Published in final edited form as:

Chem Sci. 2012 November ; 3(11): 3170–3174. doi:10.1039/C2SC20914D.

A Copper-Catalyzed Arylation of Tryptamines for the Direct Synthesis of Aryl Pyrroloindolines

Madeleine E. Kieffer, Kangway V. Chuang, and Sarah E. Reisman

The Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125 (USA)

Sarah E. Reisman: reisman@caltech.edu

Abstract

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 hodgekinsine (**1**),¹ naseaezine A (**2**),² and gliocladine C (**3**).³ As a result of their compelling bioactivities and fascinating structures, this family of alkaloids has been the subject of intense research⁴ 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-arylpyrroloindolines 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.^{9,10,11} 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•SnCl₄ catalyzes a formal (3 + 2) cycloaddition reaction between 1,3-disubstituted indoles (**4**) and benzyl 2-trifluoroacetamidoacrylate (**5**) (Scheme 1, a).¹² Good yields and high enantioselectivities

Correspondence to: Sarah E. Reisman, reisman@caltech.edu.

[†]Electronic Supplementary Information (ESI) available: experimental details, characterization data, and NMR spectral charts. See DOI: 10.1039/b000000x/

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 5 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 1, b). 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.

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 1, c). 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**.

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 *t*-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]BF₄, 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 [Ph₂I]BF₄ 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 [Ph₂I]BF₄ or other symmetric iodonium salts. On the other hand, Cu(OTf)₂ proved superior for arylation reactions 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 ~2–3:1 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).

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 [Ph₂I]BF₄ 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 [Ph₂I]BF₄.

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 (Figure 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 aryl-iodonium 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 sp³-sp² C–C bond relative to the rate of copper migration. Reductive elimination would regenerate the Cu^I 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 implementation of this transformation in natural product total synthesis are the subjects of ongoing research in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Prof. Brian Stoltz, Dr. Scott Virgil, and the Caltech Center for Catalysis and Chemical Synthesis for access to analytical equipment. We also thank Sigma-Aldrich for a kind donation of chemicals. Fellowship support was provided by the National Science Foundation (Graduate Research Fellowship, M.E.K. Grant No. DGE 1144469). Financial support from the California Institute of Technology and the NIH (NIGMS RGM097582A) is gratefully acknowledged.

Notes and references

1. Anet EFLJ, Hughes GK, Ritchie E. Aust J Chem. 1961; 14:173.
2. Raju R, Piggott AM, Conte M, Aalbersberg WGL, Feussner K, Capon RJ. Org Lett. 2009; 11:3862. [PubMed: 19655766]
3. Dong JY, He HP, Shen YM, Zhang KQ. J Nat Prod. 2005; 68:1510. [PubMed: 16252916]
4. For reviews see: Steven A, Overman LE. Angew Chem Int Edit. 2007; 46:5488. Schmidt MA, Movassaghi M. Synlett. 2008:313.
5. Selected references. From tryptophan or tryptamine derivatives: Taniguchi M, Hino T. Tetrahedron. 1981; 37:1487. Marsden SP, Depew KM, Danishefsky SJ. J Am Chem Soc. 1994; 116:11143. Austin JF, Kim SG, Sinz CJ, Xiao WJ, MacMillan DWC. Proc Nat Acad Sci USA. 2004; 101:5482. [PubMed: 15067109] Newhouse T, Baran PS. J Am Chem Soc. 2008; 130:10886. [PubMed: 18656919] Kim J, Ashenurst JA, Movassaghi M. Science. 2009; 324:238. [PubMed: 19359584] Espejo VR, Li XB, Rainier JD. J Am Chem Soc. 2010; 132:8282. [PubMed: 20518467] From oxindoles: Lee TBK, Wong GSK. J Org Chem. 1991; 56:872. Overman LE, Paone DV, Stearns BA. J Am Chem Soc. 1999; 121:7702. Trost BM, Zhang Y. J Am Chem Soc. 2006; 128:4590. [PubMed: 16594693] Bui T, Syed S, Barbas CF III. J Am Chem Soc. 2009; 131:8758. [PubMed: 19499923] He R, Ding C, Maruoka K. Angew Chem Int Ed. 2009; 48:4559. Yasui Y, Kamisaki H, Takemoto Y. Org Lett. 2008; 10:3303. [PubMed: 18582078] Ma S, Han X, Krishnan S, Virgil SC, Stoltz BM. Angew Chem Int Ed. 2009; 48:8037. Guo C, Song J, Huang JZ, Chen PH, Luo SW, Gong LZ.

- Angew Chem Int Ed. 2012; 51:1046. By interrupted Fischer indole synthesis: Boal BW, Schammel AW, Garg NK. Org Lett. 2009; 11:3458. [PubMed: 19601608]
6. Completed total syntheses of hodgekinsine: Kodanko JJ, Overman LE. Angew Chem Int Ed. 2003; 42:2528. gliocladine C: DeLorbe JE, Jabri SY, Mennen SM, Overman LE, Zhang F-L. J Am Chem Soc. 2012; 133:6549. [PubMed: 21473649] naseaeazine A: Kim J, Movassaghi M. J Am Chem Soc. 2011; 133:14940. [PubMed: 21875056]
 7. The synthesis of asperazine, a compound similar to naseaeazine A, has been reported: Govek SP, Overman LE. J Am Chem Soc. 2001; 123:9468–9469. [PubMed: 11562240]
 8. see reference 6c and: Boyer N, Movassaghi M. Chem Sci. 2012; 3:1798. [PubMed: 22844577]
 9. Allylation: Kimura M, Futamata M, Mukai R, Tamaru Y. J Am Chem Soc. 2005; 127:4592. [PubMed: 15796522] Trost BM, Quancard J. J Am Chem Soc. 2006; 128:6314. [PubMed: 16683785] Benzylation: Zhu Y, Rawal VH. J Am Chem Soc. 2011; 134:111. [PubMed: 22133348]
 10. As we were preparing this manuscript, a related, enantioselective reaction was reported. Zhu S, MacMillan DWC. J Am Chem Soc. 2012; 134:10815. [PubMed: 22716914]
 11. After the submission of this manuscript, a paper describing palladium-catalyzed intramolecular dearomative arylations of indoles was reported. Wu KJ, Dai LX, You SL. Org Lett. 2012; 14:3772.
 12. Repka LM, Ni J, Reisman SE. J Am Chem Soc. 2010; 132:14418. [PubMed: 20873714]
 13. Selected examples: Lane BS, Brown MA, Sames D. J Am Chem Soc. 2005; 127:8050. [PubMed: 15926829] Deprez NR, Kalyani D, Krause A, Sanford MS. J Am Chem Soc. 2006; 128:4972. [PubMed: 16608329] Stuart DR, Fagnou K. Science. 2007; 316:1172. [PubMed: 17525334] Stuart DR, Villemure E, Fagnou K. J Am Chem Soc. 2007; 129:12072. [PubMed: 17880083] Wang X, Gribkov DV, Sames D. J Org Chem. 2007; 72:1476. [PubMed: 17288392] Lebrasseur N, Larrosa I. J Am Chem Soc. 2008; 130:2926. [PubMed: 18278918] Phipps RJ, Grimster NP, Gaunt MJ. J Am Chem Soc. 2008; 130:8172. [PubMed: 18543910] Yang SD, Sun CL, Fang Z, Li BJ, Li YZ, Shi ZJ. Angew Chem Int Ed. 2008; 47:1473. Zhao JL, Zhang YH, Cheng K. J Org Chem. 2008; 73:7428. [PubMed: 18702549]
 14. Baran and Eastman have reported a base promoted C3-arylation of indoles using diaryliodonium electrophiles. However, they are unable to prepare the C3-aryl pyrroloindolines using this procedure. Eastman K, Baran PS. Tetrahedron. 2009; 65:3149.
 15. Kostic and coworkers have proposed a spirocyclic Pd^{II}-tryptophan complex as an intermediate in the site-specific hydrolysis of peptides, see: Kaminskaia NV, Johnson TW, Kostic NM. J Am Chem Soc. 1999; 121:8663. Kaminskaia NV, Kostic NM. Inorg Chem. 2001; 40:2368. [PubMed: 11327915]
 16. The use of *N*-benzenesulfonyl, *N*-*p*-nitrobenzenesulfonyl, and *N*-methanesulfonyl amides provided comparable yields of the pyrroloindoline product.
 17. Although the ratio of C3:C2 arylation appears to improve using Cu(OTf)₂•PhMe as the catalyst (Table 1, entry 5), control experiments determined that the decrease in C2-arylated product 17 results from the oxidative dimerization of this compound under the reaction conditions.
 18. For mechanistic studies of copper-catalyzed reactions of diaryliodonium salts, see: Lockhart TP. J Am Chem Soc. 1983; 105:1940.
 19. For studies of the structure and reactivity of aryl-Cu^{III} complexes, see: King AE, Huffman LM, Casitas A, Costas M, Ribas X, Stahl SS. J Am Chem Soc. 2010; 132:12068. [PubMed: 20690595]
 20. Although conditions have been developed for the reduction of indolyl-lactams to pyrroloindolines, in the context of highly functionalized systems, this subsequent reduction step can result in additional issues of chemoselectivity.

Figure 1.
Pyrroloindoline alkaloids: representative members.

Figure 2.
Proposed catalytic cycle.

(a) Prior Work by Our Group: Pyrroloindoline Synthesis

(b) Metal-Catalyzed Indole Arylation

(c) This Work: Metal-Catalyzed Arylation of Tryptamines

Scheme 1.
Reaction design.

Scheme 2.
Products of Pd-catalyzed arylation.

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

Table 1

Optimization of the copper-catalyzed pyrroloindoline formation.

entry	R ¹	Cu source	X	additive	C3:C2	pd ^t	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 •PhMe	BF ₄	–	3.4:1	19a	64
6	Ts	CuI	BF ₄	–	–	19a	0
7	Ts	Cu(MeCN)PF 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

^aDetermined by HPLC versus an internal standard.

^bIsolated yield.

^c[PhI-Mes]BF₄ was employed as the electrophile.

Substrate scope: tryptamine substitution.^a

Table 3

Substrate scope: iodonium substitution.^a

entry	Ar ¹	Ar ²	CuX ₂ ^b	pdt	yield (%) ^c
1	2-(Me)C ₆ H ₄	2-(Me)C ₆ H ₄	Cu(OAc) ₂	22a	50
2	4-(Me)C ₆ H ₄	4-(Me)C ₆ H ₄	Cu(OAc) ₂	22b	77
3	4-(OMe)C ₆ H ₄	4-(OMe)C ₆ H ₄	Cu(OAc) ₂	22c	66
4	4-(Cl)C ₆ H ₄	4-(Cl)C ₆ H ₄	Cu(OAc) ₂	22d	70
5	mesityl	2-(Me)C ₆ H ₄	Cu(OTf) ₂	22a	15
6	mesityl	3-(Me)C ₆ H ₄	Cu(OTf) ₂	22e	63
7	mesityl	4-(Me)C ₆ H ₄	Cu(OTf) ₂	22b	74
8	mesityl	4-(OMe)C ₆ H ₄	Cu(OTf) ₂	22c	70
9	mesityl	4-(F)C ₆ H ₄	Cu(OTf) ₂	22f	66
10	mesityl	4-(Cl)C ₆ H ₄	Cu(OTf) ₂	22d	68
11	mesityl	4-(Br)C ₆ H ₄	Cu(OTf) ₂	22g	59
12	mesityl	4-(OC ₆ H ₄)	Cu(OTf) ₂	22h	62
13	mesityl	4-(CO ₂ Et)C ₆ H ₄	Cu(OTf) ₂	22i	55

^aReactions were conducted on 0.30 mmol scale.^bCatalyst loadings: 10 mol % Cu(OAc)₂; 20 mol % Cu(OTf)₂.^cIsolated yields.