Literature Report

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

Reporter: Mu-Wang Chen
Checker: Zhang-Pei Chen
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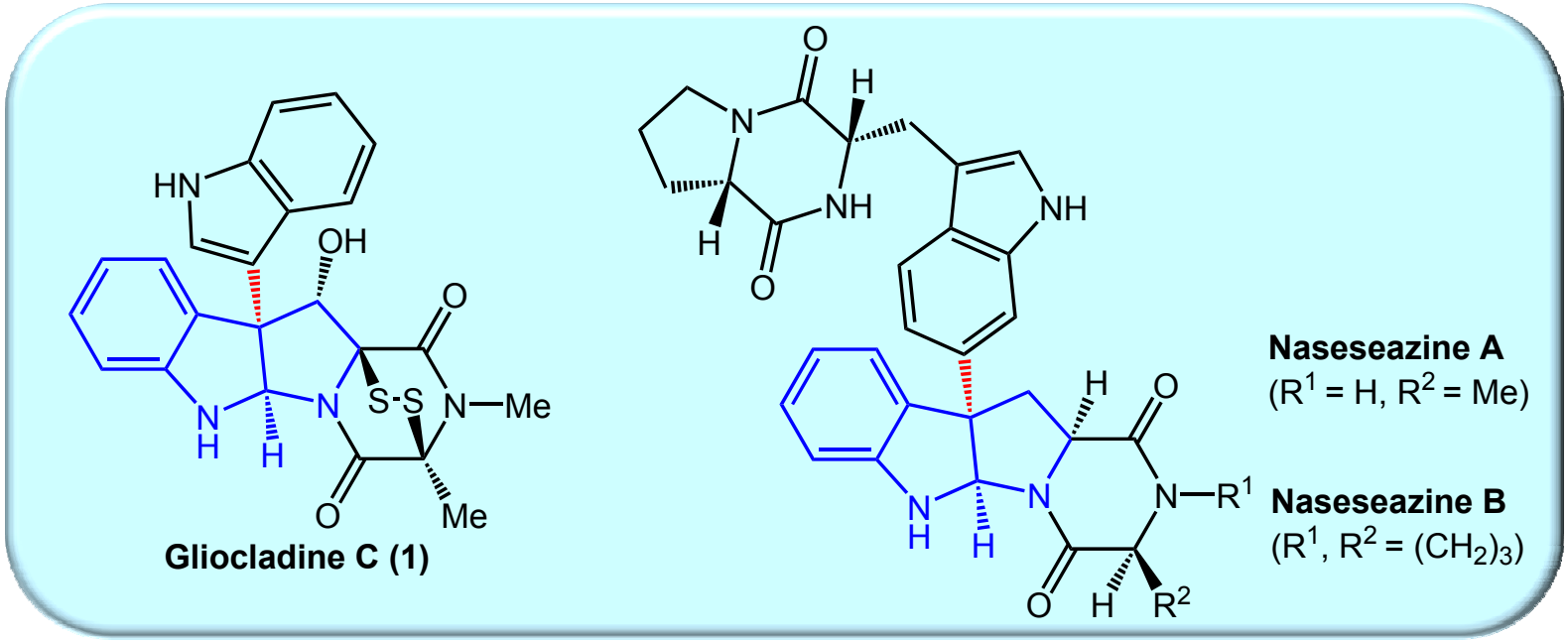
Reisman, S. E. *et al.*
J. Am. Chem. Soc. **2013,** *135,* 5557-5560.

California Institute of Technology

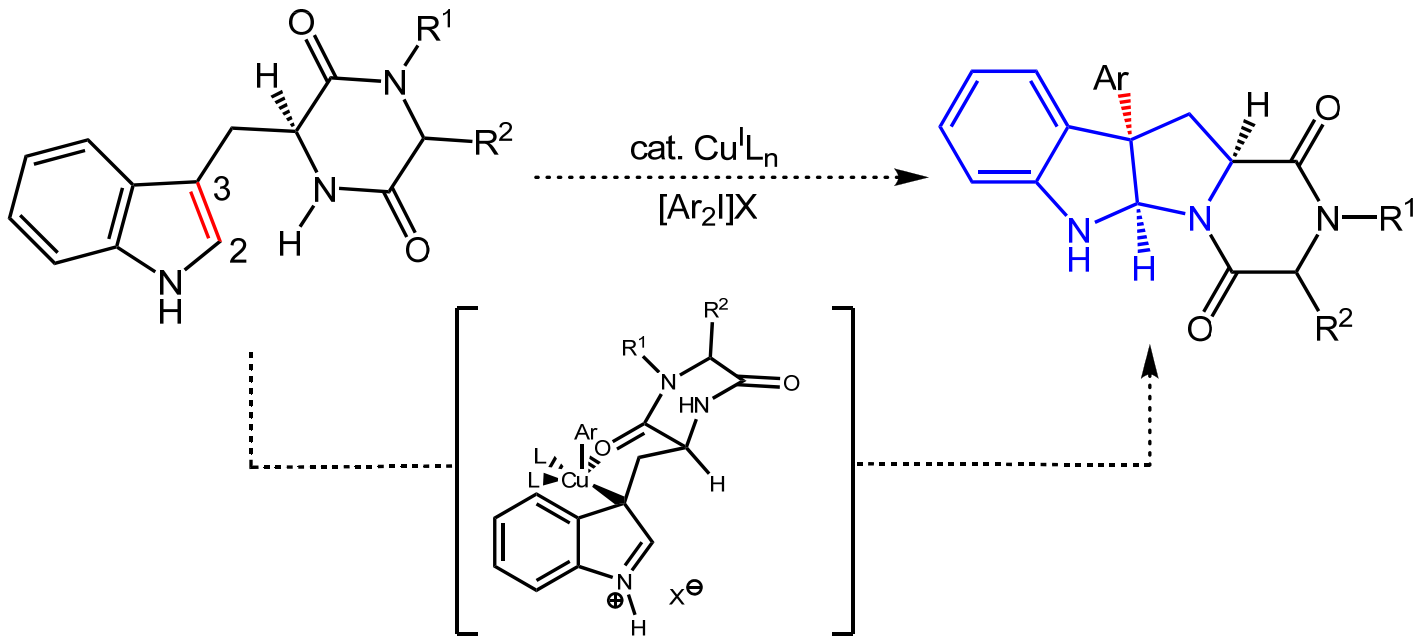
Contents

Pyrroloindoline Alkaloids

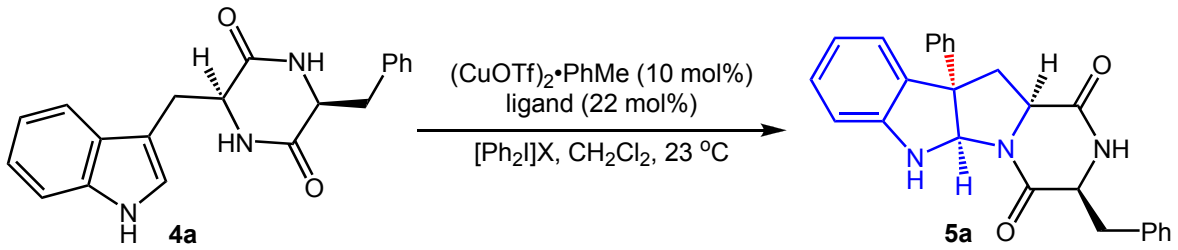


- **Oxidative cyclization reaction**
- **Organocatalyzed reaction**
- **Transition-metal-catalyzed reaction**

Copper-Catalyzed Diastereoselective C3 Arylation-Cyclization



Optimization Studies

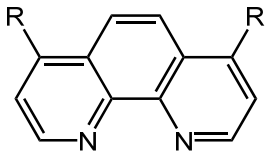


entry	ligand	$[Ph_2I]X$	C3:C2[a]	dr[a]	yield (%)[a]
1	-[b]	$[Ph_2I]PF_6$	-	-	0
2	-	$[Ph_2I]PF_6$	1:1	3:1	22
3	**L1**	$[Ph_2I]PF_6$	1:1	3:1	15
4	**L2**	$[Ph_2I]PF_6$	1:2	2:1	<5
5	**L3**	$[Ph_2I]PF_6$	6:1	10:1	20
6	**L4**	$[Ph_2I]PF_6$	12:1	12:1	38
7	**L5**	$[Ph_2I]PF_6$	2:1	5:1	26
8	**L6**	$[Ph_2I]PF_6$	1:1	4:1	24
9	**L7**	$[Ph_2I]PF_6$	>20:1	>20:1	70

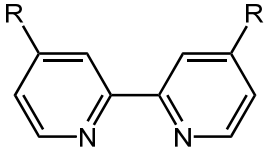
[a] Yield of major diastereomer was determined by ^1H NMR analysis of the crude reaction mixture. [b] No $(CuOTf)_2 \cdot PhMe$ was used. [c] Isolated yield

entry	ligand	$[Ph_2I]X$	C3:C2[a]	dr[a]	yield (%)[a]
10	**L8**	$[Ph_2I]PF_6$	1:1	4:1	15
11	**L9**	$[Ph_2I]PF_6$	2:1	20:1	35
12	**L7**	$[Ph_2I]PF_4$	>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])

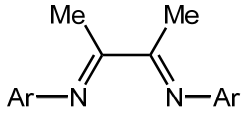
[a] Yield of major diastereomer was determined by ^1H NMR analysis of the crude reaction mixture. [b] No $(CuOTf)_2$.PhMe was used. [c] Isolated yield



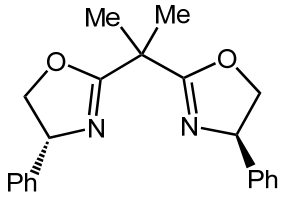
R = H (**L1**)
= Ph (**L2**)



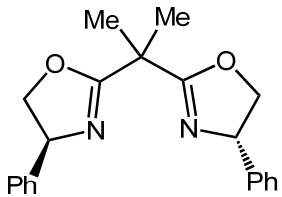
R = H (**L3**)
= *t*-Bu (**L4**)



Ar = Ph (**L5**)
= 3,5-$(t\text{-Bu})_2C_6H_3$ (**L6**)
= 2,4,6-$Me_3C_6H_2$ (**L7**)

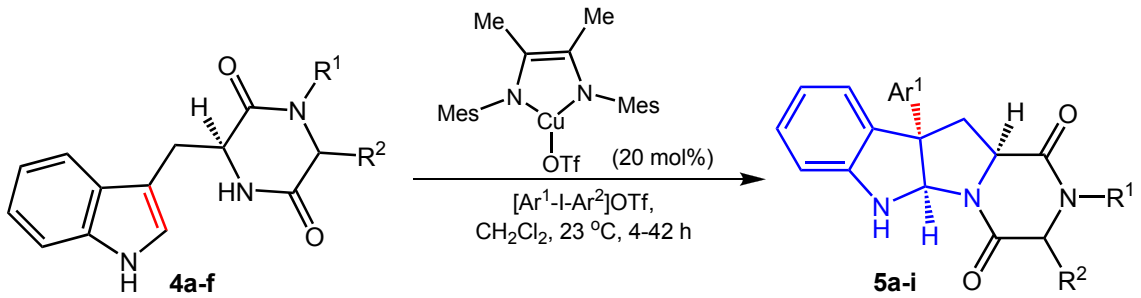


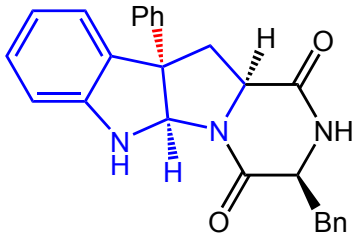
(*R,R*)-PhBox (**L8**)



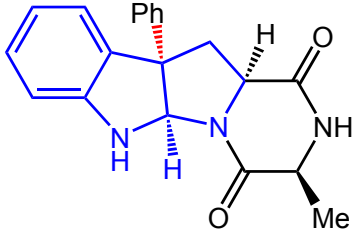
(*S,S*)-PhBox (**L9**)

Substrate Scope of Pyrroloindoline Formation

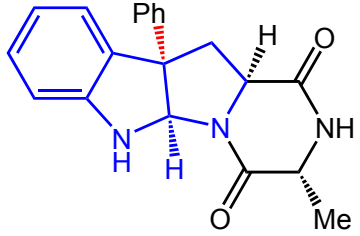




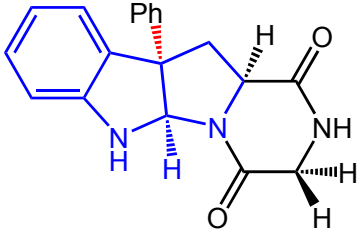
5a
85% yield



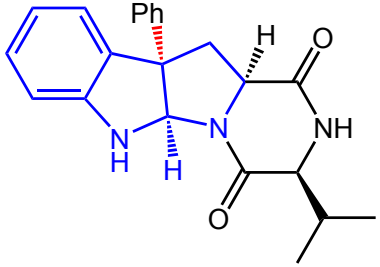
5b
66% yield



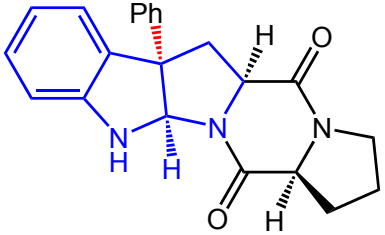
5b
50% yield



5d
64% yield

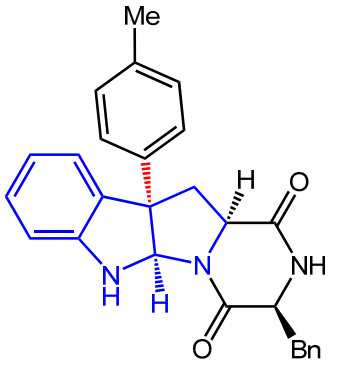


5e
51% yield

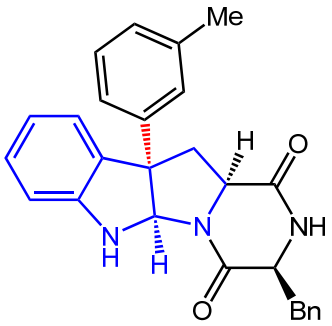


5f
71% yield[b]

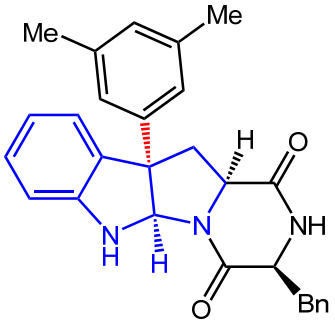
Substrate Scope of Pyrroloindoline Formation



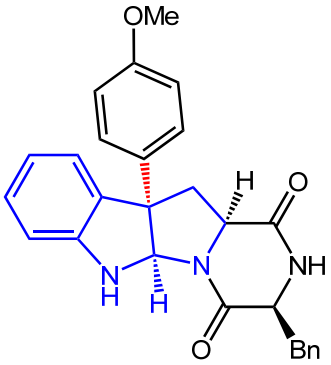
5g
77% yield



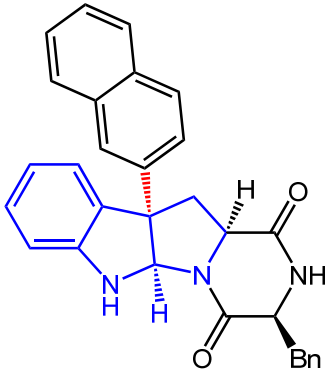
5h
94% yield



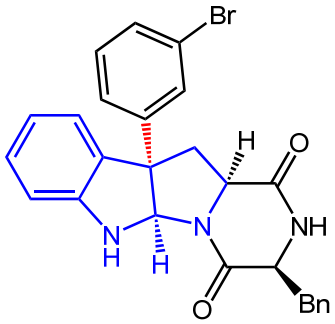
5i
91% yield



5j
67% yield



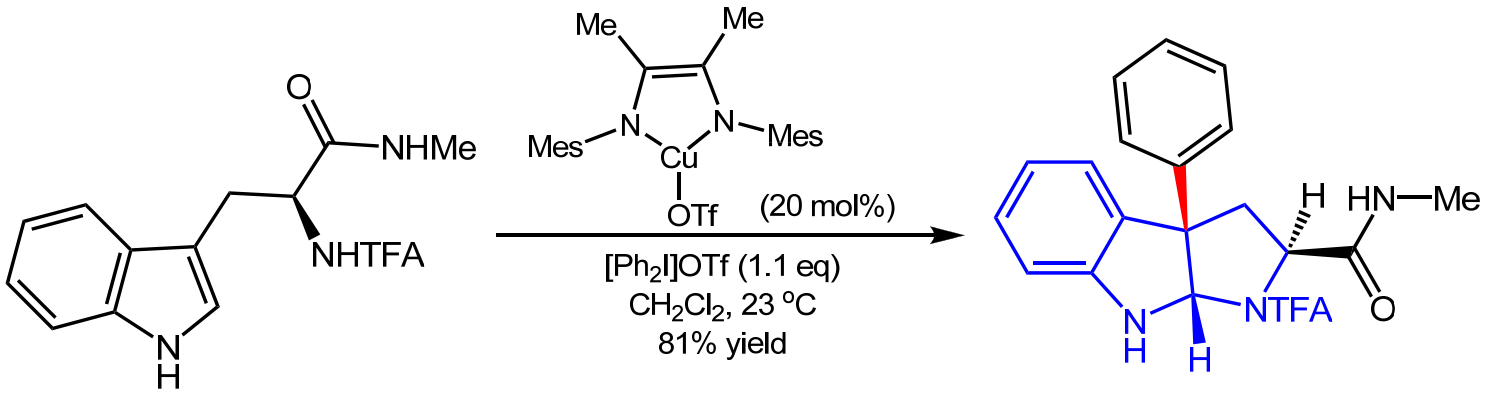
5k
81% yield[c]



5l
54% yield[c]

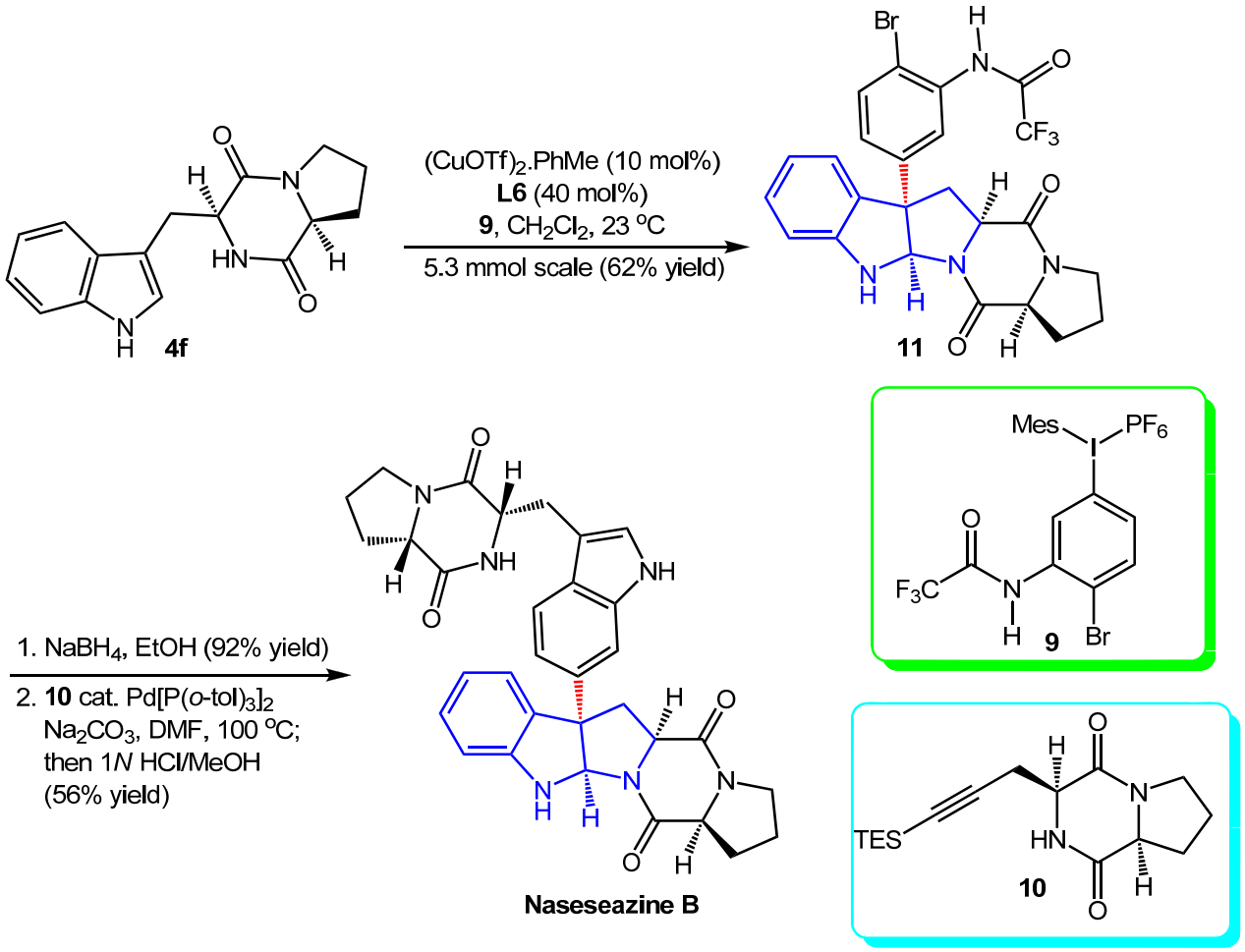
[a] Reaction were conducted on a 0.3 mmol scale using symmetric $[Ar_2I]OTf$, unless otherwise noted. Isolated yields are reported. [b] Ligand **L6** (40 mol%) was used with $[Ph_2I]PF_6$. [c] Nonsymmetric [Ar(*p*-xylyl)I]OTf was used.

Arylation of Tryptophan Carboxamide 7

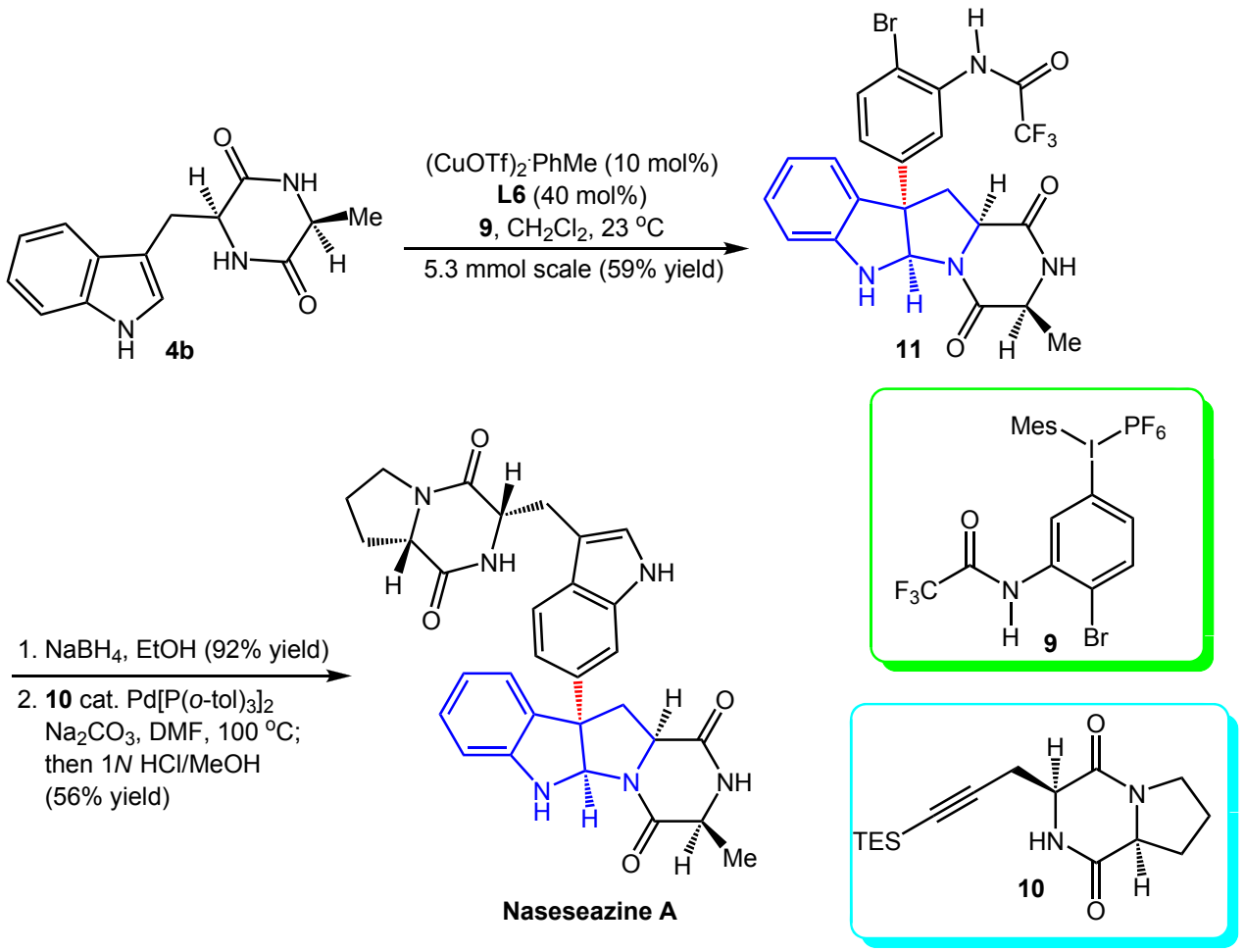


7 **8**

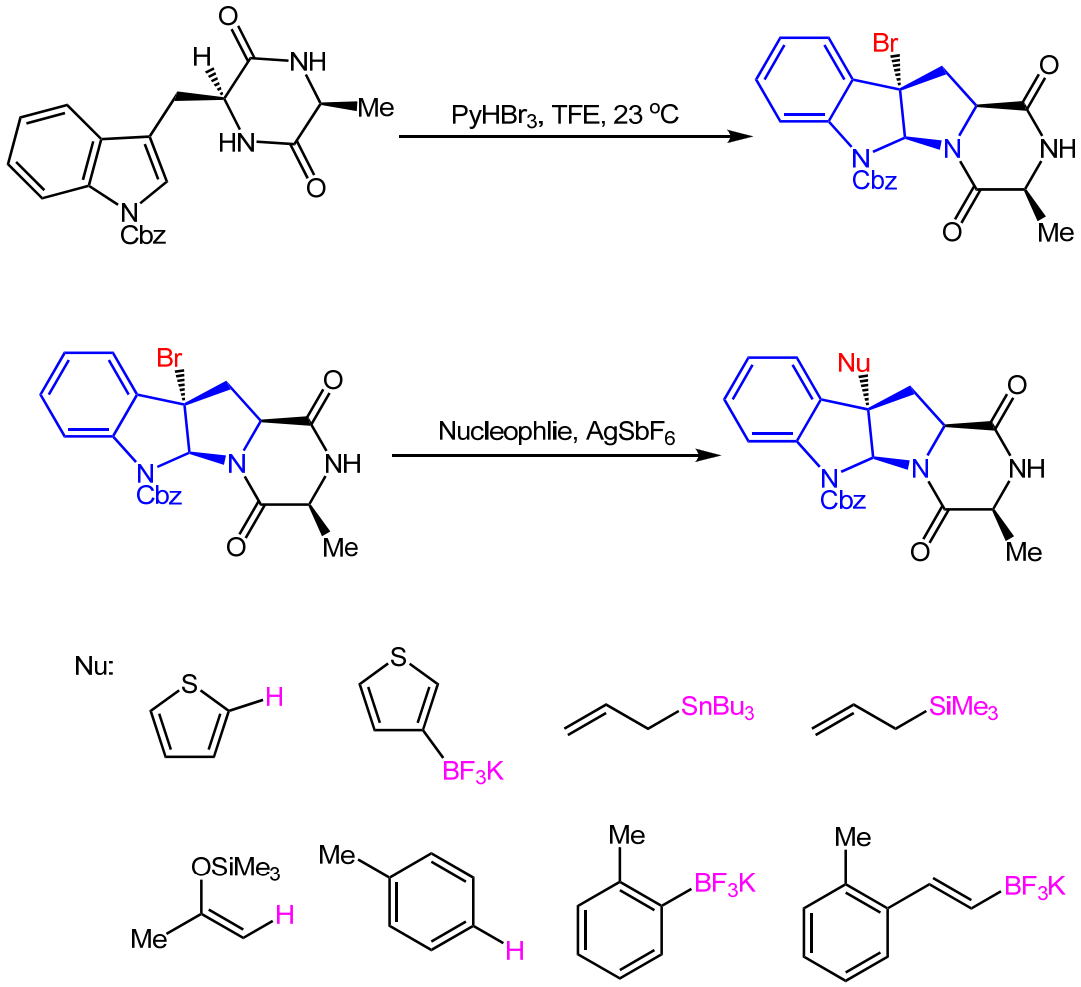
Concise Total Syntheses of (+) –Naseseazine B



Concise Total Syntheses of (+) –Naseseazine A

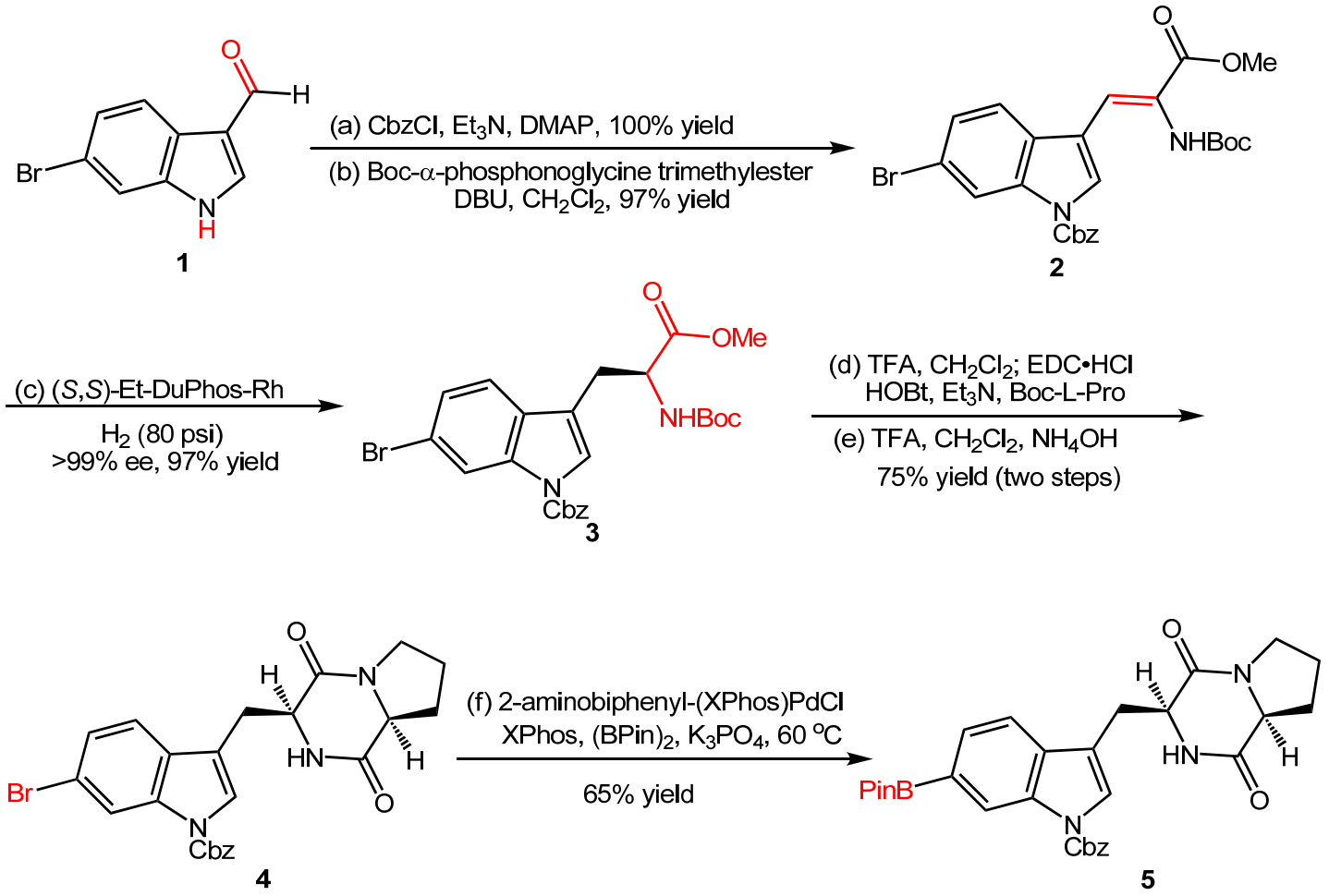


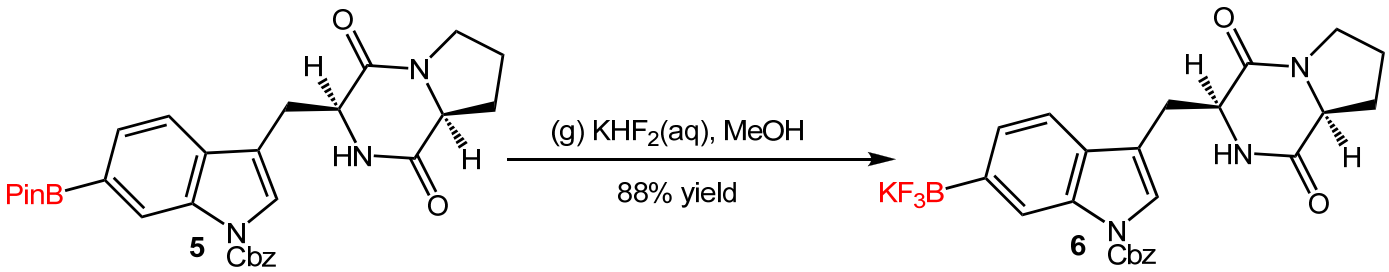
Regioselective Arylative Dimerization of Diketopiperazine Alkaloids

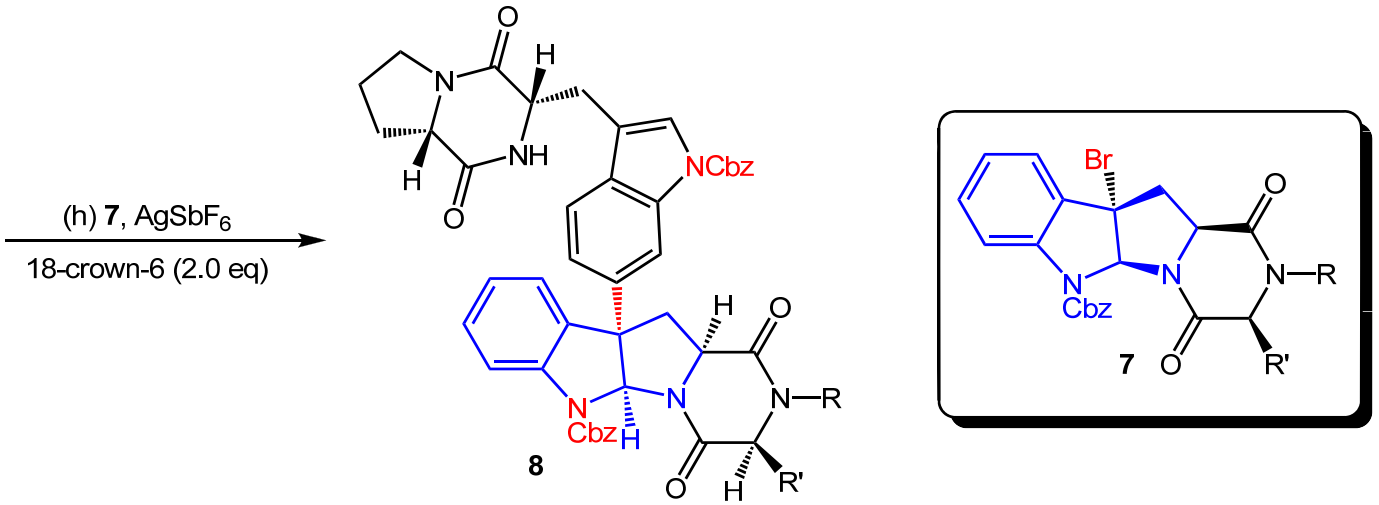


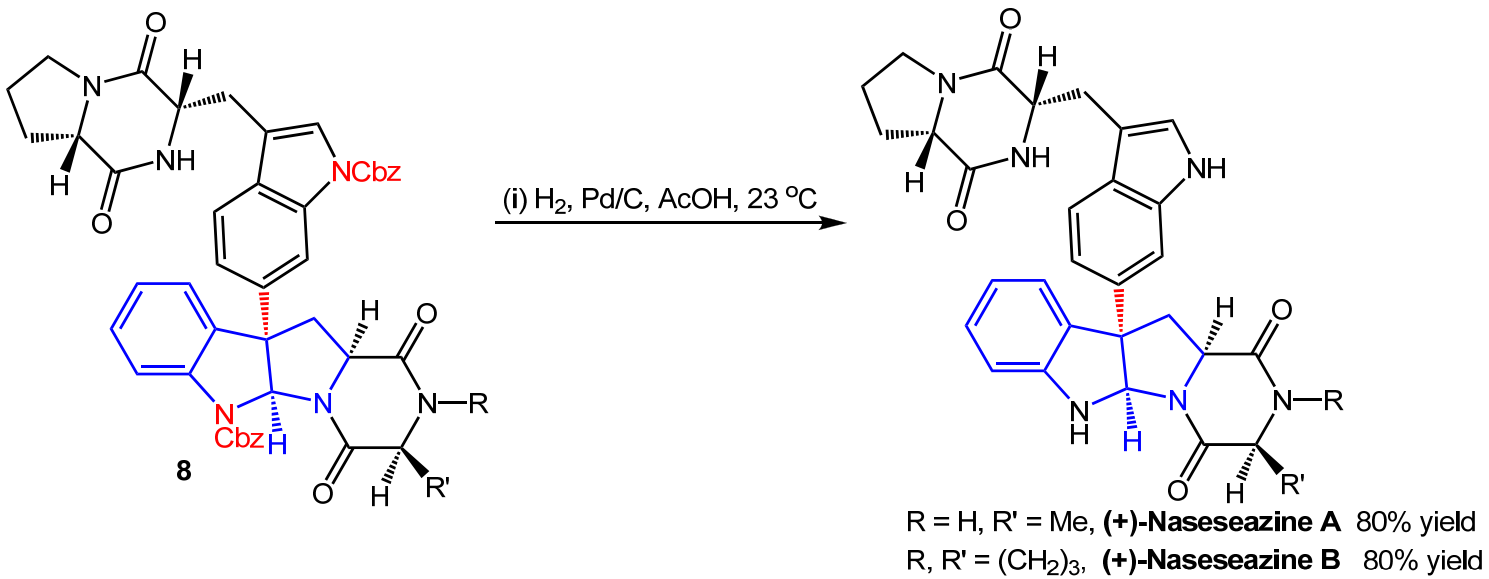
Movassaghi, M. *et al. J. Am. Chem. Soc.* **2011,** *133,* 14940-14943.

Concise and Directed Syntheses of A and B

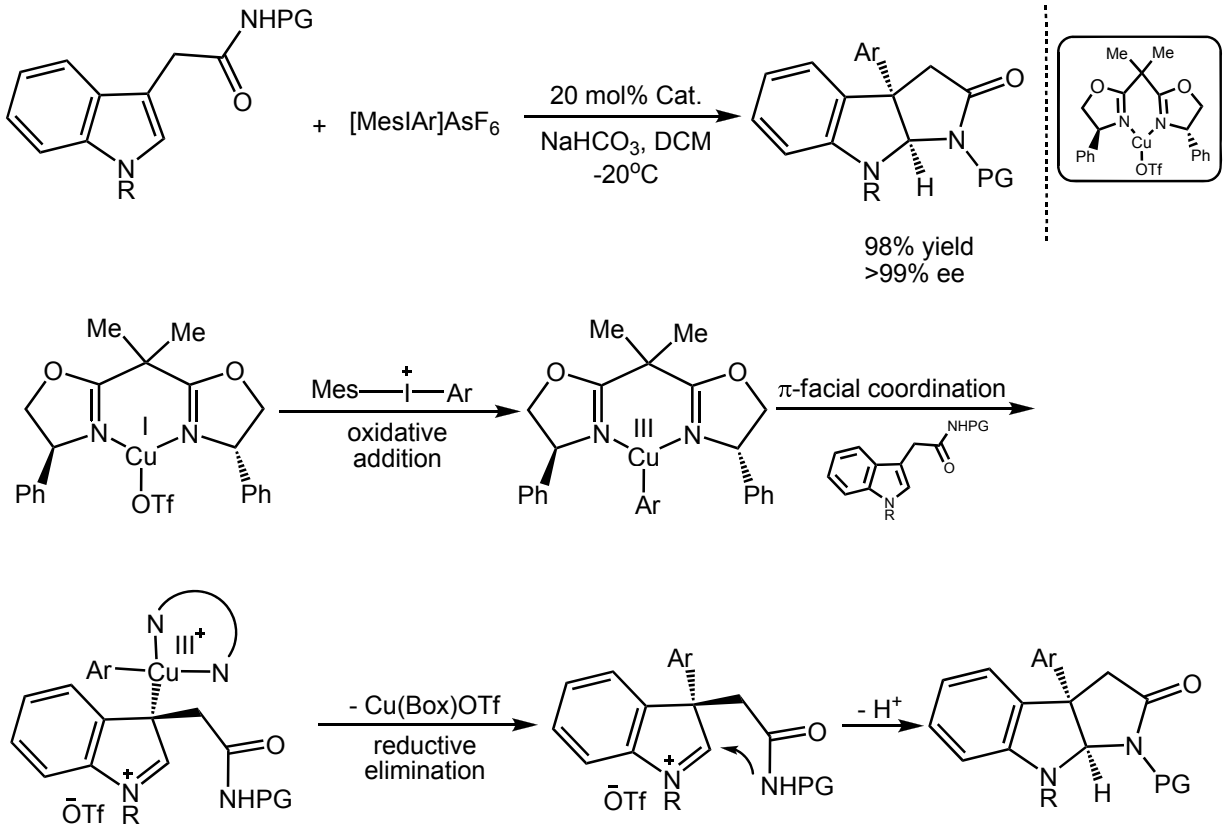



PinB
5
Cbz
(g) KHF2(aq), MeOH
88% yield
KF3B
6
Cbz


(h) 7, AgSbF6
18-crown-6 (2.0 eq)
NCbz
8
Br
7
Cbz
R = H, R' = Me 56% yield
R, R' = (CH2)3 50% yield

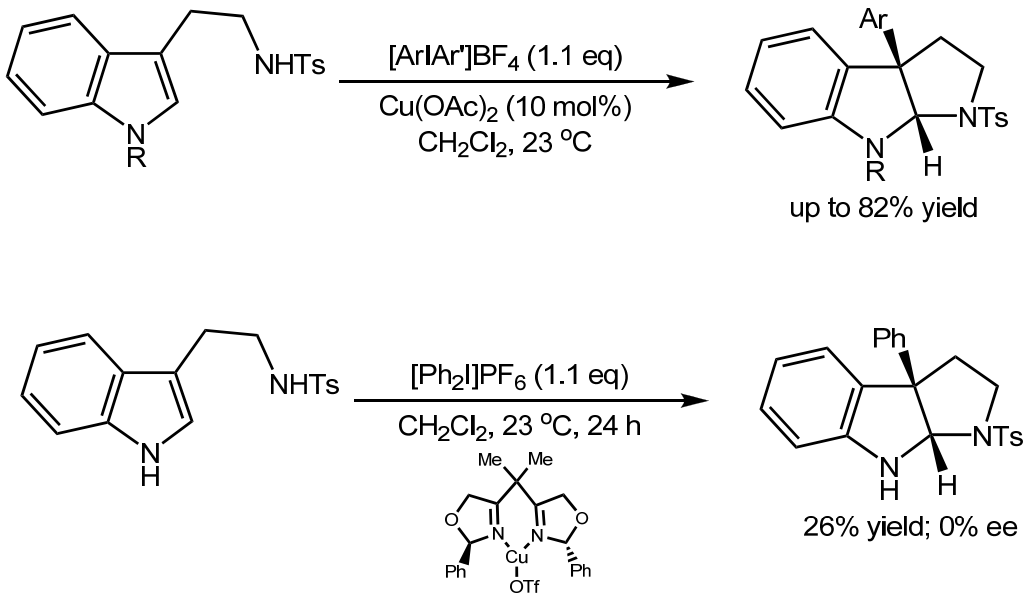

(i) H_2, Pd/C, AcOH, 23 °C
NCbz
N
Cbz
H
8
NH
R = H, R' = Me, **(+)-Naseseazine A** 80% yield
R, R' = $(CH_2)_3$, **(+)-Naseseazine B** 80% yield

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



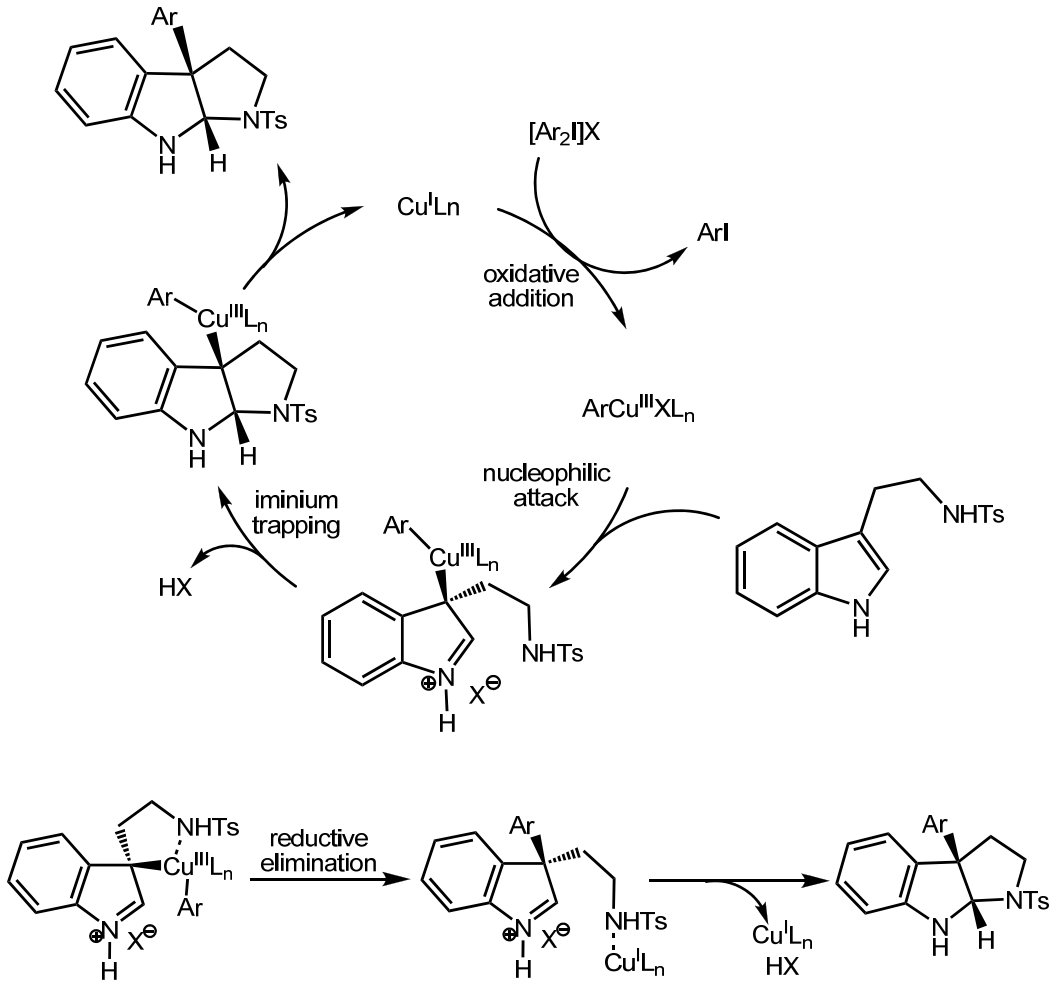
MacMillan, D. W. C. *et al. J. Am. Chem. Soc.* **2012,** *134,* 10815-10818.

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



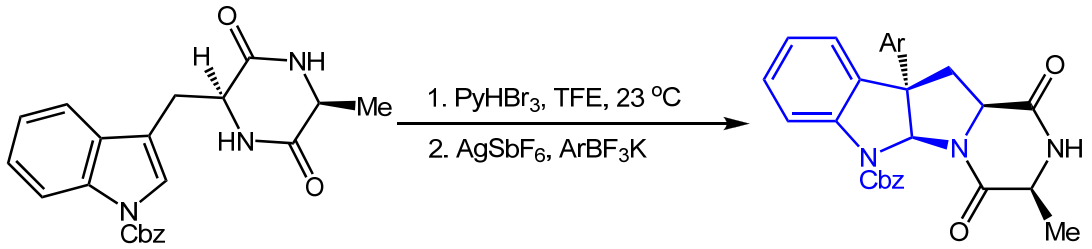
Reisman, S. E. *et al. Chem.Sci.*, **2012,** *3,* 3170-3174.

Proposed Catalytic Cycle

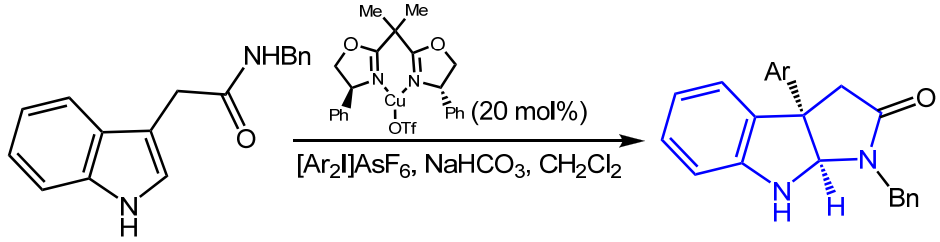


Summary

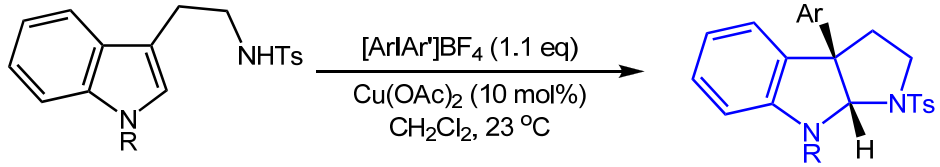
A Movassaghi and Kim (2011): Bromocyclization/Friedel-Crafts



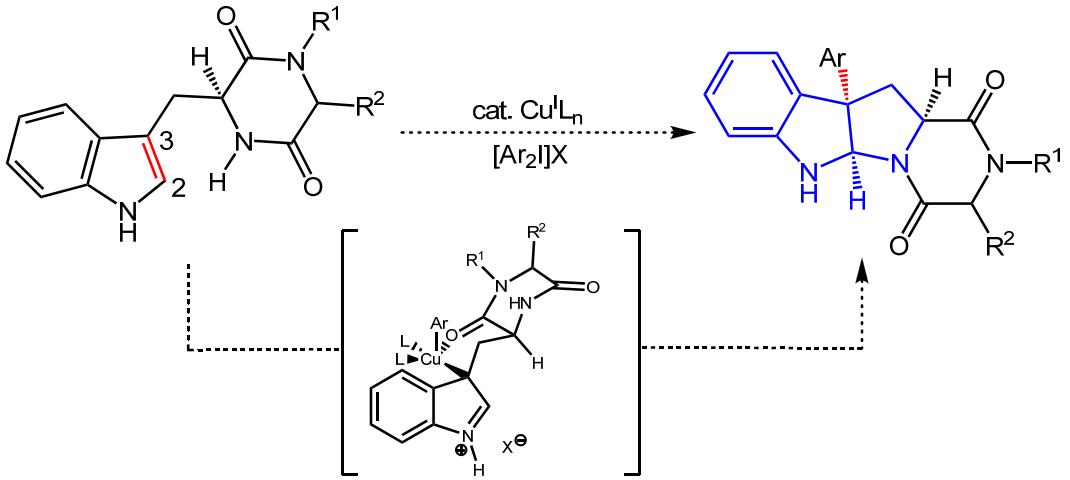
B MacMillan and Zhu (2012): Copper-Catalyzed, Enantioselective C3 Arylation-Cyclization



C Reisman and Kieffer (2012): Copper-Catalyzed C3 Arylation-Cyclization



Reisman and Kieffer (2012): Copper-Catalyzed, Diastereoselective C3 Arylation-Cyclization



The pyrroloindoline is a common structural motif that unites several biosynthetically distinct families of alkaloids. The prevalence of this indole-derived heterocyclic framework continues to inspire the development of new reactions for its construction, and these efforts have delivered increasingly efficient total syntheses of biologically active natural products. 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 as well as recently discovered organocatalyzed and transition-metal-catalyzed C−C bond-forming processes.

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.