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# *N*-Cyclopropylation of Indoles and Cyclic Amides with Copper(II) Reagent

**Takayuki Tsuritani,*,† Neil A. Strotman,‡ Yuhei Yamamoto,† Masashi Kawasaki,† Nobuyoshi Yasuda,‡ and Toshiaki Mase†**

*Process Research, PreClinical Department, Banyu Pharmaceutical Co. Ltd., 3 Okubo, Tsukuba, Ibaraki 300-2611, Japan, and Merck Research Laboratories, Department of Process Research, PO Box 2000, Rahway, New Jersey 07065*

*takayuki_tsuritani@merck.com*

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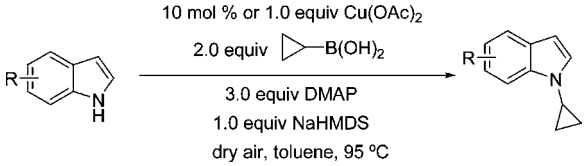
## ABSTRACT




**Copper-mediated coupling reactions of cyclopropylboronic acid with indoles and cyclic amides are described. The process utilizes catalytic or stoichiometric amounts of copper(II) acetate, DMAP, and NaHMDS at 95 °C under an atmosphere containing oxygen. A variety of functional groups remain intact throughout the reaction.**

The cyclopropyl group has received considerable attention in the field of medicinal chemistry because of its unique characteristics, such as its steric and electronic properties and metabolic stability.[1] Among the many cyclopropyl-containing compounds, *N*-cyclopropylamides and -azoles have attracted the most attention for the development of new drug candidates. Some of these compounds show antiviral,[2] antitumor,[3] and retinoic acid receptor antagonist activity.[4]

Despite the importance of *N*-cyclopropylamine derivatives, there are few methods to incorporate cyclopropyl groups on nitrogen atoms. For example, cyclopropylation of simple aniline derivatives was achieved by reductive amination with (1-ethoxycyclopropoxy)trimethylsilane,[5a−c] and through magnesium cyclopropylidene chemistry,[5d] but the yield and scope are limited. In particular, cyclopropylation of indoles, pyrroles, and amides has still remained challenging chemistry. Recently, cyclopropylation of cyclic amides and azoles was reported by Gagnon and co-workers.[6,7] This pioneering work utilized a triscyclopropylbismuth reagent with copper(II) acetate, and the reaction proceeded in good yields with broad substrate scope. A few issues with this reaction are reagent

† Banyu Pharmaceutical Co. Ltd.
‡ Merck Research Laboratories.

(1) For example, see: (a) Todo, Y.; Takagi, H.; Iino, F.; Fukuoka, Y.; Ikeda, Y.; Tanaka, K.; Saikawa, I.; Narita, H. *Chem. Pharm. Bull.* **1994**, *42*, 2049−2054. (b) Turner, W. R.; Suto, M. J. *Tetrahedron Lett.* **1993**, *34*, 281−284.

(2) (a) Chai, H.; Zhao, Y.; Zhao, C.; Gong, P. *Bioorg. Med. Chem.* **2006**, *14*, 911−917. (b) Zhao, C.; zhao, Y.; Chai, H.; Gong, P. *Bioorg. Med. Chem.* **2006**, *14*, 2552−2558.

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(4) Yoshimura, H.; Nagai, M.; Hibi, S.; Kikichi, K.; Abe, S.; Hida, T.; Higashi, S.; Hishimura, I.; Yamanaka, T. *J. Med. Chem.* **1995**, *38*, 3163−3173.

(5) (a) Kang, J.; Kim, K. S. *J. Chem. Soc., Chem. Commun.* **1987**, 897−898. (b) Gillaspy, M. L.; Lefker, B. A.; Hada, W. A.; Hoover, D. J. *Tetrahedron Lett.* **1995**, *36*, 7399−7402. (c) Yoshida, Y.; Umeza, K.; Hamada, Y.; Atsumi, N.; Tabuchi, F. *Synlett* **2003**, 2139−2142. (d) Satoh, T.; Miura, M.; Sakai, K.; Yokoyama, Y. *Tetrahedron* **2006**, *62*, 4253−4261.

(6) Gagnon, A.; St-Onge, M.; Little, K.; Duplessis, M.; Barabé, F. *J. Am. Chem. Soc.* **2007**, *129*, 44−45.

(7) Though there are a few reports of nucleophilic substitution of amide nitrogen atom with cycopropyl bromide, only one or two examples are mentioned and the yield was not clearly mentioned: (a) Liang, G.-B.; Qian, X.; Feng, D.; Biftu, T.; Eiermann, G.; He, H.; Leiting, B.; Lyons, K.; Petrov, A.; Sinha-Roy, R.; Zhang, B.; Wu, J.; Zhang, X.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1903−1907. (b) Tran, T. P.; Ellsworth, E. L.; Stier, M. A.; Domagala, J. M.; Showalter, H. D. H.; Gracheck, S. J.; Shapiro, M. A.; Joannides, T. E.; Singh, R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4405−4409.

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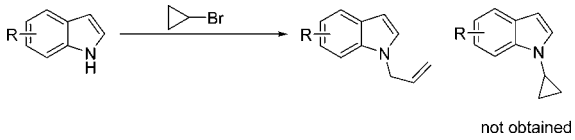
availability and atom efficiency: the triscyclopropylbismuth reagent is not commercially available and not stable for extended periods of storage, and two of the three cyclopropyl groups on bismuth do not participate in the coupling reaction.

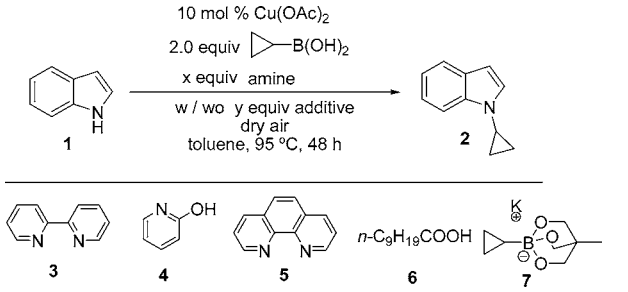
Therefore, we searched for a more facile method to introduce cyclopropyl groups on nitrogen atoms of azoles and amides. Transition-metal-catalyzed reactions between organohalides and amines constitute the most common strategy for *N*-alkylation and *N*-arylation.[8,9] Accordingly, we initially attempted the coupling reactions of indole with cyclopropyl bromide using a palladium, nickel, or copper catalyst. However, no desired coupling product was obtained, and only the *N*-allylated product derived from cyclopropane ring opening was observed, together with unreacted starting material (Scheme 1).

**Scheme 1.** Palladium-, Nickel-, or Copper-Catalyzed Reaction of Indoles with Cyclopropyl Bromide




Because of this vulnerability of cyclopropyl bromide to ring opening, we next turned our attention to the copper-mediated oxidative coupling reaction, a well-established reaction between arylmetals and amines. Thus far, arylmetals such as aryllead triacetate,[10] arylbismuth,[6,11] aryltrimethoxysilanes,[12] diaryl iodonium salts,[13] arylstannanes,[14] and arylboronic acid[15,16] have been reported to be efficient coupling partners for *N*-arylation. In particular, the coupling reactions with arylboronic acids have been studied extensively since the initial work by Chan and Lam.[15,16] We decided to focus on *N*-cyclopropylation with cyclopropylboronic acid since it is a commercially available reagent[17] and began our study with indole as a model substrate. The initial results are shown in Table 1.

**Table 1.** Conditions for the *N*-Cyclopropylation of Indole




| entry | amine | *x* | additive | *y* | yield[a] (%) |
|---|---|---|---|---|---|
| 1 | | | | | 0 |
| 2 | pyridine | 1.0 | | | 7 |
| 3 | pyridine | 3.0 | | | 40 |
| 4 | pyridine | 3.0 | **3** | 0.1 | 9 |
| 5 | pyridine | 3.0 | **4** | 0.1 | 36 |
| 6 | pyridine | 3.0 | **5** | 0.1 | 10 |
| 7 | pyridine | 3.0 | **6** | 0.2 | 20 |
| 8 | $Et_3N$ | 3.0 | | | 20 |
| 9 | lutidine | 3.0 | | | 21 |
| 10 | DMAP | 3.0 | | | 45 (43)[b] |
| 11 | DMAP | 3.0 | NaHMDS | 1.0 | 65 (62)[b] |
| 12 | | | NaHMDS | 1.0 | 0 |
| 13[c] | DMAP | 3.0 | | | 3 |

[a] HPLC assay yield. [b] Isolated yield. [c] Trialkoxyborate **7** was employed instead of cyclopropylboronic acid.

We were pleased to find that the desired coupling product was obtained in 40% assay yield under standard reaction conditions (entry 3) : $Cu(OAc)_2$ (10 mol %), pyridine (3.0 equiv), dry air, and toluene at 95 °C. DMAP and pyridine were found to be suitable amines (entries 3 and 8−10). The effect of additives was explored, and it was found that addition of an equimolar amount of NaHMDS improved the yield (entries 10 and 11), while addition of a catalytic amount (0.1 equiv) of amine ligands (entries 4−6) or addition of decanoic acid[16b,d] (0.2 equiv) did not improve the yields. This was plausibly due to the increased nucleophilicity of the indole anion. The reaction without pyridine or DMAP did not proceed at all (entries 1 and 12). Trialkoxyborate reagent **7** (see Table 1), which was recently developed by Miyaura's group as an efficient reagent for C−N bond formation as well as for Suzuki-Miyaura couplings,[18] did not work well (entry 13). Molecular oxygen was of importance in this reaction. When the reaction was conducted under a nitrogen atmosphere, no coupling product was obtained.

With these optimized conditions in hand, the scope and limitations of this reaction were examined (Table 2).

The reaction tolerated a variety of functional groups, such as chloride (entries 5 and 8), ester (entries 6), ketone (entry 7), nitrile (entry 3), and nitro (entry 4) groups. Although the reactions with electron-deficient substrates were not sufficient

(8) For reviews, see: Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. *Eur. J. Org. Chem.* **2007**, 4166−4176.

(9) (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382−2384. (b) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670−674. (c) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456. (d) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657−2640.

(10) Elliott, G. I.; Konopelski, J. P. *Org. Lett.* **2000**, *2*, 3055−3057 and references cited therein.

(11) Sorenson, R. J. *J. Org. Chem.* **2000**, *65*, 7747−7749 and references cited therein.

(12) (a) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600−7601. (b) Song, R.-J.; Deng, C.-L.; Xie, Y.-X.; Li, J.-H. *Tetrahedron Lett.* **2007**, *48*, 7845−7848.

(13) Kang, S.-K.; Lee, S.-H.; Lee, D. *Synlett* **2000**, 1022−1024.

(14) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, 674−676.

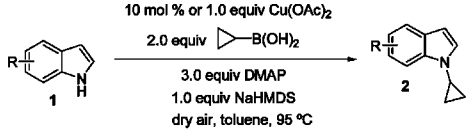
(15) (a) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941−2944. (b) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933−2936.

(16) (a) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233−1236. (b) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077−2079. (c) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397−4400. (d) Txschucke, C. C.; Murphy, J. M.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 761−764.

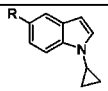
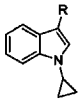
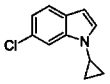
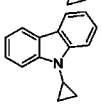
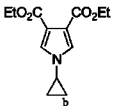
(17) Suzuki−Miyaura coupling reactions of cyclopropylboronic acid and aryl halides had already been reported. Wallace, D. J.; Chen, C. *Tetrahedron Lett.* **2002**, *43*, 6987−6990.

(18) Yamamoto, Y.; Takizawa, M.; Yu, X.-Q.; Miyaura, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 928−931.

**Table 2.** *N*-Cyclopropylation of Indole Derivatives




reaction time 16 h (stoichiometric reaction)
48 h (catalytic reaction)

| entry | product | | yield (%)[a] Cu(OAc)$_2$ [equiv] 0.1 | 1.0 |
|---|---|---|---|---|
| 1 |  | R = H, **2a** | 62 | 35 (75)[b] |
| 2 | | R = OMe, **2b** | 65 | 15 |
| 3 | | R = CN, **2c** | 28 | 86 |
| 4 | | R = $NO_2$, **2d** | 40 | 81 |
| 5 | | R = Cl, **2e** | 68 | 78 |
| 6 |  | R = $CO_2$Me **2f** | 34 | 93 |
| 7 | | R = C(O)Me **2g** | 35 | 86 |
| 8 |  | **2h** | 72 | 68 |
| 9 |  | **2i** | <5 | 40 |
| 10 |  | **2j** | 69 | 81 |
| 11 |  | **2k** | <5 | 78 |

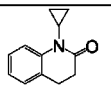
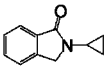
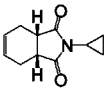
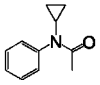
[a] Isolated yield. [b] Trialkoxy borate **7** was employed instead of cyclopropylboronic acid without NaHMDS.

(entries 3, 4, 6, 7, 9 and 11), the yields could be improved by using a stoichiometric amount of copper(II) acetate. However, surprisingly, stoichiometric reactions gave worse results in the case of electron rich substrates (entries 1 and 2),[19] and stoichiometric reactions with trialkoxyborate reagent **7** in the absence of NaHMDS furnished the desired coupling product in good yield.

We next applied this system to the cyclopropylation of amides (Table 3).

(19) In the case of indole and 5-methoxyindole, starting material was consumed completely, while starting material remained in the case of other substrates. An insoluble black tar emerged during the extractive operation in the former case.

**Table 3.** *N*-Cyclopropylation of Amides


| entry | product | | yield (%)[b] Cu(OAc)$_2$ [equiv] 0.1 | 1.0 |
|---|---|---|---|---|
| 1 |  | **9a** | 67 | 72 |
| 2 |  | **9b** | 71 | 89 |
| 3 |  | **9c** | 48 | 49 |
| 4 |  | **9d** | <5 | 93 |
| 5 |  | **9e** | 70 | 76 |
| 6 |  | **9f** | 0 | 0 |

[a] Reaction conditions are the same as those mentioned in Table 2. [b] Isolated yield

Cyclic amides and benzamide worked well (entries 1, 2, and 5), but acyclic amide did not afford the coupling product and starting material was recovered (entry 6). The poor reactivity of the acyclic amide might be due to its strong preference for the *Z*-conformation since all cyclic amides are forced to adopt the *E*-conformation. In addition, the coupling reaction proceeded well for a carbamate and imide (entries 3 and 4).

In summary, we have established a copper-mediated cyclopropylation of indoles and amides with cyclopropylboronic acid. Further development of this chemistry is currently under investigation in our laboratories.

**Acknowledgment.** We thank Dr. Kurihara H. for his helpful discussions and Drs. H. Ohsawa, M. Matsuda, and J. Sakai, Merck & Co. Inc., for HRMS measurements.

**Supporting Information Available:** Detailed experimental procedures and characterization data of each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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