

CHAPTER 1

Recent Developments in the Catalytic, Enantioselective Construction of Pyrroloindolines Bearing All-Carbon Quaternary Stereocenters[†]

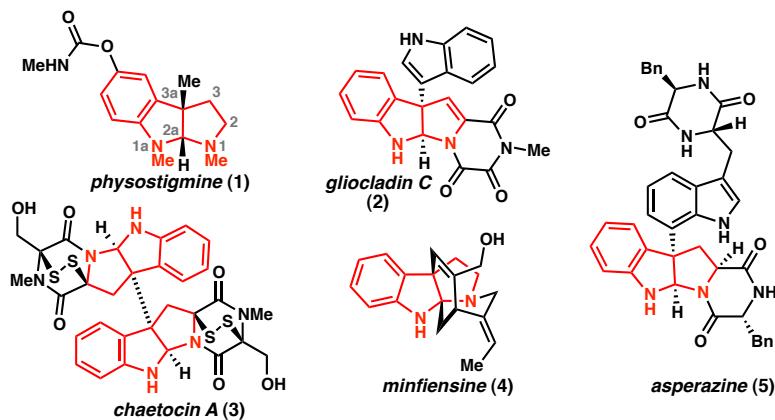
1.1 INTRODUCTION

A large family of structurally diverse natural products is characterized by the collective presence of an indoline fused at its 2 and 3 positions to a pyrrolidine, a motif commonly known as a pyrroloindoline and more precisely named hexahydropyrrolo[2,3-*b*]indole (Figure 1.1.1).¹ These alkaloids possess an array of biological properties, including cholinesterase (physostigmine (**1**)),² cancer (gliocladin C (**2**))³ and asperazine (**5**)),⁴ and histone methyltransferase (chaetocin A (**3**))⁵ inhibitory activities. Furthermore, many pyrroloindoline natural products bear C3a all-carbon quaternary stereocenters and the synthetic challenge inherent in these molecules combined with promising medicinal value has inspired a myriad of methodologies targeting the enantioenriched framework.⁶

[†] This chapter was adapted from a mini-review written in collaboration with Professor Sarah Reisman.

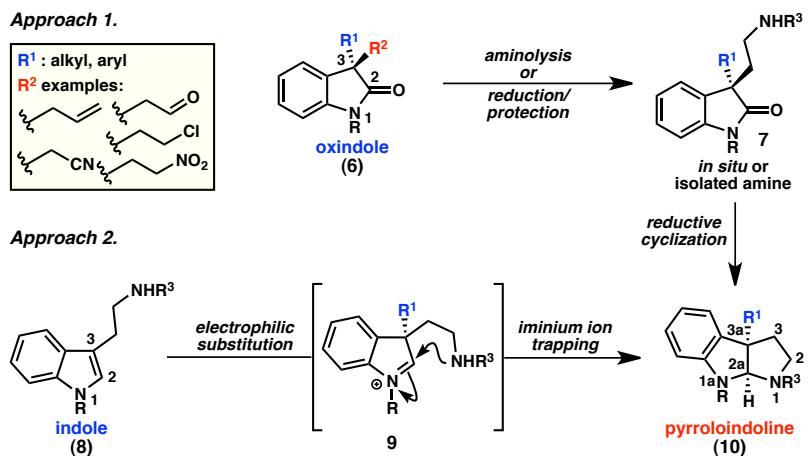
Although numerous strategies involving either chiral auxiliaries or the functionalization of L-tryptophan have been developed, this synopsis will offer an introduction to the catalytic, enantioselective approaches based on the recent growth of research within this field.

Figure 1.1.1. Representative pyrroloindoline natural products.



Catalytic, enantioselective reactions to prepare pyrroloindolines can be categorized primarily into two general approaches: (1) reactions to synthesize 3,3'-disubstituted oxindoles, which can be elaborated to the corresponding pyrroloindolines (Approach 1, Scheme 1.1.1),⁷ or (2) tandem C3-functionalization/cyclization reactions of 3-substituted indoles (Approach 2, Scheme 1.1.1). Extensive research has been conducted using both approaches, and each possesses distinct advantages. The indole functionalization approach permits direct access to pyrroloindolines, whereas the oxindole can serve as intermediates in the synthesis of both pyrroloindoline and oxindole-based natural products.⁸

Scheme 1.1.1. General approaches for pyrroloindoline synthesis.

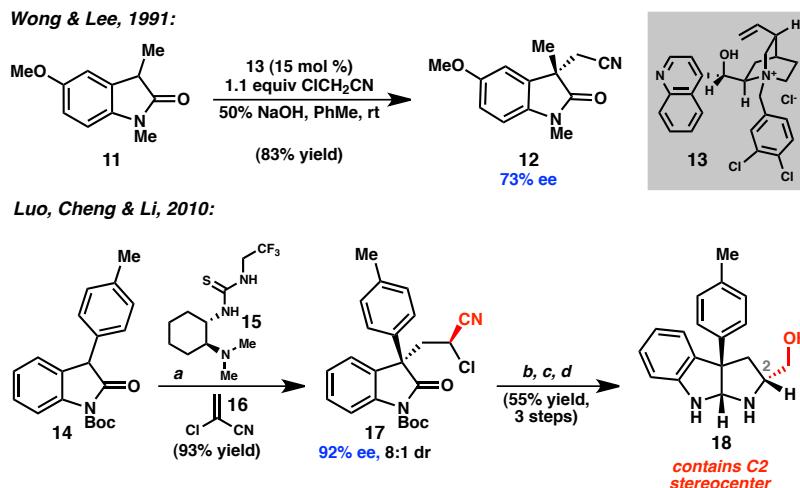


1.2 PYRROLOINDOLINE SYNTHESIS VIA 3,3'-DISUBSTITUTED OXINDOLES

3,3'-Disubstituted oxindoles are available by several methods including α -alkylation, intramolecular cyclization, and intramolecular acyl migration. The first catalytic asymmetric synthesis of a 3,3'-disubstituted oxindole was developed in 1991 at Hoechst-Roussel Pharmaceuticals Inc.⁹ Researchers Wong and Lee discovered that subjection of oxindole **11** to chloroacetonitrile in the presence of cinchoninium bromide catalyst **13** delivered enantioenriched oxindole **12** (Scheme 1.2.1). Further elaboration resulted in a formal total synthesis of the anticholinesterase natural product physostigmine (**1**, Figure 1). This approach built on the pioneering phase transfer catalysis studies of Dolling and coworkers,¹⁰ and has been succeeded by several enantioselective organocatalytic α -alkylation reactions of oxindoles.¹¹ Recently, Luo and coworkers identified a bifunctional tertiary amine thiourea (**15**) that catalyzes the conjugate addition of 3-aryl and 3-alkyloxindoles (**14**) to 2-chloroacrylonitrile (**16**).^{11c} Of the asymmetric oxindole alkylation approaches reported to date, this is the first method that directly installs an

appropriate C2-handle for advancement to diketopiperazine-based alkaloids (e.g. chaetocin A (**3**), Figure 1.1.1).

Scheme 1.2.1. Organocatalytic α -alkylation of oxindoles.

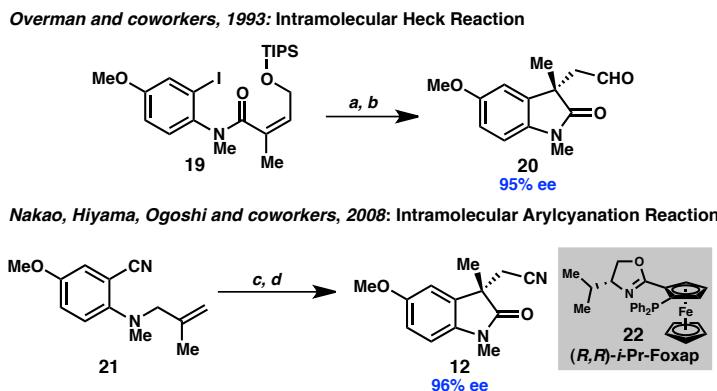


Conditions: *a.* 3.0 equiv **16**, 10 mol % **15**, 4 Å MS, $\text{ClCH}_2\text{CH}_2\text{Cl}$, $-20\text{ }^\circ\text{C}$, 48 h; *b.* NaN_3 , DMSO, $30\text{ }^\circ\text{C}$, 24 h; *c.* TMSCl , MeOH , rt, 96 h; *d.* Red-Al, PhMe , rt to $100\text{ }^\circ\text{C}$, 24 h.

A second, foundational catalytic asymmetric method to prepare 3,3-disubstituted oxindoles was the Pd-catalyzed intramolecular Heck reaction reported by Overman and coworkers in 1993 (Scheme 1.2.2).¹² In a preliminary demonstration of the synthetic utility, physostigmine (**1**, Figure 1.1.1) was prepared from Z-butenanilide **19** via oxindole carboxaldehyde **20**. Recently, this reaction was applied in more elaborate contexts including the synthesis of the alkaloids minfiensine (**4**, Figure 1.1.1)¹³ and polypyrroloindoline quadrigemine C.¹⁴ These transformations are noteworthy examples of asymmetric Heck reactions that generate all-carbon quaternary centers, and have likely inspired the development of related transition metal-catalyzed cyclization reactions for the construction of pyrroloindolines.¹⁵ For example, Nakao, Hiyama, Ogoshi and coworkers reported the synthesis of (2-oxindolyl)acetonitrile derivatives by the Ni-catalyzed enantioselective intramolecular arylcyanation of alkenes (Scheme 1.2.2).^{15c,16} A

key finding in this study was that, in addition to the nickel catalyst, a Lewis acid (AlMe_2Cl) was required to achieve indoline formation. Subsequent C-H oxidation furnishes the highly enantioenriched 3,3'-dialkyl (**12**) and 3-alkyl-3'-aryloxindoles.

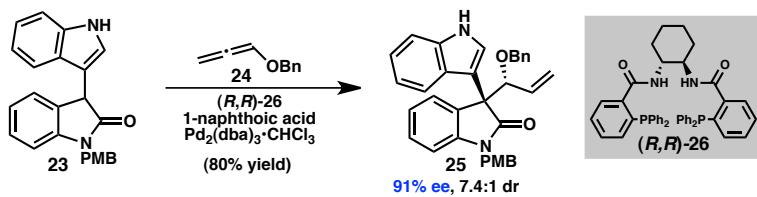
Scheme 1.2.2. Cyclization approaches to 3,3'-disubstituted oxindoles.



Conditions: *a.* 10 mol % $\text{Pd}_2\text{dba}_3\text{-CHCl}_3$, 23 mol % (*S*)-BINAP, 5.1 equiv PMP, DMA, 100 °C, 1.5 h. *b.* 3 *N* HCl, 0 to 23 °C (84 % yield, 2 steps). *c.* 10 mol % $\text{Ni}(\text{cod})_2$, 20 mol % **22**, 40 mol % AlMe_2Cl , DME, 100 °C, 10 h (88% yield); *d.* 6.0 equiv PhIO , CH_2Cl_2 , rt, 2.5 h (40% yield).

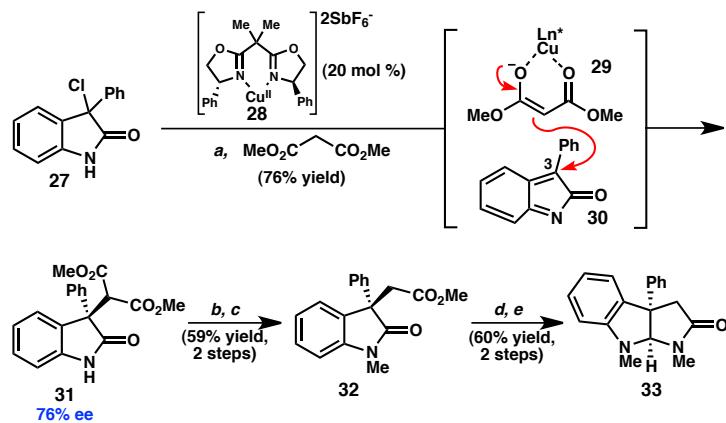
In addition to the Heck-type cyclization reactions described above, transition metal-catalyzed asymmetric allylic alkylation (AAA) reactions to prepare 3,3-disubstituted oxindoles have been developed. In 2006, Trost and coworkers reported the Mo-catalyzed AAA reaction of oxindoles using allyl carbonates as electrophiles,¹⁷ and established that these products could be easily elaborated to the corresponding pyrroloindolines. More recently, the same group developed a Pd-catalyzed AAA reaction of oxindoles using benzyloxyallene **24** as the electrophile (Scheme 1.2.3).^{18,19} The advantages of the latter reaction are that (1) it tolerates 3-indolyloxindole substrate **23**, and (2) the benzyloxy substituent in oxindole **25** provides a useful handle for the synthesis of more oxidized pyrroloindoline frameworks,²⁰ such as that found in gliocladin C and related natural products (**2**, Figure 1.1.1).

Scheme 1.2.3. *Pd*-catalyzed allylation of oxindoles with benzyloxyallene (**24**) (Trost and coworkers, 2011).



Conditions: 1.2 equiv **24**, 2.5 mol % $\text{Pd}_2(\text{dba})_3 \bullet \text{CHCl}_3$, 7.5 mol % *(R,R)*-**26**, 5 mol % 1-naphthoic acid, THF, rt, 41 h.

Scheme 1.2.4. *Cu*-catalyzed Umpolung alkylation of 3-halooxindoles (Stoltz and coworkers, 2009).

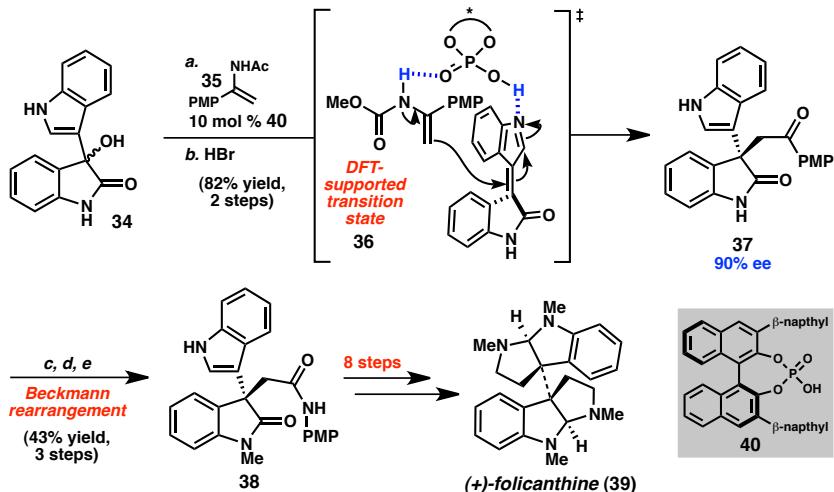


Conditions: *a*. 20 mol % *(S)*-PhBOX- $\text{Cu}(\text{II})$ - 2SbF_6 , 3.0 equiv dimethyl malonate, 2.0 equiv Et_3N , 3 Å MS, CH_2Cl_2 , -20°C (76% yield). *b*. LiCl , H_2O , DMSO, 150°C , 12 h; *c*. $t\text{BuOK}$, MeI , THF , 0°C , 1 h; *d*. AlMe_3 , $\text{MeNH}_2 \bullet \text{HCl}$, PhMe , 50°C , 5 d; *e*. LAH , THF , 0°C , 1 h.

Most oxindole α -alkylation strategies harness the intrinsic nucleophilicity of enolate intermediates; however, two recent Umpolung approaches employ oxindoles as the electrophilic component.²¹ In a 2009 report, Stoltz and coworkers describe a $\text{Cu}(\text{II})$ bisoxazoline (**28**)-catalyzed stereoablative alkylation of 3-chloro-3-aryloxindoles (**27**) with dimethylmalonate, wherein coordination of the malonate to the copper catalyst presumably generates a chiral nucleophile (**29**, Scheme 1.2.4).^{21a,22} The reaction is proposed to occur by elimination of HCl from **27** to form a transient *o*-azaxylylene (**30**); subsequent attack at C3 by **29** delivers the 3,3'-disubstituted oxindole (**31**). The utility of these products in pyrroloindoline synthesis was demonstrated for oxindole **31**, which

following Krapcho dealkoxy carbonylation, *N*-methylation, aminolysis, and reductive cyclization afforded 3-phenylpyrroloindoline **33** in an operationally straightforward manner.

Scheme 1.2.5. Phosphoric acid-catalyzed Umpolung alkylation of 3-indolyloxindoles en route to (+)-folicanthine (39) (Gong and coworkers, 2012).



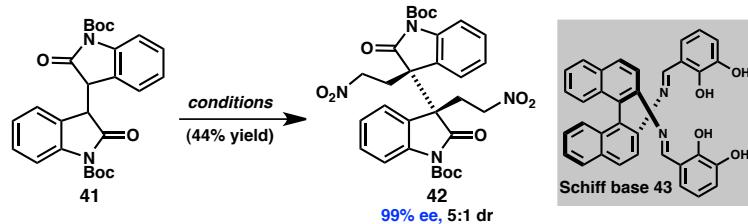
Conditions: *a.* 1.5 equiv **35**, 10 mol % **40**, Na_2SO_4 , CH_2Cl_2 , rt, 12–24 h; *b.* aqueous HBr, EtOH, rt, 8 h; *c.* $n\text{Bu}_4\text{NHSO}_4$, KOH, THF, 50 °C, 1 h; then MeI , rt, 2 h; *d.* $\text{NH}_2\text{OH}\cdot\text{HCl}$, pyridine, EtOH, rt, 2 d; *e.* HgCl_2 , MeCN, 80 °C, 2 h.

Gong and coworkers have discovered an alternative strategy for the in situ generation of electrophilic oxindole species that has proven instrumental for bispyrroloindoline synthesis.^{21b} This reaction involves indole-assisted dehydration, followed by chiral phosphoric acid (**40**)-catalyzed addition of enamine **35** to the transient azafulvene (**36**, Scheme 1.2.5). Mechanistic insight was provided by DFT calculations, which suggest a two-point binding model for the Brønsted acid that invokes hydrogen bonding of both the enamine and indole nitrogens. The necessary nitrogen functionality was installed by a Beckmann rearrangement to give **38**, which was elaborated in eight additional steps to (+)-folicanthine (**39**). Gong and coworkers further applied the asymmetric methodology

to 2-(alkyloxy)acetaldehydes by employing a cinchona alkaloid-derived co-catalyst and used this chemistry in a synthesis of gliocladin C (**2**, Figure 1.1.1).²³

The polypyrrroloindoline alkaloids present a particular synthetic challenge due to the presence of vicinal all-carbon quaternary stereocenters and, therefore, the design of methodology tailored to these molecules is an important area of research. Shortly following Gong's report of the enamine alkylation reaction described above, Kanai, Matsunaga and coworkers also reported a concise synthesis of (+)-folicanthine (**39**) (Scheme 1.2.6).²⁴ In this case, installation of the quaternary stereocenters was accomplished by sequential Mn-catalyzed Michael additions of the readily available bisoxindole **41** to nitroethylene. Although this transformation proved more practical in terms of yield as a two-step process, it is impressive that the one-flask double Michael reaction proceeds with exceptional enantioselectivity to successfully generate both stereocenters in a single step.

*Scheme 1.2.6. Mn-catalyzed double Michael reaction en route to (+)-folicanthine (**39**), (Kanai, Matsunaga and coworkers, 2012).*

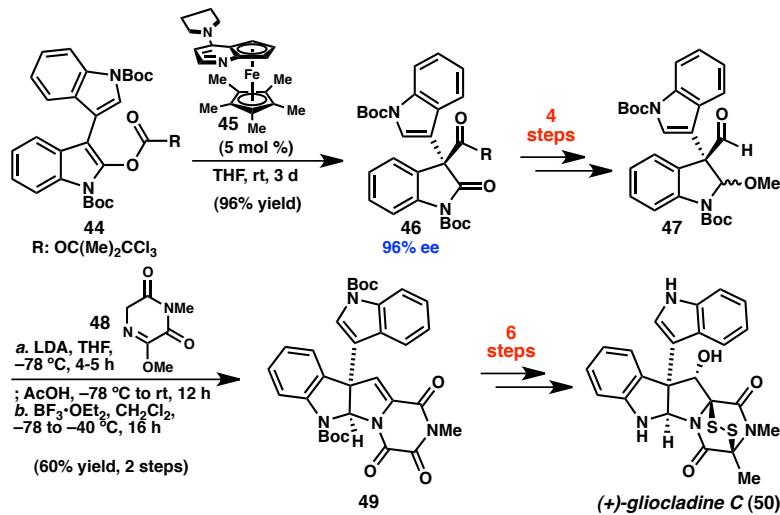


Conditions: 1.2 equiv nitroethylene, 18 mol % $\text{Mn}(4\text{-F-BzO})_2/\text{43}$ (ratio 1:1), PhMe, 5 Å MS, 50 °C, 1.5 h; then 2.0 equiv nitroethylene, 1.0 equiv 2,6-di-*tert*-butylphenol, 50 °C, 12 h.

Each of the methods discussed above depend on a reductive cyclization event as the means to access pyrroloindolines. Alternatively, the synthesis of (+)-gliocladiine C (**50**) completed by Overman and coworkers required the development of a more functional

group compatible Lewis acid-promoted cyclization reaction.²⁵ These researchers further recognized the relevant utility of the planar-chiral ferrocenyl pyridine (**45**)-catalyzed intramolecular acyl O-to-C migration of indolyl carbonates initially disclosed by Fu and coworkers.²⁶ Subjection of indolyl trichloro-*tert*-butylcarbonate **44** to the reported migration conditions provided oxindole **46** in high yield and ee (Scheme 1.2.7). Intermolecular aldol reaction of further functionalized 2-methoxyindoline **47** with trioxopiperazine **48** then installed the necessary nucleophilic amide functionality and subsequent exposure to $\text{BF}_3\text{-OEt}_2$ provided didehydropyrroloindoline **49**. This cyclization product was converted to (+)-gliocladiine C (**50**) in 6 steps,²⁷ which constitutes the first total synthesis of an epidithiodiketopiperazine (ETP) natural product incorporating a β -hydroxy-substituted stereocenter.

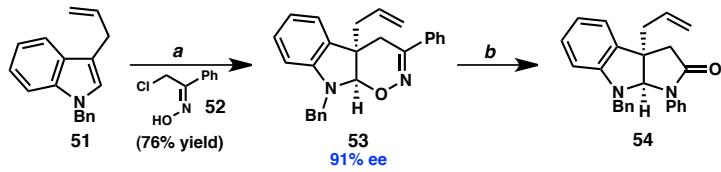
Scheme 1.2.7. First synthesis of a β -hydroxy-ETP natural product (Overman and coworkers, 2011; Fu and Hills, 2003).



As a complementary approach to asymmetric oxindole syntheses described above, Larionov and coworkers reported a strategy that invokes instead the intermediacy of an indolyl 1,2-oxazine (**53**, Scheme 1.2.8).^{28,29} Similar to the oxindole research, these studies

were driven by both the biological activity of 1,2-oxazine natural products³⁰ and the prospective conversion to pyrroloindolines. Specifically, Lewis acid-catalyzed [4+2] cycloaddition reactions of 3-alkylindoless (**51**) with nitrosoalkenes generated in situ from 2-chlorooximes (**52**) were found to afford the desired oxazines. Notably, Gilchrist and Roberts reported a related non-asymmetric NaHCO_3 -promoted reaction in 1978,³¹ but this recent addition to the literature represents the first catalytic and highly enantioselective cycloaddition of nitrosoalkenes for any dienophile.³² Beckmann rearrangement of 1,2-oxazine **53** furnished 3-allylpyrroloindoline **54**, thereby illustrating the utility of this strategy for the synthesis of both oxazines and pyrroloindolines.

Scheme 1.2.8. Nitrosoalkene [4+2]/Beckmann rearrangement approach via a 1,2-oxazine intermediate (Larionov and coworkers, 2012).



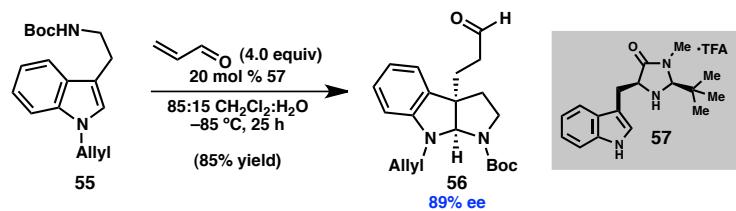
Conditions: *a.* 10 mol % $\text{CuOTf} \cdot 1/2\text{PhMe}$, 10 mol % (*S*)-DM-BINAP, 3.0 equiv Ag_2CO_3 , 3 Å MS, CH_2Cl_2 , -15°C , 48 h; *b.* 20 mol % PBr_3 , $\text{C}_6\text{H}_5\text{CF}_3$, 50°C , 16 h (79% yield).

1.3 DIRECT SYNTHESIS OF PYRROLOINDOLINES FROM INDOLES AND TRYPTAMINES

Over the past decade, direct asymmetric functionalization of 3-substituted indoles has emerged as a powerful approach for the efficient preparation of pyrroloindolines. In 2004, MacMillan and coworkers reported a chiral imidazolidinone salt (**57**)-catalyzed reaction between acrolein and tryptamine derivatives (**55**) to generate enantioenriched pyrroloindolines (**56**, Scheme 1.3.1).³³ The proposed mechanism invokes condensation of **57** with acrolein to generate a chiral iminium ion,³⁴ which undergoes a cascade conjugate

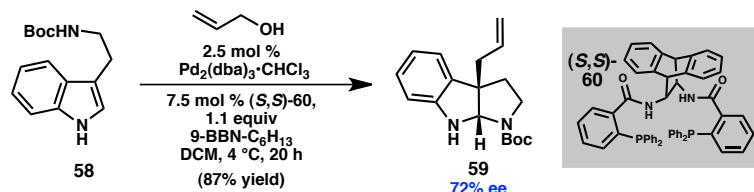
addition/cyclization reaction to deliver the pyrroloindoline framework. The appeal of this reaction is that it harnesses the intrinsic C3-nucleophilicity and provides direct access to pyrroloindolines from simple, readily available materials. The MacMillan group has utilized this organocatalytic reaction as the key step in the total syntheses of three structurally distinct pyrroloindoline alkaloids.³⁵

Scheme 1.3.1. First direct, enantioselective construction of pyrroloindolines from tryptamines (MacMillan and coworkers, 2004).



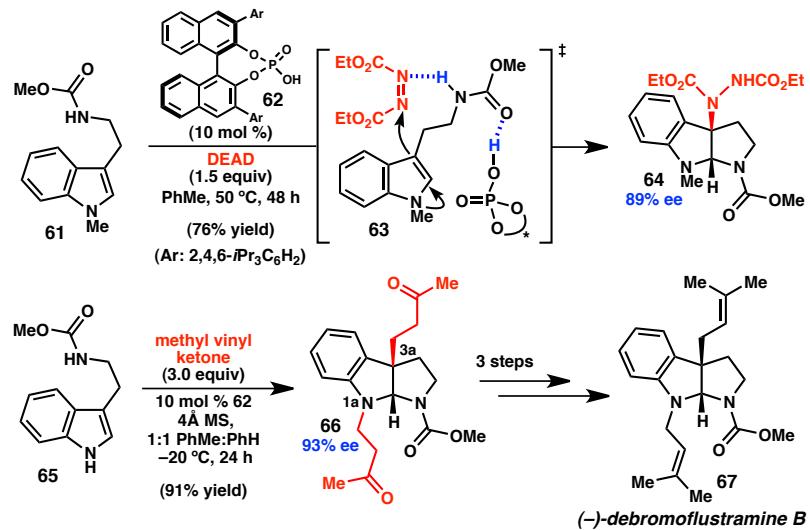
Since this initial disclosure by MacMillan and coworkers, several other methods for the direct synthesis of pyrroloindolines from tryptamine and tryptophan derivatives have been reported, and collectively these reactions provide access to a variety of enantioenriched pyrroloindoline products. In 2006, Trost and coworkers developed the first AAA reaction of allyl alcohol by including trialkylboranes as a stoichiometric promoter (Scheme 1.3.2).³⁶ Notably, the enantioselectivity of this AAA reaction is dependent on the choice of both ligand and borane, with the combination of 9-BBN- C_6H_{13} and anthracene-derived phosphine (S,S)-**60** proving optimal.

Scheme 1.3.2. Pd-catalyzed tandem allylic alkylation/cyclization reaction of tryptamines (Trost and Quancard, 2006).



Antilla and coworkers recently reported chiral phosphoric acid (**62**)-catalyzed C–N and C–C bond formation/cyclization reactions of tryptamine carbamates (**61** and **65**) (Scheme 1.3.3).³⁷ Preliminary NMR investigations suggest a mechanism involving electrophile activation by a hydrogen-bonding network (**66**). Specifically, it is proposed that coordination of the tryptamine carbonyl to the catalyst enhances the carbamate acidity and results in hydrogen bonding to the electrophile (either diethylazodicarboxylate (DEAD) or methyl vinyl ketone). This methodology constitutes the first catalytic, asymmetric construction of 3-aminopyrroloindolines, a motif present in several naturally occurring alkaloids.³⁸ Furthermore, the utility of the C–C bond forming variant has been demonstrated in the concise total synthesis of (–)-debromoflustramine B (**67**). Exposure of (*1H*)-tryptamine **65** to methyl vinyl ketone resulted in substitution at both C3a and N1a to give **66**, an intermediate primed for elaboration to **67**.

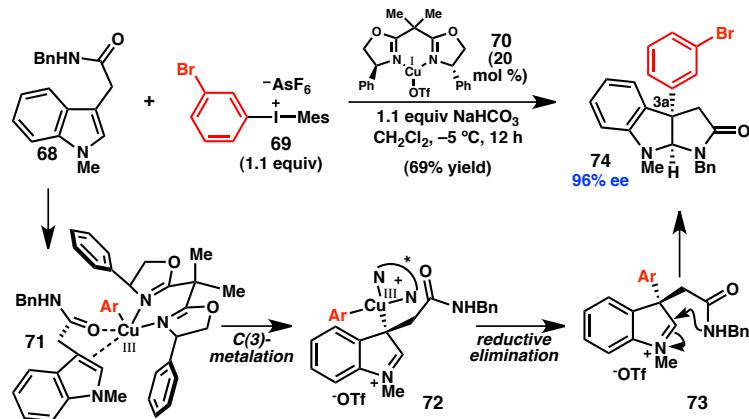
*Scheme 1.3.3. Phosphoric acid (**62**)-catalyzed preparation of two pyrroloindoline motifs (Antilla and Zhang, 2012).*



In a recent effort directed toward preparing 3a-arylpyrroloindolines, MacMillan and coworkers developed a Cu(I)-bioxazoline (**70**)-catalyzed intermolecular arylation

reaction of indole acetamides using aryliodonium salts (**69**, Scheme 1.3.4).^{39,40} The proposed mechanism involves electrophilic C3-metallation of the indole acetamide (**68**) by a Cu(III)-aryl complex, reductive elimination, and cyclization of the resultant 3-aryliindolene (**73**). The excellent enantioselectivity likely results from bidentate substrate coordination (**71**) involving both the carboxamide and C2-C3 π -bond of the indole. This reaction enables the direct preparation of highly enantioenriched derivatives including 3-(bromoaryl)pyrroloindolines (**74**) that contain a potential handle for advancement to the indolyl substitution patterns found in naturally occurring alkaloids such as asperazine (**5**, Figure 1.1.1).

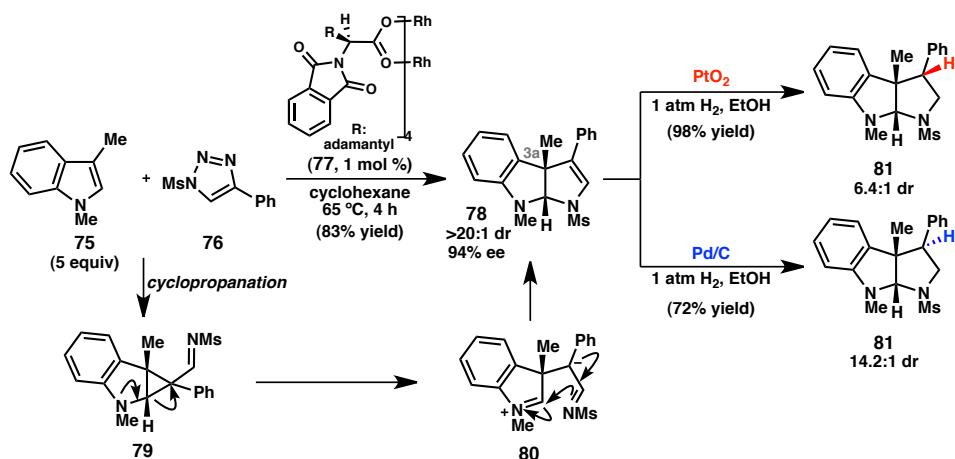
Scheme 1.3.4. Cu-catalyzed tandem arylation/cyclization reaction of indole acetamides (MacMillan and Zhu, 2012).



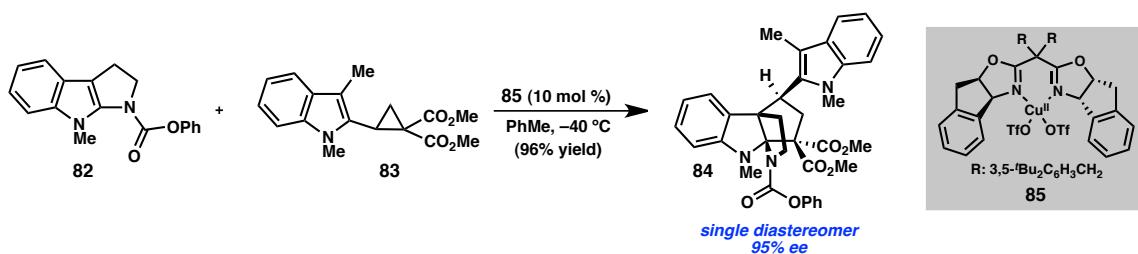
Although the majority of direct asymmetric approaches to pyrroloindolines employ tryptamine derivatives as substrates, several research groups have explored direct synthesis by formal (3 + 2) cycloaddition reactions. In 2010, we reported this approach involving the reaction of 3-substituted indoles and 2-amidoacrylates using (*R*)-BINOL·SnCl₄ as the catalyst to effect an enantiodetermining protonation (Chapter 2).⁴¹ More recently, Davies and Spangler developed a Rh₂(*S*-PTAD)₄ (**77**)-catalyzed reaction

between 3-substituted indoles (**75**) and 4-aryl-1-sulfonyl-1,2,3-triazoles (**76**) that affords didehydropyrroloindolines bearing either alkyl (**78**) or aryl substitution at C3a (Scheme 1.3.5).⁴² These products can be selectively reduced to afford either diastereomer of pyrroloindoline **81** depending on the catalyst. The formal cycloaddition to give **78** is proposed to occur by cyclopropanation of **75** with the Rh(II)-carbenoid generated in situ from **76**, followed by cyclopropane ring-opening and cyclization. An alternative formal (3 + 2) cycloaddition approach has also been disclosed by Xie, Tang, and coworkers involving the Cu(II)-bisoxazoline (**85**)-catalyzed reaction of achiral pyrroloindole **82** and donor-acceptor cyclopropane **83**, which furnishes aza-propellane **84** in excellent yield and stereoselectivity (Scheme 1.3.6).⁴³

Scheme 1.3.5. Rh-catalyzed formal (3 + 2) cycloaddition (Davies and Spangler, 2013).



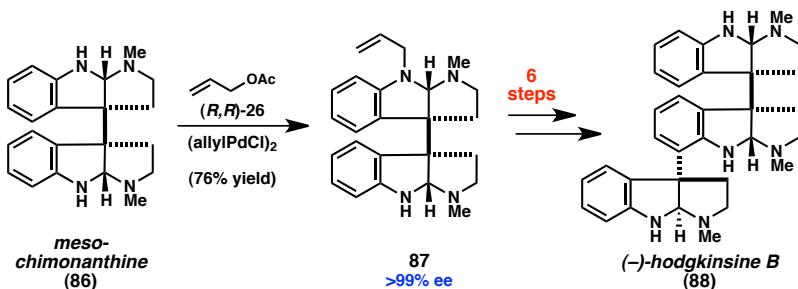
Scheme 1.3.6. Cu-catalyzed formal (3 + 2) cycloaddition (Xie, Tang, and coworkers, 2013).



1.4 SYNTHESIS OF ENANTIOENRICHED PYRROLOINDOLINES BY DESYMMETRIZATION

With the exception of the formal cycloaddition reaction, the approaches described above all rely on setting the absolute stereochemistry of the pyrroloindoline through a key, catalytic, C3-functionalization step. Alternatively, Willis and coworkers pursued a conceptually distinct strategy focused on the desymmetrization of readily accessible *meso*-chimonanthine to prepare the related trispyrroloindoline alkaloid (–)-hodgkinsine B (**88**, Scheme 1.4.1).⁴⁴ Specifically, a Pd-catalyzed *N*-allylation of the bispyrroloindoline **86** was achieved using the ligand (*R,R*)-**22**, a chiral phosphine developed by Trost and coworkers (Scheme 1.2.3).⁴⁵ This chemistry finds precedent in Taguchi and coworkers' Pd-catalyzed desymmetrization of *meso*-cyclohexane-1,2-diamides,⁴⁶ but the substrate complexity and enantioselectivity are unparalleled. In combination with the oxindole α -arylation methodology also developed by Willis and coworkers,⁴⁷ this allylic substitution-desymmetrization reaction enabled remarkably rapid access to **88**.

*Scheme 1.4.1. Allylic substitution-desymmetrization reaction en route to (–)-hodgkinsine B (**88**) (Willis and coworkers, 2011).*



Conditions: 1.2 equiv allyl acetate, 2.0 equiv Et₃N, 3.8 mol % (*R,R*)-**22**, (allylPdCl)₂ (2.5 mol % Pd), PhMe, 0 °C, 1.5 h.

1.5 CONCLUDING REMARKS

The complexity, biological activity, and remarkable variety exhibited by pyrroloindolines have long since established this family of natural products as an important target for total synthesis. In particular, the past two decades of research resulted in enantioselective, catalytic strategies for the synthesis of pyrroloindolines bearing C3a all-carbon quaternary stereocenters. Whereas early synthetic methods focused on the preparation of 3,3'-disubstituted oxindoles, more recent efforts have investigated the initial generation of 1,2-oxazines, desymmetrization, and direct functionalization of indoles. Despite the breadth of reported transformations, key restrictions exist regarding functional group incorporation and a highly divergent reaction remains elusive. These unmet challenges illustrate the demand for new methodologies and suggest that the pyrroloindoline scaffold will persist as an inspiration for future research in organic synthesis.

1.6 NOTES AND REFERENCES

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