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Enantioselective Copper-Catalyzed Construction of Aryl Pyrroloindolines via an Arylation–Cyclization Cascade

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Supporting Information

ABSTRACT: An enantioselective arylation–cyclization cascade has been accomplished using a combination of diaryliodonium salts and asymmetric copper catalysis. These mild catalytic conditions provide a new strategy for the enantioselective construction of pyrroloindolines, an important alkaloid structural motif that is commonly found among biologically active natural products.

The pyrroloindolines and polypyrroloindolines represent a diverse family of structurally complex polyindoline alkaloids that have been isolated from a widespread series of natural sources, including amphibians, plants, and marine algae.[1] An important structural subclass, the C(3)-aryl pyrroloindoline unit (Figure 1), is incorporated in a range of natural products that have been shown to be cytotoxic against both lymphocytic leukemia[2a] and lymphoblastoma[2b] cell lines. Moreover, the structurally related pyrroloindoline–thiodiketopiperazine family display nematicidal activity against pathogenic fungi such as *Pythium ultimum* and *Rhizoctonia solani*,[2c] while the C(3)-aryl-containing hodgkinsine (not shown) has been found to exhibit antinociceptive properties that are similar to morphine.[2d,3] The structural complexity of the C(3)-aryl pyrroloindolines makes them a particularly elusive and at the same time appealing target for total synthetic efforts.[4] In this context, both Overman and Movassaghi have made seminal contributions in the design of new reaction methods that allow for the rapid construction of many of these complex alkaloids. The Overman group has focused on the development of a Heck strategy for the enantioselective construction of oxindoles that were elegantly converted into quadrigemine C, psycholeine, asperazine, and idiospermuline.[4d−g] In a complementary approach, the Movassaghi group has employed Friedel–Crafts additions to enantiopure tryptophan derivatives in the synthesis of naseseazines A and B.[4a,b,5]

Recently our laboratory reported the enantioselective α-arylation of carbonyls using copper bisoxazoline catalysis and iodonium salts.[6] As a thematic extension, we postulated that this Cu(III)–aryl strategy could serve as a platform for pyrroloindoline construction via an enantioselective arylation–cyclization cascade process using indole-based nucleophiles. Herein we present the successful execution of these ideas and describe an operationally trivial asymmetric catalytic approach that allows the formation of a diverse range of C(3)-aryl pyrroloindoline architectures in only one step. We expect this new enantioselective catalysis method should be broadly applicable to natural product and medicinal agent synthesis.

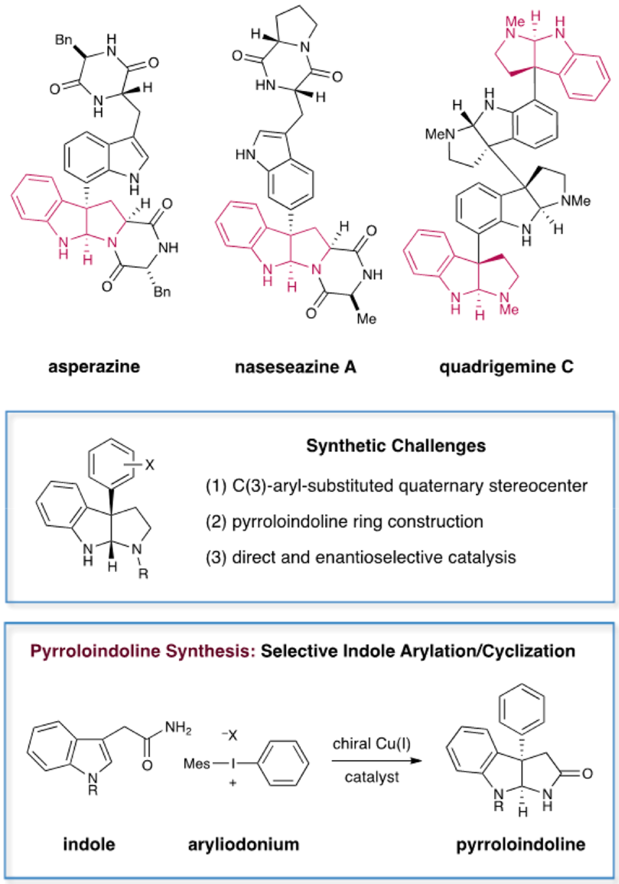

Figure 1. Representative pyrroloindolines and arylation strategy.

Our design plan is outlined in Scheme 1. We proposed that oxidative insertion of a ligand-bound Cu(I) complex into a suitable diaryliodonium salt[7,8] would result in a highly electrophilic chiral Cu(III) species.[9,10] Subsequent addition of the indole nucleophile followed by reductive elimination and amine–iminium cyclization would then yield the desired enantioenriched pyrroloindoline product while reconstituting the Cu(I) catalyst. As in our previous studies, we recognized that substrate–catalyst bidentate coordination should be important and thus sought to incorporate a pendant carbonyl on the tryptamine nucleophile unit to facilitate the formation of a square-pyramidal Cu(III) complex.[11] Given the architectural

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Scheme 1. Mechanism of Asymmetric Arylation−Cyclization

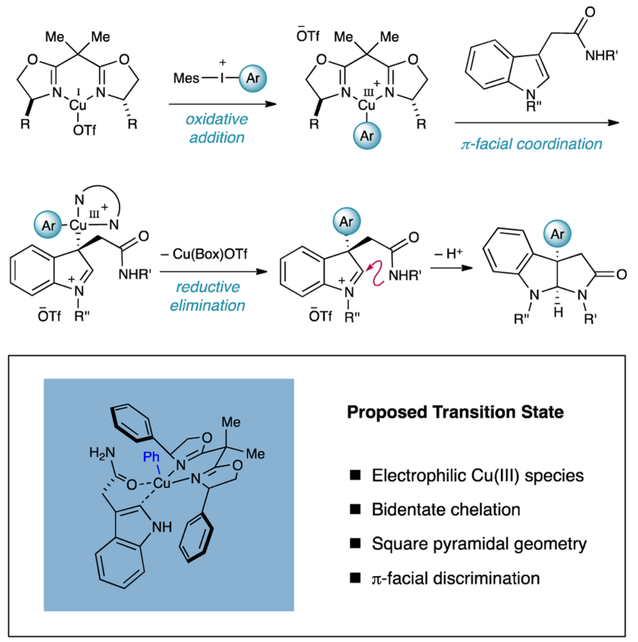
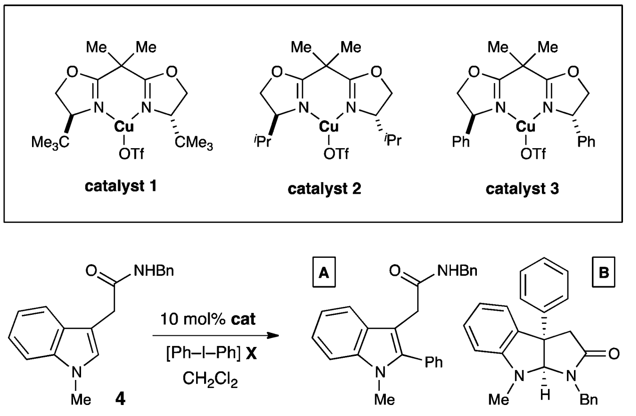


Table 1. Evaluation of Cu−Box Catalysts and Iodonium Counterions



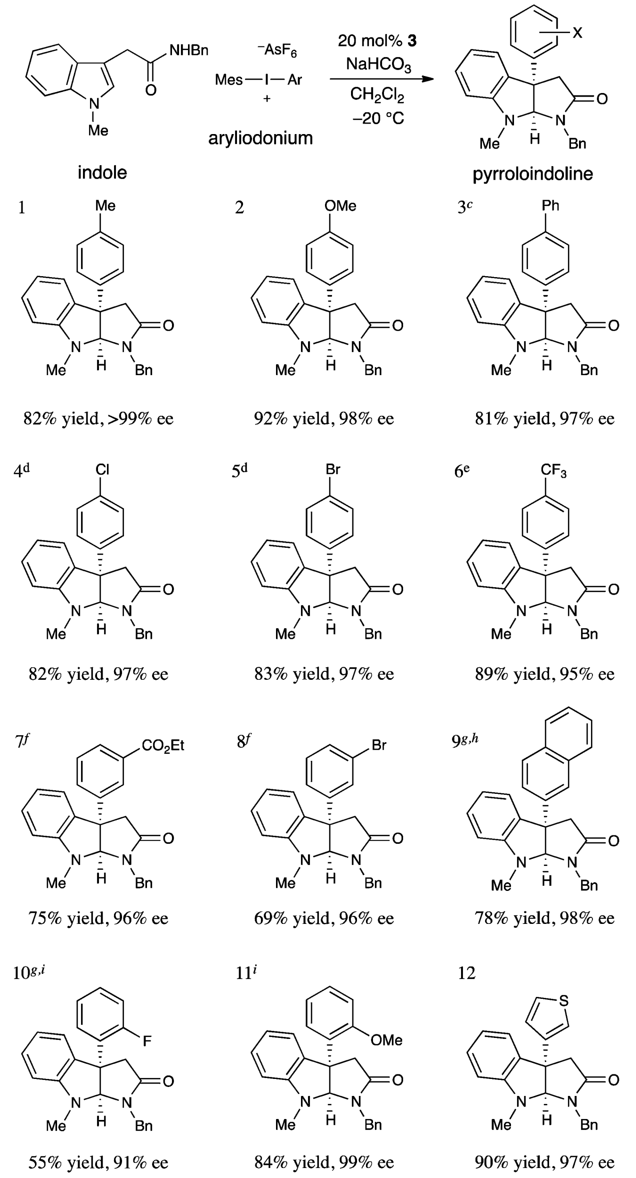
entry	catalyst	X	T (°C)	A:B	yield (%)[a]	ee (%)[b]
1	none	OTf	23	–	0	–
2	$(CuOTf)_2$·PhMe	OTf	23	29:1	69	–
3	**1**	OTf	23	4:1	20	8
4	**2**	OTf	23	3:1	71	61
5	**3**	OTf	20	1:10	90	98
6	**3**	PF_6	23	1:16	99	98
7	**3**	AsF_6	23	1:17	99	98
8	**3**	**AsF_6**	**−20**	**1:40**	**96**	**>99**

[a] Isolated yields. [b] Determined by chiral HPLC analysis; the absolute configuration was determined by chemical correlation or by analogy.

constraints of the ligand framework, this would impose a significant bias for enantiofacial coordination at the indole *Si* face (as shown), thereby enabling the required enantioselective addition and cyclization steps.

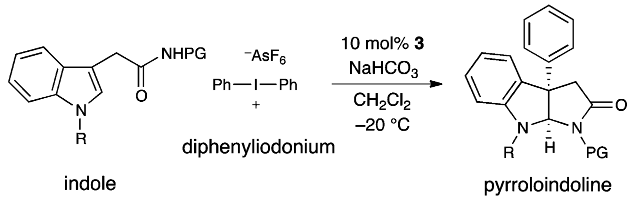
The feasibility of the proposed arylation−cyclization cascade was first examined using indole acetamide **4**, diphenyliodonium triflate, and a series of copper catalysts. As shown in Table 1, the absence of catalyst resulted in no detectable product formation. In contrast, when 5 mol % $(CuOTf)_2$·PhMe was employed, complete consumption of the iodonium was observed; however, only the undesired product of C(2)-indole arylation was observed (69% yield; entry 2). We next turned our attention to ligated copper catalysts in the hope that this would allow the Cu(III)−aryl species to participate more rapidly in the reductive elimination step, thereby circumventing a deleterious C(3) to C(2) migration step. Indeed, implementation of both the *tert*-butyl- and isopropyl-substituted bisoxazoline (Box)[12] ligands with copper yielded an improved yield of the desired C(3)-aryl adduct, albeit with modest enantiocontrol (8−61% ee; entries 3 and 4). Fortunately, when the phenyl-substituted bisoxazoline ligand was employed, a dramatic increase in regio- and enantioselectivity was observed (90% yield, 98% ee; entry 5). Moreover, further optimization of temperature and the

Table 2. Scope of the Iodonium Aryl Coupling Component[a,b]



[a] Absolute configurations were assigned by chemical correlation or by analogy. [b] Enantiomeric excesses were determined by chiral HPLC analysis of the isolated products. [c] Reaction performed at −15 °C. [d] Reaction performed at 0 °C. [e] Symmetrical diaryliodonium salt was used. [f] Reaction performed at −5 °C. [g] Using PF_6 counterion. [h] Reaction performed at −10 °C. [i] Reaction performed at room temperature.

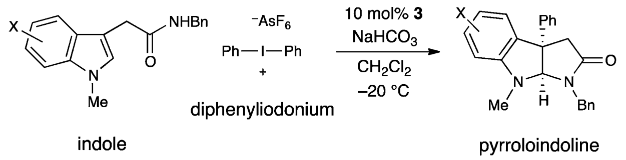
Table 3. Scope of the Indole Acetamide Component[a,b]



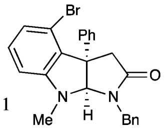
entry	R	PG	yield (%)	ee (%)
1	Me	Bn	96	>99
2	Bn	Bn	96	>99
3[c]	allyl	Bn	92	>99
4	H	Bn	80	90
5	H	Me	98	93
6	H	H	86	95
7	Me	H	92	>99
8	Me	Me	96	97

[a] Absolute configurations were assigned by chemical correlation or analogy. [b] Enantiomeric excesses were determined by chiral HPLC analysis. [c] Reaction performed at room temperature.

Table 4. Scope of the Indole Nucleophile Coupling Component[a,b]

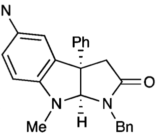


1



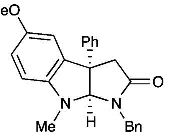
88% yield, >99% ee

2[c]



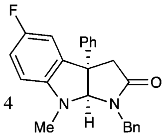
80% yield, 99% ee

3



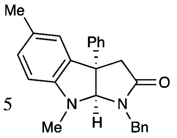
91% yield, >99% ee

4



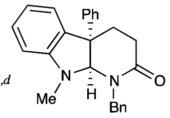
93% yield, >99% ee

5



96% yield, 97% ee

6[c,d]



67% yield, 97% ee

[a] Absolute configurations were assigned by chemical correlation or analogy. [b] Enantiomeric excesses were determined by chiral HPLC analysis. [c] Using 30 mol % catalyst. [d] Using PF_6 counterion at 0 °C.

iodonium counterion afforded the desired C(3)-aryl pyrroloindoline in 96% yield and >99% ee as essentially a single regioisomer (entries 6−8).

With these optimized conditions in hand, we next turned our attention to the scope of the aryl or heteroaryl coupling partner in this new pyrroloindoline-forming reaction (Table 2). While symmetrical diaryliodonium salts can be successfully employed in this context, the approach pioneered by Gaunt in which aryl−mesityl reagents are used to generate Ar−Cu(III) intermediates is preferred for reasons of practicality.[9b] Importantly, both electron-rich (82−92% yield, ≥98% ee; entries 1, 2, and 11) and electron-deficient arenes (55−89% yield, 91−98% ee; entries 4−8 and 10) were found to be suitable coupling partners in this new protocol. Moreover, a broad range of ortho-, meta- and para-substituted aryl rings with diverse steric and electronic properties can be readily exploited (55−92% yield, 91−99% ee; entries 2, 4, 5, 7, 8, 10, and 11). Notably, halogen-substituted aryl rings are tolerated in this Cu(I)-catalyzed transformation, a critical consideration for further elaboration of these pharmacophores in medicinal chemistry or natural product studies (83% yield, 97% ee; entry 5).

As revealed in Tables 3 and 4, this enantioselective arylation−cyclization technology tolerates a wide range of substituents on the indole component. Initial examination of the possible substitution on the indolic nitrogen[13] demonstrated that a range of alkyl protecting groups are compatible; for example, *N*-methyl-, *N*-benzyl-, and *N*-allyl-substituted indole acetamides undergo addition−cyclization in >92% yield with nearly perfect enantiocontrol (92−96% yield, 97−99% ee; Table 3, entries 1−3 and 8). Moreover, unsubstituted indolic nitrogens were tolerated with little or no effect (80−98% yield, 90−95% ee; entries 4−6). Examination of the substituent patterns on the nucleophile framework revealed that this protocol is amenable to both electron-rich (91−96% yield, 97−99% ee; Table 4, entries 3 and 5) and electron-poor indoles (80−93% yield, ≥99% ee; Table 4, entries 1, 2, 4). As was the case for the aryl coupling partner, this addition−cyclization sequence proceeds with perfect chemoselectivity for oxidative addition into the iodonium C−I bond in the presence of halogens on the nucleophilic substrate (88% yield, >99% ee; Table 4, entry 1). Finally, we were delighted to find that this mechanism can be translated to the formation of six-membered piperidinyl indolines with excellent enantiocontrol using an indole propionamide substrate (67% yield, 97% ee; Table 4, entry 6). This result suggests that a variety of alkaloid pharmacophores might be readily generated using this new asymmetric arylation strategy.

In conclusion, we have developed a new copper-catalyzed cascade protocol that allows the rapid and enantioselective construction of C(3)-aryl pyrroloindoline architectures. Further investigations into the mechanistic details of this transformation, including models for asymmetric induction, are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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