ORGANIC LETTERS

2012
Vol. 14, No. 17
4525–4527

Copper(I)-Catalyzed Cascade Dearomatization of 2-Substituted Tryptophols with Arylidonium Salts

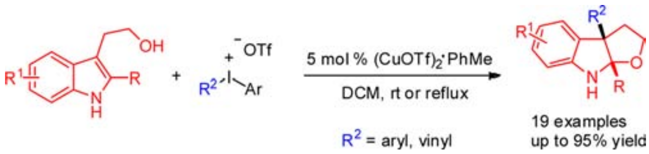
Chuan Liu, Wei Zhang, Li-Xin Dai, and Shu-Li You*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

slyou@sioc.ac.cn

Received July 12, 2012

ABSTRACT



Copper(I)-catalyzed dearomative arylation and vinylation of 2-substituted tryptophols were realized with a subsequent cyclization reaction. The cascade dearomatization sequence provided versatile furoindoline derivatives with two quaternary carbon centers in good to excellent yields.

Furoindolines are frequently existing structural fragments in natural products (Figure 1). However, substituted furoindolines with a quaternary carbon center at the C-3 position represent a synthetic challenge and still mainly rely on Fischer indole synthesis.[1] We recently developed an efficient cascade dearomatization protocol of *N*-substituted tryptophols to synthesize functionalized furoindolines *via* a Lewis acid catalyzed Michael addition reaction and a subsequent iminium ion trapping step.[2] Compared with the fully developed synthesis of pyrrolidinoindolines with a quaternary carbon center at the C-3 position utilizing various cascade dearomatization sequences,[3] the application of cascade dearomatization of tryptophols for the construction of furoindoline derivatives[4] still needs further exploration.[3d,5]

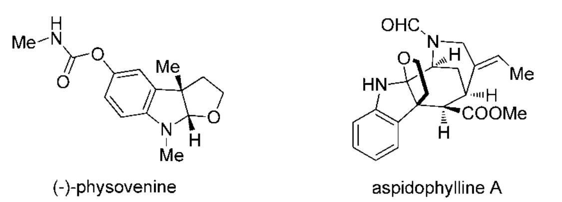


Figure 1. Representative furoindoline natural products.

Transition-metal-catalyzed direct arylation of aromatic rings with diarylidonium salts have made significant progress.[6]

(1) (a) ElAzab, A. S.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 2757. (b) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687. (c) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877.

(2) For a cascade dearomatization of *N*-substituted tryptophols *via* a Lewis acid catalyzed Michael reaction, see: Liu, C.; Zhang, W.; Dai L.-X.; You, S.-L. *Org. Biomol. Chem.* **2012**10.1039/C2OB26139A.

(3) For selected dearomatization reaction of indoles: (a) Lévy, J.; Sapi, J.; Laronze, J.-Y.; Royer, D.; Toupet, L. *Synlett* **1992**, 601.(b) Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964. (c) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482. (d) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (e) Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc.* **2010**, *132*, 14418. (f) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606. (g) Knowles, R. R.; Carpenter, J.; Blakey, S. B.; Kayano, A.; Mangion, I. K.; Sinz, C. J.; MacMillan, D. W. C. *Chem. Sci.* **2011**, *2*, 308.

(4) (a) Kim, S.-G. *Bull. Korean Chem. Soc.* **2009**, *30*, 2519. (b) Liu, Y.; Xu, W.; Wang, X. *Org. Lett.* **2010**, *12*, 1448. (c) Cera, G.; Crispino, P.; Monari, M.; Bandini, M. *Chem. Commun.* **2011**, *47*, 7803. (d) Noey, E. L.; Wang, X.; Houk, K. N. *J. Org. Chem.* **2011**, *76*, 3477. (e) Cera, G.; Chiarucci, M.; Mazzanti, A.; Mancinelli, M.; Bandini, M. *Org. Lett.* **2012**, *14*, 1350. (f) Fan, F.; Xie, W.; Ma, D. *Org. Lett.* **2012**, *14*, 1405.

(5) For selected cascade dearomatization reaction of tryptophols: (a) Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Ōmura, S.; Smith, A. B., III. *J. Am. Chem. Soc.* **2000**, *122*, 2122. (b) Sunazuka, T.; Yoshida, K.; Kojima, N.; Shirahata, T.; Hirose, T.; Handa, M.; Yamamoto, D.; Harigaya, Y.; Kuwajima, I.; Ōmura, S. *Tetrahedron Lett.* **2005**, *46*, 1459. (c) Lozano, O.; Blessley, G.; Martinez del Campo, T.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 8105.

10.1021/ol301939w
Published on Web 08/14/2012

In 2008, Gaunt et al. reported a copper-catalyzed arylation of indoles with a favorable C-3 selectivity.[6c] Inspired by this pioneering work, we envisioned that a copper-catalyzed cascade dearomatization reaction of 2-substituted tryptophols including the direct arylation at the indole C-3 position and a subsequent iminium ion trapping would afford the furoindoline derivatives with two quaternary carbon centers (Scheme 1). Herein, we report the preliminary results on such a copper-catalyzed dearomatization reaction of 2-substituted tryptophols affording furoindoline derivatives.[7,8]

Scheme 1. Proposed Cascade Dearomatization of 2-Substituted Tryptophols *via* Copper-Catalyzed Arylation Reaction with Diarylidonium Salts

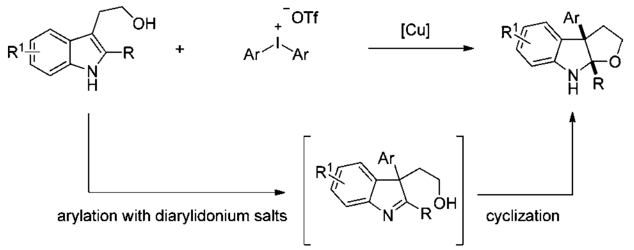
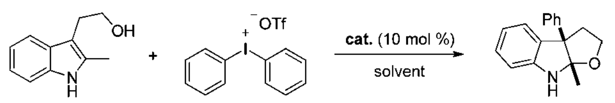


Table 1. Evaluation of Catalysts and Reaction Conditions



1a 2a 3a

entry[a]	catalyst	solvent	time (h)	yield (%)[b]
1	$Cu(OTf)_2$	CH_2Cl_2	1	91
2	$Cu(OAc)_2$	CH_2Cl_2	1	82
3	$Cu(ClO_4)_2 \cdot 6H_2O$	CH_2Cl_2	28	80
4[c]	$(CuOTf)_2 \cdot PhMe$	CH_2Cl_2	1	94
5	$CuPF_6(CH_3CN)_4$	CH_2Cl_2	20	90
6	CuCl	CH_2Cl_2	18	75
7	$Sc(OTf)_3$	CH_2Cl_2	48	<5
8	$Zn(OTf)_2$	CH_2Cl_2	48	N.R.
9	$Sn(OTf)_3$	CH_2Cl_2	48	<5
10	$Bi(OTf)_3$	CH_2Cl_2	48	N.R.
11	$Pd(OAc)_2$	CH_2Cl_2	48	<5
12[d]	$(CuOTf)_2 \cdot PhMe$	CH_2Cl_2	12	90
13[e]	$(CuOTf)_2 \cdot PhMe$	CH_2Cl_2	12	84
14[c]	$(CuOTf)_2 \cdot PhMe$	Et_2O	24	80
15[c]	$(CuOTf)_2 \cdot PhMe$	THF	24	63
16[c]	$(CuOTf)_2 \cdot PhMe$	toluene	48	71
17[c]	$(CuOTf)_2 \cdot PhMe$	DCE	3	86
18[c]	$(CuOTf)_2 \cdot PhMe$	$CHCl_3$	3	73
19[c]	$(CuOTf)_2 \cdot PhMe$	CH_3CN	48	N.R.

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), catalyst (0.03 mmol) in solvent (3 mL) at rt. [b] Isolated yield. [c] 5 mol % of $(CuOTf)_2 \cdot PhMe$ was used. [d] 2.5 mol % of $(CuOTf)_2 \cdot PhMe$ was used. [e] 1 mol % of $(CuOTf)_2 \cdot PhMe$ was used.

We began our exploration by testing model substrate **1a** with diphenylidonium salt (**2a**) under the catalysis of various copper sources. To our great delight, the reaction proceeded smoothly in dichloromethane at room temperature to afford the desired dearomative product **3a** in satisfactory yields (entries 1–6, Table 1). Among these tested copper sources, $(CuOTf)_2 \cdot PhMe$ performed best (94% yield, entry 4, Table 1). To further explore this cascade sequence, several frequently used Lewis acids were also examined. However, none of them could catalyze this reaction efficiently (entries 7–11, Table 1).

With $(CuOTf)_2 \cdot PhMe$ as the catalyst, the catalyst loading was then examined. With 2.5 or 1 mol % of the catalyst, the reaction could also proceed smoothly but with a prolonged reaction time (entries 12–13, Table 1). With 5 mol % of $(CuOTf)_2 \cdot PhMe$, the reaction conditions were further optimized. Various solvents ($CHCl_3$, DCE, toluene, Et_2O, THF, and CH_3CN) were tested, and all led to the formation of the desired product **3a** except for CH_3CN (entries 14–19, Table 1). The reaction in CH_2Cl_2 gave the best yield (entry 4, Table 1). The *syn* stereochemistry of product **3a** was established by an X-ray crystallographic analysis (see the Supporting Information for details).

Under the optimized reaction conditions (5 mol % of $(CuOTf)_2 \cdot PhMe$ in CH_2Cl_2, rt), the scope of the reaction was explored. The results are summarized in Scheme 2. First, the substituent at the C-2 position of tryptophol was tested.[9] The phenyl group could be tolerated, and **3b** was obtained in 87% yield after refluxing for 48 h. Second,

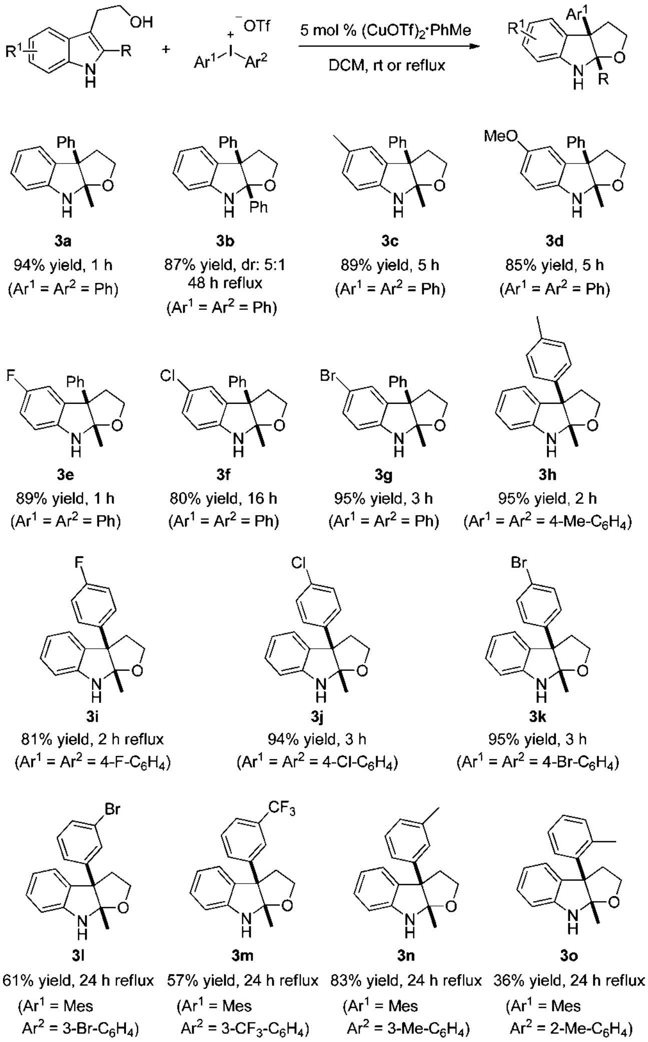
(6) For recent reviews on diaryliodonium salts, see: (a) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924. (b) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052. For selected Cu-catalyzed arylation with diaryliodonium salts: (c) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (d) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (e) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F. M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 458. (f) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 463. (g) Bigot, A.; Williamson, A. E.; Gaunt, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13778. (h) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260. (i) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 13782. (j) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773. For selected Pd-catalyzed arylation with diaryliodonium salts: (k) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (l) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234. (m) Xiao, B.; Fu, Y.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 468. For an organic base promoted C-3 arylation of 3-substituted indole with diaryliodonium salts: (n) Eastman, K.; Baran, P. S. *Tetrahedron* **2009**, *65*, 3149.

(7) For recent reviews on dearomatization reaction, see: (a) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (b) Roche, S. P.; Porco, J. A., Jr *Angew. Chem., Int. Ed.* **2011**, *50*, 4068. (c) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447. For selected dearomatization reactions from our group, see: (d) Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 11418. (e) Wu, Q.-F.; Liu, W.-B.; Zhuo, C.-X.; Rong, Z.-Q.; Ye, K.-Y.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4455. (f) Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8665. (g) Zhuo, C.-X.; Liu, W.-B.; Wu, Q.-F.; You, S.-L. *Chem. Sci.* **2012**, *3*, 205. (h) Wu, Q.-F.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1680. (i) Cai, Q.; You, S.-L. *Org. Lett.* **2012**, *14*, 3040. (j) Wu, K.-J.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2012**, *14*, 3772.

(8) During the preparation of the manuscript, Zhu and MacMillan reported an enantioselective copper-catalyzed construction of arylpyrroloindolines *via* an arylation–cyclization cascade; see: Zhu, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 10815.

(9) Under the optimized reaction conditions, 2-(2-phenyl-1*H*-indol-3-yl)ethanol was isolated in 86% yield when tryptophol was used.

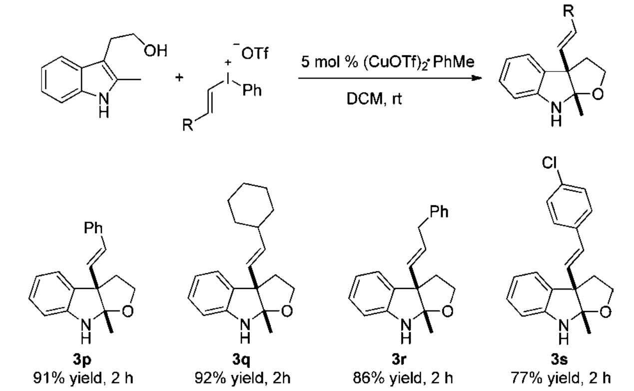
Scheme 2. Substrate Scope for Cu(I)-Catalyzed Arylation



2-methyl tryptophols with various substituents on the indole core all reacted with diphenyliodonium salt (**2a**) smoothly. The substrates bearing either an electron-donating group (5-Me, 5-MeO) or an electron-withdrawing group (5-Cl, 5-Br, 5-F) were found suitable to afford dearomative products in 80−95% yield (**3c** to **3g**, Scheme 2). Further exploration of the substrate scope involved various diaryliodonium salts. Diarylidonium salts having either an electron-donating group (2-Me, 3-Me, 4-Me) or an electron-

(10) For selected reactions of vinylphenylidonium salts, see: (a) Beringer, F. M.; Galton, S. A. *J. Org. Chem.* **1965**, *30*, 1930. (b) Ochiai, M.; Sumi, K.; Takaoka, Y.; Kunushima, M.; Nagao, Y.; Shiro, M.; Fujita, E. *Tetrahedron* **1988**, *44*, 4095. (c) Ochiai, M.; Oshima, K.; Masaki, Y. *J. Am. Chem. Soc.* **1991**, *113*, 7059. (d) Zefirov, N. S.; Kozmin, A. S.; Kasumov, T.; Potekhin, K. A.; Sorokin, V. D.; Brel, V. K.; Abramkin, E. V.; Struchkov, Y. T.; Zhdankin, V. V.; Stang, P. J. *J. Org. Chem.* **1992**, *57*, 2433. (e) Ochiai, M.; Shu, T.; Nagaoka, T.; Kitagawa, Y. *J. Org. Chem.* **1997**, *62*, 2130. (f) Skucas, E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 9090.

Scheme 3. Substrate Scope for Cu(I)-Catalyzed Vinylation



withdrawing group (4-Cl, 4-Br, 4-F, 3-Br, 3-CF_3) could be employed. In most cases, good to excellent yields were achieved (81−95%, **3h** to **3k**, and **3n**). However, **3l** (3-Br), **3m** (3-CF_3), and **3o** (2-Me) were obtained in only moderate yields, due to either the strong *meta*-electron-withdrawing groups or the steric hindrance.

Finally, to further broaden the substrate scope, vinylation of 2-methyl tryptophol (**1a**) was also explored. The results are summarized in Scheme 3. To our great delight, various vinylphenylidonium salts[10] were good partners for this cascade sequence (**3p** to **3s**, Scheme 3). In general, the vinylphenylidonium salts display higher reactivity compared to the diarylidonium salts. The reactions with vinylphenylidonium salts proceed to completion in 2 h at room temperature.

In summary, we have developed an efficient method to provide functionalized furoindolines *via* Cu(I)-catalyzed arylation or vinylation of 2-substituted tryptophols and the subsequent cyclization reaction. This cascade dearomatization sequence of tryptophols provided versatile furoindoline derivatives with two quaternary carbon centers in excellent yields under mild conditions. Further development of an enantioselective version of this reaction is currently underway in our laboratory.

Acknowledgment. We thank the National Basic Research Program of China (973 Program 2009CB825300) and the National Natural Science Foundation of China (21025209, 20932008, 21102160, 21121062) for generous financial support.

Supporting Information Available. Detailed experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.