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

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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.[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 coworkers reported a Friedel–Crafts-type arylation of 3-bromocyclotryptophans, which provides access to aryl pyrroloindolines in two steps from the corresponding tryptophan derivatives (Figure 2, a).[8] In an effort to further streamline this overall transformation, we subsequently developed a one-step synthesis of aryl pyrroloindolines by the Cu-catalyzed arylation of *N*-tosyltryptamines (Figure 2, b).[9] Concomitant to our studies, MacMillan and coworkers reported a catalytic asymmetric arylation of indole-3-carboxamides to generate arylated 2-oxo-pyrroloindolines in high yields and ee's (Figure 2, c).[10] Although the latter two methodologies both provide direct access to aryl pyrroloindolines from simple starting materials, in neither case do the products obtained contain an appropriate carboxylate functionality for 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 2, d). We hypothesized that reductive elimination from a Cu^{III}-aryl complex involving bidentate

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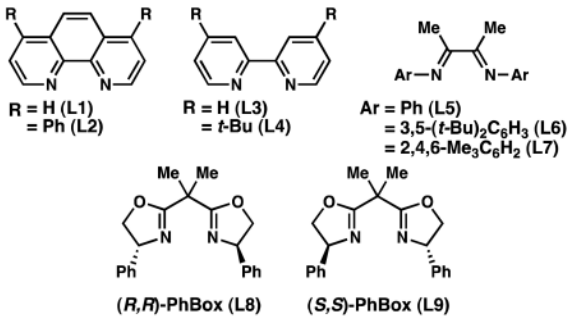
ASSOCIATED CONTENT
Supporting Information. Detailed experimental procedures, compound characterization data, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

substrate coordination (e.g. **6**) could permit transmission of the stereochemical information from the tryptophan α-carbon to the newly formed quaternary center. In this communication, we report the successful execution of this synthetic plan, which has 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**, readily accessible by cyclocondensation of the corresponding amino acids.[13] Exposure of **4a** to 10 mol % $(CuOTf)_2$•PhMe and 1.1 equivalents of diphenyliodonium hexafluorophosphate in dichloromethane furnished pyrroloindoline **5a** in low yield as a mixture of diastereomers (Table 1, entry 2). Under these conditions, pyrroloindoline **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 diastereoselectivity, a survey of several achiral, bidentate ligands was conducted. We were pleased to find that use of readily available bis-mesityl-α-diimine ligand **L7**[14] ($^{Mes}DAB_{Me}$) delivers pyrroloindoline **5a** in 70% yield, with high C3:C2 selectivity and excellent levels 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 could be further improved by using diphenyliodonium triflate (entry 14). Under our optimal conditions, pyrroloindoline **5a** is isolated in 85% yield as a single diastereomer. Interestingly, use of either enantiomer of the chiral bisoxazoline ligand (**L8** or **L9**) previously employed by MacMillan for enantioselective pyrroloindoline formation[10] gave poor yields and low C3:C2 arylation ratios (entries 10 and 11). As might be expected, a clear matching and mismatching between the diketopiperazine substrate and chiral ligand was observed, with **L9** providing higher dr and C3 selectivity.

As demonstrated in Table 2, a variety of arylated pyrroloindolines can be prepared in one step from the corresponding diketopiperazines. 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 obtained for the formation of **5b** and **5c** reflect the poor solubility and slower reaction rates for these substrates; in both cases, high site- and diastereoselectivity is still observed. In contrast, the cyclo-(Pro-Trp) diketopiperazine (**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 encumberance at the *ortho* positions revealed that use of Cu^I(**L6**)OTf in conjunction

with diphenyliodonium hexafluorophosphate 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 non-transferable group[15] exhibited slower reaction rates and diminished C3:C2 selectivity under the standard conditions. Fortunately, mitigating the steric demand of these non-symmetric iodonium salts by using a *p*-xylyl substituent as a non-transferable group restores both reaction rates and site selectivity.[16] Thus, using either the symmetric or *p*-xylyl-substituted non-symmetric iodonium salts, a variety of arenes bearing either electron-donating or electron-withdrawing substituents at the *p*- or *m*-positions could be coupled, providing the pyrroloindolines in moderate to excellent yields as single diastereomers. Unfortunately, *o*-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 subjection of **7** to our optimized reaction conditions affords 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.

In order 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 naseseazines A (**3a**) and B (**3b**). To this end, diaryliodonium salt **9**, containing a protected *o*-bromoaniline, was efficiently prepared on gram scale from 2-bromo-5-iodoaniline in 70% overall yield. Addition of diketopiperazine **4f** and iodonium **9** to a pre-stirred solution of $(CuOTf)_2$•PhMe (10 mol %) and **L6** (40 mol %) in dichloromethane – 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 due to competitive transfer of the *p*-xylyl group. The coupling of cyclo-(Ala-Trp) **4b** and iodonium **9** under the same conditions provided the related pyrroloindoline **12** in 59% yield.

To complete the synthesis 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**, coupling with alkyne **10** by a modified Larock indolization[17,18] procedure provided, upon acidic workup, naseseazine B in 51% yield. Elaboration of **12** by the same sequence delivered naseseazine A in 56% yield. Enabled by 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 and with good functional group tolerance. Using this transformation to assemble

the pyrroloindoline core, concise, stereoselective syntheses of the bisindole alkaloids (+)-naseseazines A and B were completed in 25% and 19% overall yield, respectively. The further development and application of this transformation in natural product synthesis is the subject of ongoing research in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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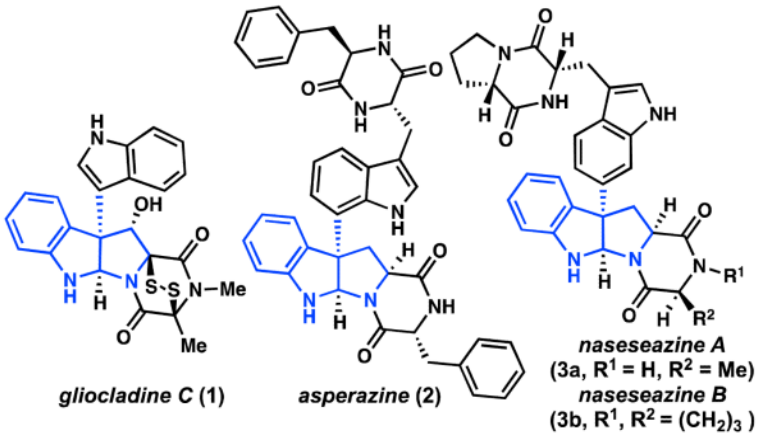


Figure 1.
Pyrroloindoline alkaloids.

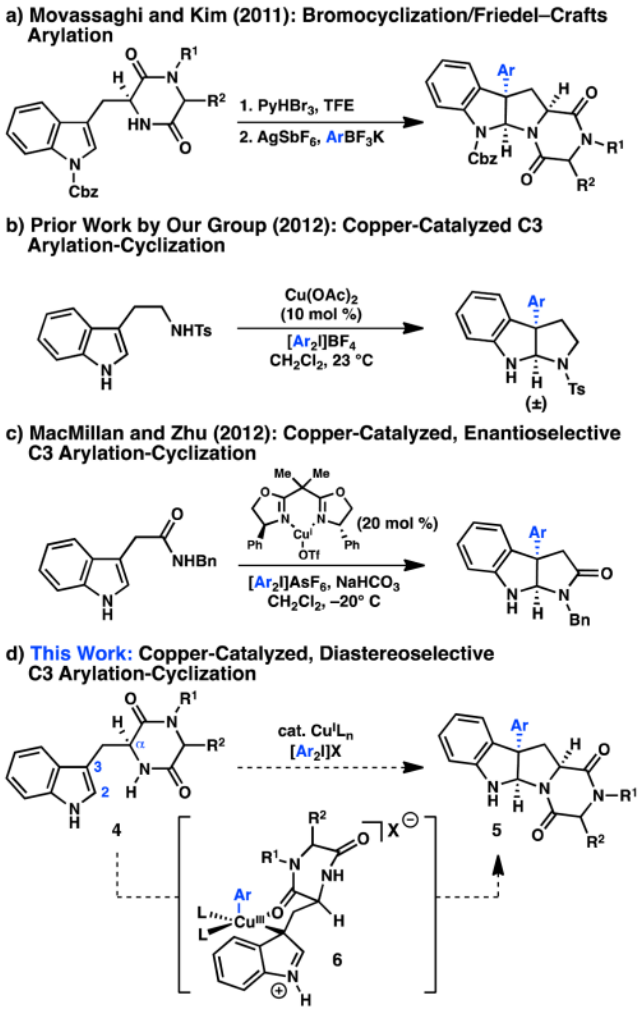
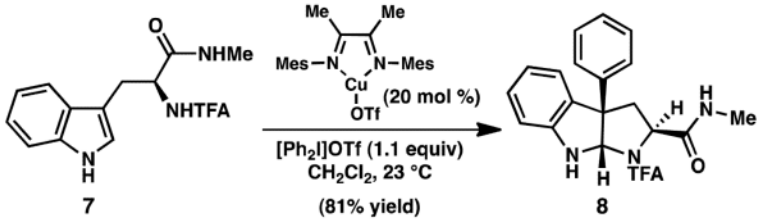
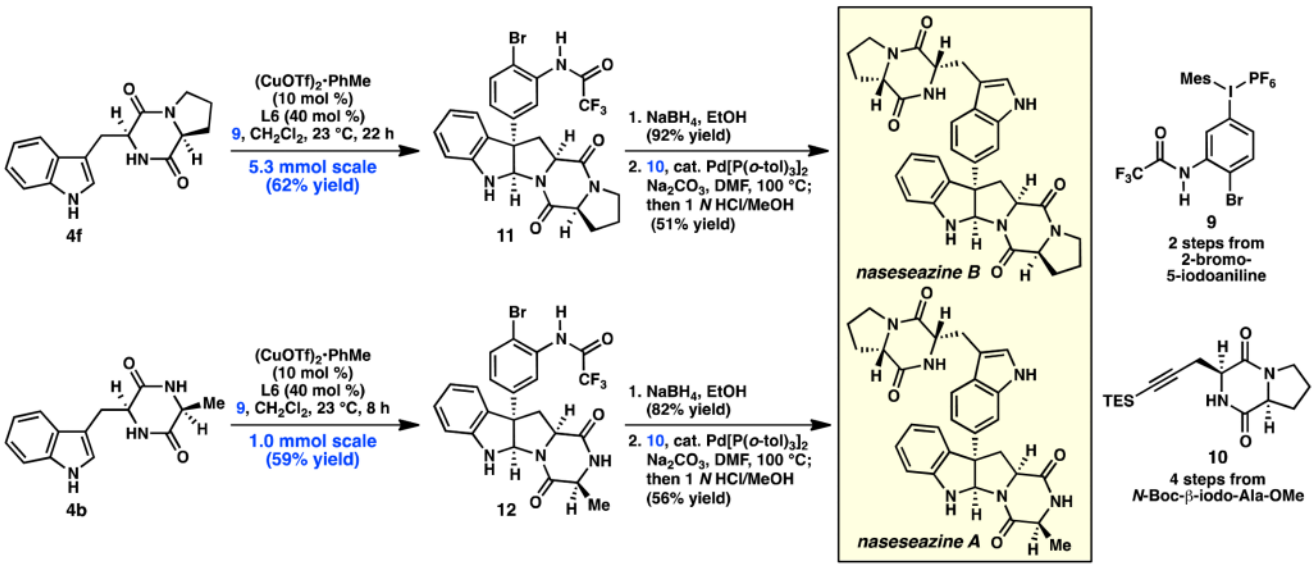


Figure 2.
Strategies for aryl pyrroloindoline formation.



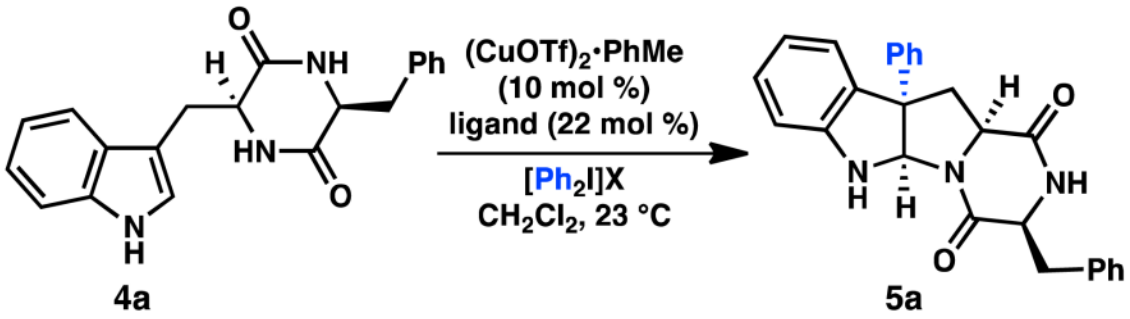
Scheme 1.
Arylation of tryptophan carboxamide **7**.



Scheme 2.
Concise total synthesis of (+)-naseseazines A (**3a**) and B (**3b**).

Table 1

Optimization studies.



Entry	Ligand	[Ph_2I]X	C3:C2[a]	dr[a]	yield (%)[a]
1	_ [b]	[Ph_2I]PF_6	–	–	0
2	–	[Ph_2I]PF_6	1:1	3:1	22
3	**L1**	[Ph_2I]PF_6	1:1	3:1	15
4	**L2**	[Ph_2I]PF_6	1:2	2:1	<5
5	**L3**	[Ph_2I]PF_6	6:1	10:1	20
6	**L4**	[Ph_2I]PF_6	12:1	12:1	38
7	**L5**	[Ph_2I]PF_6	2:1	5:1	26
8	**L6**	[Ph_2I]PF_6	1:1	4:1	24
9	**L7**	[Ph_2I]PF_6	>20:1	>20:1	70
10	**L8**	[Ph_2I]PF_6	1:1	4:1	15
11	**L9**	[Ph_2I]PF_6	2:1	20:1	35
12	**L7**	[Ph_2I]BF_4	>20:1	>20:1	76
13	**L7**	[Ph_2I]AsF_6	>20:1	>20:1	81
14	**L7**	[Ph_2I]OTf	>20:1	>20:1	83 (85)[c]

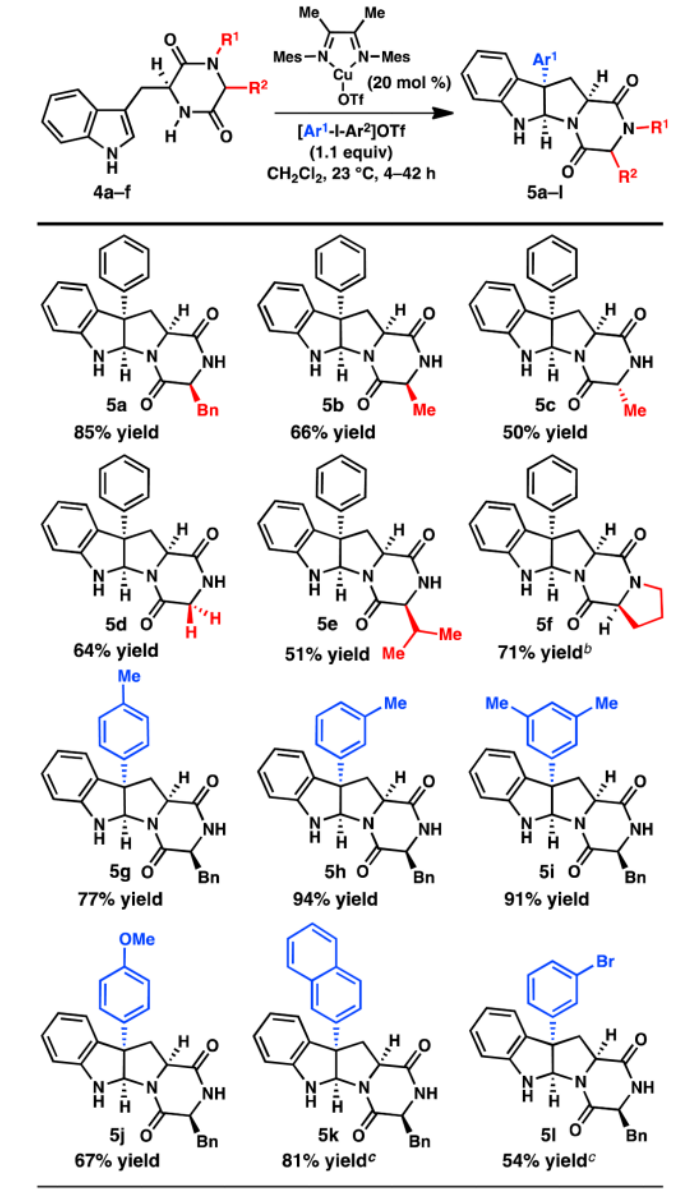
[a]Yield of major diastereomer as determined by ^{1}H NMR analysis of the crude reaction mixture.

[b]No $(CuOTf)_2$•PhMe was used.

[c] Isolated yield.

Table 2

Substrate scope of pyrroloindoline formation.[a]



[a]Reactions conducted on 0.3 mmol scale using symmetric diaryliodonium triflate unless otherwise noted. Isolated yields are reported.

[b]40 mol % Ligand **L6** was used with diphenyliodonium hexafluorophosphate.

[c]Non-symmetric aryl[*p*-xylyl]iodonium triflate was used.