

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

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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 derivatives⁴ still needs further exploration.^{3d,5}

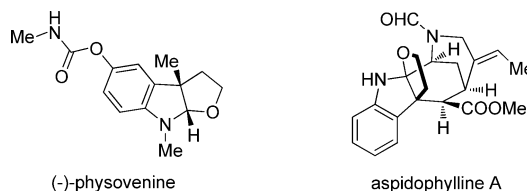


Figure 1. Representative furoindoline natural products.

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

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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 Diaryliodonium Salts

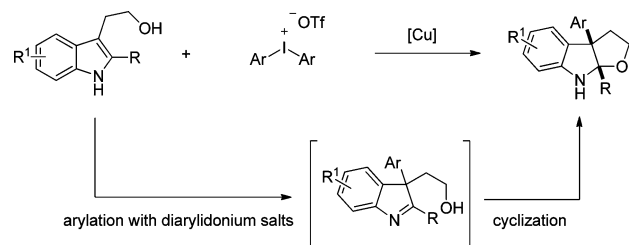
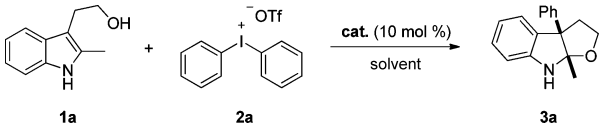


Table 1. Evaluation of Catalysts and Reaction Conditions



entry ^a	catalyst	solvent	time (h)	yield (%) ^b
1	Cu(OTf) ₂	CH ₂ Cl ₂	1	91
2	Cu(OAc) ₂	CH ₂ Cl ₂	1	82
3	Cu(ClO ₄) ₂ ·6H ₂ O	CH ₂ Cl ₂	28	80
4 ^c	(CuOTf) ₂ ·PhMe	CH ₂ Cl ₂	1	94
5	CuPF ₆ (CH ₃ CN) ₄	CH ₂ Cl ₂	20	90
6	CuCl	CH ₂ Cl ₂	18	75
7	Sc(OTf) ₃	CH ₂ Cl ₂	48	<5
8	Zn(OTf) ₂	CH ₂ Cl ₂	48	N.R.
9	Sn(OTf) ₃	CH ₂ Cl ₂	48	<5
10	Bi(OTf) ₃	CH ₂ Cl ₂	48	N.R.
11	Pd(OAc) ₂	CH ₂ Cl ₂	48	<5
12 ^d	(CuOTf) ₂ ·PhMe	CH ₂ Cl ₂	12	90
13 ^e	(CuOTf) ₂ ·PhMe	CH ₂ Cl ₂	12	84
14 ^c	(CuOTf) ₂ ·PhMe	Et ₂ O	24	80
15 ^c	(CuOTf) ₂ ·PhMe	THF	24	63
16 ^c	(CuOTf) ₂ ·PhMe	toluene	48	71
17 ^c	(CuOTf) ₂ ·PhMe	DCE	3	86
18 ^c	(CuOTf) ₂ ·PhMe	CHCl ₃	3	73
19 ^c	(CuOTf) ₂ ·PhMe	CH ₃ CN	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·PhMe was used. ^d 2.5 mol % of (CuOTf)₂·PhMe was used. ^e 1 mol % of (CuOTf)₂·PhMe was used.

We began our exploration by testing model substrate **1a** with diphenyliodonium 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 dearomatative product **3a** in satisfactory yields (entries 1–6, Table 1). Among these tested copper sources, (CuOTf)₂·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·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·PhMe, the reaction conditions were further optimized. Various solvents (CHCl₃, DCE, toluene, Et₂O, THF, and CH₃CN) were tested, and all led to the formation of the desired product **3a** except for CH₃CN (entries 14–19, Table 1). The reaction in CH₂Cl₂ 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·PhMe in CH₂Cl₂, 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,

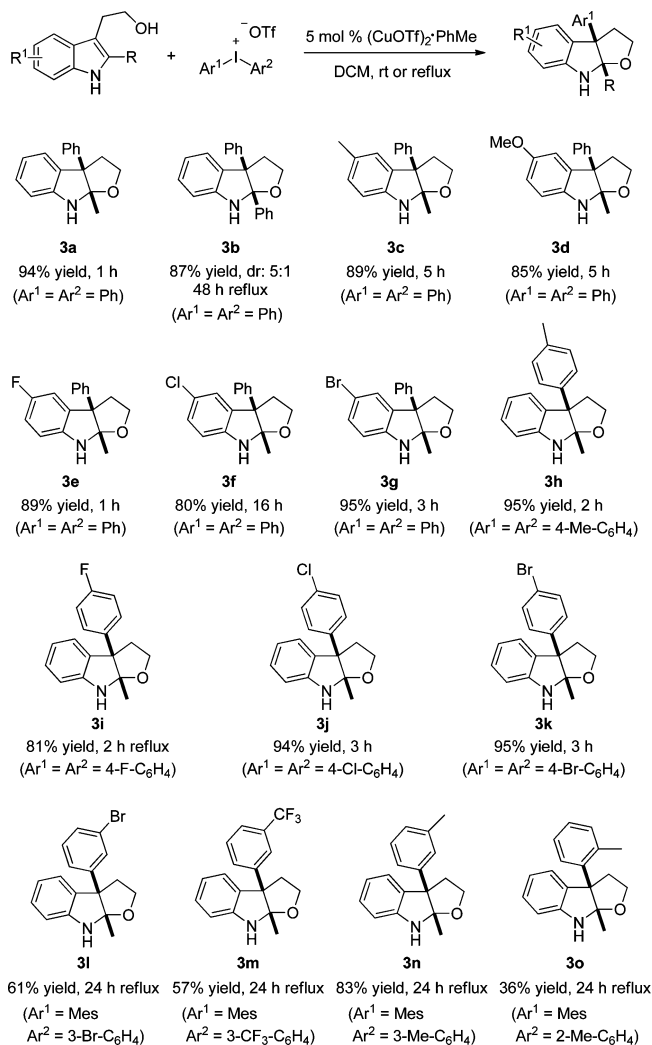
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(9) Under the optimized reaction conditions, 2-(2-phenyl-1*H*-indol-3-yl)ethanol was isolated in 86% yield when tryptophol was used.

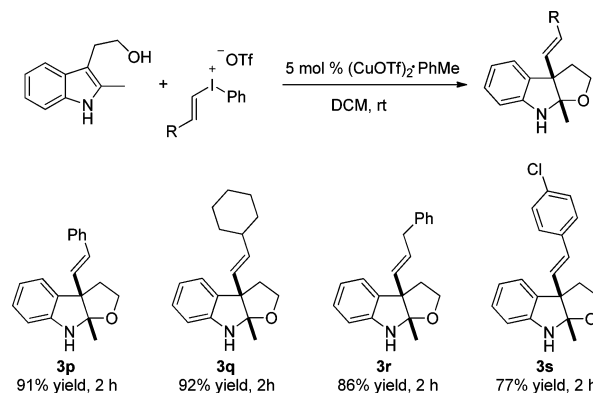
Scheme 2. Substrate Scope for Cu(I)-Catalyzed Arylation



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. Diaryliodonium salts having either an electron-donating group (2-Me, 3-Me, 4-Me) or an electron-

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



withdrawing group (4-Cl, 4-Br, 4-F, 3-Br, 3-CF₃) 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-CF₃), 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 vinylphenyliodonium salts¹⁰ were good partners for this cascade sequence (**3p** to **3s**, Scheme 3). In general, the vinylphenyliodonium salts display higher reactivity compared to the diaryliodonium salts. The reactions with vinylphenyliodonium 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.