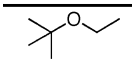
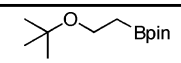
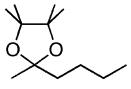
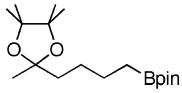
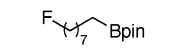
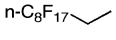
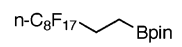
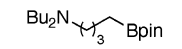
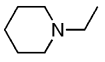
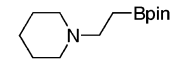
We have reported the regiospecific reaction of bis(pinacolato)-diborane(4) (B_2pin_2) and pinacolborane (HBpin) with the terminal C−H bonds of alkanes catalyzed by Cp*Rh(η^4-C_6Me_6) (eqs 1 and 2).[5,6] If the boryl group could be installed with similar selectivity at the end of an alkyl chain in a molecule with additional functionality (eq 3), then the versatility of organoborane reagents[7] could be exploited to generate a variety of bifunctional and polyfunctional products with one of the groups at the terminal position of an alkyl chain. We report that the rhodium-catalyzed borylation of methyl C−H bonds is compatible with several heteroatom-containing moieties, that the selectivity for reaction at methyl vs methylene or methine groups occurs without a dependence on the position or the binding ability of the heteroatom, and that the borylated product can be converted to bifunctional alkylarenes, alcohols, or alkylfluoroborates directly in the crude reaction mixture.



Rhodium-catalyzed borylations[5] of the pinacol acetal of 2-hexanone, *tert*-butyl-protected ethanol, 1-fluorooctane, (perfluoro-*n*-octyl)ethane, tributylamine, and *N*-ethyl piperidine are summarized in Table 1. Reactions of B_2pin_2 with an excess of these reactants without solvent gave the alkylboronate ester and HBpin in >70% yield. (Cp*$RhCl_2$)$_2$, Cp*Rh(η^2-ethylene)$_2$, and Cp*Rh(η^4-C_6Me_6) (**1**) all catalyzed these reactions, but **1** was the most active.

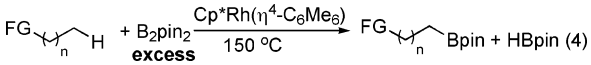
The borylation of C−H bonds with B_2pin_2 generates an equivalent of HBpin. HBpin reacts with neat linear alkanes to generate a second equivalent of borylated product and H_2, but little reaction between HBpin and the acetal, ether, or either fluoroalkane was observed. Thus, the yields in Table 1 refer to those for the reaction of B_2pin_2 to form RBpin and HBpin. In contrast, borylation of the amines with HBpin was observed, as indicated by the consumption of HBpin and the formation of >100% yield of product based on the single-step reaction of B_2pin_2 with R−H to form the alkylboronate ester and HBpin.

Table 1. Rhodium-Catalyzed Terminal Borylation of Alkyl Groups[a]

Reactant	Product	reactant: B_2pin_2	mol% **1**	Yield(%)[b]
		10:1	5	91
		1:1	10	48[c]
		10:1	5	74
		1:2	17	70
		10:1	5	83[d]
		1:2	10	46
		10:1	5	90
		1:2	10	84
		10:1	5	75[e]
		1:1	10	33
		10:1	5	55[e]
		1:2	10	67

[a] Conditions: B_2pin_2, **1**, neat, 150 °C, 24 h. [b] Yields calculated by GC areas. [c] In cyclohexane solvent (3 equiv). [d] 140 °C, 12 h. [e] Yield based on conversion to H_2.

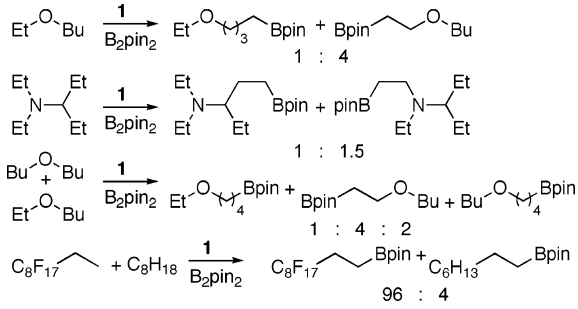
The acetal, ether, and alkyl fluoride contain several types of C−H bonds that could undergo borylation. Only the hydrogens of the methyl group of the butyl chain in the acetal reacted, as determined by GC−MS of the crude reaction and NMR spectroscopy of the isolated products. Similarly, no product from activation of the hydrogens of the *tert*-butyl substituent or hydrogens α to oxygen in the ether was observed by these techniques. More surprising, no product was observed from functionalization of 1-fluorooctane α to fluorine. Reaction at the hydrogens α to fluorine might have occurred competitively with reaction at the methyl group because fluorine is small and the α-C−H bonds are weaker and more acidic than the methyl C−H bonds. Reaction of a substrate with equivalent methyl groups, such a triethylamine, did generate a mixture of mono- and difunctionalized products when the organic substrate was the limiting reagent.



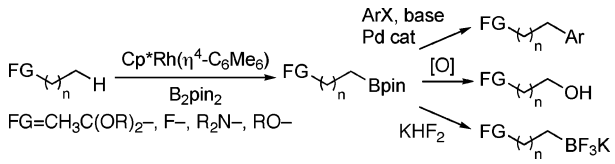
The use of methyl borylation in a synthetic sequence would require that the organic substrate be the limiting reagent, as shown in eq 4. Reactions in cyclohexane solvent occurred with the reagent and not the alkane, but reactions in the absence of a solvent with 10−17 mol % **1** (Table 1) generally occurred in higher yields (see Supporting Information). These reactions were limited by conversion; the balance of the material consisted of the two unreacted starting materials. B_2pin_3, pinBOBpin, or both were formed eventually from the B_2pin_2. Nevertheless, substantial yields of functionalized product were obtained under conditions of limiting ether, acetal, amine, or fluoroalkane substrate.

10.1021/ja044933x CCC: $27.50

Scheme 1



Scheme 2



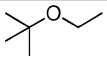
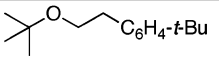
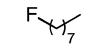
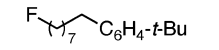
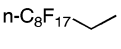
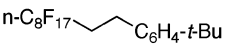
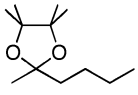
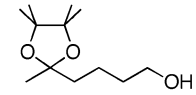
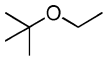
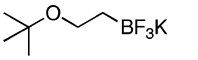
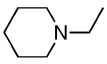
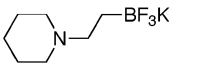
The difference between the reactions with excess of substrate and with substrate as limiting reagent can be rationalized by the relative rates for reaction of an unsaturated rhodium boryl intermediate with the HBpin side product and with the organic reagent. In separate work,[8] we have shown that the catalytic process occurs by dissociation of HBpin from Cp*Rh(Bpin)$_2$(H)(X) to generate Cp*Rh(Bpin)(X) (X = H, Bpin) and that the partitioning of this intermediate between reaction with alkane and HBpin affects the rate. When the organic substrate is neat and present in excess quantities, it competes more effectively with HBpin for the binding site on the catalyst than when it is the limiting reagent. In this case, the conversion of the organic substrate to the alkylboronate ester is higher.

To investigate the electronic effects of the heteroatoms on the borylation process, we conducted reactions in ethyl butyl ether and in *N*,*N*-diethyl-3-aminopentane. As shown in Scheme 1, the reactions occurred preferentially at the methyl group closer to the heteroatom, and the effect of the more electronegative oxygen in the ether was larger than that of the more coordinating and basic nitrogen in the amine. The same selectivity was observed from an intermolecular competition between ethyl butyl ether and dibutyl ether, after correcting for the ratio of alkyl groups. Consistent with preferential reaction at the less electron-rich methyl group, reaction of a mixture of (perfluoro-*n*-octyl)ethane and octane formed a 94:6 ratio of products that favored borylation of the fluoroalkane.

To exploit the diverse reactivity of organoboranes, we developed procedures to conduct sequential borylations of alkyl groups and conversion of the boronate esters to alkylarenes,[9] alcohols, and alkyltrifluoroborates, which are more reactive than boronate esters[10] (Scheme 2 and Table 2). The coupling of alkyl boronate esters with aryl halides is not straightforward, and previous coupling of pinacol alkylboronic esters required thallium[9b] or alkyllithium[9c] reagents. However, treatment of the crude reaction with 4-*tert*-butylbromobenzene, 1,1′-bis(diisopropylphosphino)ferrocene, Pd(dba)$_2$, and base led to a moderate to excellent yield of product from sequential C−H functionalization and cross-coupling (entries 1−3). Alternatively, the products from the functionalization process were converted to the corresponding alcohol by addition of aqueous alkaline H_2O_2 (entry 4) to the crude reaction solution or to the corresponding alkyl trifluoroborates by analogous addition of methanolic KHF_2 (entries 5 and 6).

In summary, we have shown that molecules containing nitrogen, oxygen, and fluorine undergo rhodium-catalyzed C−H activation and borylation at the least hindered and least electron-rich methyl group. The products from these reactions can be converted directly from the crude reactions to alcohols, alkylarenes, and alkyltrifluoroborates.

Table 2. Tandem Functionalization of Methyl Groups

Entry	Reactant	Product	Cond.[a]	Yield(%)
1			A,B	87[b]
2			A,C	29[b]
3			A,B	64[b]
4			A,D	68[c]
5			A,E	86[c]
6			A,E	69[c,d]

[a] Conditions: (A) B_2pin_2, 5 mol % **1**, neat, 150 °C; (B) 1-bromo-4-*tert*-butylbenzene (2 equiv), CsOH (4 equiv), Pd(dba)$_2$ (10 mol %), and Fc(P^{i}Pr$_2$)$_2$ (10 mol %) in toluene, 100 °C; (C) Same as B, but CsF and DMF used in place of CsOH and toluene; (D) H_2O_2 and KOH in THF and H_2O; (E) KHF_2 in MeOH. [b] Yields calculated by GC. [c] Yields calculated by ^{1}H NMR. [d] Yield based on the reaction of B_2pin_2 with R−H to form R−Bpin and H_2.

Acknowledgment. We thank the NSF (CHE-03019071) and Shell Chemicals for support of this work. J.L. thanks the NIH (GM069172) for a postdoctoral fellowship, and M.T. thanks Mitsubishi for partial support.

Supporting Information Available: Procedures for synthesis and characterization of reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (c) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (d) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (e) Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2000**, *122*, 6321. (f) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149. (g) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900. (h) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.

(2) Luo, Y. R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, FL, 2003.

(3) (a) Goldberg, K. I., Goldman, A. S., Eds. *Activation and Functionalization of C−H Bonds*; American Chemical Society: Washington, DC, 2004; Vol. 885. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (c) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437. (d) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (e) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154.

(4) Ethyl sulfonates, carboxylates, and phosphates undergo platinum-catalyzed oxidation at the terminal methyl group, but higher analogues react at the ω and $\omega-1$ positions: Lin, M.; Shen, C.; Garcia-Zayas, E. A.; Sen, A. *J. Am. Chem. Soc.* **2001**, *123*, 1000.

(5) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995.

(6) For concurrent borylation of arenes, see: (a) Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **1999**, *121*, 7696. (b) Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168.

(7) (a) Ramachandran, P. V., Brown, H. C., Eds. *Organoboranes for Syntheses*; American Chemical Society: Washington, DC, 2001; Vol. 783. (b) Pelter, A., Smith, K., Brown, H. C. *Borane Reagents*; Academic: London, 1988.

(8) Hartwig, J. F.; Cook, K. S.; Hapke, M.; Incarvito, C. D.; Fan, Y.; Webster, C. E.; Hall, M. B. Submitted for publication.

(9) (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (b) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405. (c) Zou, G.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 5817.

(10) (a) Fang, G.-H.; Yan, Z.-J.; Deng, M.-Z. *Org. Lett.* **2004**, *6*, 357. (b) Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534.

JA044933X