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Copper(I)-Catalyzed Asymmetric Dearomatization of Indole Acetamides with 3-Indolylphenyliodonium Salts

Chuan Liu,[a] Ji-Cheng Yi,[a] Xiao-Wei Liang,[a] Ren-Qi Xu,[a] Li-Xin Dai,[a] and Shu-Li You*[a]

Abstract: An intermolecular asymmetric cascade dearomatization reaction of indole acetamides with 3-indolylphenyliodonium salts has been developed. This protocol provides a straightforward access to 3-(3a-indolyl)hexahydropyrroloindolines bearing an all-carbon quaternary stereocenter at the C3 position of indoline with high enantioselectivity, and the utility of which has been demonstrated by a formal asymmetric synthesis of folicanthine.

The 3-(3a-indolyl)hexahydropyrroloindoline (structure **A**) with a quaternary carbon stereocenter at the C3 position exits in a large array of indole alkaloids (Figure 1).[1] With the interesting structural features and a wide range of significant biological activities,[1] these alkaloids have attracted considerable attention of synthetic chemists to develop diverse methods for the construction of the 3-(3a-indolyl)hexahydropyrroloindoline ring system.[2] These methods include planar-chiral ferrocenyl pyridine derivative catalyzed Steglich-type rearrangement of indolyl carbonates,[2b] visible-light-mediated radical coupling of bromopyrroloindoline with indoles[2c] and a stereoretentive Friedel–Crafts alkylation of indoles[2e] (Scheme 1a, 1b). Despite of these significant achievements, development of a rapid and direct catalytic asymmetric reaction to access such a core structure **A** still holds extremely important position in the total

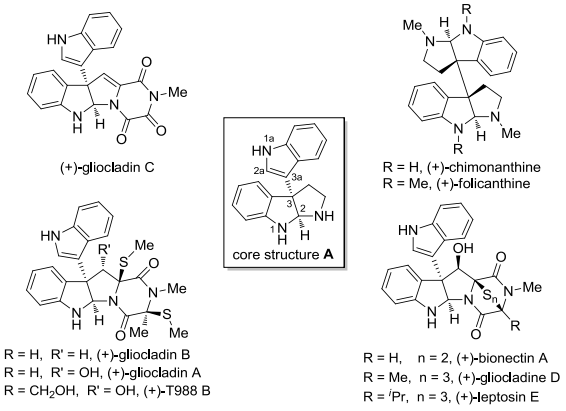
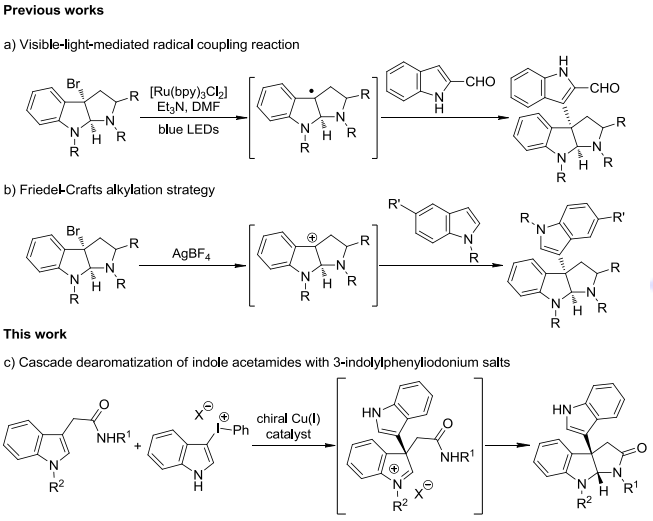


Figure 1. Selected 3-(3a-indolyl)hexahydropyrroloindoline natural products.



Scheme 1. Approaches to 3-(3a-indolyl)hexahydropyrroloindolines

synthesis of the 3-(3a-indolyl)hexahydropyrroloindoline alkaloid family products.

On the other hand, catalytic asymmetric dearomatization (CADA) reactions of indoles[3-5] have emerged as powerful organic transformations for the construction of pyrroloindoline alkaloids.[6] Among them, Cu-catalyzed cascade dearomatization reactions between indole derivatives with a pendant nucleophile incorporated at the C3 position and diaryliodonium salts have witnessed significant development.[7] In 2012, Zhu and MacMillan[7a] reported an elegant cascade reaction of tryptramine derivatives with diaryliodonium salts providing a direct strategy for the enantioselective construction of pyrroloindolines. We envisioned that indolylphenyliodonium salts[8] could be applied in this type of reactions, leading to a significant step forward in both hypervalent iodonium salt chemistry and indole functionalization. Notably, this is an unprecedented umpolung of the highly nucleophilic C3 position of indoles. As part of our ongoing research program towards the development of CADA reactions,[3d, 9] we recently realized a cascade reaction between indole acetamides and 3-indolylphenyliodonium salts by a chiral copper bisoxazoline complex, affording enantioenriched 3-(3a-indolyl)hexahydropyrroloindolines within one single step (Scheme 1c)[10] A formal total synthesis of folicanthine was accomplished based on this method. Herein, we report the preliminary results of this study.

Our initial studies focused on the preparation of 3-indolylphenyliodonium salts **2**. After elaboration of the reported procedure,[8a] the desired 3-indolylphenyliodonium salts could be obtained by straightforward transformations from indole (see the Supporting Information). Next, we began our study by evaluating the reaction of indole acetamide **1** and newly synthesized 3-indolylphenyliodonium salts **2** in the presence of a catalytic amount of $[Cu(CH_3CN)_4]PF_6$ combined with a series of chiral Box ligands (Table 1). When **1a'** was chosen as model substrate,

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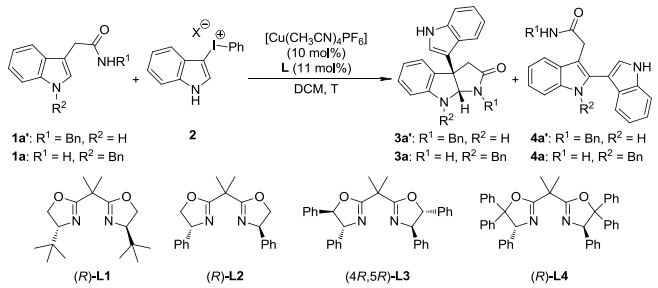
and 10 mol% $[Cu(CH_3CN)_4]PF_6$ was employed in the absence of a ligand, only an undesired product of **4a'** was obtained in 48% yield (entry 1, Table 1). To our delight, the reaction in dichloromethane at room temperature proceeded smoothly to afford the desired product **3a'** in the presence of phenyl-substituted bisoxazoline ligands (entries 3-4, Table 1). When **L3** was employed, moderate regio- and enantioselectivities were observed (50% yield, 23% ee, entry 4, Table 1). Further optimization of the reaction temperature and the counterions of the iodonium salts (entries 5-8, Table 1) disclosed that the reaction at -10 °C with the AsF_6 salt gave an increased **3a'/4a'** ratio and enantioselectivity of **3a'** (**3a'/4a'** 3/1, 74% ee, entry 8, Table 1). Fortunately, changing the protecting group resulted in a dramatic impovement in enantioselectivity (**3a**/**4a**: 20/1, 87% ee, entry 9, Table 1). Moreover, examining the counterions of the iodonium salts and the solvents revealed that the reaction with the iodonium salt containing SbF_6 counterion in EtOAc gave the best results (56% yield, 95% ee, entry 11, Table 1). Meanwhile, the absolute configuration of product **3a** was assigned as (*R, R*) by vibrational circular dichroism (VCD) spectroscopy (see the Supporting Information for details). Notably, in all cases, exclusive chemoselectivity was observed and no side product by the transfer of phenyl group was detected.

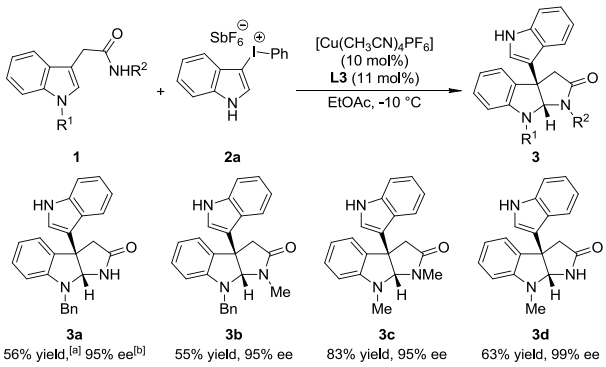
Table 1. Optimization of reaction conditions.[a]



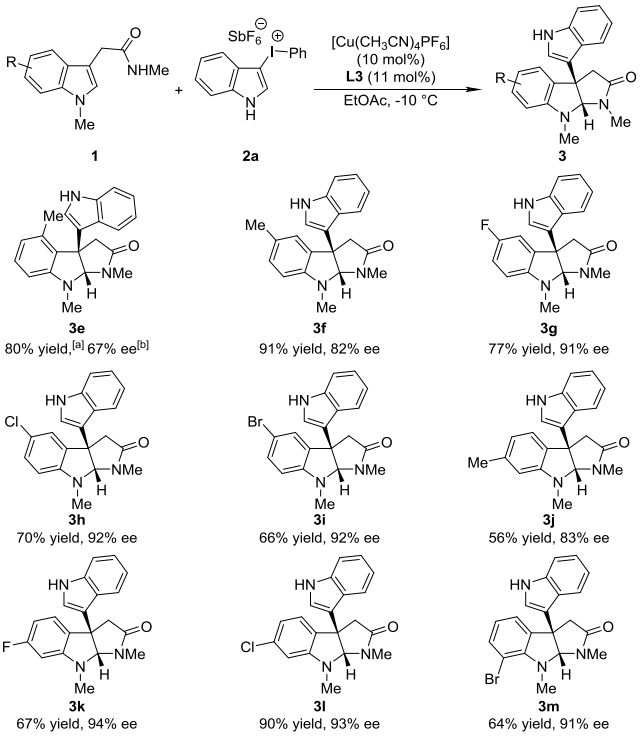
Entry	L	R^1	R^2	Temp (°C)	X	3a'(a)/ 4a'(a)	Yield [%][b]	*ee* [%][c]
1	-	Bn	H	25	OTf	1/20	48	-
2	**L1**	Bn	H	25	OTf	1/20	38	-
3	**L2**	Bn	H	25	OTf	2/1	41	21
4	**L3**	Bn	H	25	OTf	1/1	50	23
5	**L3**	Bn	H	25	PF_6	1/1	42	55
6	**L3**	Bn	H	0	PF_6	1.5/1	50	61
7	**L3**	Bn	H	0	AsF_6	2/1	46	64
8	**L3**	Bn	H	-10	AsF_6	3/1	39	74
9	**L3**	H	Bn	-10	AsF_6	20/1	54	87
10	**L3**	H	Bn	-10	SbF_6	20/1	46	89
11[d]	**L3**	**H**	**Bn**	**-10**	**SbF_6**	**20/1**	**56**	**95**
12[d]	**L4**	H	Bn	-10	SbF_6	20/1	53	92
13[d]	**L2**	H	Bn	-10	SbF_6	20/1	32	79

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $[Cu(CH_3CN)_4PF_6]$ (0.02 mmol), **L** (0.022 mmol), solvent (3.0 mL). [b] Isolated yield of both products. [c] Determined by HPLC analysis. [d] EtOAc was used as solvent.

With the optimized conditions in hand, we turned our attention to explore the generality of the protecting groups on indole acetamides. As shown in Scheme 2, the protecting groups on indole or acetamide nitrogen could be varied. For example, *N*-methyl-substituted indole acetamide and *N*-methyl acetamidyl indole participated in this cascade dearomatization with high levels of enantioselectivity (55−83% yield, 95−99% ee; **3a** to **3d**, Scheme 2). Notably, the reaction with *N*-methyl-2-(1-methyl-1H-indol-3-yl) acetamide **1c** proceeded smoothly to give cascade dearomatized product in the highest yield and excellent enantioselectivity (83% yield, 95% ee, **3c**, Scheme 2). Then the *N*-methyl group was used as protecting group on both indolic and acetamidyl nitrogens for testing the generality for indole acetamides and 3-indolylphenyliodonium salts.



Scheme 2. Scope of the indole acetamides. Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), $[Cu(CH_3CN)_4PF_6]$ (0.02 mmol), **L3** (0.022 mmol) in EtOAc (3.0 mL) at -10 °C. [a] Isolated yield. [b] Determined by HPLC analysis.

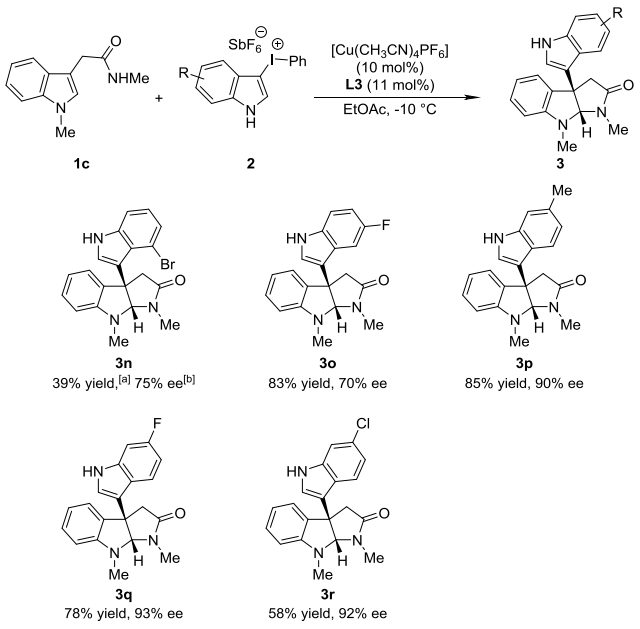


Scheme 3. Scope of the indole acetamides. Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), $[Cu(CH_3CN)_4PF_6]$ (0.03 mmol), **L3** (0.033 mmol) in EtOAc (5.0 mL) at -10 °C. [a] Isolated yield. [b] Determined by HPLC analysis.

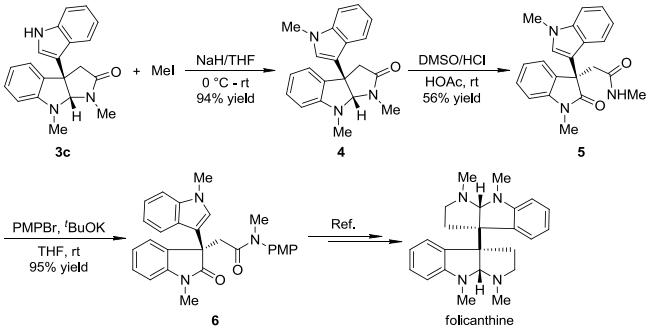
Next, the scope of substituent patterns on the nucleophile framework was explored. Indole acetamides bearing substituent at the C4, C5, C6 or C7 position all led to their corresponding products (**3e** to **3m**, Scheme 3). Generally, the substrates with electron-withdrawing group (5-F, 5-Cl, 5-Br, 6-F, 6-Cl, 7-Br) gave products with excellent enantioselectivity (91-94% ee) and high yields (64−90%), but indole acetamide derivatives bearing an electron-donating group (4-Me, 5-Me, 6-Me) afforded the corresponding products in lower enantioselectivity (67-83% ee, **3e**, **3f** and **3j**, Scheme 3).

To further broaden the substrate scope, several 3-indolylphenyliodonium salts varying substituents on the indole ring were also examined (Scheme 4). It was found that 3-indolylphenyliodonium salts bearing substituent at the C6 position (6-Me, 6-F, 6-Cl) all led to their corresponding products in good yields with excellent enantioselectivity (58-85% yields, 90-93% ee, **3p** to **3r**, Scheme 4). The reaction of substituent at the C5 position also proceeded smoothly to afford the desired product in 83% yield and 70% ee (**3o**, Scheme 4). However, introduction of a Br at the C4 position of indole resulted in low yield and moderate enantioselectivity likely due to the steric hinderance (39% yields, 75% ee, **3n**, Scheme 4).

To highlight the synthetic value of this methodology, the utility of this cascade dearomatization reaction in a formal total synthesis of folicanthine is demonstrated. As depicted in Scheme 5, under basic conditions, *N*-methylation of indole in **3c** furnished compound **4** in 94% yield. Subsequent oxidation by DMSO/HCl afforded compound **5** in 56% yield. Then, introducing a PMP group to the amide nitrogen atom gave rise to compound **6** in 95% yield, from which folicanthine could be synthesized following the procedures reported by Gong and co-workers.[11]



Scheme 4. Scope of the indolylphenyliodonium salts. Reaction conditions: **1c** (0.3 mmol), **2** (0.36 mmol), $[Cu(CH_3CN)_4PF_6]$ (0.03 mmol), **L3** (0.033 mmol) in EtOAc (5.0 mL) at -10 °C. [a] Isolated yield. [b] Determined by HPLC analysis.



Scheme 5. Formal synthesis of folicanthine.

In summary, we have developed a copper-catalyzed asymmetric cascade dearomatization reaction of indole acetamide derivatives with 3-indolylphenyliodonium salts. This protocol provides a straightforward synthesis of 3-(3a-indolyl)hexahydropyrrolo-indolines bearing an all-carbon quaternary stereocenter at the C3 position of indoline with high enantioselectivity. The synthetic value of this transformation has been demonstrated by the formal total synthesis of folicanthine. Further application of this methodology in the total synthesis of complex indole alkaloids is under investigation in our laboratory.

Experimental Section

In a glove box, $[Cu(CH_3CN)_4PF_6]$ (11.1 mg, 0.03 mmol, 10 mol%) and **L3** (16.0 mg, 0.033 mmol, 11 mol%) were added to an oven dried Schlenk tube. The Schlenk tube was then sealed and taken out from the glove-box, and then EtOAc (5.0 mL) was added. The mixture was stirred for 1 h before the appropriate indolylphenyliodonium salt **2** (0.36 mmol, 1.2 equiv), and indole acetamide **1** (0.3 mmol, 1.0 equiv) were added at -10 °C under argon. The reaction mixture was allowed to stir for 5-7 days at -10 °C. After the reaction was complete (monitored by TLC), it was quenched by adding saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified by silica gel column chromatography (PE/EA = 1/1) to afford the desired product **3**.

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Keywords: asymmetric catalysis • dearomatization • hexahydropyrroloindoline • indole • iodonium salt

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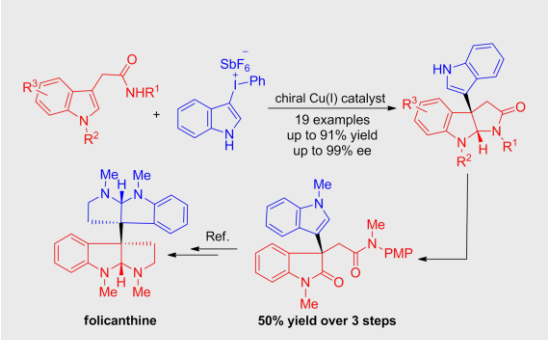
Entry for the Table of Contents

Layout :

COMMUNICATION

An intermolecular asymmetric cascade dearomatization reaction of indole acetamides with 3-indolylphenyliodonium salts has been developed. This protocol provides a straightforward access to 3-(3a-indolyl)hexahydropyrroloindolines bearing an all-carbon quaternary stereocenter at the C3 position of indoline with high enantioselectivity, and the utility of which has been demonstrated by a formal asymmetric synthesis of folicanthine.



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