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Copper-Catalyzed Diastereoselective Arylation of Tryptophan Derivatives: Total Synthesis of (+)-Naseseazines A and B

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Supporting Information

ABSTRACT: A copper-catalyzed arylation of tryptophan derivatives is reported. The reaction proceeds with high site- and diastereoselectivity to provide aryl pyrroloindoline products in one step from simple starting materials. The utility of this transformation is highlighted in the five-step syntheses of the natural products (+)-naseseazine A and B.

The pyrroloindoline is a common structural motif that unites several biosynthetically distinct families of alkaloids (Figure 1).[1] The prevalence of this indole-derived heterocyclic framework continues to inspire the development of new reactions for its construction,[2] and these efforts have delivered increasingly efficient total syntheses of biologically active natural products.[3] Specifically, the development of tandem C3-functionalization/cyclization reactions of tryptamine and tryptophan derivatives has proven to be a particularly fruitful line of research. Such methods include a variety of oxidative cyclization reactions[4] as well as recently discovered organocatalyzed[5] and transition-metal-catalyzed[6] C−C bond-forming processes.

Despite the advances described above, the direct preparation of aryl-substituted pyrroloindolines has until recently remained a challenge.[7] In 2011, Movassaghi and co-workers reported a Friedel−Crafts-type arylation of 3-bromocyclotryptophans that provides access to aryl pyrroloindolines in two steps from the corresponding tryptophan derivatives (Figure 2a).[8] In an effort to streamline this overall transformation further, we subsequently developed a one-step synthesis of aryl pyrroloindolines via Cu-catalyzed arylation of *N*-tosyltryptamines (Figure 2b).[9] Concomitant with our studies, Zhu and MacMillan reported a catalytic asymmetric arylation of indole-3-carboxamides to generate arylated 2-oxopyrroloindolines in high yields and ee's (Figure 2c).[10] Although the latter two methodologies provide direct access to aryl pyrroloindolines from simple starting materials, in neither case do the products obtained contain an appropriate carboxylate functionality for

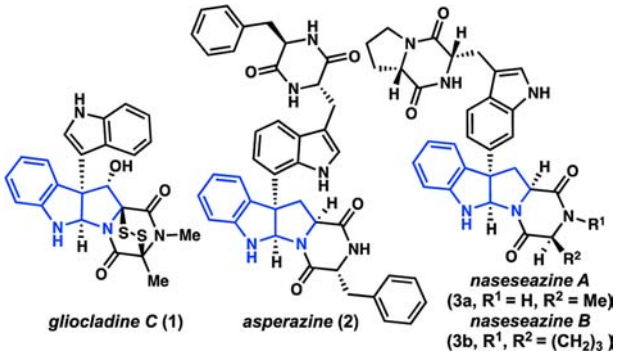

Figure 1. Pyrroloindoline alkaloids.

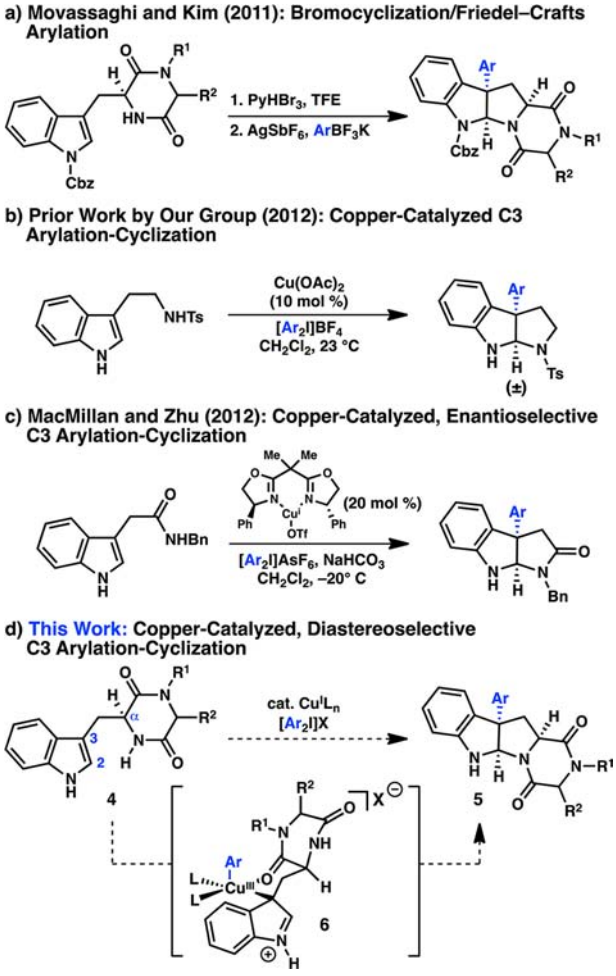

Figure 2. Strategies for the formation of aryl pyrroloindolines.

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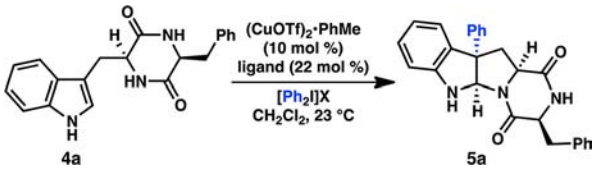
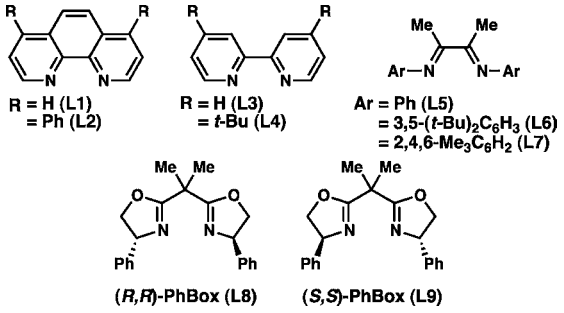
Table 1. Optimization Studies



entry	ligand	[Ph$_2$I]X	C3:C2[a]	dr[a]	yield (%)[a]
1	–[b]	[Ph$_2$I]PF$_6$	–	–	0
2	–	[Ph$_2$I]PF$_6$	1:1	3:1	22
3	**L1**	[Ph$_2$I]PF$_6$	1:1	3:1	15
4	**L2**	[Ph$_2$I]PF$_6$	1:2	2:1	<5
5	**L3**	[Ph$_2$I]PF$_6$	6:1	10:1	20
6	**L4**	[Ph$_2$I]PF$_6$	12:1	12:1	38
7	**L5**	[Ph$_2$I]PF$_6$	2:1	5:1	26
8	**L6**	[Ph$_2$I]PF$_6$	1:1	4:1	24
9	**L7**	[Ph$_2$I]PF$_6$	>20:1	>20:1	70
10	**L8**	[Ph$_2$I]PF$_6$	1:1	4:1	15
11	**L9**	[Ph$_2$I]PF$_6$	2:1	20:1	35
12	**L7**	[Ph$_2$I]BF$_4$	>20:1	>20:1	76
13	**L7**	[Ph$_2$I]AsF$_6$	>20:1	>20:1	81
14	**L7**	[Ph$_2$I]OTf	>20:1	>20:1	83 (85[c])

[a]Yield of major diastereomer as determined by ^{1}H NMR analysis of the crude reaction mixture. [b]No (CuOTf)$_2$·PhMe was used. [c]Isolated yield.



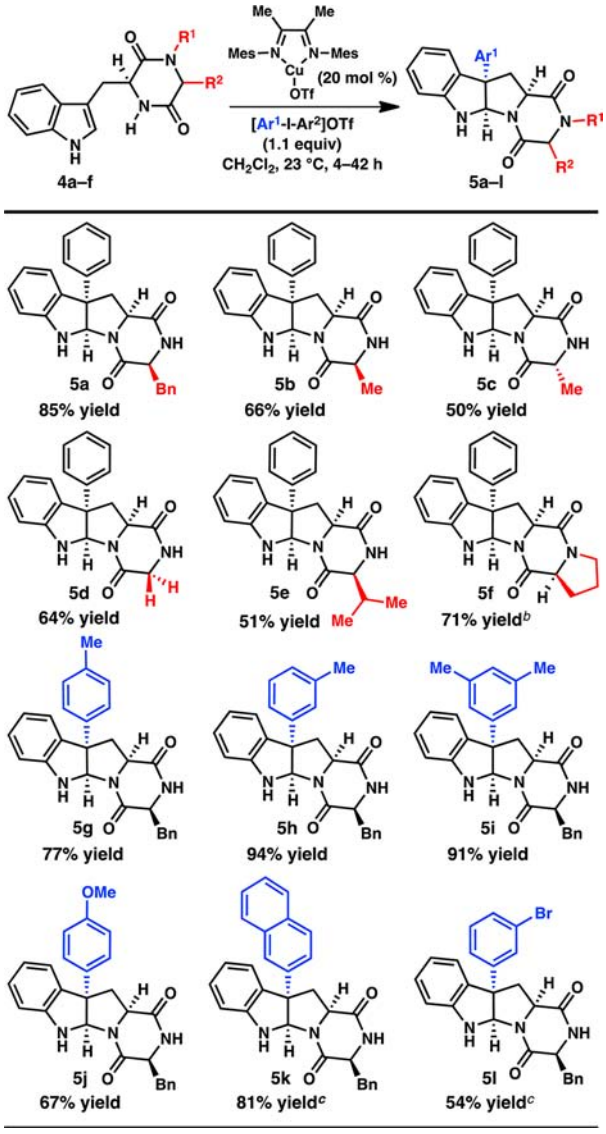
direct elaboration to diketopiperazine-containing natural products such as **1**–**3** (Figure 1).[11,12]

Given our interest in the synthesis of such compounds, we sought to develop a complementary *diastereoselective* arylation of tryptophan derivatives (Figure 2d). We hypothesized that reductive elimination from a Cu^{III}–aryl complex involving bidentate substrate coordination (e.g., **6**) could permit transmission of the stereochemical information from the tryptophan α-carbon to the newly formed quaternary center. Here we report the successful execution of this synthetic plan, which enabled a concise diastereoselective synthesis of the pyrroloindoline alkaloids (+)-naseseazines A and B.

We began our studies by investigating the Cu-catalyzed arylation of *cyclo*-(Trp-Phe) (**4a**), which is readily accessible by cyclocondensation of the corresponding amino acids.[13] Exposure of **4a** to 10 mol % (CuOTf)$_2$·PhMe and 1.1 equiv of diphenyliodonium hexafluorophosphate ([Ph$_2$I]PF$_6$) in CH_2Cl_2 furnished pyrroloindoline **5a** in low yield as a mixture of diastereomers (Table 1, entry 2). Under these conditions, **5a** was formed in an equimolar ratio with the corresponding C2-arylated product (not shown). A control experiment confirmed that no reaction occurs in the absence of copper (entry 1).

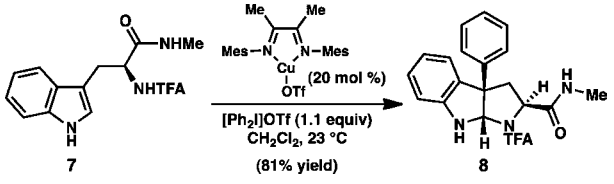
In an effort to improve both the C3:C2 arylation ratio and the diastereoselectivity, a survey of several achiral bidentate ligands was conducted. We were pleased to find that use of

Table 2. Substrate Scope of Pyrroloindoline Formation[a]



[a]Reactions were conducted on a 0.3 mmol scale using symmetric [Ar$_2$I]OTf, unless otherwise noted. Isolated yields are reported. [b]Ligand **L6** (40 mol %) was used with [Ph$_2$I]PF$_6$. [c]Nonsymmetric [Ar(*p*-xylyl)I]OTf was used.

Scheme 1. Arylation of Tryptophan Carboxamide 7



readily available bis(mesityl)-α-diimine ligand **L7**[14] (^{Mes}DAB$_{Me}$) delivers **5a** in 70% yield with high C3:C2 selectivity and an excellent level of diastereocontrol (Table 1, entry 9). Comparison of a series of α-diimine ligands revealed that the aryl substitution pattern exerts a significant effect on both the yield and the C3:C2 selectivity (entries 7–9). The yield of the reaction was further improved by using diphenyliodonium triflate ([Ph$_2$I]OTf) (entry 14). Under our optimal conditions, **5a** was isolated in 85% yield as a single diastereomer.

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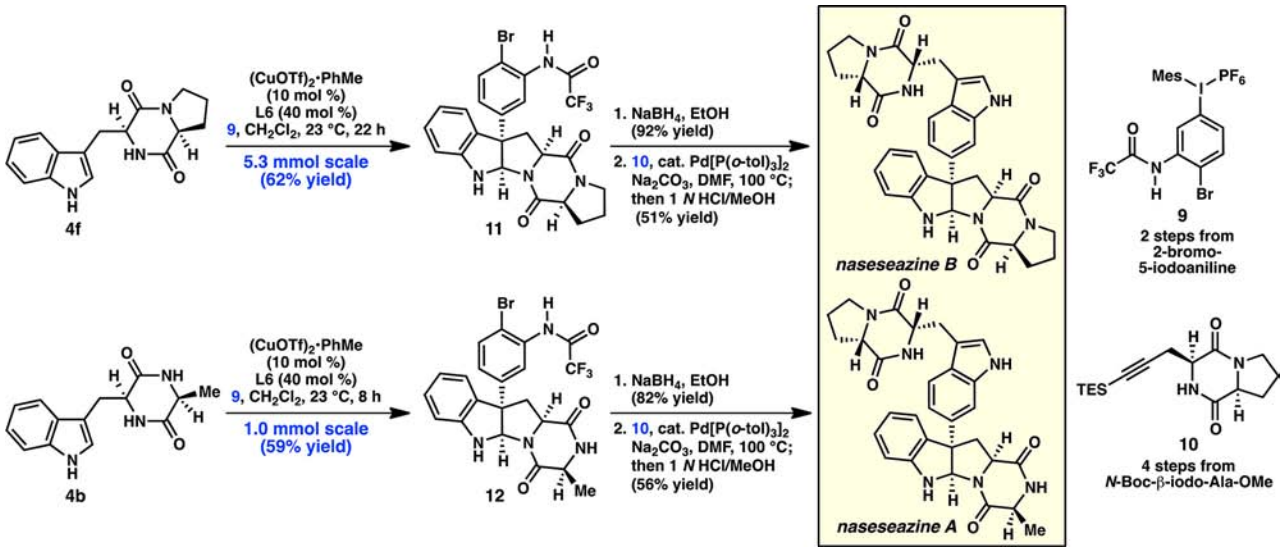
Scheme 2. Concise Total Syntheses of (+)-Naseseazines A and B



Interestingly, use of either enantiomer of the chiral bisoxazoline ligand previously employed by Zhu and MacMillan for enantioselective pyrroloindoline formation[10] (**L8** or **L9**) gave poor yields and low C3:C2 arylation ratio (entries 10 and 11). As might be expected, clear matching and mismatching between the diketopiperazine substrate and the chiral ligand was observed, with **L9** providing higher dr and C3 selectivity.

A variety of arylated pyrroloindolines can be prepared in one step from the corresponding diketopiperazines (Table 2). The diketopiperazines derived from either L- or D-alanine react to deliver diastereomeric pyrroloindolines **5b** and **5c**, respectively, which possess the same configuration at the newly formed quaternary center. This observation indicates that the chirality at the tryptophan-derived stereogenic center is the dominant stereocontrolling factor. The relatively modest yields of **5b** and **5c** reflect the poor solubility and lower reaction rates for these substrates; in both cases, high site- and diastereoselectivity were still observed. In contrast, the diketopiperazine *cyclo*-(Pro-Trp) (**4f**) proved to be a challenging substrate, providing **5f** in low yield as a result of poor C3:C2 selectivity under our standard conditions. We hypothesized that the increased rigidity of the bicyclic diketopiperazine may result in destabilizing non-bonding interactions with the Cu^{I}(**L7**)OTf catalyst. A screen of α-diimine ligands possessing less steric encumbrance at the ortho positions revealed that the use of Cu^{I}(**L6**)OTf in conjunction with $[Ph_2I]PF_6$ restores the C3:C2 selectivity and delivers pyrroloindoline **5f** in 71% yield.

The scope of the aryl coupling partner was also investigated. Whereas symmetric diaryliodonium salts reacted smoothly under the reaction conditions (Table 2, products **5g–j**), the use of iodonium salts containing the more hindered mesityl substituent as a nontransferable group[15] exhibited lower reaction rates and diminished C3:C2 selectivity under the standard conditions. Fortunately, mitigating the steric demand of these nonsymmetric iodonium salts by using a *p*-xylyl substituent as a nontransferable group restored both the reaction rate and site selectivity.[16] Thus, with either symmetric or *p*-xylyl-substituted nonsymmetric iodonium salts, a variety of arenes bearing either electron-donating or -withdrawing substituents at the para or meta positions could be coupled, providing the pyrroloindolines in moderate to excellent yields as single diastereomers. Unfortunately, ortho-substituted arenes are not transferred efficiently and represent one limitation of the existing methodology.

Although our initial studies focused on the arylation of tryptophan-derived diketopiperazines, we wondered whether the simple tryptophan carboxamide **7** would be a suitable substrate. We were pleased to find that subjecting **7** to our optimized reaction conditions afforded arylated pyrroloindoline **8** in 81% yield as a single diastereomer (Scheme 1). However, upon careful analysis by a variety of NMR spectroscopic methods, we determined that **8** possesses the opposite configuration at the newly formed quaternary center relative to the diketopiperazine-containing products in Table 2. At this time, the origin of this stereodivergent reactivity remains unclear. Nonetheless, this finding presents the exciting opportunity to generate either enantiomeric series of pyrroloindoline products from naturally occurring L-tryptophan.

To highlight the utility and efficiency of this direct arylation methodology for the synthesis of pyrroloindoline natural products, we sought to complete a total synthesis of the bisindole alkaloids naseseazine A (**3a**) and B (**3b**) (Scheme 2). To this end, diaryliodonium salt **9** containing a protected *o*-bromoaniline was efficiently prepared on a gram scale from 2-bromo-5-iodoaniline in 70% overall yield. Addition of **9** and diketopiperazine **4f** and to a prestirred solution of $(CuOTf)_2$·PhMe (10 mol %) and **L6** (40 mol %) in CH_2Cl_2 (the conditions previously developed for the arylation of **4f**) delivered the desired pyrroloindoline **11** in 62% yield. This direct and efficient procedure is easily performed on large scale and provides the desired pyrroloindoline with excellent levels of diastereocontrol. Although reactions conducted with the corresponding *p*-xylyl iodonium salt provided higher conversions of **4f**, the yields of **11** were lower because of competitive transfer of the *p*-xylyl group. The coupling of **9** and *cyclo*-(Ala-Trp) (**4b**) under the same conditions provided the related pyrroloindoline **12** in 59% yield.

To complete the syntheses of **3a** and **3b**, diketopiperazine-containing alkyne **10** was prepared in four steps from commercially available *N*-Boc-β-iodoalanine methyl ester. Following cleavage of the trifluoroacetamide group in **11**,

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coupling with alkyne **10** by a modified Larock indolization procedure[17,18] provided **3b** in 51% yield upon acidic workup. Elaboration of **12** by the same sequence delivered **3a** in 56% yield. Through the Cu-catalyzed arylation chemistry developed herein, these complex polycyclic alkaloids are available in five steps (longest linear sequence) from commercially available starting materials.

In conclusion, a Cu-catalyzed site- and diastereoselective arylation of tryptophan derivatives has been developed. This reaction provides direct access to aryl pyrroloindolines under mild conditions with good functional group tolerance. Using this transformation to assemble the pyrroloindoline core enables the concise, stereoselective syntheses of the bisindole alkaloids (+)-naseseazines A and B in overall yields of 25 and 19%, respectively. The further development and application of this transformation in natural product synthesis is the subject of ongoing research in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, compound characterization data, and ^{1}H and ^{13}C NMR spectra. 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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