J|A|C|S
COMMUNICATIONS

Published on Web 01/05/2006

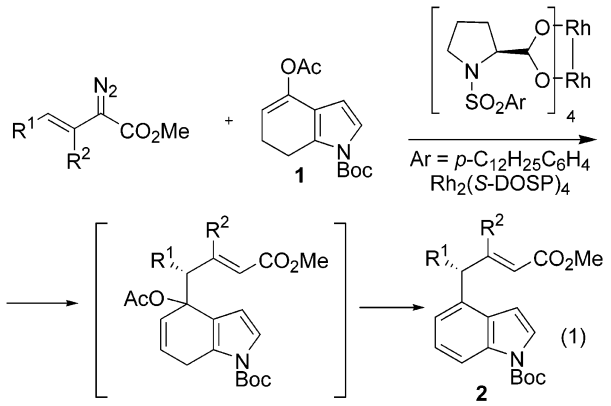
C−H Activation as a Strategic Reaction: Enantioselective Synthesis of 4-Substituted Indoles

Huw M. L. Davies* and James R. Manning

Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, New York 14260-3000

Received November 29, 2005; E-mail: hdavies@buffalo.edu

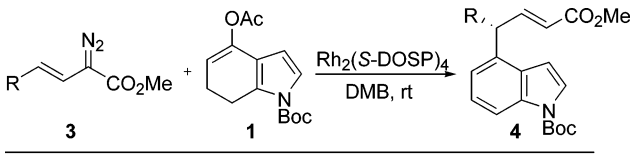
The indole nucleus has long been of great interest to synthetic chemists owing to its ubiquity in a large number of biologically active alkaloids[1] and pharmaceutical agents.[2] Traditional strategies for the synthesis of functionalized variants of this "privileged" moiety have relied largely upon cyclization of an appropriately substituted precursor,[3] metalation followed by electrophilic trapping of the anion,[4] and cross-coupling reactions.[5] Recently, attention has been focused on the asymmetric functionalization of the indole core.[6] While these examples take advantage of the relatively nucleophilic 3-position of the indole nucleus to add electrophiles via a Friedel−Crafts type reaction, there are comparatively few methods for selective functionalization of the less reactive 4-position. Such methods include a thallation/iodination reaction,[7] directed lithiation of 3-substituted gramines,[4a] and cross-coupling reactions.[8] We herein disclose a novel strategy for the highly enantioselective synthesis of 4-substituted indoles **2** from a 4-acetoxy-6,7-dihydroindole (**1**) via a rhodium(II)-catalyzed combined C−H activation/Cope rearrangement−elimination reaction (eq 1).

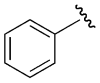
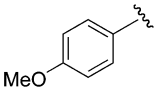
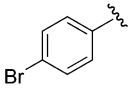
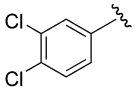
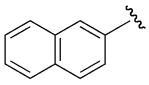
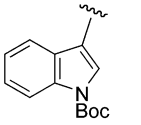
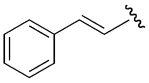


The development of catalytic methods for C−H activation is of considerable current interest.[9,10] The combined C−H activation/Cope rearrangement is an impressive example because it proceeds with excellent stereocontrol.[11] The rhodium prolinate catalyst, Rh_2(*S*-DOSP)$_4$, is very effective in this chemistry, routinely resulting in very high enantioselectivity. 1,2-Dihydronaphthalenes have been versatile substrates for the C−H activation, leading to the synthesis of formal Michael addition products,[11b] naphthalene derivatives,[11b] double C−H functionalization,[11f] and the synthesis of the natural products, (+)-erogorgiaene,[11e] (−)-colombiasin A,[11g] and (−)-elisapterosin B.[11g] This current study demonstrates that dihydroindoles are also effective substrates for this unusual chemistry.

The Rh_2(*S*-DOSP)$_4$-catalyzed reaction with 4-acetoxy-6,7-dihydroindole (**1**) is applicable to a range of terminally substituted vinyldiazoacetates **3** as illustrated in Table 1. The standard reaction conditions used 1 mol % of catalyst and 2,2-dimethylbutane (DMB) as solvent. Electron-rich and electron-deficient aryl substituents are compatible with this chemistry (entries 1−5), as well as an indolylvinyldiazoacetate (entry 6). A dienyldiazoacetate is equally effective (entry 7), and even an alkyl substituent can be accommodated (entry 8). In all instances the new stereogenic centers in the 4-substituted indoles **4** are formed in >97% ee. The absolute configuration of the bromophenyl derivative **4c** (entry 3) was determined by X-ray crystallography of the reduced analogue,[12] while the others are tentatively assigned by assuming an analogous enantioinduction. The yields in these reactions ranged from 45 to 65% because there was some competing reaction initiated at the pyrrole ring.[13]

Table 1. Synthesis of 4-Substituted Indoles

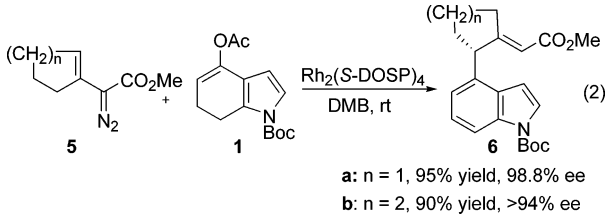


entry	compound	R	yield, %	ee, %
1	**a**		65	98.5
2	**b**		52	98.0
3	**c**		53	98.7
4	**d**		45	98.0
5	**e**		56	98.0
6	**f**		64	97.7
7	**g**		56	99.0
8	**h**		61	98.6

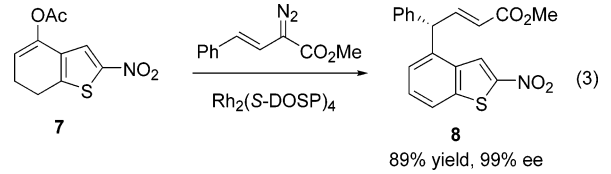
4-Substituted indoles can also be formed in the reaction of cyclic vinyldiazoacetates **5** as illustrated in eq 2. In these cases, competing reactions on the pyrrole ring were not observed and the 4-substituted

10.1021/ja057768+ CCC: $33.50

indoles **6** were formed in 90−95% yields. Once again, the enantioselectivities in these reactions were very high.



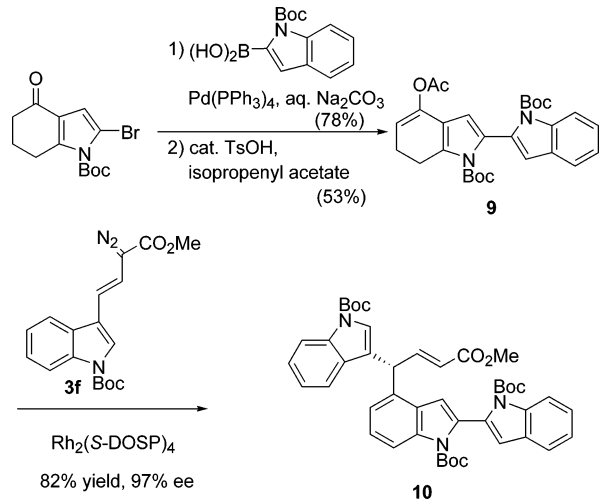
The C−H activation can be extended to a 4-substituted 6,7-dihydrobenzothiophene **7** as illustrated in eq 3. Thiophenes are common reaction partners with rhodium carbenoids,[14] but in this case the C−H activation is the dominant reaction, generating the 4-substituted benzothiophene **8** in 89% yield and 99% ee.



The C−H activation strategy to prepare 4-substituted indoles compliments some of the more conventional methods for indole synthesis as illustrated in Scheme 1. Palladium-catalyzed coupling[15] followed by acylation[16] readily forms the 2-indole derivative **9**. Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **9** with the 3-indolylvinyldiazoacetate **3f** generates the trisindole derivative **10** in 82% yield and 97% ee. In **10**, one indole is 2-substituted, another is 3-substituted, and the third is 2,4-disubstituted. The successful outcome of this reaction underscores the facility of the combined C−H activation/Cope rearrangement because indoles have often been shown to be reactive partners in carbenoid chemistry.[17]

In conclusion, we have reported a novel methodology for the asymmetric synthesis of 4-substituted and 2,4-disubstituted indoles from the Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of vinyldiazoacetates in the presence of a 4-acetoxy-6,7-dihydroindole precursor. The reaction proceeds via a combined C−H activation/Cope rearrangement−elimination mechanism, resulting in good yields and very high asymmetric induction. The further application of this chemistry to the synthesis of novel pharmaceutical targets is currently in progress.

Scheme 1



Acknowledgment. This work was supported by the National Science Foundation (CHE-0350536). We thank Cara L. Nygren for the X-ray crystallographic analysis.

Supporting Information Available: Full experimental data for the compounds described in this paper; X-ray crystallographic files in CIF format.

References

(1) (a) Sundberg, R. J. *Indoles*; Academic Press: London, 1996. (b) Saxton, J. E. *Nat. Prod. Rep.* **1997**, 559. (c) Borschberg, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1465.
(2) Kleeman, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 4th ed.; Thieme: New York, 2001.
(3) (a) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776. (b) Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1986**, *27*, 1837.
(4) (a) Iwao, M. *Heterocycles* **1993**, *36*, 29. (b) Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett.* **2002**, *4*, 815.
(5) For comprehensive reviews of indole syntheses: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, *7*, 1045. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.
(6) (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (b) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (c) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780. (d) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942. (e) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154.
(7) Somei, M.; Yamkada, F.; Kunimoto, M.; Kaneko, C. *Heterocycles* **1984**, *22*, 7801.
(8) (a) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657. (b) Kalinin, A. V.; Chauder, B. A.; Rakhit, S.; Snieckus, V. *Org. Lett.* **2003**, *5*, 3519.
(9) For reviews on catalytic methods for C−H functionalization, see: (a) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (c) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (e) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (f) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003,** *103*, 2861.
(10) For recent examples of catalytic C−H functionalization, see: (a) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496. (b) Dangel, B. D.: Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856. (c) Wehn, P. M.; DuBois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950. (d) Waltz, K. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 11358. (e) Desai, L. V.: Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (f) Davies, H. M. L.; Jin, Q. *Org. Lett.* **2004**, *6*, 1769.
(11) (a) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233. (b) Davies, H. M. L.; Jin, Q. *J. Am. Chem. Soc.* **2004**, *126*, 10862. (c) Davies, H. M. L.; Jin, Q. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5472. (d) Davies, H. M. L.; Beckwith, R. E. J. *J. Org. Chem.* **2004**, *69*, 9241. (e) Davies, H. M. L.; Walji, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1733. (f) Davies, H. M. L.; Jin, Q. *Org. Lett.* **2005**, *7*, 2293. (g) Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**. In press.
(12) The X-ray crystallographic data have been submitted to the Cambridge Structure Database [Nygren, C. L.; Coppens, P. *Private Communication* 2005, CCDC 279134].
(13) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095.
(14) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1989**, *54*, 299.
(15) Thoresen, L. H.; Kim, H.; Welch, M. B.; Burghart, A.; Burgess, K. *Synlett* **1998**, 1276.
(16) Maekawa, H.; Itoh, K.; Goda, S.; Nishiguchi, I. *Chirality* **2003**, *15*, 95.
(17) Davies, H. M. L. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: London 1995; Vol. 1, pp 1−18.

JA057768+