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

Shaolin Zhu and David W. C. MacMillan*

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States

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 leukemia2a and lymphoblastoma2b 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 naseezaines A and B.4a,b,5

Recently our laboratory reported the enantioselective α-arylation of carbonyls using copper bisoazoline 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 in particular the 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.

Our design plan is outlined in Scheme 1. We proposed that oxidative insertion of a ligand-bound Cu(I) complex into a suitable diaryliodonium salt7,8 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

Figure 1. Representative pyrroloindolines and arylation strategy.

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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

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aAbsolute configurations were assigned by chemical correlation or by analogy. bEnantiomeric excesses were determined by chiral HPLC analysis of the isolated products. cReaction performed at −15 °C. dReaction performed at 0 °C. eSymmetrical diaryliodonium salt was used. fReaction performed at −5 °C. gUsing PF6 counterion. hReaction performed at −10 °C. iReaction performed at room temperature.

Table 2. Scope of the Iodonium Aryl Coupling Component

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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. 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 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 naphthyl 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 naphthyl 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.

AUTHOR INFORMATION

Corresponding Author
dmacmill@princeton.edu

Notes
The authors declare no competing financial interest.

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REFERENCES


S.Z. thanks the Shanghai Institute of Organic Chemistry for a postdoctoral fellowship.
(3) Additionally, the bionectin family of C(3)-aryl pyrroloindolines has been shown to possess anti-MRSA activity. See: Zheng, C.-J.; Kim, C.-J.; Bae, K. S.; Kim, Y.-H.; Kim, W.-G. J. Nat. Prod. 2006, 69, 1816.


(5) For additional strategies to construct C(3)-aryl pyrroloindolines involving visible-light photoredox catalysis, palladium-catalyzed cross-coupling, and a Steglich-type rearrangement, see refs 4c, 4i, and 4h, respectively.


(c) Grushin, V. V. Chem. Soc. Rev. 2000, 29, 315.


(13) The use of carbamate protecting groups (e.g., Boc or CBz) on the indolic or acetamidyl nitrogens resulted in complete suppression of the desired reaction under the conditions outlined.