Chapter 1

An Introduction to Tryptophan

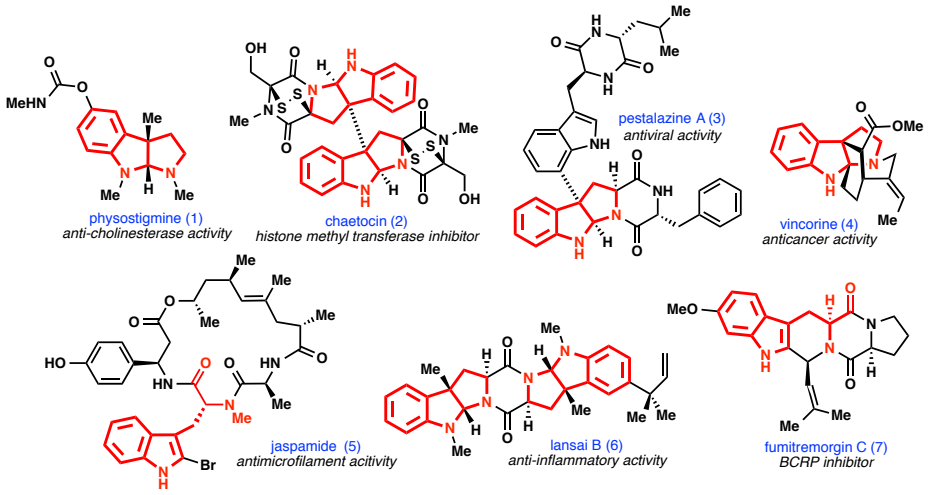
1.1 INTRODUCTION

Tryptophan and unnatural tryptophan derivatives are important building blocks in the total synthesis of natural products, as well as for the development of new drugs,[1] biological probes,[2] and chiral small molecule catalysts.[3] The central tryptophan motif can be found within numerous biologically active natural products, either explicitly or implicitly, some of which are shown in **Figure 1.1**. Furthermore, the utilization of functionalized tryptophans for the study of complex biological systems has served as an important strategy for studying protein conformational dynamics as well as elucidating key protein interactions, such as the identification of a critical cation–π interaction of the nicotinic acetylcholine receptor.[2c]

Biosynthetically, these key amino acids serve as the basis for another fascinating class of natural products, the pyrroloindoline alkaloids.[4] This family comprises a large class of compounds characterized by their unique indoline fused pyrrolidine core (**Figure**

1.1). These compounds have been shown to exhibit a broad array of biological activity across a range of cell lines that is intricately related to their broad structural diversity. Given their promising medicinal relevance, these products have inspired innovative work on new synthetic methodologies to access the central pyrroloindoline framework that have culminated in the total synthesis of a number of these challenging natural products.[5]

Figure 1.1. *Trytophan and cyclotryptophan natural products*



Together, these molecules have served as topics of intense interest from synthetic chemists and chemical biologists alike. The following introductory chapter serves to briefly summarize and highlight modern synthetic strategies and tactics to access unnatural tryptophan derivatives as well as pyrroloindoline alkaloids with selected examples in total synthesis.

1.2 SYNTHESIS OF TRYPTOPHAN DERIVATIVES

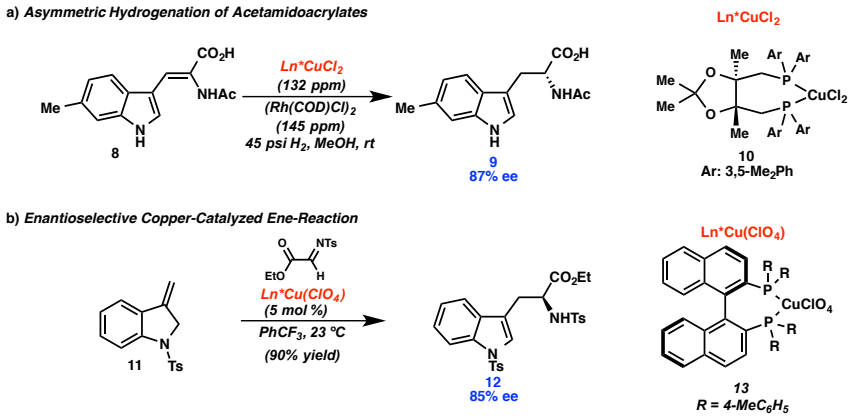
Due to their pervasiveness across many fields, the development of new methods to access enantioenriched tryptophan derivatives represents an important endeavor in synthetic chemistry.[1,2,3] This is particularly true due the inherent challenges associated

with selective backbone functionalization of the indole nucleus, making simple derivatization of natural (*L*)-tryptophan largely untenable. As a result, a range of methods for the preparation of enantioenriched unnatural tryptophans, including auxiliary controlled, enantiospecific, and enantioselective methods, have been reported.[6]

Surprisingly, to date, there exist relatively few convergent and enantioselective syntheses of tryptophan derivatives lacking β-substitution. Perhaps the most common method to access unnatural amino acids is through the asymmetric hydrogenation of dehydroamino acids. In 1980, Townsend and co-workers demonstrated that subjection of 6-methyl dehydrotryptophan to $[Rh(COD)Cl]_2$, copper-phosphine complex **10**, and 45 psi of hydrogen gas gave 6-methyl tryptophan (**9**) in high enantiomeric excess (**Scheme 1.1**, **a**).[7] Subsequent work on asymmetric hydrogenation has further streamlined this process to provide excellent ee's at low Rh-catalyst loadings, making it an efficient choice in many instances. Still, the preparation of the dehydroamino acids, often from the corresponding carboxyaldehyde, can sometimes require a laborious synthetic undertaking.

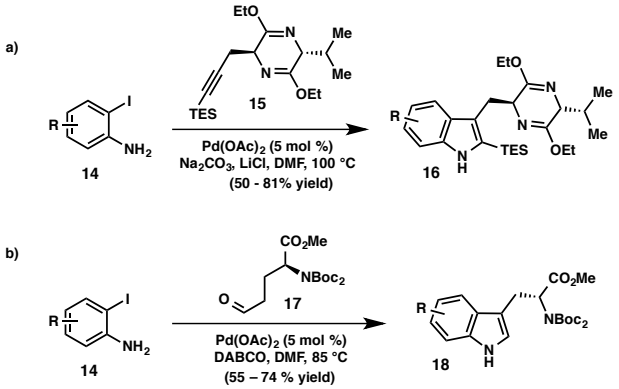
An alternative enantioselective method was described by Leckta and co-workers in 1998. By employing 5 mol % of copper-BINAP catalyst **13,** tosylindoline **11** can undergo an enantioselective imino-ene reaction to furnish tosyl tryptophan derivative **12** in 90% yield and 85% ee (**Scheme 1.1**, **b**).[8] While this method offers access to enantioenriched products, strict substrate requirements limit the generality of this approach and thus this method has largely not been broadly adopted for tryptophan synthesis.

Scheme 1.1. *Enantioselective methods for the synthesis of unnatural tryptophans*



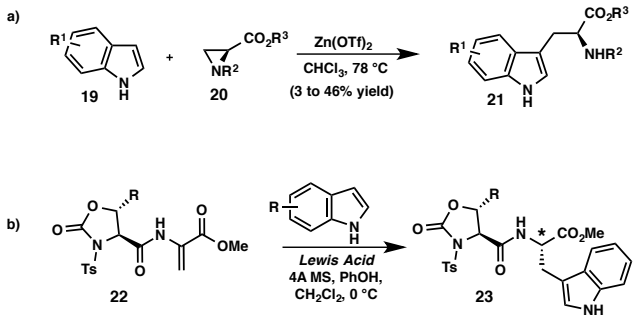
Given the dearth of catalytic, enantioselective methods reported to date, alternative strategies are also commonly employed, including enantiospecific and auxiliary-controlled methods. One such enantiospecific approach utilizes *ortho*-iodoanlines (**14**) in conjunction with an amino-acid derived coupling partner (**Scheme 1.2**, **a**).[9] In 1999, Cook and co-workers reported the Pd(0)-catalyzed heteroannulation (Larock indole synthesis) of *o*-iodoaniline with Schöllkpf-auxiliary derived triethylsilyl alkyne **15**. Utilizing Larock's originally reported conditions, functionalized indoles containing the amino acid moiety masked as a bis-imidate are efficiently synthesized (**16**). These products can be readily advanced to the parent amino acid through sequential acid-mediated hydrolysis followed by saponification. A complementary approach to the Larock indole synthesis was reported by Jia and Zhu in 2005, utilizing an aldehyde coupling partner (**17**) in place of a disubstituted alkyne (**Scheme 1.2**, **b**).[10] Operating through the intermediacy of the aldimine, Pd-mediated heteroannulation affords 2-unsubstituted tryptophans in moderate to good yield. Importantly, this method requires the formation of reactive aliphatic aldehyde intermediates and therefore necessitates protection of the amine as an imide.

Scheme 1.2. *Enantiospecific methods for the synthesis of unnatural tryptophans*



Lewis-acid mediated coupling strategies have also been employed for tryptophan synthesis from enantiopure starting materials. In 1989, Sato and Kozikowski reported a $Zn(OTf)_2$-mediated stereospecific opening of enantiopure aziridines to directly provide functionalized tryptophans, albeit in modest yields (**Scheme 1.3**, **a**). Subsequent work by Bennani[11] and Isobe[12] have illustrated that improved yields of this process may be achieved by utilizing scandium-based Lewis acids. An alternative, auxiliary-based approach has also been developed by Gentilucci and coworkers, employing oxazolidinone-based acetamidoacrylates with a variety of Lewis-acids to effect 1,4-addition of an indole nucleophile (**Scheme 1.3**, **b**).[13] Using this approach, moderate diastereoselectivities are achieved depending on the indole nucleophile and Lewis acid employed.

Scheme 1.3. *Enantiospecific and auxiliary based approaches for the synthesis of unnatural tryptophans*



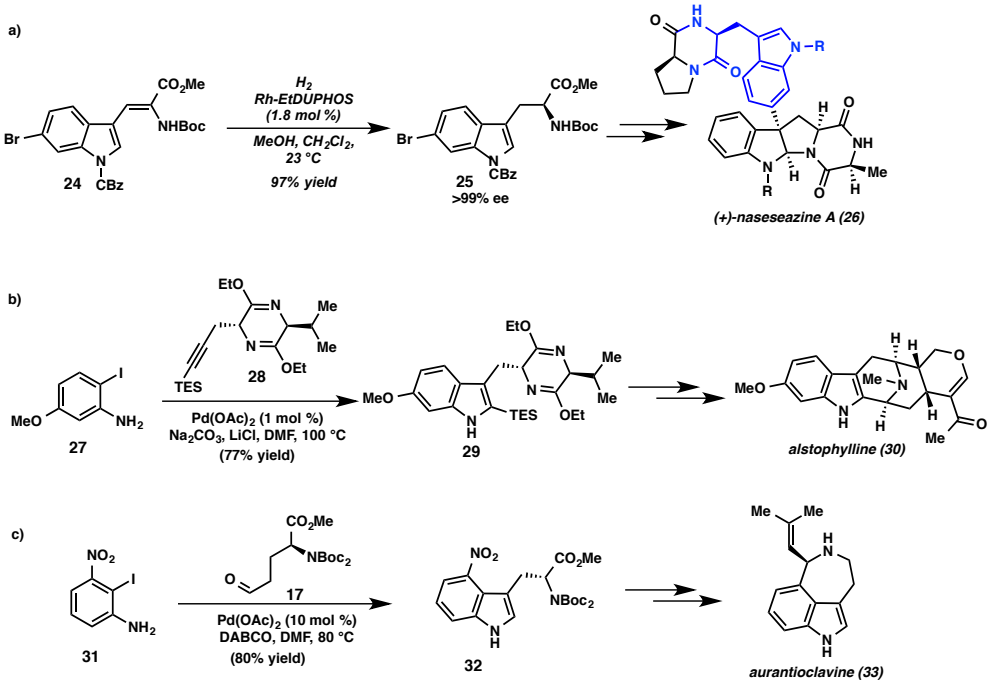
1.3 TRYPTOPHAN DERIVATIVES IN TOTAL SYNTHESIS

As highlighted above, the tryptophan motif is prevalent in many natural product scaffolds and it is therefore unsurprising that the methods outlined previously have been widely adopted in total synthesis. In most instances, the assembly of a requisite tryptophan moiety occurs at an early stage of the synthesis, and is subsequently functionalized or appended to more complex fragments in order to complete the total synthesis. Far fewer examples exist in the literature of late-stage tryptophan synthesis, a likely consequence of limitations in the existing methodology in functional group tolerance.

For example, **Scheme 1.4** illustrates the preparation of three unnatural tryptophans. In their synthesis of the (+)-naseseazines, Movassaghi and Kim utilize a highly selective Rh-EtDUPHOS catalyzed asymmetric hydrogenation in order to prepare 6-bromotryptophan **25** for elaboration to the northern diketopiperazine of (+)-naseseazine A (**26**).[14] This hydrogenation is not only high yielding and enantioselective, it occurs in the presence of other potentially reactive groups such as a CBz protecting group and the

aryl bromide. Cook and co-workers have also utilized their methodology in their total synthesis of the complex polycyclic alkaloid alstophylline (**Scheme 1.4**, **b**). Employing a Larock indole synthesis on 300-gram scale with only 1 mol % $Pd(OAc)_2$, aniline **27** is readily advanced to 6-methoxytryptophan *en route* to the natural product.[15] Similarly, Jia and co-workers have utilized their Pd-catalyzed aldehyde-aniline coupling to synthesize 4-nitrotrytophan derivative **32**, which is then advanced to the natural product aurantioclavine (**33**).[16]

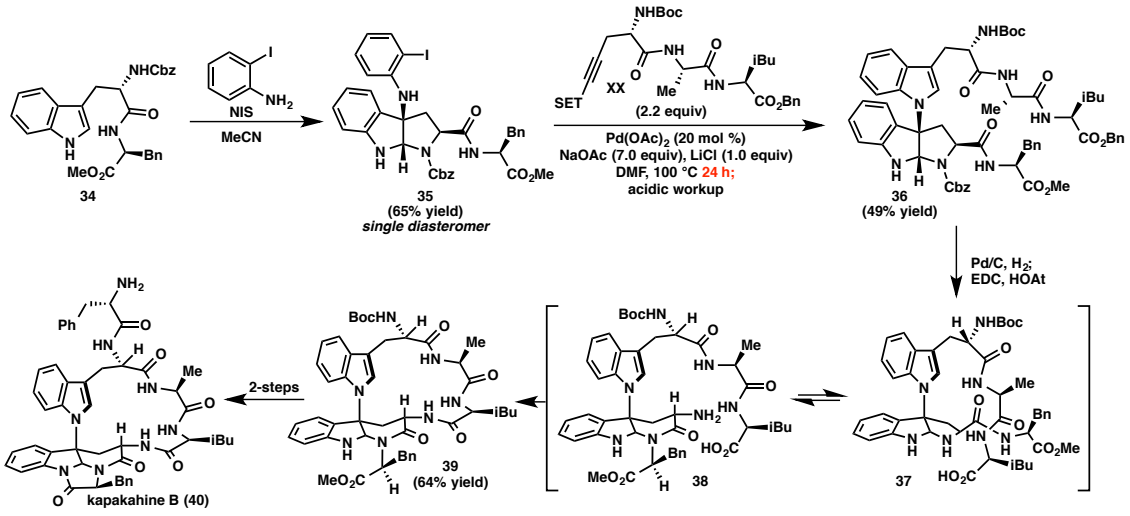
Scheme 1.4. *Tryptophan in total synthesis*



Although early-stage tryptophan synthesis is the most common, several remarkable examples of late-stage tryptophan assembly via Larock indolization have been reported in the literature. In 2009 Baran and co-workers reported the total synthesis of kapakahine B, utilizing a Larock indole synthesis to assemble the key tryptophan motif.[17] Beginning with tryptophan-derived peptide **24**, subjection to *o*-iodoaniline and NIS provided pyrroloindoline **35** as a single diastereomer. Under palladium catalysis,

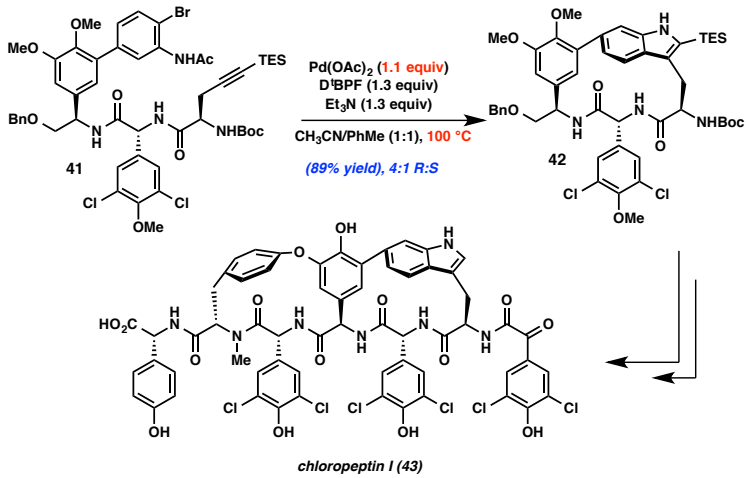
iodoaniline **35** underwent a Larock indole synthesis with a serine-derived derived alkyne in a moderate 49% yield. Debenzylation and concomitant Cbz deprotection furnished pyrroloindoline **37**, which existed in equilibrium with α-carboline **38**. Addition of EDC and HOAt resulted in facile and selective macrocycle formation from α-carboline **38**, providing the product in 64% yield. The synthesis of kapakahine B was completed in a further two-steps. This elegant synthesis, which assembles the key tryptophan moiety in an exceptionally complex setting, illustrates both the power of the Larock indole synthesis, but also its limitations – the key step requires upwards of 20 mol % catalyst for prolonged reaction times (24 h) in order to achieve two productive turnovers.

Scheme 1.5. *Baran's synthesis of kapakahine B*



An equally impressive Larock indole synthesis was used as the key step in Boger's fabulous synthesis of the chloropeptins (**Scheme 1.6**).[18] Utilizing an intramolecular macrocyclization strategy, treatment with 1.1 equiv $Pd(OAc)_2$ in the presence of 1,1'-di-tertbutylphosphinoferrocene in a mixed solvent system provided 89% yield of indolization product **42** in favor of the desired atropisomer.

Scheme 1.6. *Boger's late stage tryptophan synthesis*

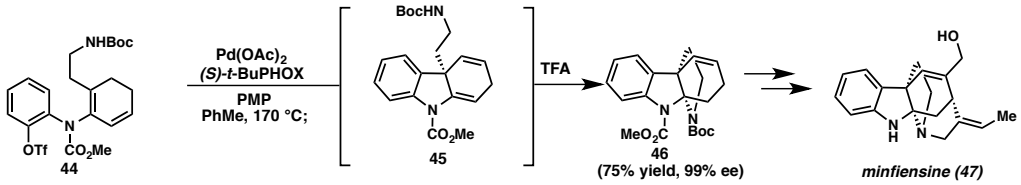


1.4 STRATEGIES FOR THE SYNTHESIS OF PYRROLOINDOLINES

The abundance of pyrroloindoline natural products and the breadth of structural diversity, coupled intricately with their biological activities, has sparked a tremendous interest from the synthetic community, both in methodology develop and in total synthesis.[5] Due to intense interest in this area of research, the structure, activity, and synthesis of pyrroloindolines has been reviewed in detail.[19]

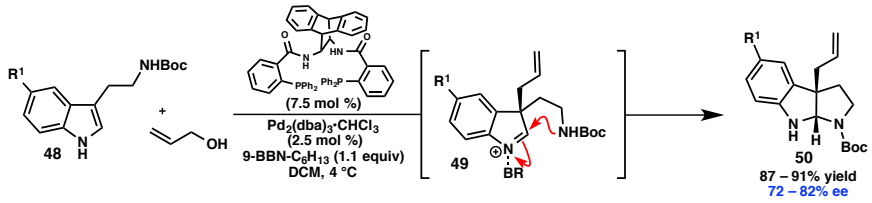
From a strategic standpoint, there are numerous disconnections to arrive at the pyrroloindoline motif. Instrumental in enabling the enantioselective synthesis of pyrroloindolines, however, has been the adoption of chiral transition metal complexes. One such approach is exemplified in work by Overman and co-workers on the enantioselective, intramolecular Heck cyclization (**Scheme 1.7**).[20] Treatment of aryl triflate **44** in the presence $Pd(OAc)_2$, (*S*)-^{t}BuPHOX, and pentamethylpiperidine as base resulted in clean Heck cyclization to provide 1,3-cyclohexadiene intermediate **45**. Immediate quenching with TFA then effected cyclization of the pendant amine, thereby providing the pyrroloindoline framework (**46**) in 75% overall yield and 99% ee.

Scheme 1.7. *Overman's Heck strategy to access pyrroloindolines*



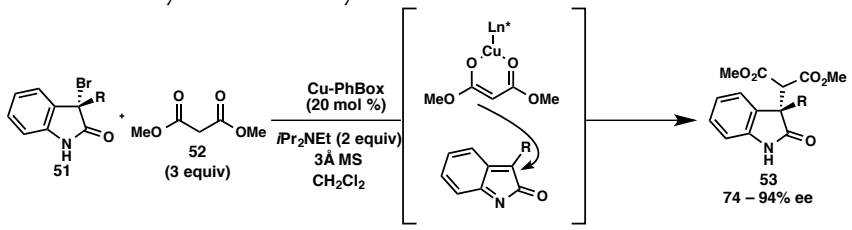
A mechanistically distinct approach using a Pd-catalyst was reported by Trost in 2006, utilizing allyl alcohols in conjunction with trialkylborates to effect C3-allylation in high yields and good enantioselectivities (**Scheme 1.8**).[21] The reaction is presumed to occur *via* an electrophilic, chiral Pd-π-allyl complex, thus providing high enantiofacial bias of the prochiral electrophile. This reaction, which provides the pyrroloindoline directly from a corresponding tryptamine, follows up previous work from the Trost lab on the asymmetric allylic alkylation of oxindole nucleophiles, the products of which can also be elaborated to the pyrroloindoline motif *via* reductive functionalization.[22]

Scheme 1.8. *Trost's transition metal strategy to access pyrroloindolines*



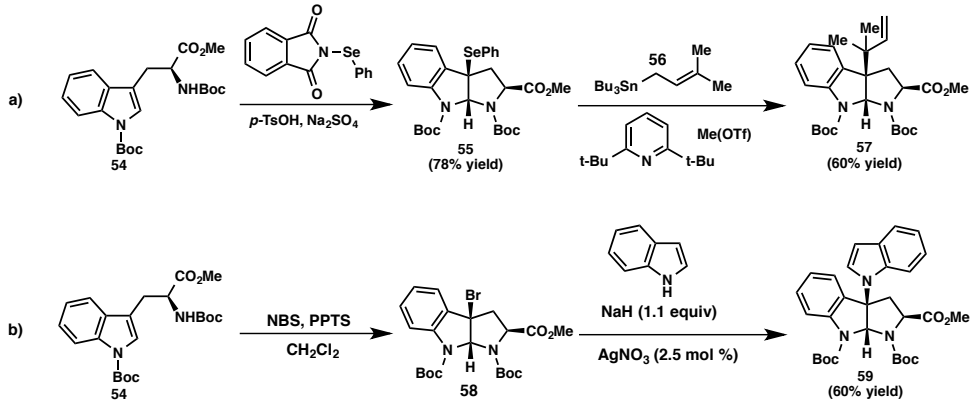
The application of a chiral Pd-π-allyl complex constitutes a chiral electrophile strategy to access pyrroloindolines. Alternatively, a chiral nucleophile strategy can be employed as reported by Stoltz in 2009.[23] Utilizing a CuPhBOX complex in the presence of excess base, dimethylmalonate **52** can be efficiently alkylated in excellent yields and enantioselectivities to afford functionalized oxindole products (**Scheme 1.9**). Reductive elaboration of these oxindole products affords the pyrroloindoline scaffolds in high ee.

Scheme 1.9. *Stoltz's asymmetric alkylation of oxindoles*



Perhaps one of the most widely adopted strategies to date is that of C3-oxidative functionalization *via* an electrophilic heteroatom. This versatile approach has been utilized extensively on tryptamine and tryptophan scaffolds, and occurs through direct C3-functionalization followed by cyclization of a pendant nucleophile onto the resulting iminium ion. The C3-substituent can often act as a leaving group, enabling subsequent functionalization in a highly selective manner. Two such examples are illustrated in **Scheme 1.10**. An early report by Danishefsky and co-workers illustrated the ability of electrophilic selenation to enable the highly diastereoselective selenocyclization of Boc-tryptophan derivative **54** in 78% yield.[24] Subsequent activation with MeOTf in the presence of a prenylstannane reagent provides reverse prenylated pyrroloindoline **57** in 60% yield.

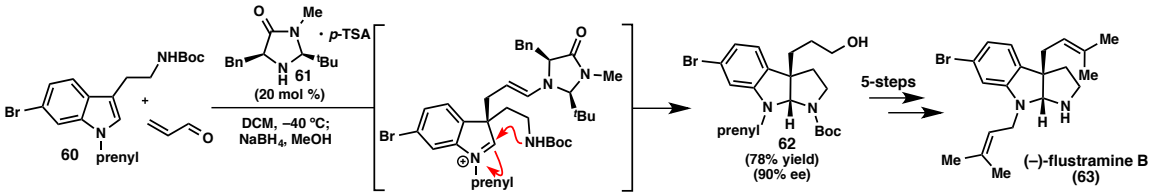
Scheme 1.10. *C3-functionalization/cyclization to access pyrroloindolines*



This strategy is applicable with a range of electrophiles. As shown in scheme **1.10**, addition of *N*-bromosuccinimide and pyridinium *p*-toluensulfonate to tryptophan **54** results in clean formation of bromopyrroloindoline **58**. Subsequent treatment with excess base and catalytic $AgNO_3$ results in stereoretentive substitution by an indole nucleophile. Extension of this strategy to other electrophilic atom sources as well as a range of enantioselective variants have been reported.[25]

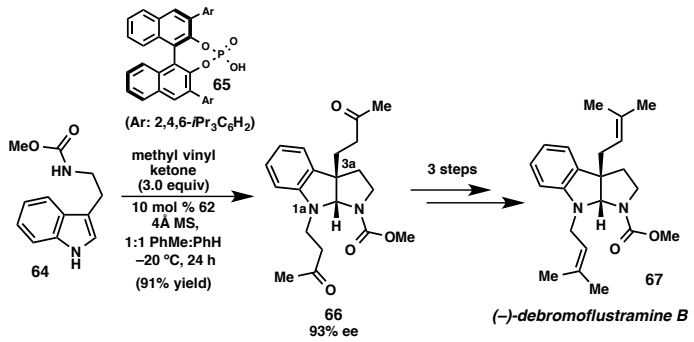
In contrast to heteroatom based electrophiles, carbon-based electrophiles can also be utilized with great success. In 2004, MacMillan and coworkers illustrated the success of this strategy *via* iminium activation. Utilizing imidazolinone catalyst **61** with acrolein as an electrophile, a highly enantioselective preparation of C3-alkylated pyrroloindolines was achieved (**Scheme 1.11**).[26]

Scheme 1.11. *MacMillan's organocatalyzed pyrroloindoline synthesis*



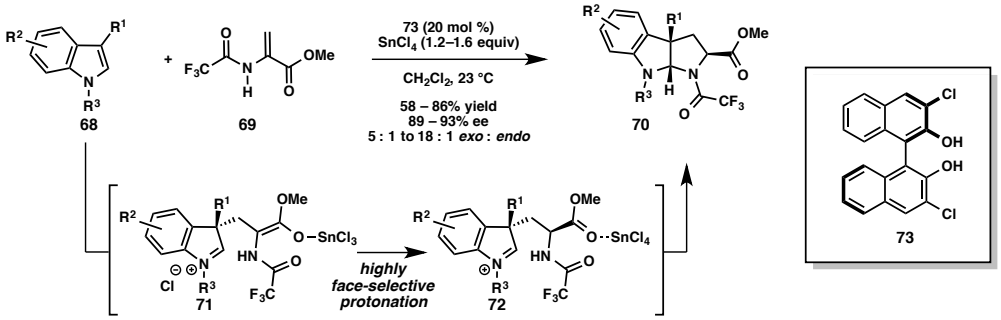
Activation of Michael acceptors can also be realized utilizing chiral Brønsted acids, such as *(R)*-TRIP (**Scheme 1.12**). As demonstrated by Antilla and co-workers, addition of catalytic *(R)*-TRIP phosphoric acid **65** to an excess of methyl vinyl ketone resulted in a highly enantioselective, double conjugate addition to provide pyrroloindoline **66**, which was readily advanced to the natural product (–)-debromoflustramine B in an additional three steps.[27]

Scheme 1.12. *Antilla's organocatalyzed pyrroloindoline synthesis*



Distinct from the two reactions shown above, Reisman and co-workers reported a highly enantioselective, formal (3 + 2) cycloaddition reaction between 3-substituted indoles and acetamidoacrylates (**Scheme 1.13**).[28] Employing stoichiometric $SnCl_4$ and catalytic (*R*)-BINOL, which together presumably generate a Lewis-acid assisted Brønsted acid, pyrroloindolines **70** are convergently synthesized in a single step from simple starting materials. It is proposed that this reaction proceeds *via* a highly face-selective protonation reaction, which resolves two diastereomeric conjugate addition complexes (**71**–**72**). From a synthetic standpoint, a key distinction of this method compared to others is that the pendant amine nucleophile resides on the electrophilic coupling partner, rather than on the nucleophile.

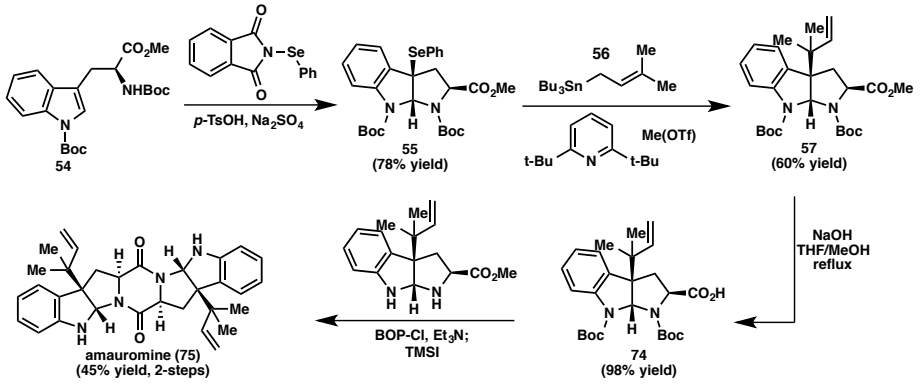
Scheme 1.13. *Reisman's formal (3+2) cycloaddition to access pyrroloindlines*



1.5 PYRROLOINDOLINES IN TOTAL SYNTHESIS

Given the enormous body of research dedicated to the total synthesis of pyrroloindolines, only a small sampling of total syntheses will be presented in the section below. One of the first successful examples employing a diastereoselective pyrroloindoline synthesis comes from the Danishefsky lab (**Scheme 1.14**).[24] Beginning with Boc protected tryptophan **54**, they were able to effect a selenation/cyclization sequence to furnish *exo*-pyrroloindoline **55** as a 9:1 diastereomeric mixture. Activation of the phenyl selenide with MeOTf and exposure to prenyl stannane **56**, provided the reverse prenyl adduct in 60% yield. Saponification of the methyl ester, peptide coupling with the free amine, and successive diketopiperazine formation provided amauromine in only four-steps from tryptophan **54**.

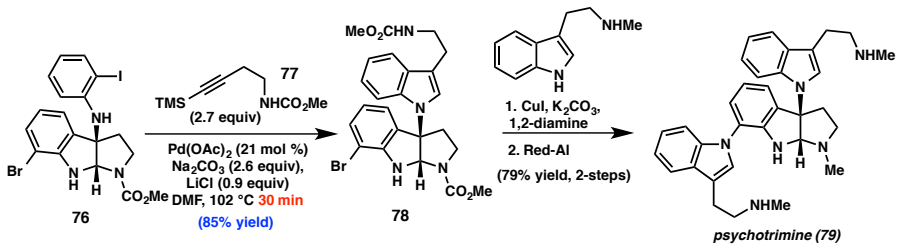
Scheme 1.14. *Danishefsky's synthesis of amauromine*



In 2008, Baran and co-workers demonstrated the diastereoselective cyclization of tryptamines with nitrogen-based electrophiles.[29] Beginning with tryptamine, treatment with the unique combination of *N*-iodosuccinimide, 2-iodoaniline, and Et_3N at –45°C results in an electrophilic, C3-amination of the tryptamine to afford pyrroloindoline **76**. Under palladium catalysis, iodoaniline **76** underwent a Larock indole synthesis with

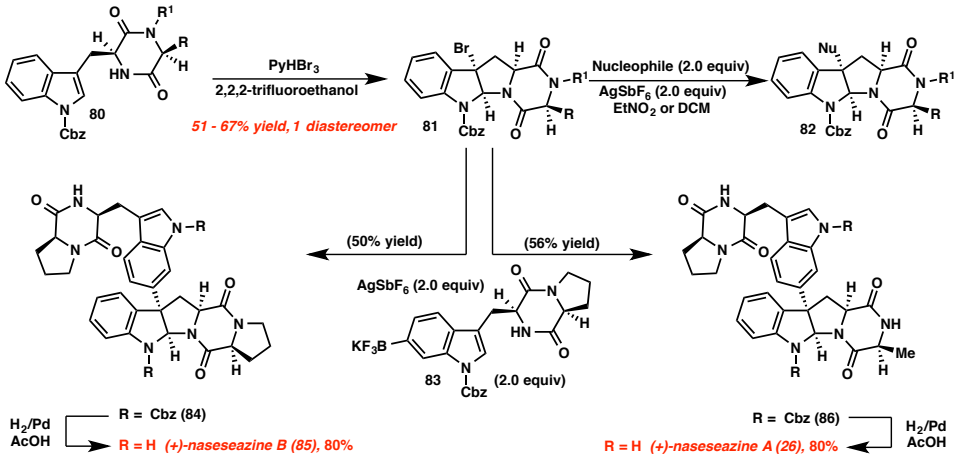
alkyne **77** in excellent yield. C–N bond formation, followed by treatment with Red-Al provided the natural product psychotrimine (**79**) in excellent overall yield.

Scheme 1.15. *Baran's synthesis of psychotrimine*



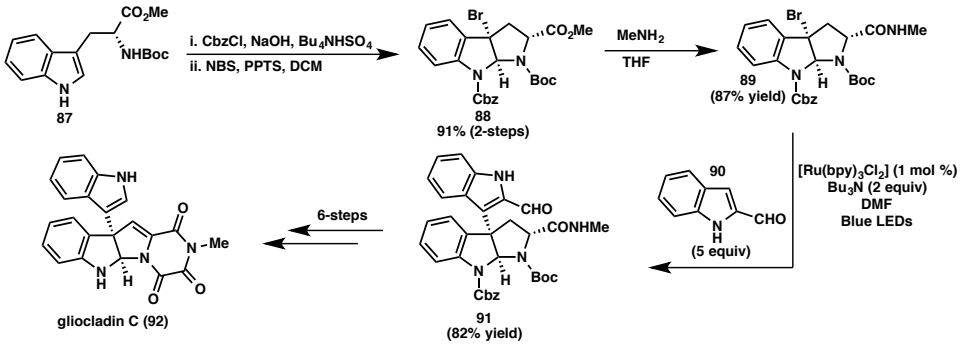
In 2011, Movassaghi and Kim reported a general strategy for the synthesis of 3-arylpyrroloindolines *via* a two-step bromocyclization/Friedel-Crafts sequence of tryptophan-derived diketopiperazines (**Scheme 1.16**).[14] Treatment of protected diketopiperazine **80** with $PyHBr_3$ in 2,2,2-trifluoroethanol effected an oxidative cyclization to form C3-bromopyrrolodinoline **81** in moderate yield and as a single diastereomer. In a subsequent step, addition of superstoichiometric silver salts resulted in halide abstraction to form a benzylic cation, which is then readily trapped in a stereoretentive fashion with excess nucleophile (**82**). Using this strategy, a variety of C3-substituted pyrroloindolines are readily prepared, accomodating C3-allyl, aryl, and hetereoaryl substitution. Although a number of arenes react to form a mixture of positional isomers during the Friedel-Crafts step in this reaction, the corresponding potassium trifluoroborate salts can be used to adequately restore regioselectivity. Using this method, the authors advanced bromotetracycle **81** to 3-arylpyrroloindolines **84** and **86** in 50 and 56% yield, respectively, utilizing an excess of functionalized potassium trifluoroborate salt **83**, derived from 6-bromotryptophan. Subsequent global deprotection provided (+)-naseseazines A and B in 80% yield and 9-steps longest linear sequence.

Scheme 1.16. *Movassaghi's synthesis of (+)-naseseazines A and B*



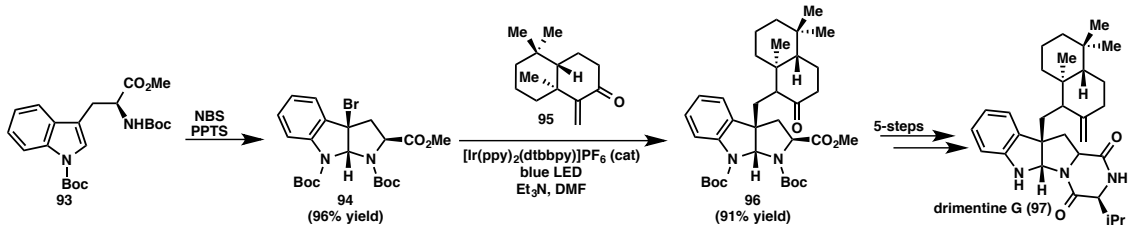
A similar approach was adopted by Stephenson and co-workers in their synthesis of gliocladin C using photoredox catalysis.[30] Following an oxidative cyclization of protected tryptophan **87**, the bromopyrroloindoline underwent amidation to furnish carboximide **89**. Subsequent exposure to $[Ru(bpy)_3Cl_2]$ and visible light generated a tertiary benzylic radical, which was trapped with five equivalents of indole **90** to form the desired C3–C3' aryl linkage. Notably, C2 substitution of the indole nucleophile is imperative to achieve the desired regioselectivity in the transformation. Additional elaboration to the natural product was accomplished in six-steps.

Scheme 1.17. *Stephenson's synthesis of gliocladin C*



An intermediate bromopyrroloindoline **94**, formed *via* the oxidative bromocyclization of tryptophan, was also utilized in Li's synthesis of drimentine G.[31] Employing a photoredox strategy similar to Stephenson's, generation of a tertiary benzylic radical followed by conjugate addition into enone **95** provided complex pyrroloindoine **96** in excellent yield. An additional five-steps is subsequently required to construct the diketopiperazine moiety and effect deoxygenation to provide the natural product.

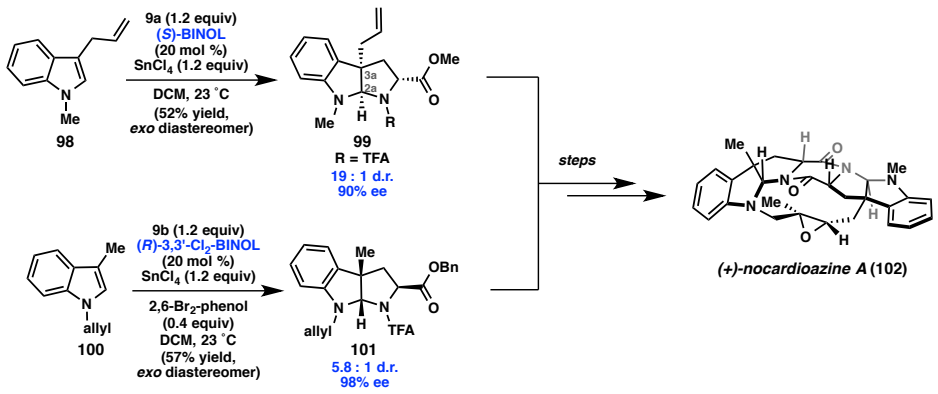
Scheme 1.18. *Li's synthesis of drimentine G*



In 2014, Reisman and co-workers reported a concise total synthesis of the complex macrocyclic bispyrroloindoline (+)-nocardioazine A (**102**) utilizing their previously reported $SnCl_4$•BINOL catalyzed formal (3 + 2) cycloaddition.[32] Importantly, this complex natural product contains two pyrroloindoline units, each of *opposite stereochemical configuration* at the 5/5-ring junction, making an excellent case for convergent asymmetric synthesis. To this end, 3-allyl-*N*-methylindole (**98**) was subjected to the previously optimized reaction conditions to afford pyrroloindoline **99** in 52% yield, 19:1 dr, and 90% ee. Simultaneously, treatment of 3-methyl-*N*-allylindole (**100**) under newly optimized conditions provided pyrroloindoline **101** in 57% yield, 5.8 : 1 dr, and 98% ee. Subsequent functionalization of each fragment followed by coupling and

cyclocondensation to prepare the diketopiperazine assembles the natural product in short order.

Scheme 1.19. *Reisman's synthesis of nocardioazine A*



1.6 CONCLUSIONS

These interesting scaffolds still serve as fascinating motivations for new synthetic methodologies and the basis for novel chemistry in total synthesis. Although much work has been done, the implementation and actualization of new synthetic strategies to meet unmet challenges will clearly be of interest in the coming times.

1.7 NOTES AND REFERENCES

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