J|A|C|S
COMMUNICATIONS

Published on Web 11/15/2006

Ir-Catalyzed Functionalization of 2-Substituted Indoles at the 7-Position: Nitrogen-Directed Aromatic Borylation

Sulagna Paul, Ghayoor A. Chotana, Daniel Holmes, Rebecca C. Reichle, Robert E. Maleczka, Jr.,* and Milton R. Smith, III*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824-1322

Received May 5, 2006; E-mail: smithmil@msu.edu

Indoles have important biological functions. Traditionally, substituted indole syntheses fall into two classes:[1] (i) construction of the indole ring system from other substrates,[1a] and (ii) direct functionalizations of an existing indole.[1b] The Fischer indole synthesis is an example of the former class, while electrophilic addition is an example of the latter. In this regard, metal-mediated C−H functionalizations of indoles are particularly attractive because elaborations of unprotected indoles are possible.[2]

7-Functionalized indoles exist in some intriguing natural products,[3] such as asperazine,[3a] chloropeptin I,[3b] diazonamide A,[3c] dragmacidin D,[3d] and TMC-95A and B.[3e] Because most of these have aryl or alkyl substituents at C7, cross-coupling reactions have been linchpins in synthetic approaches, as indicated in Scheme 1. Since C7 of indole is difficult to functionalize selectively, construction of the requisite coupling partners can be a nontrivial synthetic bottleneck.

For N-unprotected, 2-substituted indoles, reactions that selectively functionalize C7 are extremely rare.[4,5] Snieckus and co-workers have developed the most general method for functionalizing 2-substituted indoles. Theirs is a directed metalation approach that requires N-protection/deprotection.[6] Certainly, direct functionalization of *unprotected* 2-substituted indoles at C7 would have appeal. In this communication, we offer Ir-catalyzed borylation as one means toward this end.

In our studies on borylations of heterocycles,[7] we noted that small quantities of a single diborylated product arose when indole borylation was carried out with pinacolborane (HBPin) at elevated temperatures. This product could be obtained in good yield by adjusting the HBPin stoichiometry. A series of NMR experiments conclusively identified C7 as the site of the second borylation.

To assess the reaction scope, various substrates and conditions were examined. Bipyridine-ligated catalysts disclosed by Ishiyama, Miyaura, and Hartwig performed best.[8] The conversion of reactants to products was clean, as judged by ^{1}H and ^{11}B NMR, and intermediates were not detected. Of note, moderately elevated temperatures shortened reaction times *and* improved isolated yields. As shown in Table 1, borylation yields and functional group tolerance are good. Because substrates unsubstituted at C2 gave diborylated products (entries 13 and 14), most of the indoles in Table 1 are 2-substituted. Entry 11 is noteworthy as selective removal of the $SiMe_3$ allows access to the 7-borylated indole.[9] Entry 12 indicates that, for 2-phenylindole, borylation is favored at the indole 7-position over the phenyl sites. Significant N-borylation likely accounts for the low yield in entry 10.

Borylations at positions flanking the indole N hint at its participation in the reaction. Three possibilities that we envision are depicted in Scheme 2. In the first pathway, initial N−H scission affords an Ir−N intermediate. Subsequent Ir insertion into the C−H bond at C7 (not shown) would precede product formation. In the second pathway, hydrogen bonding between the hydrogen on the indole nitrogen and a pinacolate oxygen directs C−H insertion. In the third mechanism, coordination of the indole N to Ir directs C−H insertion.[10]

Scheme 1. Approaches to C7-Arylated Indole Natural Products

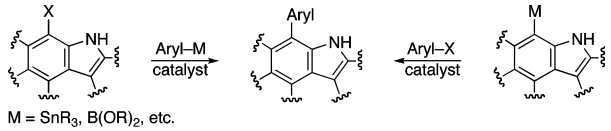
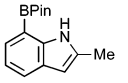
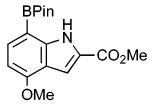
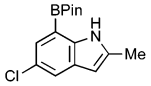
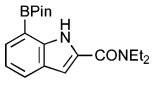
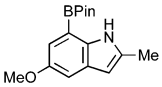
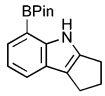
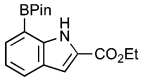
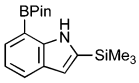
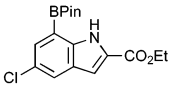
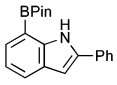
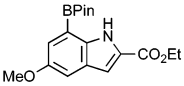
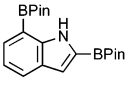
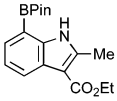
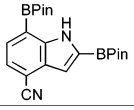


Table 1. Ir-Catalyzed Synthesis of 7-Borylated Indoles[a]

entry	product	time, yield	entry	product	time, yield
1		4 h, 78%	8		8 h, 79%
2[b]		20 h, 91%	9[d]		2.5 h, 90%
3		4 h, 88%	10[c]		36 h, 45%
4		1 h, 87%	11[c]		1 h, 76%
5[c]		6 h, 83%	12		3 h, 69%
6[c]		3 h, 82%	13[e]		4 h, 90%
7[d]		18 h, 64%	14[f]		10 h, 92%

[a] Typically, a solution containing the indole, 1.5 equiv of HBPin, and 3 mol % of pregenerated Ir catalyst[8b] was heated at 60 °C until the indole was consumed. Yields are for isolated products. See Supporting Information for details. [b] Reaction at room temperature. [c] 2.0 equiv of HBPin used. [d] B_2Pin_2 (1.0 equiv) was the borylating reagent. [e] 2.2 equiv of HBPin used. [f] 2.5 equiv of HBPin used.

To test the first mechanism in Scheme 2, catalytic borylation of *N*-d_1-5-chloro-2-methylindole using HBPin was examined. At 50% conversion, deuterium incorporation in HBPin or H_2 could not be detected by ^{1}H and ^{11}B NMR. Hence, the N−H activation mechanism can be excluded.

Diborylation of *N*-methyl indole was initially examined to exclude the second mechanism in Scheme 2. Like indole, initial borylation at C2 predominated, but 58 and 22% of the second borylation occurred at C6 and C5, respectively.[11] This outcome could be construed as support for H bonding, but a N coordination pathway could also be sterically sensitive to methylation.

10.1021/ja0631652 CCC: $33.50

Scheme 2. Potential N-Directed Mechanisms for Indole Borylation. Positions Affected by N-Deuteration are Indicated in Red

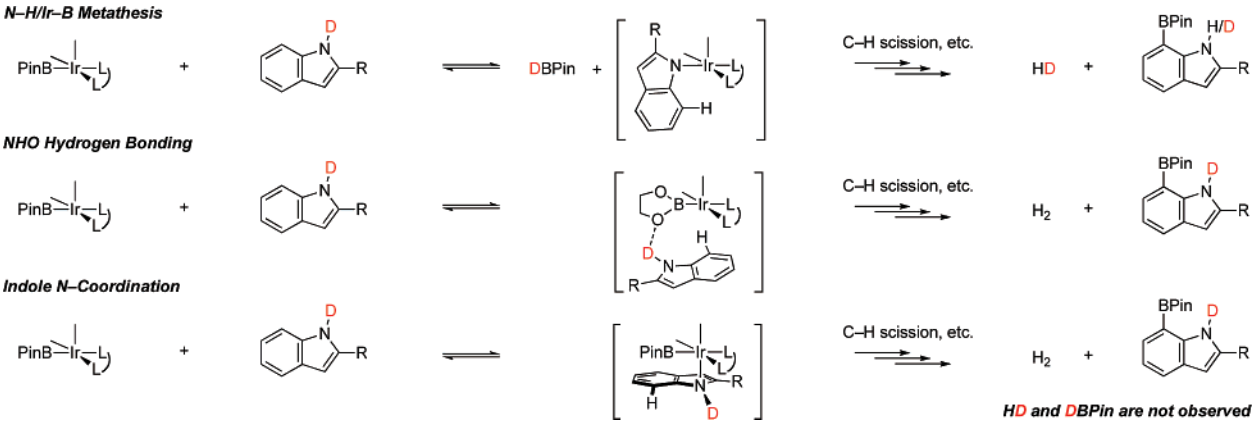
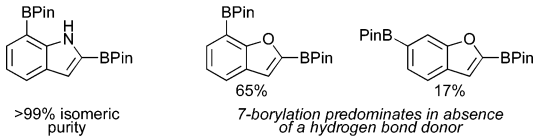
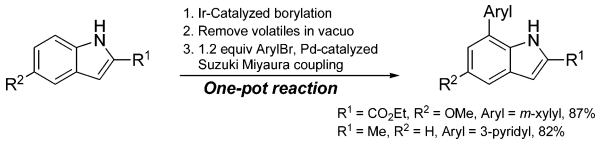


Chart 1. Regiochemistry for Diborylation of Benzofuran and Indole



Scheme 3. One-Pot, 7-Arylation of 2-Substituted Indoles



Because benzofuran is an isosteric analogue of indole absent the heteroatom-attached proton, its reactivity can address whether hydrogen bonding is a prerequisite for borylation at C7. As shown in Chart 1, the 2,7- and 2,6-isomers comprise 65 and 17% of the diborylated isomers of benzofuran. Even though the respective *meta* and *para* directing effects of OMe and BPin suggest that the second borylation should be favored at C6,[12] the 7-borylated isomer dominates, as was the case for indole.[13] Thus, hydrogen bonding to an acidic substrate proton is not absolutely required for the observed regioselectivity. On the basis of these observations, we presently favor the last mechanism in Scheme 2, where N-chelation to Ir (or B) directs borylation.[14]

A recent study raises concerns that the products in Table 1 might perform poorly in Suzuki−Miyaura cross-couplings.[15] Thus, two one-pot transformations were attempted, where the crude product from Ir-catalyzed borylation was subjected to Pd-catalyzed cross-coupling with two aryl bromides (Scheme 3). On the basis of the starting indoles, the arylated products were isolated in 87 and 82% yield, bolstering the prospects for synthetic utility.

In conclusion, Ir-catalyzed borylation provides the first general approach to functionalizing unprotected indoles at C7. Efforts toward further validating the mechanism, expanding the substrate scope, and elaborating the resulting boronate esters are ongoing.

Acknowledgment. We thank Professors Aaron Odom and Babak Borhan for helpful discussions, BASF, Inc. and Frontier Scientific, Inc. for generous gifts of HBPin and B_2Pin_2, and the Michigan Economic Development Corp., NSF REU (R.C.R.), NIH (GM63188 to M.R.S.), and the Astellas USA Foundation for generous financial support.

Supporting Information Available: Spectral data for all new compounds, as well as general experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, pp 314−476. (b) Jones, R. A. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, pp 201−312.

(2) (a) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972−4973. (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050−8057. (c) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996−4997. (d) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, 2924−2925. (e) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649−5651. (f) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056−3058.

(3) (a) Govek, S. P.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 9468−9469. (b) Deng, H. B.; Jung, J. K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032−9034. (c) Nicolaou, K. C.; Chen, D. Y. K.; Huang, X. H.; Ling, T. T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888−12896. (d) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179−13184. (e) Lin, S.; Yang, Z.-Q.; Kwok, B. H. B.; Koldobskiy, M.; Crews, C. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6347−6355.

(4) Aluminum anilide has been reported to mediate ethylene insertion into the C7 C−H bond of 2-methylindole at 280−300 °C: (a) Stroh, R.; Hahn, W. *Justus Liebigs Ann. Chem.* **1959**, *623*, 176−183. Low-yielding Rh-catalyzed carbene insertion into the C7 C−H of a 3-substituted indole has been claimed: (b) Kennedy, A. R.; Taday, M. H.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2407−2409.

(5) While indole itself has not been selectively functionalized at C7, enzymatic chlorinations at C7 in indole[5a] and tryptophan[5b] are known: (a) Wiesner, W.; Vanpee, K. H.; Lingens, F. *FEBS Lett.* **1986**, *209*, 321−324. (b) Dong, C. J.; Flecks, S.; Unversucht, S.; Haupt, C.; van Pee, K. H.; Naismith, J. H. *Science* **2005**, *309*, 2216−2219.

(6) (a) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899−1902. (b) Regioselectivity of this type, previously ascribed to directed ortho metalation, is now attributed to a complex-induced proximity effect (CIPE). See: Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206−2225.

(7) (a) Tse, M. K.; Cho, J.-Y.; Smith, M. R., III. *Org. Lett.* **2001**, *3*, 2831−2833. (b) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305−308.

(8) (a) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390−391. (b) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263−14278.

(9) TBAF cleaves the $SiMe_3$ group, affording the 7-borylated indole in 88% yield. See Supporting Information for details.

(10) An intriguing alternative to this latter mechanism, involving coordination of the indole N to B in one of the boryl ligands, is not shown.

(11) GC−MS indicates 20% of a third isomer. It was not obtained sufficiently pure for assignment of regiochemistry to be made.

(12) Chotana, G. A.; Rak, M. A.; Smith, M. R., III. *J. Am. Chem. Soc.* **2005**, *127*, 10539−10544.

(13) A decrease in selectivity for benzofuran versus indole is consistent with replacing the indole NH with a less basic O in a heteroatom chelation mechanism.

(14) Though C3 is the thermodynamic site of protonation in indole,[14a] kinetic accessibility of the N lone pair is reflected by the fact that acid-catalyzed deuterium exchange at N is ca. 100 times faster than at C3.[14b] For both sites, experimental data strongly support exchange via an S_E2 mechanism: [14b] (a) Hinman, R. L.; Whipple, E. B. *J. Am. Chem. Soc.* **1962**, *84*, 2534−2539. (b) Muir, D. M.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1976**, 388−392.

(15) Prieto, M.; Zurita, E.; Rosa, E.; Munoz, L.; Lloyd-Williams, P.; Giralt, E. *J. Org. Chem.* **2004**, *69*, 6812−6820.

JA0631652