

# Synthesis of Oxindoles by Palladium-catalyzed C–H Bond Amidation

Tomoya Miura, Yoshiteru Ito, and Masahiro Murakami\*

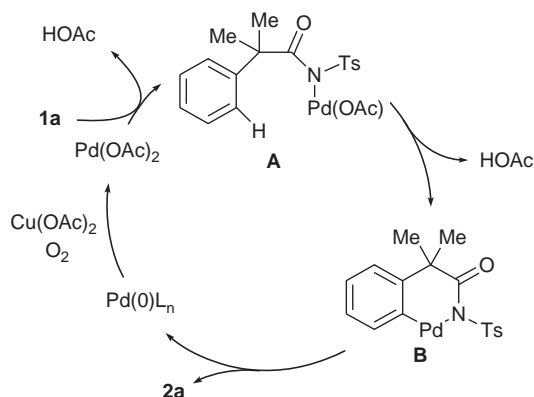
Department of Synthetic Chemistry and Biological Chemistry, Kyoto University, Katsura, Kyoto 615-8510

(Received January 15, 2009; CL-090055; E-mail: murakami@sbchem.kyoto-u.ac.jp)

Treatment of *N*-tosylphenylacetamide derivatives with copper(II) acetate in the presence of a catalytic amount of palladium(II) acetate affords 3,3-disubstituted oxindoles. The reaction proceeds through the intramolecular metallation of an aromatic C–H bond and the following C–N bond formation by reductive elimination.

The development of efficient methods for the synthesis of nitrogen-containing heterocycles using transition-metal catalysts is of immense interest owing to the ubiquity of heterocyclic cores in natural products and pharmaceuticals.<sup>1</sup> Cyclization through the direct conversion of C–H bonds into C–N bonds would be attractive for the construction of these ring systems in view of atom economy and synthetic simplicity.<sup>2</sup> In 2005, Buchwald and co-workers reported a palladium-catalyzed synthesis of carbazoles from acetylated 2-phenylaniline via C–H functionalization forming a C–N bond.<sup>3</sup> Since then, the method has been applied to the synthesis of other classes of heterocycles using palladium- and/or copper-catalysts.<sup>4</sup> Herein, we describe a synthesis of oxindoles from *N*-tosylphenylacetamide derivatives facilitated by a combination of Pd(OAc)<sub>2</sub> and Cu(OAc)<sub>2</sub>.<sup>5</sup>

When *N*-tosyl-2-methyl-2-phenylpropanamide (**1a**) was treated with Pd(OAc)<sub>2</sub> (10 mol%) in *p*-xylene at 140 °C for 14 h under an O<sub>2</sub> atmosphere, the oxindole **2a** was obtained in 15% yield (Table 1, Entry 1).<sup>6</sup> The effect of reoxidants as additives was examined (Entries 2–5) to reveal that the reaction in the presence of Cu(OAc)<sub>2</sub> (1 equiv) gave **2a** in 82% yield. Reducing the amount of Cu(OAc)<sub>2</sub> to 0.3 equiv and lowering the reaction temperature to 100 °C decreased the yield of **2a** (Entries 6 and 7). The reaction under an O<sub>2</sub> atmosphere proceeded faster than that under an Ar atmosphere (Entry 8). Although 4-nitrobenzenesulfonyl was also suitable as the protecting group of



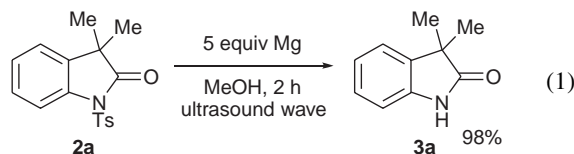
Scheme 1. A plausible reaction pathway.

the amide (Entry 9), no reaction took place with 4-methoxybenzyl-protected amide **1c** (Entry 10).

A proposed reaction pathway for the production of **2a** from **1a** is depicted in Scheme 1. Initially, the amide moiety of **1a** binds to Pd(OAc)<sub>2</sub> forming the palladium amide **A** with concomitant loss of a molecule of acetic acid. Then, cyclopalladation of **A** occurs to produce the six-membered-ring palladacycle **B** together with another molecule of acetic acid.<sup>7</sup> Finally, reductive elimination affords **2a** and a palladium(0) species, which is re-oxidized to Pd(OAc)<sub>2</sub> in the presence of Cu(OAc)<sub>2</sub> under an O<sub>2</sub> atmosphere.

Under optimized reaction conditions, a variety of *N*-tosylphenylacetamide derivatives reacted to afford the corresponding oxindoles in yields ranging from 30% to 97% (Table 2).<sup>8</sup> However, nonsubstituted substrates on the methylene carbon such as *N*-tosylphenylacetamide failed to participate in the cyclization, presumably due to the *gem*-dialkyl effect.<sup>9</sup> The reaction of **1g** and **1h** bearing a substituent at the para position gave the desired oxindoles in good yields (Entries 4 and 5). Whereas an electron-withdrawing chloro group was suitable as the meta substituent (Entry 6), an electron-donating methoxy group retarded the process (Entry 7). Notably, the C–H bond activation occurred exclusively at the less hindered 6-position of **1i** and **1j**. A similar electronic and steric effect was observed in the carbazole synthesis reported by Buchwald *et al.*<sup>3</sup>

The removal of the *N*-tosyl group in the products was readily achieved on treatment with magnesium in methanol under ultrasonic radiation (eq 1).<sup>10</sup>



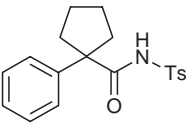
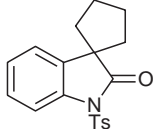
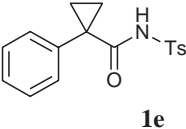
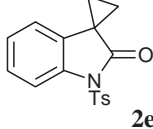
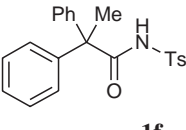
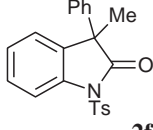
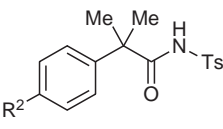
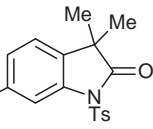
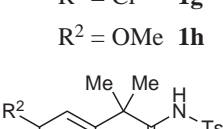
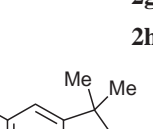
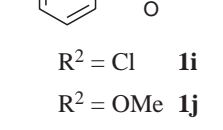
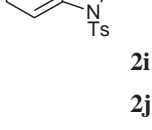
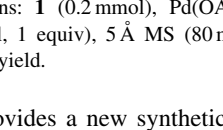
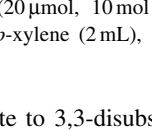
In summary, we have demonstrated that the palladium-catalyzed C–H bond amidation of *N*-tosylphenylacetamide deriva-

Table 1. Optimization of reaction conditions<sup>a</sup>

| Entry | <b>1</b>  | R <sup>1</sup> | Reoxidant (equiv)                   | Gas            | T/°C | Yield/% <sup>b</sup> |
|-------|-----------|----------------|-------------------------------------|----------------|------|----------------------|
| 1     | <b>1a</b> | Ts             | none                                | O <sub>2</sub> | 140  | 15                   |
| 2     | <b>1a</b> | Ts             | PhI(OAc) <sub>2</sub> (1)           | O <sub>2</sub> | 140  | <5                   |
| 3     | <b>1a</b> | Ts             | Benzoquinone (1)                    | O <sub>2</sub> | 140  | <5                   |
| 4     | <b>1a</b> | Ts             | Ag <sub>2</sub> CO <sub>3</sub> (1) | O <sub>2</sub> | 140  | 81                   |
| 5     | <b>1a</b> | Ts             | Cu(OAc) <sub>2</sub> (1)            | O <sub>2</sub> | 140  | 82                   |
| 6     | <b>1a</b> | Ts             | Cu(OAc) <sub>2</sub> (0.3)          | O <sub>2</sub> | 140  | 63                   |
| 7     | <b>1a</b> | Ts             | Cu(OAc) <sub>2</sub> (1)            | O <sub>2</sub> | 100  | 35                   |
| 8     | <b>1a</b> | Ts             | Cu(OAc) <sub>2</sub> (1)            | Ar             | 140  | 47                   |
| 9     | <b>1b</b> | Ns             | Cu(OAc) <sub>2</sub> (1)            | O <sub>2</sub> | 140  | 84                   |
| 10    | <b>1c</b> | PMB            | Cu(OAc) <sub>2</sub> (1)            | O <sub>2</sub> | 140  | 0                    |

<sup>a</sup>Reactions conducted on a 0.2 mmol scale. <sup>b</sup>Isolated yield. Ns = 4-nitrobenzenesulfonyl.

**Table 2.** Synthesis of 3,3-disubstituted oxindoles **2**<sup>a</sup>

| Entry | Substrate   | Product   | Yield/% <sup>b</sup> |
|-------|---|---|----------------------|
| 1     |                                      |    | 84                   |
| 2     |                                      |    | 39                   |
| 3     |                                      |    | 97                   |
| 4     | <br>R <sup>2</sup> = Cl <b>1g</b>    |    | 65                   |
| 5     | <br>R <sup>2</sup> = OMe <b>1h</b>  |   | 61                   |
| 6     | <br>R <sup>2</sup> = Cl <b>1i</b>  |  | 63                   |
| 7     | <br>R <sup>2</sup> = OMe <b>1j</b> |  | 30                   |

<sup>a</sup>Conditions: **1** (0.2 mmol), Pd(OAc)<sub>2</sub> (20 μmol, 10 mol %), Cu(OAc)<sub>2</sub> (0.2 mmol, 1 equiv), 5 Å MS (80 mg), *p*-xylene (2 mL), 14 h under O<sub>2</sub>.

<sup>b</sup>Isolated yield.

tives provides a new synthetic route to 3,3-disubstituted oxindoles,<sup>11</sup> which are important structural elements of indole alkaloids and pharmacologically active compounds.<sup>12</sup>

This work was partly supported by Grant-in-Aid for Scientific Research (A) No. 19205013 from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

## References and Notes

- Reviews: a) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, 36, 1095. b) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.* **2008**, 108, 3174. c) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, 108, 3395.
- Reviews: a) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, 62, 2439. b) H. M. L. Davies, J. R. Manning, *Nature* **2008**, 451, 417.
- a) W. C. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, 127, 14560. b) W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng, S. L. Buchwald, *J. Org. Chem.* **2008**, 73, 7603.
- C–N bond formation: a) K. Inamoto, T. Saito, M. Katsuno, T. Sakamoto, K. Hiroya, *Org. Lett.* **2007**, 9, 2931. b) B.-J. Li, S.-L. Tian, Z. Fang, Z.-J. Shi, *Angew. Chem., Int. Ed.* **2008**, 47, 1115. c) G. Brasche, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2008**, 47, 1932. d) J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem., Int. Ed.* **2008**, 47, 6452. e) J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, 130, 16184. C–O bond formation: f) S. Ueda, H. Nagasawa, *Angew. Chem., Int. Ed.* **2008**, 47, 6411. C–S bond formation: g) K. Inamoto, Y. Arai, K. Hiroya, T. Doi, *Chem. Commun.* **2008**, 5529. h) K. Inamoto, C. Hasegawa, K. Hiroya, T. Doi, *Org. Lett.* **2008**, 10, 5147.
- During the preparation of this manuscript, a C–H bond amidation reaction of *N*-methoxyphenylacetamide derivatives in the presence of Pd(OAc)<sub>2</sub>/CuCl<sub>2</sub>/AgOAc was disclosed by Yu: M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, 130, 14058. Unlike the Yu case, no silver salt was required as a reoxidant in the present reaction.
- No reaction took place with substrate **1a** under the Yu conditions reported in reference 5.
- Both the proton-abstraction mechanism and the S<sub>E</sub>Ar mechanism are conceivable for the C–H activation step. In reference 3b, other cyclization mechanisms via a Heck-type process and a Wacker-type process onto the arene ring were proposed by Buchwald and co-workers.
- General procedure:** To an oven-dried flask was added anhydrous Cu(OAc)<sub>2</sub> (36.3 mg, 0.2 mmol, 1 equiv), powdered molecular sieves (80 mg, activated 5 Å), Pd(OAc)<sub>2</sub> (4.5 mg, 20 μmol, 10 mol %), and *N*-tosylphenylacetamide derivative **1** (0.2 mmol, 1 equiv). The flask was evacuated and filled with O<sub>2</sub>. Freshly-distilled *p*-xylene (2 mL) was added via syringe. The reaction mixture was stirred at 140 °C for 14 h, and then quenched with addition of saturated aqueous NH<sub>4</sub>Cl solution (30 mL). The resulting solution was extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed with brine, dried over MgSO<sub>4</sub>, and filtered through Florisil. The solvent was removed under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 3/1 or CHCl<sub>3</sub> only) to give the corresponding oxindole **2**.
- a) M. E. Jung, J. Gervay, *J. Am. Chem. Soc.* **1991**, 113, 224. b) J. B. Sperry, D. L. Wright, *J. Am. Chem. Soc.* **2005**, 127, 8034. c) S. M. Bachrach, *J. Org. Chem.* **2008**, 73, 2466.
- D. A. Alonso, P. G. Andersson, *J. Org. Chem.* **1998**, 63, 9455.
- For recent reports on the synthesis of 3,3-disubstituted oxindoles, see: a) C. V. Galliford, J. S. Martenson, C. Stern, K. A. Scheidt, *Chem. Commun.* **2007**, 631. b) D. B. England, G. Merey, A. Padwa, *Org. Lett.* **2007**, 9, 3805. c) J. Huang, E. Bunel, M. M. Faul, *Org. Lett.* **2007**, 9, 4343. d) K. G. Liu, A. J. Robichaud, *Tetrahedron Lett.* **2007**, 48, 461. e) Y.-X. Jia, J. M. Hillgren, E. L. Watson, S. P. Marsden, E. P. Kündig, *Chem. Commun.* **2008**, 4040. f) Y. Yasui, H. Kamisaki, Y. Takemoto, *Org. Lett.* **2008**, 10, 3303. g) R. A. Altman, A. M. Hyde, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, 130, 9613.
- Reviews: a) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209. b) C. V. Galliford, K. A. Scheidt, *Angew. Chem., Int. Ed.* **2007**, 46, 8748.