

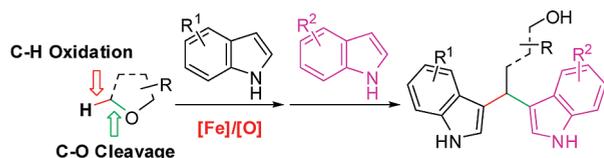
One-Pot Synthesis of Symmetric and Unsymmetric 1,1-Bis-indolylmethanes via Tandem Iron-Catalyzed C–H Bond Oxidation and C–O Bond Cleavage

Xingwei Guo, Shiguang Pan, Jinhua Liu, and Zhiping Li*

Department of Chemistry, Renmin University of China,
Beijing 100872, China

zhipingli@ruc.edu.cn

Received September 29, 2009



The reactions of indoles with ethers give a variety of symmetric and unsymmetric 1,1-bis-indolylmethane derivatives via iron-catalyzed C–H bond oxidation and C–O bond cleavage.

1,1-Bis-indolylmethane derivatives are found in bioactive metabolites of terrestrial and marine natural sources.¹ The condensation of carbonyl compounds with indoles is the most practical method of synthesizing symmetric 1,1-bis-indolylmethane compounds. However, a multistep synthesis had to be used for the synthesis of unsymmetric 1,1-bis-indolylmethanes.² The conversion of aromatic C–H bonds into C–C bonds classically has involved Friedel–Crafts reactions, which generally require a stoichiometric amount of the Lewis acids. Selective and efficient functionalization of C–H bonds has attracted much attention in both academia and industry in the past decades.³ The challenge of direct functionalization of indoles stimulated us to investigate the present oxidative coupling reactions.

(1) (a) Fahy, E.; Potts, B. C. M.; Faulkner, D. J.; Smith, K. *J. Nat. Prod.* **1991**, *54*, 564. (b) Garbe, T. R.; Kobayashi, M.; Shimizu, N.; Takesue, N.; Ozawa, M.; Yukawa, H. *J. Nat. Prod.* **2000**, *63*, 596.

(2) (a) Yu, H.; Yu, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 2929. (b) Bandgar, B. P.; Patil, A. V.; Kamble, V. T. *Arkivoc* **2007**, 252. (c) Ma, S.; Yu, S. *Org. Lett.* **2005**, *7*, 5063. (d) Zeng, X.-F.; Ji, S.-J.; Wang, S.-Y. *Tetrahedron* **2005**, *61*, 10235. (e) Kumar, S.; Kumar, V.; Chimni, S. S. *Tetrahedron Lett.* **2003**, *44*, 2101.

(3) For representative reviews, see: (a) Bergman, R. G. *Nature* **2007**, *446*, 391. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (d) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (e) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (f) *Handbook of C-H Transformations*; Dyker, D., Ed.; Wiley-VCH: Weinheim, Germany, 2005.

(4) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497.

(5) (a) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949. (b) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242. (c) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

Recently, we⁴ and others⁵ reported catalytic oxidative coupling reactions of the sp^3 C–H bond adjacent to an oxygen atom with the sp^3 C–H bond. However, the catalytic oxidative coupling reaction of the sp^3 C–H bond adjacent to an oxygen atom with the sp^2 C–H bond has virtually been untouched.⁶ Herein, we report a novel, simple, and efficient method to construct both symmetric and unsymmetric 1,1-bis-indolylmethanes using simple iron catalyst,⁷ which is the formal oxidative coupling reaction of the sp^2 C–H bond and the sp^3 C–H bond.

An extensive investigation of reaction conditions with a range of catalysts and oxidants⁸ was carried out and some representative results were shown in Table 1. The information for 1,1-bis-indolylmethane product **3a** was not observed in the presence of $Fe_2(CO)_9$, $Fe(OAc)_2$, $Fe(acac)_2$, or $Fe(acac)_3$ (Table 1, entries 1–4). Comparable yields were obtained when $FeCl_2$, $FeBr_2$, and $FeCl_3$ were used as catalysts (Table 1, entries 5–7).⁹ However, FeI_2 was a less effective catalyst (Table 1, entry 8). *tert*-Butyl hydroperoxide (TBHP) and *tert*-butyl peroxybenzoate were less effective oxidants for the formation of **3a** compared with di-*tert*-butyl peroxide (Table 1, entries 9 and 10). The information for the desired product **3a** was not observed in the absence of an oxidant or a catalyst (Table 1, entries 11 and 12). The reaction was completely suppressed by adding 1.0 equiv of TEMPO, a radical trapping reagent (Table 1, entry 13). This result indicates that a radical intermediate is most likely involved in the initial steps of the present transformation. It should be noted that **3a** was obtained exclusively even at room temperature, albeit in a low yield.

Subsequently, the scope of the present transformation was investigated with $FeCl_2$ as a catalyst. The desired 1,1-bis-indolylmethane derivatives **3** were obtained with good to excellent yields (Table 2). The reaction appears general with respect to the structural variation of **1** and **2**. Both *N*-H and *N*-Me indoles reacted smoothly with THF (Table 2, entries 1–5). Two regioisomers were obtained in a ratio of 1:1 when 2-methyl tetrahydrofuran **2b** was used (Table 2, entry 6).¹⁰ 1,3-Dihydroisobenzofuran **2c** and isochroman **2d** reacted with various indoles selectively (Table 2, entries 7 and 8).

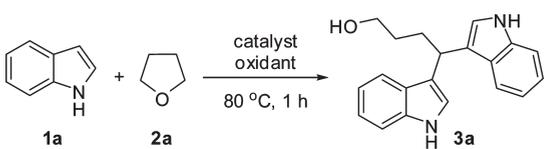
(6) Oxidative coupling reactions of the indolyl sp^2 C–H bond and the sp^3 C–H bond, see: (a) Shenvi, R. A.; O'Malley, D. P.; Baran, P. S. *Acc. Chem. Res.* **2009**, *42*, 530. (b) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857. (c) Baran, P. S.; DeMartino, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7083. (d) Baran, P. S.; Ambhaikar, N. B.; Guerrero, C. A.; Hafensteiner, B. D.; Lin, D. W.; Richter, J. M. *Arkivoc* **2006**, 310. (e) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968.

(7) For representative reviews on iron catalyst, see: (a) Sherry, B. D.; Furstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (b) Correa, A.; Mancheno, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (c) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317. (d) Furstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (e) Bolm, C.; Legros, J.; Le Pailh, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

(8) The combination of an iron catalyst and peroxide is well-known in Gif chemistry: (a) Stavropoulos, P.; Celenligil-Cetin, R.; Tapper, A. E. *Acc. Chem. Res.* **2001**, *34*, 745. (b) Barton, D. H. R. *Tetrahedron* **1998**, *54*, 5805. (c) Barton, D. H. R.; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504.

(9) A low yield of **3a** was obtained by a condensation reaction of aldehyde and indole, see: Giannini, G.; Marzi, M.; Moretti, G. P.; Penco, S.; Tinti, M. O.; Pesci, S.; Lazzaro, F.; De Angelis, F. *Eur. J. Org. Chem.* **2004**, 2411.

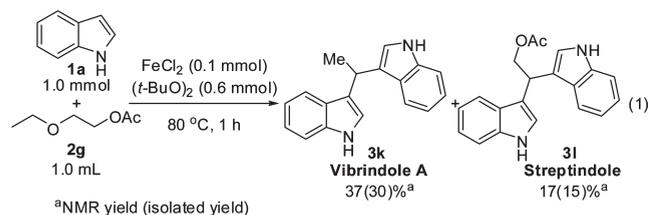
(10) Monoindolyl products were not observed, see: Bhuvanewari, S.; Jeganmohan, M.; Cheng, C. H. *Chem.—Eur. J.* **2007**, *13*, 8285.

TABLE 1. Optimization of Reaction Conditions^a


entry	catalyst	oxidant	isolated yield (%)
1	Fe ₂ (CO) ₉	(<i>t</i> -BuO) ₂	N.D. ^b
2	Fe(OAc) ₂	(<i>t</i> -BuO) ₂	N.D.
3	Fe(acac) ₂	(<i>t</i> -BuO) ₂	N.D.
4	Fe(acac) ₃	(<i>t</i> -BuO) ₂	N.D.
5	FeCl ₂	(<i>t</i> -BuO) ₂	86
6	FeBr ₂	(<i>t</i> -BuO) ₂	85
7	FeCl ₃	(<i>t</i> -BuO) ₂	85
8	FeI ₂	(<i>t</i> -BuO) ₂	37
9	FeCl ₂	<i>t</i> -BuOOH	50
10	FeCl ₂	PhCOOO- <i>t</i> -Bu	< 5
11	FeCl ₂		N.D.
12		(<i>t</i> -BuO) ₂	N.D.
13 ^c	FeCl ₂	(<i>t</i> -BuO) ₂	N.D.

^a1a (1.0 mmol), 2a (1 mL), catalyst (0.1 mmol), and oxidant (0.6 mmol). ^bNot detected by TLC. ^cTEMPO (0.5 mmol) was added.

Linear ethers reacted with 5-nitroindole **1f** and **1a** to give the dealkoxyl products with moderate to excellent yields (Table 2, entries 9–11). Importantly, two natural products, Vibrindole A **3k**¹¹ and Streptindole **3l**,¹² were obtained in 37% and 17% yield, respectively, in one reaction under the present reaction conditions (eq 1).



When the reaction of indole **1a** with **2c** was performed in the presence of 1.2 equiv of peroxide at 60 °C, the monoindolation product **4a** was formed in 13% together with a 83% yield of **3g** (Scheme 1). Interestingly, the monoindolation products, **4b** and **4c**, were obtained as major products when electron-withdrawing substituted indoles, **1c** and **1f**, were applied (Scheme 1). These results clearly demonstrated that (1) the second indolation step is a Friedel–Craft alkylation reaction and (2) the second indolation step is the rate-limiting step due to the energy being increased in the heterolysis of the benzylic C–O bond.

With highly selective product **4c** in hand, we envisioned that the synthesis of unsymmetric bis-indolylmethane derivatives might be achieved using our methodology. Indeed, unsymmetric bis-indolylmethanes **5** were selectively obtained by simply adding the second indole into the reaction mixture in one pot (Scheme 2). The second indolation step proceeds smoothly without the extra isolation step and the additional catalyst. It is noteworthy that iron catalyst is indispensable for the formation of **5**. The information for **5** was not observed in the reactions of

TABLE 2. Synthesis of Symmetric Bis-indolylmethanes^a

entry	1	2	3	yield (%)
1				86
2				74
3				75
4				76 ^b
5				84
6				75(1:1) ^c
7				90
8				62
9				95
10				91 ^d
11				55 ^d

^a1 (1.0 mmol), 2 (1 mL), FeCl₂ (0.1 mmol), and (*t*-BuO)₂ (0.6 mmol); 80 °C, 1 h. ^b5 h. ^cThe ratio of two isomers is given in parentheses. ^d50 °C, 12 h.

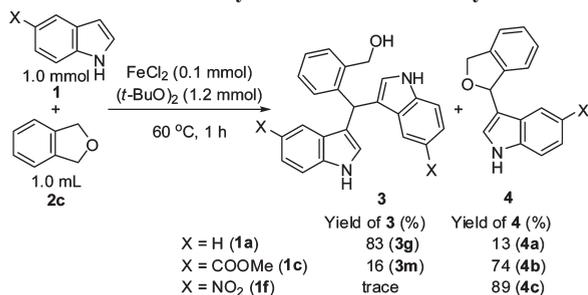
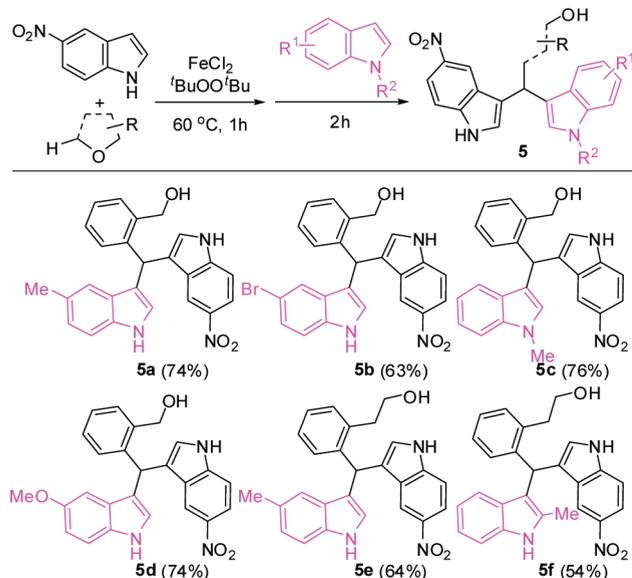
4 with other indoles without a catalyst. Not only 1,3-dihydroisobenzofuran **2c** but also isochroman **2d** could be used under the present reaction conditions. In all cases, the information for symmetric 1,1-bis-indolylmethane products generated from the second indoles was not observed. Given the importance of nitro groups in organic synthesis,¹³ the current procedure presents an alternative method to construct various unsymmetric bis-indolylmethane derivatives, which are difficult to obtain by other methods.

To investigate the possible mechanism of the present double indolation, 1,3-deuterated indole **1a-D** was synthesized and subjected to the reaction under the standard conditions. **3a** was exclusively obtained in 61% yield

(11) Bell, R.; Carmeli, S.; Sar, N. *J. Nat. Prod.* **1994**, *57*, 1587.
 (12) Osawa, T.; Namiki, M. *Tetrahedron Lett.* **1983**, *24*, 4719.

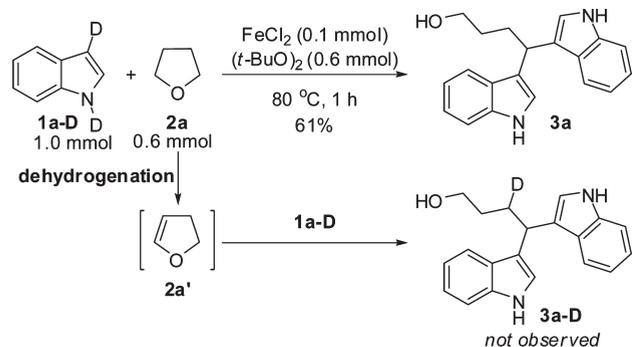
(13) *The Nitro Group in Organic Synthesis*; Ono, N., Ed.; Wiley-VCH: New York, 2001.

SCHEME 1. Monoindolation vs. Double Indolation

SCHEME 2. Synthesis of Unsymmetric Bis-indolylmethanes^a

^aReaction conditions: The first indole (0.5 mmol), **2** (0.5 mL), FeCl₂ (0.05 mol), and (t-BuO)₂ (0.6 mmol) and the second indole (0.5 mmol). The overall yield was provided.

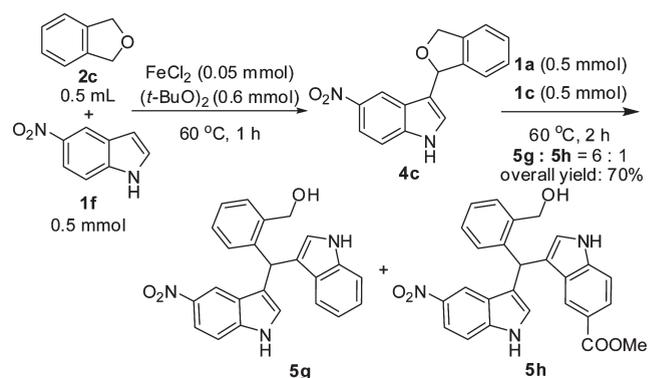
SCHEME 3. The Reactions of 1,3-Deuterated Indole 1a-D and THF



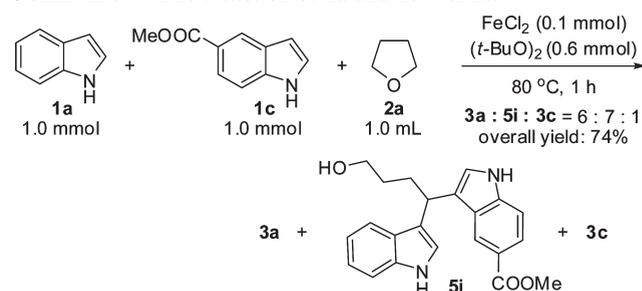
(Scheme 3). The deuterated product **3a-D** was not observed. Therefore, the possible intermediate of 2,3-dihydrofuran **2a'** was excluded.¹⁴

Furthermore, a series of competition experiments were investigated to address the influences of the electronic

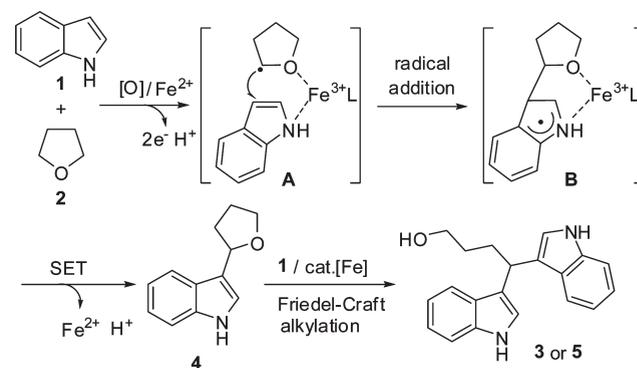
SCHEME 4. The Reaction of 1a and 1c with 4c



SCHEME 5. The Reaction of 1a and 1c with 2a



SCHEME 6. A Tentative Mechanism for the Formation of 3 and 5



properties of indoles in two indolation steps. The results indicated that the second indolation step depended on the electronic effect of indoles, which agrees with the Friedel–Crafts aromatic alkylation (Schemes 4 and 1). However, the first indolation step is less influenced by the electronic properties of indoles (Scheme 5).¹⁵ In other words, the first C–C bond formation is likely a radical process rather than an ionic one.

On the basis of the above results, a tentative mechanism was proposed (Scheme 6). H-abstraction gives an intermediate **A**. Radical addition offers an intermediate **B**, followed by oxidation leading to the oxidative coupling product **4**.¹⁶ The

(15) See the details in the Supporting Information.

(16) (a) *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001. (b) Guerrero, M. A.; Miranda, L. D. *Tetrahedron Lett.* **2006**, *47*, 2517. (c) Miranda, L. D.; Cruz-Almanza, R.; Pavon, M. *Arkivoc* **2002**, 15.

(14) Yadav, J. S.; Reddy, B. V. S.; Satheesh, G.; Prabhakar, A.; Kunwar, A. C. *Tetrahedron Lett.* **2003**, *44*, 2221.

double indolation product **3** or **5** is formed by Friedel–Craft alkylation reaction in the presence of iron catalyst.¹⁷

In summary, we demonstrated an efficient method to synthesize symmetric and unsymmetric bis-indolylmethane derivatives. These results demonstrate the dichotomous catalytic behavior of the iron catalysts, which are transition metal catalyst in C–C bond oxidative coupling and Lewis acid in C–O bond cleavage. The knowledge should prompt a broad range of applications of iron-catalyzed C–H bond oxidation and C–O bond cleavage.

Experimental Section

General Procedure for Products 3. To a mixture of indole **1a** (1 mmol), THF **2a** (1.0 mL, 12 mmol), and FeCl₂ (0.1 mmol) was dropped di-*tert*-butyl peroxide (0.6 mmol) under nitrogen at room temperature. The resulting mixture was stirred at 80 °C for 1 h. The reaction temperature was cooled to room temperature; the resulting reaction solution was mixed with some silica gel. Solvent was evaporated and the residue was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether (1:3) as eluent. The fraction with a *R_f* 0.4 (ethyl acetate/petroleum ether = 1:1) was collected to give the desired product **3a**. ¹H NMR (ppm) δ 7.75 (s, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 7.6 Hz, 2H), 6.99 (t, *J* = 7.6 Hz, 2H), 6.74 (s, 2H), 4.40 (t, *J* = 7.2 Hz, 1H), 3.52 (t, *J* = 6.4 Hz, 2H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.56 (q, *J* = 7.2 Hz, 2H); ¹³C NMR (ppm) δ 136.5, 127.0, 121.6, 121.5, 119.8, 119.5, 118.9, 111.1, 62.9, 33.7, 31.9, 31.3.

General Procedure for Products 5. To a mixture of 5-nitroindole **1f** (0.5 mmol), 1,3-dihydroisobenzofuran **2c** (0.5 mL,

5 mmol), and FeCl₂ (0.05 mmol) was dropped di-*tert*-butyl peroxide (0.6 mmol) under nitrogen at room temperature. The resulting mixture was stirred at 60 °C for 1 h. 5-Methylindole **1d** (0.5 mmol) was added into the reaction mixture. The resulting mixture was stirred at 60 °C for 2 h. The reaction temperature was cooled to room temperature; the resulting reaction solution was mixed with some silica gel. Solvent was evaporated and the residue was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether (1:3) as eluent. The fraction with a *R_f* 0.3 (ethyl acetate/petroleum ether = 1:1) was collected to give the desired product **5a**. IR (neat) ν_{\max} 3393, 3321, 3283, 3084, 3034, 2982, 2918, 1722, 1626, 1518, 1468, 1325, 1250, 1098, 1038, 1009, 797, 752, 606 cm⁻¹; ¹H NMR (ppm) δ 11.60 (s, 1H), 10.74 (s, 1H), 8.35 (s, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.18–7.09 (m, 3H), 6.95 (s, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.65 (s, 1H), 6.27 (s, 1H), 5.31 (t, *J* = 5.2 Hz, 1H), 4.69 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.62 (dd, *J* = 13.2, 5.2 Hz, 1H), 2.30 (s, 3H); ¹³C NMR (ppm) δ 141.8, 140.7, 140.4, 140.0, 135.5, 128.4, 128.1, 127.8, 127.3, 127.2, 127.1, 126.5, 124.5, 123.2, 121.3, 118.9, 117.0, 116.7, 112.5, 111.8, 61.3, 34.7, 21.8; MS (EI) *m/z* (%) 411, 393(100), 376, 361, 346, 331, 304, 280, 263, 232, 231, 204, 189, 165, 144, 131, 119, 91, 84, 66, 46; HRMS calcd for C₂₅H₂₀N₃O₃ [M – H] 410.1499, found 410.1493.

Acknowledgment. We thank the NSFC (20602038 and 20832002) and the State Key Laboratory of Fine Chemicals (No. KF0704) for financial support. We also thank the program for New Century Excellent Talents in University. We are indebted to Prof. Zhenfeng Xi, Peking University.

Supporting Information Available: Representative experimental procedures, characterization of all new compounds, and the copies of ¹H NMR and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(17) Indolation by Lewis acid-catalyzed C–O bond cleavage: (a) References 11 and 15. (b) Barluenga, J.; Fernandez, A.; Rodriguez, F.; Fanans, F. J. *J. Organomet. Chem.* **2009**, *694*, 546. (c) Yadav, J. S.; Reddy, B. V. S.; Aravind, S.; Kumar, G. G. K. S. N.; Reddy, A. S. *Tetrahedron Lett.* **2007**, *48*, 6117. (d) Zeng, X.-F.; Ji, S.-J.; Wang, S.-Y. *Tetrahedron* **2005**, *61*, 10235. Indolation by protic acid-catalyzed C–O bond cleavage: (e) Reference 2b.