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Benzylic Substitution of Gramines with Boronic Acids and Rhodium or Iridium Catalysts†

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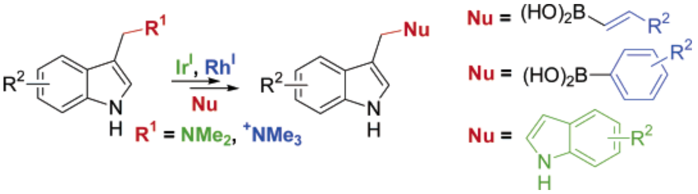
ABSTRACT



Gramine–MeI salts were useful starting materials for the synthesis of 3-benzyl- and 3-allylindoles by the 1,4-addition of boronic acids to the C═C–C═N linkages generated in situ under Rh(I)-catalysis. On the other hand, under Ir(I) catalysis, the reaction of gramines with indoles was used to produce nonsymmetrical diindolylmethanes.

The indole scaffold is one of the most medicinally relevant cores. Substituted indoles have been referred to as *privileged structures* since they are capable of binding to many receptors with high affinity. Therefore, the synthesis and selective functionalization of indoles have been the focus of active research over the years.[1] Currently, the implementation of new mild, selective procedures with ample functional group tolerance for the preparation of indoles is of high interest. Methods which use readily available starting materials and make use of aqueous media are particularly welcome to design new manufacturing processes.

Gramines (3-aminomethylindoles) are readily prepared by the Mannich reaction[2] and constitute valuable intermediates in the synthesis of complex indole-containing molecules (Figure 1).

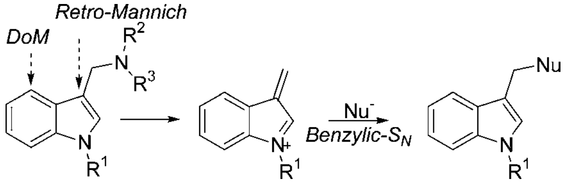


Figure 1. Gramines as versatile starting materials for the functionalization of indoles.

Gramines can be used to assist functionalization at C-4 of the indole ring by directed ortho-metalation[3] and of C-3 by retro-Mannich sequences.[4] In addition, the amino func-

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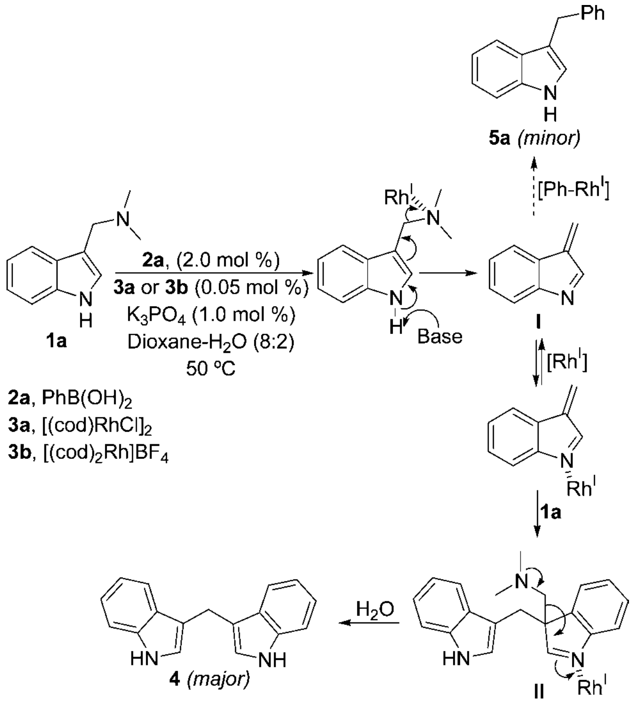
tionality can be made to depart as the leaving group to furnish stabilized benzylic-type cations (indolium ions) which can be trapped by heteronucleophiles and by stabilized carbon nucleophiles.[5,6] However, their reaction with nonstabilized carbon nucleophiles has been scarcely considered[7] and has found limited success only in the case of N-protected indoles.

The transition-metal-catalyzed conjugate addition of organometallic reagents to electron-deficient olefins is one of the most reliable methods for selective C−C bond formation.[8] In particular, the Rh(I)-catalyzed conjugate addition of aryl- and alkenylboronic acids can be carried out in water-tolerant solvents and is compatible with the presence of unprotected OH and NH groups.[9] This method of C−C bond formation has been applied to a variety of substrates including α,*β*-unsaturated ketones, esters, amides, aldehydes, alkenylphosphonates, nitroalkenes, and alkenyl sulfones. However, the conjugate addition to C═C−C═N systems has not been reported. Recently, Ir(I) complexes have also been shown to catalyze conjugate addition reactions of boronic acids.[10]

We report herein a new approach to the benzylic functionalization of indoles by the conjugate addition to the C═C−C═N linkages generated in situ under Rh(I) or Ir(I) catalysis, without the need of protection of the indole nitrogen.

Scheme 1 depicts the attempted benzylic substitution of the Me_2N group of gramine (**1a**) with Ph when treated with $PhB(OH)_2$ (**2a**) and the Rh(I) complexes **3a** or **3b** in the presence of K_3PO_4 as the base. Under these reaction conditions, diindolylmethane (**4**) was isolated (75%) together with minor amounts (10%) of the expected product **5a**.

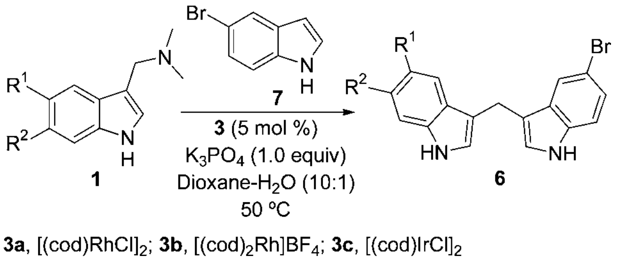
Scheme 1. Attempted Benzylic Substitution of **1a** with $PhB(OH)_2$ under Rh(I) Catalysis



We observed that **4** was also produced in the absence of $PhB(OH)_2$, but no reaction took place without a Rh(I) complex or a base. Therefore, it was reasonable to assume that coordination of the exocyclic nitrogen with the Rh(I) complexes will be slowing down transmetalation from boron to rhodium, thus preventing the formation of enough concentration of the [Ph−Rh^I] species required for the addition of Ph.[11,12] At the same time, this type of coordination will be assisting the formation of intermediate **I**. Under these circumstances, another gramine molecule will act as a nucleophile to generate compound **II**. Retro-Mannich reaction on intermediate **II** and final protonation will explain the formation of **4** as the major reaction product.

On this basis, we devised a new method[13,14] for the synthesis of nonsymmetrical diindolylmethanes **6** (Scheme 2).

Scheme 2. Synthesis of Nonsymmetrical Diindolylmethanes



Reaction of gramines **1** with 5-bromoindole[15] (**7**) and K_3PO_4 under Rh(I) or Ir(I) catalysis (complexes **3**) led to compounds **6** (Table 1). In addition to Rh(I) catalysis (**3a**, **3b**), Ir(I) catalysis was found to promote this transformation,

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(3) First report on DoM-functionalization of gramines at C-4: (a) Iwao, A. *Heterocycles* **1993**, *36*, 29. See also: (b) Fukuda, T.; Akashima, H.; Iwao, M. *Tetrahedron* **2005**, *61*, 6886.

(4) For the functionalization at C-3 by a halonium-induced retro-Mannich reaction, see: Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett.* **2002**, *4*, 815 and references cited therein.

(5) (a) Howe, E. E.; Zambito, A. J.; Snyder, H. R.; Tishler, M. *J. Am. Chem. Soc.* **1945**, *67*, 38. (b) Thesing, J.; Schülde, F. *Chem. Ber.* **1952**, *85*, 324. (c) Brewster, J. H.; Eliel, E. L. *Org. React.* **1953**, *7*, 99. (d) Allbright, J. D.; Snyder, H. R. *J. Am. Chem. Soc.* **1959**, *81*, 2239. (e) Baciocchi, E.; Schiroli, A. *J. Chem. Soc. B* **1968**, 401. (f) Somei, M.; Karasawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*, 941. (g) Iwao, M.; Motoi, O. *Tetrahedron Lett.* **1995**, *36*, 5929.

(6) For examples of combined applications of benzylic, C-3 and C-4 functionalizations of gramines in the synthesis of complex indoles, see: (a) Shinohara, H.; Fukuda, T.; Iwao, M. *Tetrahedron* **1999**, *55*, 10989. (b) Hurt, C. R.; Lin, R.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 225. (c) Smith, A. B.; Kanoh, N.; Ishiyama, H; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254.

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(8) For recent reviews, see: (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.1. (b) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; p 569. (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (d) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (e) Lipshutz, B. H. In *Organometallics in Organic Synthesis. A Manual*, 2nd ed.; Schlosser, M., Ed.; Wiley: Chichester, 2002; p 665.

(9) For reviews, see: (a) Hayashi, T. *Synlett* **2001**, 879. (b) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (d) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (e) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13.

Table 1. Synthesis of Nonsymmetrical Diindolylmethanes[a]

no.	**1**	**3**[b]	**6** (%)[c]
1	**1a**, R^1= H, R^2 = H	**3a**	**6a** (62)
2	**1a**, R^1= H, R^2 = H	**3b**	**6a** (73)
3	**1a**, R^1= H, R^2 = H	**3c**	**6a** (81)
4	**1b**, R^1= CH_3O, R^2 = H	**3c**	**6b** (79)
5	**1c**, R^1= H, R^2 = CH_3O	**3c**	**6c** (74)

[a] Reaction conditions: **1** (0.2 mol %), **3** (0.01 mol %), **7** (0.25 mol %), K_3PO_4 (0.2 mol %), dioxane−H_2O 10:1 (1.0 mL), 50 °C. [b] **3a**, $[(cod)RhCl]_2$; **3b**, $[(cod)_2Rh]BF_4$; **3c**, $[(cod)IrCl]_2$. [c] Yield of the isolated product after column chromatography on silica gel.

and in fact, the Ir(I) complex **3c** was found to be superior to the Rh(I) compounds **3a** or **3b**.

Scheme 3. Rh(I)-Catalyzed Benzylic Substitution of Methiodides **8** with Boronic Acids **2**

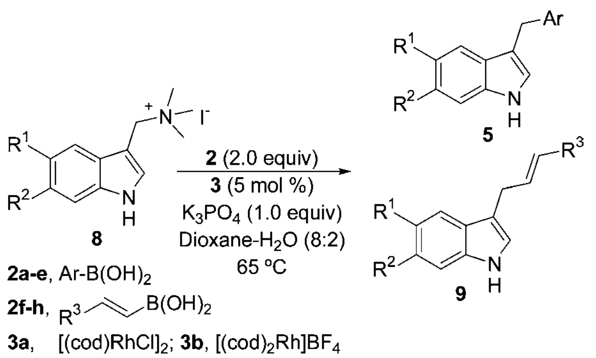

Table 2. Synthesis of 3-Benzyl- and 3-Allylindoles from Methiodides **8**[a]

no.	**8**	**2**	**5**, **9** (%)[b]
1	**8a**, R^1= H, R^2 = H	**2a**, Ar = Ph	**5a** (65)[c]
2	**8a**, R^1= H, R^2 = H	**2a**, Ar = Ph	**5a** (85)[d]
3	**8a**, R^1= H, R^2 = H	**2b**, Ar = 4-$MeOC_6H_4$	**5b** (77)[d]
4	**8a**, R^1= H, R^2 = H	**2c**, Ar = 2-$MeOC_6H_4$	**5c** (75)[d]
5	**8a**, R^1= H, R^2 = H	**2d**, Ar = 4-$CF_3C_6H_4$	**5d** (82)[d]
6	**8b**, R^1= CH_3O, R^2 = H	**2d**, Ar = 4-$CF_3C_6H_4$	**5e** (80)[d]
7	**8c**, R^1= H, R^2 = CH_3O	**2d**, Ar = 4-$CF_3C_6H_4$	**5f** (76)[d]
8	**8a**, R^1= H, R^2 = H	**2e**, Ar = 2-BrC_6H_4	**5g** (85)[d]
9	**8a**, R^1= H, R^2 = H	**2f**, R^3 = Ph	**9a** (82)[d]
10	**8a**, R^1= H, R^2 = H	**2g**, R^3 = 4-$CF_3C_6H_4$	**9b** (78)[d]
11	**8a**, R^1= H, R^2 = H	**2h**, R^3 = 4-ClC_6H_4	**9c** (65)[d]
12	**8b**, R^1= CH_3O, R^2 = H	**2f**, R^3 = Ph	**9d** (80)[d]
13	**8c**, R^1= H, R^2 = CH_3O	**2f**, R^3 = Ph	**9e** (75)[d]

[a] Reaction conditions: **1** (0.2 mol %), **2** (0.4 mol %), **3** (0.01 mol %), K_3PO_4 (0.2 mol %), dioxane-H_2O 8:2 (1.0 mL), 65 °C. [b] Yield of the isolated product after column chromatography on silica gel. [c] Catalyst **3a**, $[(cod)RhCl]_2$. [d] Catalyst **3b**, $[(cod)_2Rh]BF_4$.

Benzylic substitution of gramines **1** with boronic acids was made possible when quaternizing the amino group in the form of methiodides **8**. The Me_3N^+ group in **8** is not able to coordinate Rh(I), thus allowing for successful formation of $[R-Rh^I]$ species by transmetalation from boron to rhodium (Scheme 3, Table 2). Reaction of compounds **8** with arylboronic acids **2a**−**e** in the presence of K_3PO_4 under Rh(I) catalysis afforded the benzylic substitution products **5**. In this reaction, Rh(I) catalysis was superior to Ir(I) catalysis, as in the latter case, only **4** was isolated. We also observed better performance of the cationic Rh(I) complex **3b** over the chloride dimer **3a** (Table 2, entries 1 and 2). The reaction was general for electron-rich, electron-deficient, or sterically hindered ortho-substituted arylboronic acids (entries 2−8). Similarly, the reaction with alkenylboronic acids **2f**−**h** produced the allylindoles **9** (entries 9−13).

This method for the synthesis of C-3 benzyl and allylindoles is devoid from competition with the regioselectivity problems usually found in some other synthetic procedures.[16]

In conclusion, this paper demonstrates that under Rh(I) catalysis, $RB(OH)_2$ compounds are able to afford conjugate addition products with the C═C−C═N linkages generated in situ from the readily available gramine−MeI salts used as starting materials, leading to C-3 benzyl and allyl indole derivatives. Additionally, a new method for the synthesis of nonsymmetrical diindolylmethanes has been described, making use of gramines as starting materials in combination with Ir(I) catalysis. All of these transformations are carried out in a water-containing solvent, which can be of interest from environmental and manufacturing standpoints.

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(12) For a related coordination of the CH_2NMe_2 group of **1a** with Pd(II) salts leading to cyclometalation to the 2-position of the indole moiety, see: Tollari, S.; Demartin, F.; Cenini, S.; Palmisano, G.; Raimondi, P. *J. Organomet. Chem.* **1997**, *527*, 93.

(13) For a review on the synthesis and medicinal relevance of diindolylalkanes, see: Chakrabarty, M.; Basak, R.; Harigaya, Y. *Heterocycles* **2001**, *55*, 2431.

(14) To the best of our knowledge, there is only one previously reported synthesis of nonsymmetrical diindolylmethanes. See: Chalaye-Mauger, H.; Denis, J.-N.; Averbuch-Pouchot, M.-T.; Vallée, Y. *Tetrahedron* **2000**, *56*, 791.

(15) 5-Bromoindole (**7**) was chosen as model example for the synthesis of non-symmetrical diindolylmethanes. Further applications derived from halogen-metal exchange or transition-metal-catalyzed couplings can be foreseen for compounds **6**.

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

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