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EDGE ARTICLE

A copper-catalyzed arylation of tryptamines for the direct synthesis of aryl pyrroloindolines†

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An operationally simple, copper-catalyzed arylation of *N*-tosyltryptamines provides direct access to C3-aryl pyrroloindolines. A range of electron-donating and electron-withdrawing substituents is tolerated on both the indole backbone and the aryl electrophile. These reactions occur under ambient temperatures and with equimolar quantities of the coupling partners.

Introduction

The pyrroloindoline alkaloids are a structurally diverse family of biologically active natural products, which include compounds such as hodgkinsine (**1**),[1] naseseazine A (**2**),[2] and gliocladine C (**3**) [3] (Fig. 1). As a result of their compelling bioactivities and fascinating structures, this family of alkaloids has been the subject of intense research[4] and has inspired the development of a variety of new synthetic methods to prepare the key heterocyclic ring system.[5] In particular, pyrroloindolines that possess an aryl substituent at C3 (such as **1–3**) are uniquely challenging.[6,7] The current state-of-the-art is Movassaghi and Kim's recently reported and highly practical Friedel–Crafts type arylation of 3-bromocyclotryptophans, which provides access to C3-aryl pyrroloindolines in two steps from the corresponding tryptophan derivatives.[8] Conceptually, we sought to further streamline the synthesis of C3-aryl pyrroloindolines to a one-step process by developing a transition metal-catalyzed arylative cyclization of tryptamine or tryptophan derivatives, thereby circumventing the need to prepare a brominated intermediate. This type of transformation has been realized by Pd-catalyzed allylation and benzylation processes; however, the corresponding transition metal-catalyzed *arylation* reactions of tryptamines have remained elusive.[9–11] Herein, we report a copper-catalyzed arylation of readily available tryptamine derivatives as an operationally simple, direct approach to prepare C3-aryl pyrroloindolines.

Reaction design

As part of our studies in the area of alkaloid total synthesis, we have been interested in the development of new reactions to prepare pyrroloindolines from C3-substituted indoles by direct C–C bond formation. Recently, we reported a new method for the preparation of enantioenriched pyrroloindolines (**6**) in which (*R*)-BINOL·$SnCl_4$ catalyzes a formal (3 + 2) cycloaddition reaction between 1,3-disubstituted indoles (**4**) and benzyl 2-trifluoroacetamidoacrylate (**5**) (Scheme 1a).[12] Good yields and high enantioselectivities were obtained for a variety of indole substrates. Unfortunately, under the optimal reaction conditions, C3-aryl substrates were unreactive and failed to provide the desired pyrroloindoline product.

Given our long-term objective of preparing natural products such as **1–3**, we sought to develop a complementary approach to synthesize C3-aryl pyrroloindolines. There have been several recent reports describing both Pd- and Cu-catalyzed direct arylation of simple indole substrates.[13] Depending on the substitution pattern and the reaction conditions, the indole starting materials can be selectively arylated at either C2 or C3 (Scheme 1b). A general mechanism for these reactions invokes nucleophilic attack of the electrophilic metal by the indole at C3 to give metal complex **8**. The C3-arylated product **9** is formed by rearomatization of **8** followed by reductive elimination. On the other hand, metal complex **8** can give rise to the C2-arylated product **10** if migration of the metal from C3 to C2 precedes rearomatization and reductive elimination.

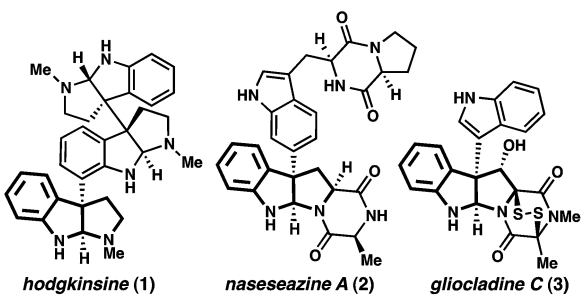

Fig. 1 Pyrroloindoline alkaloids: representative members.

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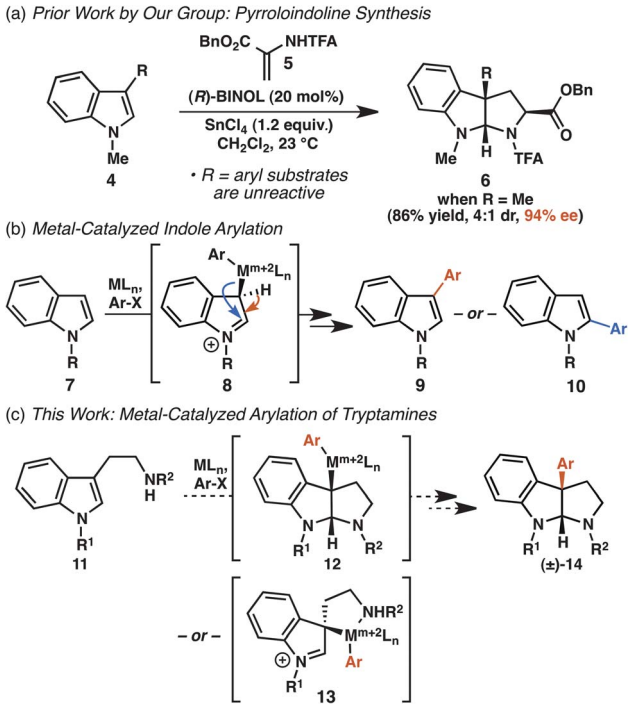
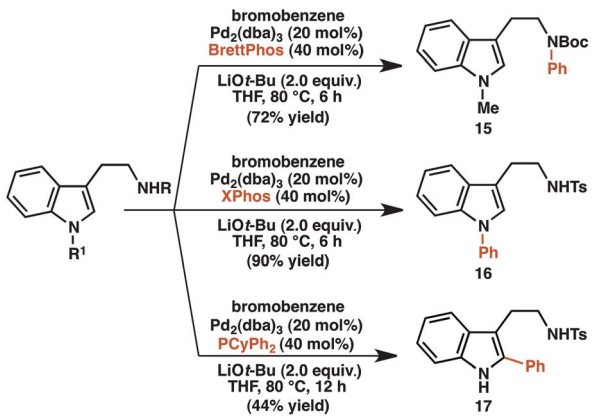


Scheme 1 Reaction design.

We wondered whether this type of reaction pathway could be diverted to instead generate C3-aryl pyrroloindolines.[14] Specifically, we hypothesized that use of a tryptamine derivative may result in trapping of the intermediate iminium ion, stabilizing the C3-metalated species **12** (Scheme 1c). Alternatively, the protected amine could serve as a ligand to stabilize the C3-metalated species **13** through chelation.[15] In either scenario, subsequent reductive elimination could provide the C3-aryl pyrroloindoline **14**.

Results and discussion

Our studies commenced with a survey of several Pd- and Cu-catalyzed arylation conditions using various tryptamine derivatives as substrates. Depending on the substrate and ligand, Pd-catalyzed reactions furnished *N*-phenyl products **15** or **16**, or C2-phenyl product **17** (Scheme 2). We hypothesized that a more electrophilic metal complex could prove beneficial, and turned to the $Cu(OTf)_2$/diphenyliodonium conditions originally published by Gaunt and coworkers for the C3 arylation of simple indoles.[13g] We were pleased to find that treatment of **18a** with 10 mol% $Cu(OTf)_2$ and 1.1 equiv. of diphenyliodonium tetrafluoroborate in dichloromethane at room temperature provided C3-phenyl pyrroloindoline **19a** in 62% yield (Table 1, entry 1). The major side product of the reaction was 2-phenyltryptamine **17**.

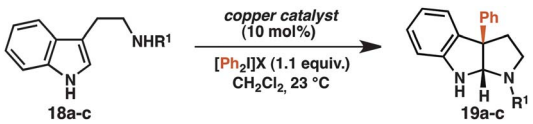


Scheme 2 Products of Pd-catalyzed arylation.

In an effort to further optimize the reaction, the effects of several reaction parameters were systematically evaluated. A brief screen of protecting groups revealed that sulfonamide groups on the tryptamine nitrogen were uniquely effective for the formation of **19**.[16] For example, use of the *tert*-butylcarbamate (Boc) or acetamide (Ac) protecting groups delivered only trace quantities of pyrroloindoline **19b** or **19c**, respectively (Table 1, entries 3 and 4).

A survey of copper catalysts demonstrated that both Cu^I and Cu^{II} triflate salts furnish **19a** in good yields (Table 1, entries 1 and 5). However, the ligand on copper dramatically affects the reactivity toward pyrroloindoline formation (entries 6 and 7). In terms of the iodonium salts, the best results were obtained using the non-coordinating tetrafluoroborate counterion. The non-symmetric iodonium salt [Ph-I-Mes]BF_4, for which the mesityl group serves as a non-transferable ligand, is also a competent coupling partner, although longer reaction times are required (entry 13). Although both $Cu(OTf)_2$ and $Cu(OAc)_2$ furnished comparable yields of pyrroloindoline **19a** when using $[Ph_2I]BF_4$ as the electrophile, the $Cu(OAc)_2$-catalyzed reaction profile was cleaner overall, thereby simplifying purification. As a result, $Cu(OAc)_2$ was the catalyst of choice for arylation reactions employing $[Ph_2I]BF_4$ or other symmetric iodonium salts. On the other hand, $Cu(OTf)_2$ proved superior for arylation reactions

Table 1 Optimization of the copper-catalyzed pyrroloindoline formation



Entry	R^1	Cu source	X	Additive	C3 : C2	Pdt	Yield[a](%)
1	Ts	$Cu(OTf)_2$	BF_4	—	2.3 : 1	**19a**	62[b]
2	Ts	—	BF_4	—	—	**19a**	0
3	Boc	$Cu(OTf)_2$	BF_4	—	—	**19b**	<5
4	Ac	$Cu(OTf)_2$	BF_4	—	—	**19c**	<5
5	Ts	$(CuOTf)_2 \cdot PhMe$	BF_4	—	3.4 : 1	**19a**	64
6	Ts	CuI	BF_4	—	—	**19a**	0
7	Ts	$Cu(MeCN)_4PF_6$	BF_4	—	—	**19a**	0
8	Ts	$Cu(OAc)_2$	BF_4	—	2.9 : 1	**19a**	64
9	Ts	$Cu(OTf)_2$	PF_6	—	2.5 : 1	**19a**	28
10	Ts	$Cu(OTf)_2$	OTf	—	2.9 : 1	**19a**	32
11	Ts	$Cu(OTf)_2$	Cl	—	—	**19a**	0
12	Ts	$Cu(OTf)_2$	BF_4	dtbpy	—	**19a**	<5
13[c]	Ts	$Cu(OTf)_2$	BF_4	—	2.6 : 1	**19a**	65[b]

[a] Determined by HPLC *versus* an internal standard. [b] Isolated yield. [c] [Ph-I-Mes]BF_4 was employed as the electrophile.

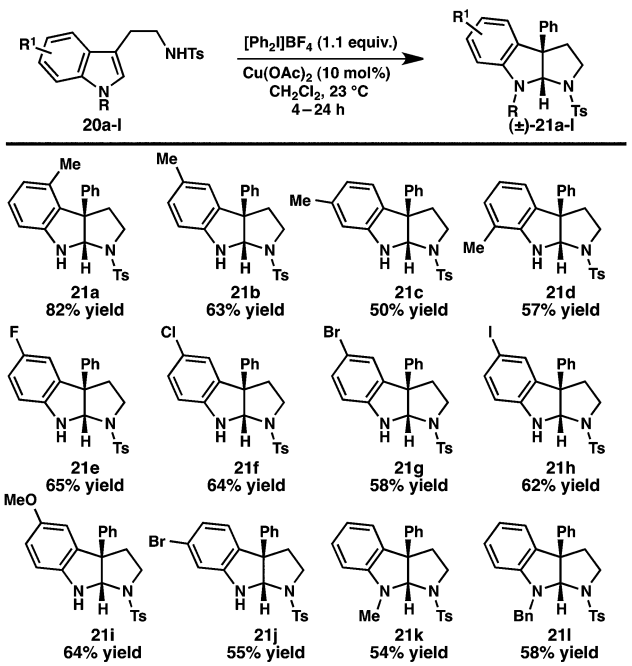
that employed less reactive, mesityl-substituted iodonium salts (*vide infra*).

Whereas Gaunt and coworkers found that 2,6-di-*tert*-butylpyridine (dtbpy) improved the yields of copper-catalyzed C3-arylation reactions of simple indole derivatives, the same additive completely inhibited the formation of pyrroloindoline **19a** (entry 12). Although the Cu sources and iodonium salts screened in Table 1 clearly influence the *reactivity* of the system, they did not significantly alter the C3 : C2 arylation ratio: the ratio of **19a** to **17** was ~2 to 3 : 1 in all cases.[17]

With the optimal conditions in hand, the scope of the reaction with respect to substitution of the indole backbone was explored (Table 2). We were pleased to find that tryptamine substrates bearing alkyl substitution at C4, C5, C6, and C7 are accommodated, providing the corresponding pyrroloindolines in good yields. Additionally, a variety of electron-donating and electron-withdrawing substituents are tolerated at C5. Although comparable yields are obtained, slower rates are observed in the reactions of indoles substituted with electron-withdrawing groups. *N*-Tosyltryptamines bearing alkyl substitution on the indole nitrogen are also competent reaction partners.

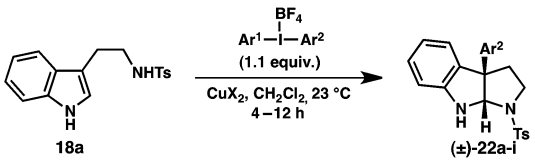
In order to evaluate the scope of substituents tolerated on the aryl electrophile, the coupling between *N*-tosyltryptamine **18a** and several functionalized iodonium salts was also conducted. A range of electron-donating and electron-withdrawing substituents is tolerated using either the symmetric diaryliodonium salts (Table 3, entries 1–4) or the mesityl-substituted iodonium salts (entries 5–13). In the latter case, the reactions are considerably slower and require the use of 20 mol % of the more reactive $Cu(OTf)_2$ in order to obtain good yields of **22** in reasonable reaction times. The *o*-methylphenyl group is the only example that we identified for which substantially higher yields were obtained using the symmetric iodonium salt instead of the corresponding mesityl-substituted iodonium salt (Table 3, entry 1 *vs.* entry 5).

Table 2 Substrate scope: tryptamine substitution[a]



[a] Reactions were conducted on 0.30 mmol scale. Isolated yields are reported.

Table 3 Substrate scope: iodonium substitution[a]



Entry	Ar^1	Ar^2	CuX_2[b]	Pdt	Yield[c](%)
1	2-(Me)C_6H_4	2-(Me)C_6H_4	$Cu(OAc)_2$	**22a**	50
2	4-(Me)C_6H_4	4-(Me)C_6H_4	$Cu(OAc)_2$	**22b**	77
3	4-(OMe)C_6H_4	4-(OMe)C_6H_4	$Cu(OAc)_2$	**22c**	66
4	4-(Cl)C_6H_4	4-(Cl)C_6H_4	$Cu(OAc)_2$	**22d**	70
5	Mesityl	2-(Me)C_6H_4	$Cu(OTf)_2$	**22a**	15
6	Mesityl	3-(Me)C_6H_4	$Cu(OTf)_2$	**22e**	63
7	Mesityl	4-(Me)C_6H_4	$Cu(OTf)_2$	**22b**	74
8	Mesityl	4-(OMe)C_6H_4	$Cu(OTf)_2$	**22c**	70
9	Mesityl	4-(F)C_6H_4	$Cu(OTf)_2$	**22f**	66
10	Mesityl	4-(Cl)C_6H_4	$Cu(OTf)_2$	**22d**	68
11	Mesityl	4-(Br)C_6H_4	$Cu(OTf)_2$	**22g**	59
12	Mesityl	4-(I)C_6H_4	$Cu(OTf)_2$	**22h**	62
13	Mesityl	4-(CO_2Et)C_6H_4	$Cu(OTf)_2$	**22i**	55

[a] Reactions were conducted on 0.30 mmol scale. [b] Catalyst loadings: 10 mol% $Cu(OAc)_2$; 20 mol% $Cu(OTf)_2$. [c] Isolated yields.

Our screening protocol was conducted using 10–20 mol% catalyst loading to ensure uniformly good yields over a range of substrates. However, to demonstrate the scalability and efficiency of this transformation, the reaction has been carried out on a 3 g scale using *N*-tosyltryptamine (**18a**) and $[Ph_2I]BF_4$ with only 2.5 mol% catalyst loading. Purification by trituration provides analytically pure pyrroloindoline **19a** in 63% yield, without the need for column chromatography. Notably, the reaction proceeds at ambient temperature with nearly equimolar ratios of indole and $[Ph_2I]BF_4$.

The mechanism of this reaction is still under investigation; however, in analogy to that proposed by Gaunt for the Cu-catalyzed C3-arylation of unsubstituted indoles, we currently favor a Cu^I–Cu^{III} catalytic cycle (Fig. 2).[13g,18,19] Although our optimized conditions utilize Cu^{II} salts due to their ease of handling, a catalytically active Cu^I species is presumably generated by *in situ* reduction. Oxidative addition of the aryliodonium to the Cu^I catalyst would give a highly electrophilic Cu^{III}–aryl species. Nucleophilic attack by C3 of tryptamine **18a** would provide iminium ion **24**, which could undergo cyclization of the sulfonamide to generate Cu^{III}–pyrroloindoline complex **25**. Reductive elimination would regenerate the Cu^I catalyst and provide arylated pyrroloindoline **22**.

Alternatively, it is possible that the sulfonamide serves as a ligand to facilitate the nucleophilic attack by indole at the Cu^{III}–aryl complex to give spiro-metallacycle **26**. Moreover, this ligand coordination could accelerate the rate of reductive elimination to form the sp^3–sp^2 C–C bond relative to the rate of copper migration. Reductive elimination would regenerate the Cu^I

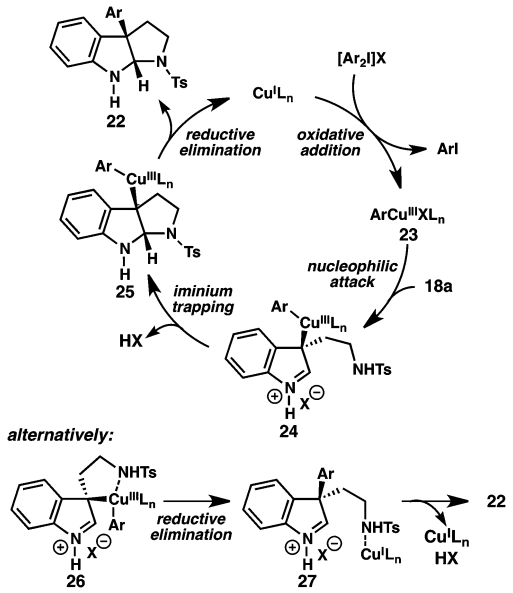
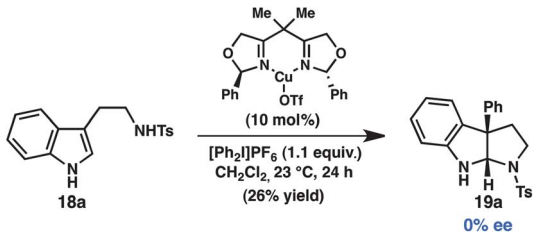


Fig. 2 Proposed catalytic cycle.



Scheme 3 Arylation of **18a** using a chiral copper catalyst.

catalyst, and cyclization would furnish arylated pyrroloindoline **22**. Our substrate studies clearly indicate the sulfonamide group plays a critical role in promoting C3-arylation, which could be attributed to its participation as a ligand.

Concurrent with the preparation of this manuscript, MacMillan and coworkers reported a similar, Cu-catalyzed enantioselective arylation of indole-3-yl acetamides.[10] Interestingly, application of the MacMillan conditions to *N*-tosyltryptamine **18a** provides pyrroloindoline **19a** in 26% yield and 0% ee (Scheme 3). This contrast in both the reactivity and selectivity could also implicate the importance of a "ligand-directed" metalation step. Moreover, comparison of our results suggest that both the ligand *and* the substrate influence the ratio of C3 to C2 arylation. Whereas the MacMillan system has advantages in terms of asymmetric catalysis, the arylation of *tryptamine* derivatives represents an important complementary reaction, as it provides the parent pyrroloindoline directly.[20]

Conclusions

In conclusion, we have developed a copper-catalyzed direct arylation of tryptamine derivatives to prepare C3-aryl pyrroloindolines. A range of electron-donating and electron-withdrawing substituents is tolerated on both the indole backbone and the aryl iodonium salts. These reactions occur under ambient temperatures and with equimolar quantities of the coupling partners. We have demonstrated that this reaction can be conducted on multigram scale to give **19a**, and in this case the product can be purified without the need for chromatography. Efforts toward diastereo- and enantioselective arylation, as well as the implentation of this transformation in natural product total synthesis are the subjects of ongoing research in our laboratory.

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