CHAPTER 1

Natural Products and Pharmaceuticals as Inspiration for the Development of Enantioselective Catalysis[†]

1.1 INTRODUCTION

Biologically active natural products and pharmaceuticals often contain particularly challenging structural features and functionalities in terms of synthesis. Perhaps the greatest difficulties are those caused by issues of stereochemistry. A useful strategy for synthesizing such molecules is to devise methods of bond formation that provide opportunities for using enantioselective catalysis. In using this tactic, the desire for a particular target structure ultimately drives the development of catalytic methods. New enantioselective catalytic methods contribute to a greater fundamental understanding of how bonds can be constructed and lead to valuable synthetic technologies that are useful for a variety of applications. The lack of methods available for installing functionalities or structural motifs during chemical synthesis can at first be frustrating. However,

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[†] This review was written in collaboration with Justin T. Mohr and a similar version has been published. See: Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323–332.

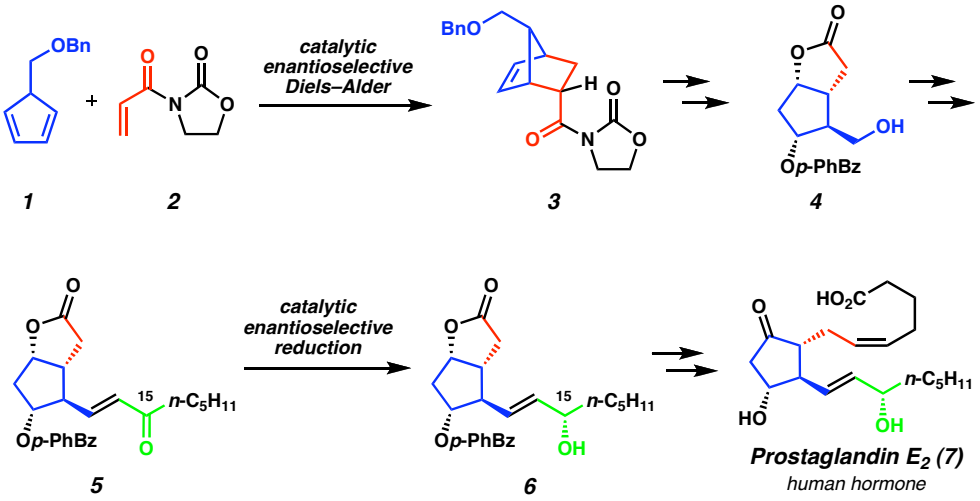
retrosynthetic analysis,[1] a way of viewing the target molecule as a series of structurally simpler precursors, can greatly aid in planning how to generate a valuable chemical substance. Despite this, difficulties in preparing materials enriched in a particular enantiomer persist because of the limited number of catalytic enantioselective transformations available.[2] One fruitful strategy is to design a synthesis that depends on a bond-forming reaction for which there is no known enantioselective variant. This approach thus provides the impetus for developing novel transformations and leads to a greater understanding of methods of bond construction and catalysis. Herein, several recent examples of novel catalytic enantioselective transformations are described in order to illustrate the effectiveness of this strategy for preparing important structural motifs found in biologically active molecules. Each of these transformations has contributed not only an effective means of generating a particular target structure but also a useful new tool for a variety of applications in synthetic chemistry.

1.2 HISTORICAL OVERVIEW OF ENANTIOSELECTIVE METHODS

To provide an overview of established catalytic enantioselective methods that have been developed for total synthesis, several notable examples of enantioselective reactions in total synthesis are highlighted in Scheme 1.2.1 through Scheme 1.2.4. In each of these cases, the target molecules posed particular challenges that had yet to be solved by enantioselective catalysis. Although, in some instances (e.g., the Diels–Alder reaction, Scheme 1.2.1), the methods were developed before their first application in total synthesis, the demonstrated value of the transformation highlighted the need for enantioselective variants. Following the development of the [4 + 2] cycloaddition

reaction in the 1920s,[3] studies of this transformation elucidated several key facets of the stereochemical outcome of the reaction (e.g., the "endo rule," regioselectivity, and diastereoselectivity). These intrinsic stereochemical control elements proved useful when the Diels–Alder reaction was first featured in a total synthesis with Stork's stereocontrolled synthesis of cantharidin[4] in 1951. Subsequently, the thermal Diels–Alder reaction was used for several total syntheses, perhaps most famously in Woodward's landmark synthesis of reserpine.[5] Enantioselectivity in this transformation remained elusive, however, and perhaps was considered unattainable at the time.

Scheme 1.2.1. Enantioselective Diels–Alder cycloaddition and enantioselective ketone reduction en route to prostaglandins



One key practical improvement in the Diels–Alder reaction was the discovery that Lewis acids markedly increased the reaction rate.[6] Many laboratories sought to exploit this and to develop asymmetric versions of the Diels–Alder reaction catalyzed by chiral Lewis acids, culminating in a report of the first highly enantioselective catalytic Diels–

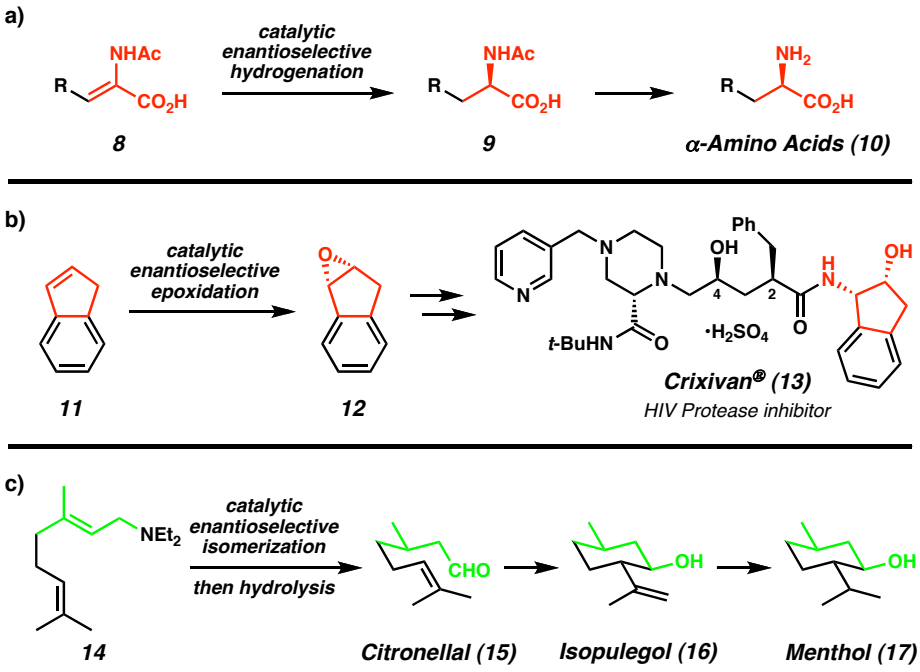
Alder reaction in 1979.[7] The interface between reaction development, study of the mechanism, and synthesis is readily apparent from the multitude of chiral Diels–Alder catalysts and accompanying enantioselective total syntheses that have been reported.[8] These successes validate the extensive efforts directed at realizing this important goal.

Other methods were developed to address more general problems in synthesis (e.g., synthesis of chiral alcohols by means of enantioselective ketone reduction, Scheme 1.2.1); however, the key structures are embedded in a variety of important natural products and pharmaceutical compounds. In the case of Corey's approach to the synthesis of prostaglandins[9] first reported in the 1960s, control of the configuration of the sidechain allylic alcohol at C(15) required stoichiometric chiral reducing agents until a solution to this long-standing problem was found in the 1980s.[10] Interestingly, the oxazaborolidine catalyst discovered in these explorations has had other varied applications in synthesis and catalysis,[8b,11] demonstrating the versatility of privileged molecular frameworks[12] for enantioselective catalysis.

The practical application of enantioselective catalysis is apparent in myriad industrial applications (e.g., Scheme 1.2.2), for which the limits of catalysis must be examined to minimize costs. Important industrial applications include the synthesis of chiral building blocks (e.g., amino acids[13] (**10**)), novel biologically active pharmaceuticals (e.g., Crixivan[14] (indinavir sulfate, **13**)), and commodity chemicals (cheap chemicals sold in bulk) with various important uses (e.g., menthol[15] (**17**)). Only the most efficient methods are feasible for large-scale industrial synthesis, and in many ways these protocols represent the pinnacle of modern enantioselective catalysis.[16] A viable commercial operation must account for more than simply effective asymmetric induction; factors

including turnover frequency, catalyst availability, catalyst recovery, catalyst toxicity, and feasible large-scale handling procedures must all be considered for industrial applications. These daunting challenges underscore the demand for increasingly efficient catalyst systems.

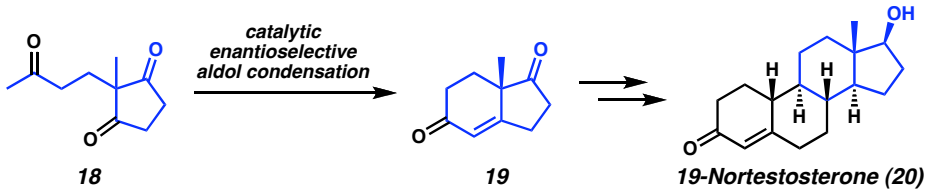
Scheme 1.2.2. a) Enantioselective enamide hydrogenation toward α-amino acids. b) Enantioselective alkene epoxidation toward Crixivan. c) Enantioselective isomerization of an allyl amine toward menthol



To maximize the usefulness of the stereochemistry attained by these key asymmetric transformations, subsequent diastereoselective reactions may be used to control the formation of many stereocenters based on a single enantioselective transformation (e.g., Scheme 1.2.3). The Hajos–Parrish ketone (**19**), first prepared in the context of steroid synthesis, has been used extensively in other synthetic efforts and has proved to be a

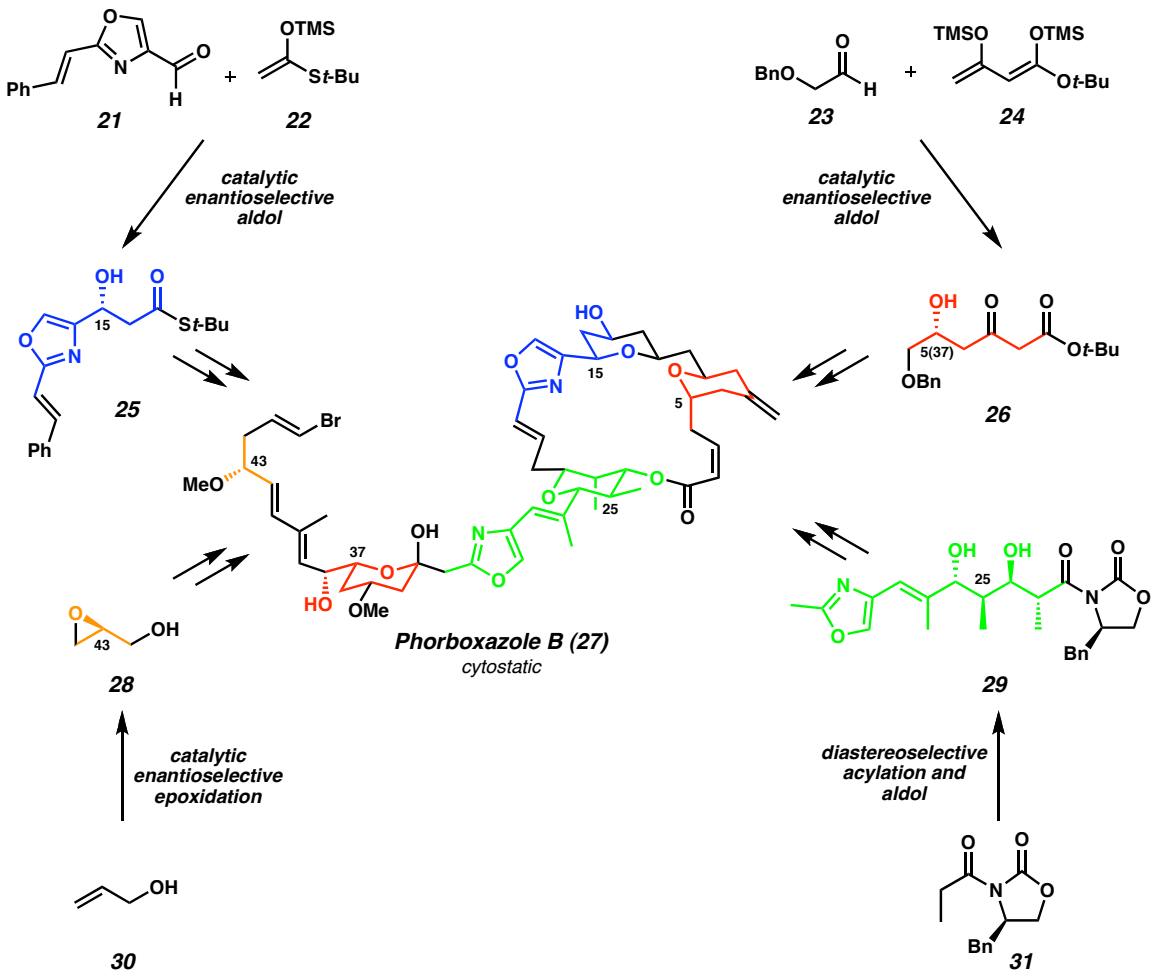
versatile chiral-pool starting material.[17] The amino acid catalyst system developed for this intramolecular aldol condensation provided a sound basis for the recent use of organic molecules as catalysts for a variety of enantioselective transformations (see subsection 1.3.4).

Scheme 1.2.3. Enantioselective intramolecular aldol condensation toward steroids



The use of several different enantioselective reactions to prepare enantioenriched fragments of complex molecules improves efficiency through convergency. The importance of this strategy is shown by the variety of extraordinarily complex polyketide natural products that have been prepared through asymmetric intermolecular aldol reactions (e.g., phorboxazole B[18] (**27**), Scheme 1.2.4). The challenging structure of these molecules has required the development of several related protocols to address the subtle differences in substitution patterns and functionality present in substrates, and, despite many successes, studies are ongoing.[19]

Scheme 1.2.4. Convergent application of various enantioselective methods toward the synthesis of phorboxazole B



1.3 RECENT DEVELOPMENTS IN ENANTIOSELECTIVE CATALYSIS

In this section, recent representative developments made by using this approach—that is, by using target structures to inspire the development of enantioselective catalysts—for the construction of biologically important target molecules are described. Most of these methods involve the formation of a carbon–carbon bond, the fundamental structure of organic molecules. These cases were selected to illustrate some of the latest developments in enantioselective catalysis for complex molecule synthesis. Special

attention has been given to reactions that address some of the most important challenges in synthetic chemistry today: increasing functional group tolerance, generating new carbocyclic and heterocyclic rings, and forming all-carbon quaternary stereocenters. The examples are also intended to show the important symbiosis between total synthesis and method development, and to show that improvements in one branch of synthetic chemistry have an impact on the others.

1.3.1 β-ENAMINO AMIDE HYDROGENATIONS — JANUVIA

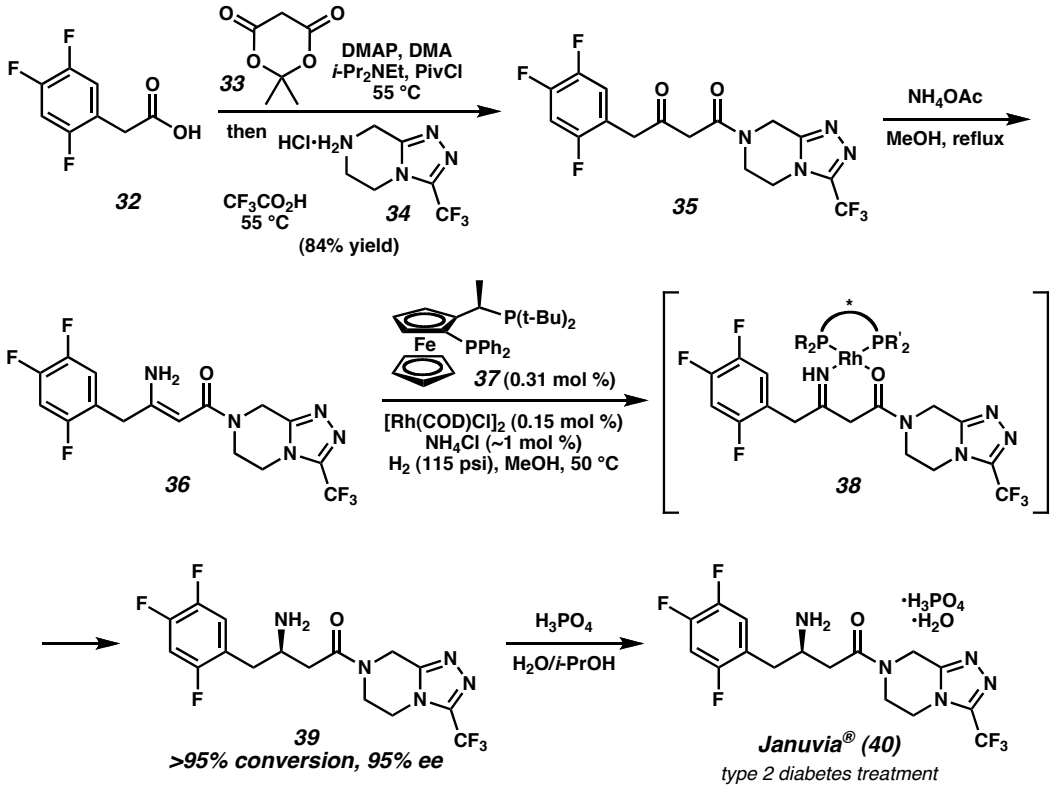
Catalytic enantioselective hydrogenation has become one of the most effective and powerful methods for the synthesis of chiral α-amino acids for numerous applications.[13] Over the past decade, the usefulness of the homologous building blocks, β-amino acids, in pharmaceutical, agrochemical, β-peptide, and natural substances has become evident, highlighting the need for a general and effective means for their preparation.[20] Undoubtedly, the implementation of a catalytic asymmetric hydrogenation of *N*-acyl-β-enamino esters seemed to be the most efficient pathway toward their synthesis, although initial investigations achieved poor selectivities.[21] Additional syntheses using the chiral pool, auxiliaries, and more recently the catalytic asymmetric generation of C–C and C–N bonds have been successful in satisfying the increased demand for β-amino acids.[20b] These valuable methods allow flexible strategies for the synthesis of a variety of analogs; however, most examples are limited by the requirement for further chemical manipulation that is often necessary to produce the functionality of the desired β-amino acids.

Despite initial difficulties, the asymmetric hydrogenation of *N*-acyl-β-enamino esters has been developed into a useful method over the past 15 years.[22] This fruitful endeavor has demonstrated that several transition metal and ligand combinations are competent for preparing *N*-acyl-β-amino acids with good-to-excellent enantioselectivities. A notable drawback to this strategy, however, is the requirement for the seemingly indispensable *N*-acyl group on the β-enamino esters; this group is needed for metal chelation, which improves reactivity and selectivity. The introduction of this moiety often produces enamine alkene isomers that can be difficult to separate, and, importantly, the individual isomers are typically hydrogenated with differing rates and selectivities. Moreover, these difficulties are magnified by the necessary removal of this group, a seemingly cumbersome artifact of an otherwise powerful strategy. Nonetheless, this advance has allowed a variety of β-amino acids to be prepared.[20b]

An innovative solution to this problem was demonstrated by a group at Merck en route to synthesizing Januvia (sitagliptin phosphate; **40**, Scheme 1.3.1), which has recently been approved by the U. S. Food and Drug Administration for the treatment of type 2 diabetes.[23] The optimal target contains an unfunctionalized β-amino amide. A strategy was sought to install this moiety directly by asymmetric hydrogenation of unsubstituted β-enamino ester and amide derivatives[24] (e.g., **36**). A traditional hydrogenation route for the production of amino acids is a proven, cost-effective method for the synthesis of chiral building blocks. The industrial infrastructure is already in place to realize this goal; however, in this case, the reduction of unprotected β-enamino acids was not effective with existing chiral catalysts. A crucial component in addressing such limitations was Merck's high-throughput screening facility, which allowed rapid

screening of catalyst structures and reaction conditions (an essential component for the success of any asymmetric catalytic process).[25] One potential complication for this hydrogenation strategy was avoided when it was observed that the preparation of the β-enamino ester and amide substrates (e.g., **35** → **36**) proceeded with complete selectivity for the Z-isomer, presumably owing to hydrogen bonding in the products.

Scheme 1.3.1. Enantioselective hydrogenation of a β-enamino amide toward the synthesis of Januvia



During the screening, a survey of transition metals and ligands revealed that rhodium complexes of the Josiphos (e.g., **37**, Scheme 1.3.1) family of ligands efficiently catalyze the hydrogenation of a variety of substrates to give high yields with excellent enantioselectivities. The remarkable functional-group tolerance of this catalyst allowed

the strategic implementation of this asymmetric transformation as the penultimate step of the synthesis, thereby maximizing the usefulness of the process and materials. Thus, phenylacetic acid derivative **32** was converted into β-ketoamide **35** in a one-pot procedure via acylation of Meldrum's acid (**33**), followed by treatment with triazole salt **34**.[26] Exposure to ammonium acetate converted this into β-enamino amide **36** as a single enamine isomer. Hydrogenation of amide **36** in the presence of 0.30 mol % of rhodium(I) and ligand **37** provided β-amino amide **39** in >95% conversion and 95% enantiomeric excess. Subsequent recrystallization and salt formation with phosphoric acid gave Januvia (**40**). Efforts to optimize efficiency and examine the mechanism of the asymmetric process revealed that reactivity and selectivity were dependent on the pH of the reaction solution.[27] It was found that ~1 mol % of a mild acid (i.e., ammonium chloride) was essential for the reaction to proceed reproducibly on a large scale. In addition, it was observed that hydrogenation of a related substrate under identical conditions with a deuterium gas atmosphere resulted in deuterium incorporation at the β-position only, suggesting that an imine is an intermediate (**38**) and that an enamine–imine tautomerization process plays an important part in the mechanism.[24] Interestingly, intermediates such as **38** have a striking similarity to asymmetric β-carbonyl hydrogenations pioneered by Noyori and co-workers.[28]

This example demonstrates the development of asymmetric catalysis into a state-of-the-art science through maximizing the efficiency by minimizing unnecessary functionality, by using atom economy, and by using extremely active catalysts. Moreover, the development of the catalyst system for the synthesis of Januvia exemplifies the continued need for subtly different catalysts to meet new synthetic

demands. Building on the experience obtained during the development of a highly efficient enamide reduction toward α-amino acids, such large-scale industrial synthesis of important β-amino acids has been a relatively rapid process.

1.3.2 $C(sp^3)$–$C(sp^3)$ CROSS-COUPLINGS — FLUVIRUCININE A_1

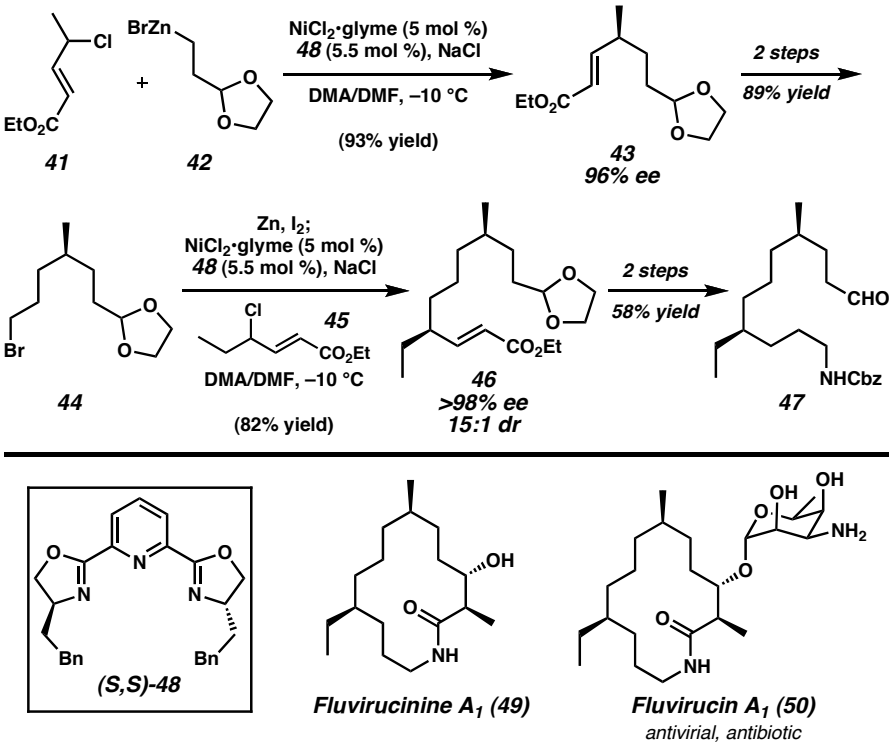
Transition metal-catalyzed cross-coupling reactions have been used extensively for constructing C–C bonds and, consequently, have had a substantial effect on the field of complex molecule synthesis.[29] The predominance of palladium and nickel catalysts in cross-coupling technologies and their extraordinary functional-group tolerance increases the efficiency of this process by allowing a large degree of functionalization before coupling. Moreover, the efficacy of this cross-coupling strategy for streamlining synthesis has allowed retrosynthetic analyses that had been thought impossible with standard, nonmetal reactions. Until recently, however, most cross-coupling methods involved $C(sp^2)$–$C(sp^2)$ or $C(sp^2)$–C(sp) centers, limiting the application potential. Two crucial issues associated with expanding the substrate scope to include $C(sp^3)$–$C(sp^3)$ couplings are the relatively low reactivity of alkyl halides toward oxidative addition and the propensity of σ-alkyl organometallic complexes to undergo rapid β-hydrogen elimination reactions.[30] Practical solutions to this problem were first presented by Suzuki and Knochel, followed more recently by Fu.[30b,31] In general, the reaction scope now encompasses a variety of primary and secondary halides and pseudohalides as the electrophilic component, with organoboranes, boronic acids, alkylmagnesium halides and alkylzinc halides as the nucleophilic component.[30b] Although perhaps not developed in the context of a particular target molecule, progress in these cross-coupling methods has

allowed retrosynthetic disconnections that were not practical previously. Asymmetric cross-coupling protocols could, in turn, allow the direct formation of remote stereocenters in relatively unfunctionalized molecules.

Early examples of catalytic asymmetric cross-coupling reactions involving $C(sp^3)$–$C(sp^2)$ centers were explored by Kumada and co-workers in the late 1970s and produced moderate enantioselectivities.[32] Despite these initial reports and the subsequent evolution of cross-coupling methods and asymmetric catalysis, a deficiency in the development of catalytic asymmetric methods for $C(sp^3)$–$C(sp^3)$ couplings existed until Fu and co-workers[33] reported an asymmetric Negishi coupling in 2005. Before this report, researchers in the Fu laboratory observed the proficiency of tridentate pybox ligands (e.g., **48**, Scheme 1.3.2) at enabling the room temperature nickel-catalyzed Negishi coupling of symmetric secondary alkyl bromides and iodides.[34] It was postulated that the tridentate nature of pybox ligands prevented the undesired β-hydrogen-elimination pathway, which would require a vacant coordination site. Reaction optimization facilitated the development of several asymmetric variations that generate challenging stereocenters applicable to complex molecule synthesis, as demonstrated in Fu's formal total synthesis of fluvirucinine A_1 (**49**), the aglycon of the macrolactam antibiotic fluvirucin A_1 (**50**).[35] A key nickel(II)-catalyzed asymmetric cross-coupling of racemic allylic chloride **41** and alkylzinc reagent **42** in the presence of (*S*,*S*)-**48** generated γ-disubstituted enone **43** in an excellent yield and 96% enantiomeric excess. Elaboration over two steps to a bromide (**44**), followed by conversion to the alkylzinc form and a second nickel(II)-catalyzed asymmetric Negishi cross-coupling with racemic allylic chloride **45**, provided the ester **46** in a good yield and with >98% enantiomeric excess

and a 15:1 ratio of diastereomers. A subsequent two-step conversion to the aldehyde **47** intersected Suh's synthesis of fluvirucinine A_1 (**49**).[36] This method exemplifies the efficiency of the $C(sp^3)$–$C(sp^3)$ cross-coupling and presents a creative solution to the particularly difficult challenge of remote stereochemical control.

Scheme 1.3.2 Enantioselective $C(sp^3)$–$C(sp^3)$ cross-couplings toward fluvirucinine A_1



At present, most examples of this technology require a stabilizing group adjacent to the site of the putative carbon-centered radical. Eliminating this condition would further improve the utility of this asymmetric cross-coupling method. In addition, stereogenic organometallic coupling partners (e.g., secondary alkylzinc reagents) have not yet been reported in this asymmetric transformation. A potential goal for this synthetic method would be the combination of a racemic secondary alkyl halide and a racemic secondary

alkylmetal reagent to form vicinal stereocenters along an alkyl chain with high levels of enantioselectivity and diastereoselectivity.

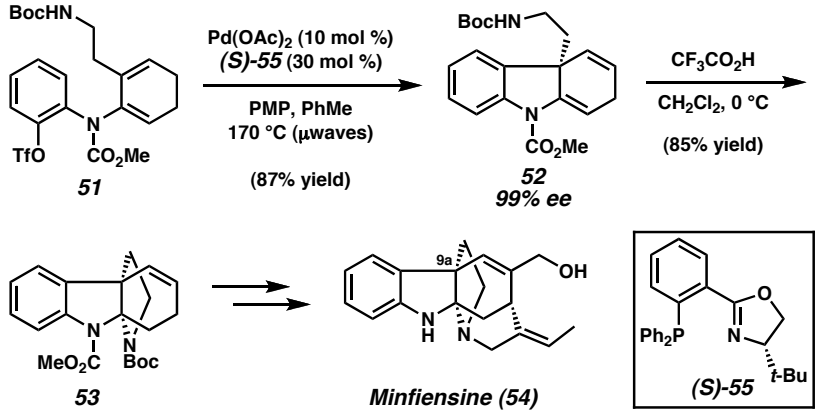
1.3.3 INTRAMOLECULAR HECK CYCLIZATIONS — MINFIENSINE

The enantioselective generation of all-carbon quaternary stereocenters is a considerable challenge for synthetic chemists.[37] As quaternary stereocenters are found in many natural product structures, convenient enantioselective methods for their formation would be useful. One such method is the Heck reaction,[38] in which a palladium(0) catalyst promotes the vinylation of an aryl halide, vinyl halide, or trifluoromethane sulfonate. The large body of literature on palladium catalysis and mechanisms,[29] as well as an ever-growing collection of chiral ligands for transition-metal catalysis, greatly increased the potential of using this method to carry out asymmetric catalysis. In addition, many synthetic endeavors using diastereoselective or nonstereoselective intramolecular Heck reactions have been reported,[39] increasing the significance of an enantioselective process. In 1989, the laboratories of Shibasaki[40] and Overman[41] independently reported the first variants of an intramolecular catalytic asymmetric Heck reaction. Initial levels of enantioselectivity were moderate; however, subsequent optimizations realized good-to-excellent selectivities in the generation of tertiary and all-carbon quaternary stereocenters.[42]

Indole alkaloids encompass a large number of natural and pharmaceutical substances with a wide range of biological activities.[43] The plant alkaloid minfiensine (**54**, Scheme 1.3.3) is a compelling example of the all-carbon quaternary stereocenter motif in biologically active natural products. Minfiensine and related alkaloids have been used in

traditional medicines and have promising anticancer activity.[44] The intriguing polycyclic structure and biological relevance of minfiensine prompted the Overman laboratory[45] to explore a catalytic enantioselective Heck reaction to generate the sole quaternary stereocenter at C(9a). It was discovered that the palladium-catalyzed intramolecular Heck reaction of dienyl aryl trifluoromethane sulfonate **51** in the presence of the phosphinooxazoline ligand (*S*)-**55** under microwave conditions produced indoline **52** in good yield and with 99% enantiomeric excess. Subsequent acid-promoted carbamate cyclization produced the tricyclic core of minfiensine (**53**), which was then converted to the natural product. The efficiency and selectivity of the catalytic asymmetric Heck reaction facilitated completion of the target, where the remaining stereocenters are derived from this initial transformation.

Scheme 1.3.3. Enantioselective intramolecular Heck reaction toward minfiensine



Despite numerous examples of the asymmetric Heck reaction in total synthesis,[42] there are several features that could be improved. Reactions typically require high temperatures and relatively high catalyst loadings, and the development of chiral ligands

that greatly increase the reactivity of the transition metal while maintaining an adequate asymmetric environment would be greatly beneficial.

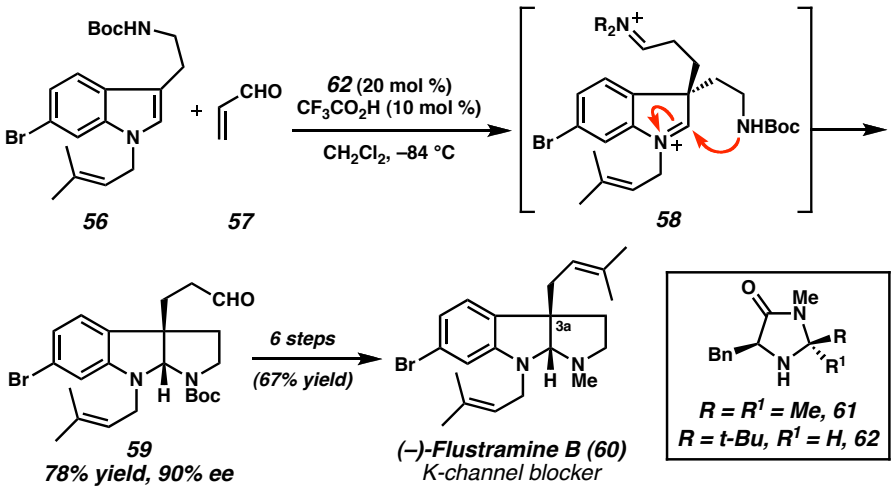
As most enantioselective Heck reactions use an sp^2-hybridized organohalide component, another frontier lies in the application of unactivated alkyl carbon electrophiles that have β-hydrogens in both intramolecular and intermolecular cases, an area currently in its infancy.[46]

1.3.4 INDOLE FRIEDEL–CRAFTS ALKYLATIONS — FLUSTRAMINE B

Numerous methods have been developed for the generation of substituted indoles;[47] however, enantioselective indole functionalization has been far less explored. To address the deficiencies in the indole functionalization literature, Jørgensen[48] and MacMillan[49] independently developed strategies for asymmetric Friedel–Crafts alkylation of conjugate acceptors with electron-rich heteroaromatics. MacMillan's method uses a secondary amine catalyst (**61**, Scheme 1.3.4) that facilitates the LUMO-lowering activation of α,β-unsaturated aldehydes for a variety of transformations.[50] Although imidazolidinone **61** was a sufficient catalyst for the Friedel–Crafts alkylation of pyrroles, generating good yields and excellent enantioselectivities,[49] application of less-activated indole substrates resulted in sluggish reactivity with considerably diminished selectivities.[51] Kinetic investigations of iminium-catalyzed reactions revealed that the overall reaction rate was influenced by the efficiency of formation for both the iminium ion and the C–C bond, prompting the development of a modified imidazolidinone catalyst (**62**). This refinement minimized the steric bulk around one face of the catalyst, thereby exposing the lone pair of electrons on the secondary amine nitrogen. This structural change translated into

increased reactivity that enabled the asymmetric Friedel–Crafts alkylation of a variety of indoles with good-to-excellent yields and very high enantioselectivities.[51]

Scheme 1.3.4. Enantioselective Friedel–Crafts alkylation toward flustramine B



Pyrroloindoline alkaloids are a family of polyindole alkaloids of diverse structural complexity and biological relevance.[52] Diastereoselective syntheses of the core of these compounds have focused on the control of the C(3a) all-carbon quaternary stereocenter as a key design element.[53] With a powerful and mild indole alkylation method in hand, MacMillan and co-workers[54] devised a cascade strategy for the catalytic asymmetric preparation of the C(3a) stereocenter and the pyrroloindoline core of the potassium-channel blocker (–)-flustramine B (**60**, Scheme 1.3.4) in one step. In this key transformation, tryptamine derivative **56** and 2-propenal (acrolein, **57**), in the presence of catalyst **62**, underwent the asymmetric Friedel–Crafts alkylation to provide iminium intermediate **58**. Subsequent carbamate cyclization and hydrolysis to regenerate the catalyst provided the core (**59**) with a good yield and 90% enantiomeric excess.

Importantly, this allowed completion of (–)-flustramine B (**60**) in just six steps and with good overall yield, highlighting the efficiency of this cascade approach. It is noteworthy that this strategy also has the potential to be applied to the synthesis of various polycyclic indolines such as the diazonamide family of cytotoxic alkaloids.[54] It is also interesting to note that both the intramolecular Heck reaction (see subsection 1.3.3) and the indole Friedel–Crafts alkylation can generate similar indoline structural motifs despite the markedly different bond-connecting strategies of these reactions. The success of these dissimilar strategies allows a great deal of flexibility in the planning of syntheses.

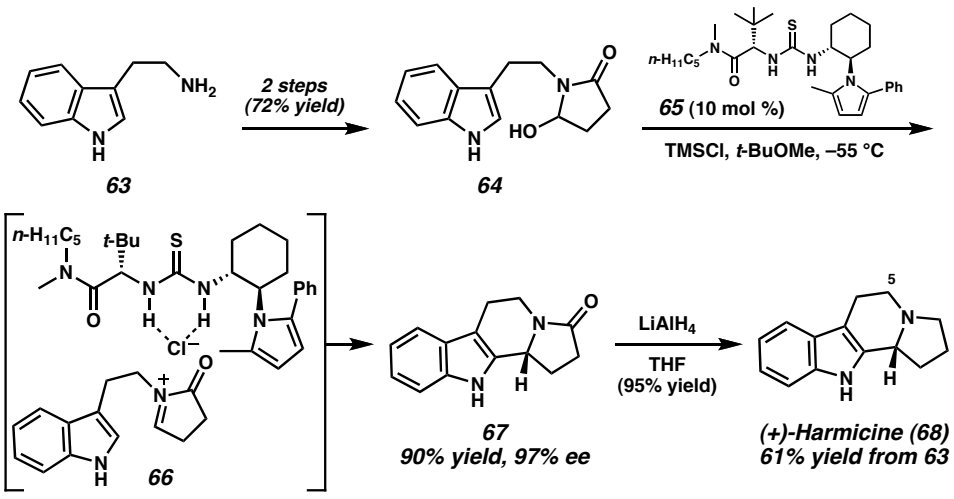
Iminium-activation methods with chiral amine catalysts have been successful for numerous transformations, but catalyst loading, turnover frequency, and excesses of certain reagents limit the large-scale industrial application of these methods. In addition, in some cases, the organic catalyst may be more difficult to remove from the reaction products than a metal catalyst. However, the typically air- and moisture-stable reaction conditions, low cost of some catalysts, and often metal-free conditions are attractive. The variety of asymmetric transformations (some proceeding through substantially different reaction pathways) that have been realized with chiral amine catalysts so far indicates a burgeoning field in which there are many useful enantioselective catalysts.

1.3.5 PICTET–SPENGLER CYCLIZATIONS — HARMICINE

Since Pictet and Spengler reported the intramolecular cyclization of an aromatic ring onto an iminium species in 1911,[55] this transformation has been of great use in the synthesis of many important alkaloid natural products.[56] Indeed, the need for asymmetric variants of this reaction was recognized, and several diastereoselective protocols have

been devised.[56] A common approach to diastereoselective Pictet–Spengler cyclization has been to use tryptophan derivatives to control the stereochemistry of the cyclization. However, using this type of technique for the synthesis of a natural product such as harmicine (**68**, Scheme 1.3.5), which is active against the disease leishmaniasis, necessitates the removal of the stereocontrol element at C(5), following the diastereoselective cyclization. Nonetheless, Allin and co-workers[57] proved this to be a viable method in 2007. This particular structure, however, highlighted a challenge for enantioselective catalysis and an opportunity to improve synthetic efficiency.

Scheme 1.3.5. Enantioselective Pictet–Spengler cyclization toward harmicine



When considering prospects for asymmetric induction, Jacobsen and Taylor considered activated *N*-acyl-iminium ions as a template and reasoned that a chiral thiourea derivative might be effective in promoting cyclization.[58] In practice, these Brønsted acids,[58] as well as other Brønsted acids investigated later by other groups,[59] proved to be excellent catalysts for enantioselective indole annulations with in situ-

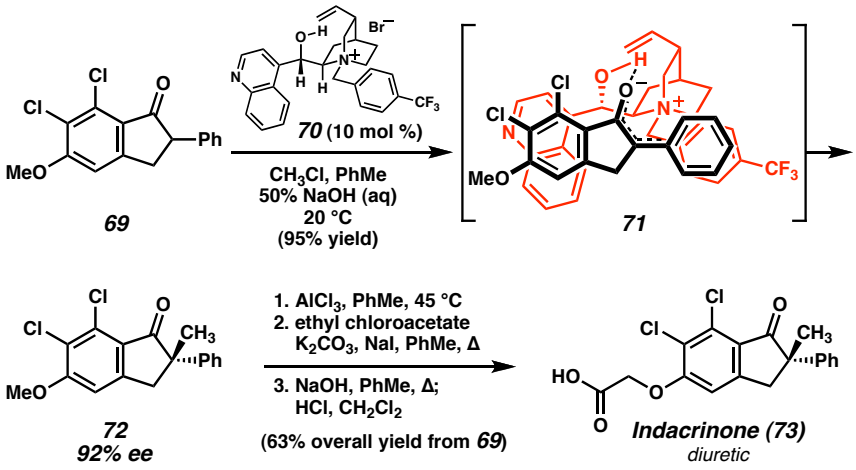
generated *N*-acyl-iminium species (e.g., **66**, Scheme 1.3.5). In later studies by Jacobsen and co-workers, it was found that hydroxylactams (e.g., **64**) are convenient precursors to *N*-acyl-iminium ions, which in turn enable access to various polycyclic structures.[60] Given this effective protocol, an efficient catalytic asymmetric synthesis of harmicine (**68**) was realized in four steps from tryptamine (**63**). Several mechanistic experiments have suggested that asymmetric induction is controlled by a complex of the Brønsted acid catalyst (**65**) and a chloride counterion closely associated with the iminium ion (e.g., **66**) that effectively blocks approach to one face of the electrophile, providing annulated products (e.g., **67**) with excellent enantiomeric excesses. This insight into the remarkable mechanism of this transformation has led to a related C–C bond-forming process using oxocarbenium ions.[61] Further exploitation of this unusual proposed catalyst–anion interaction could lead to a variety of other asymmetric addition reactions, such as intermolecular alkylation of *N*-acyl-iminium ions. In common with the history of the Diels–Alder reaction (see section 1.2), the exploration of the Pictet–Spengler cyclization has provided a useful method to access many heterocyclic structures embedded in alkaloid natural products using a classical reaction with well-established synthetic applications.

1.3.6 PHASE TRANSFER ALKYLATIONS — INDACRINONE

Enolate alkylations exemplify the fundamental usefulness of the carbonyl group for C–C bond formation. Strategies to induce asymmetry in these reactions have included chiral auxiliaries and chiral ligands, although few examples are catalytic. A particularly challenging class of product targets is all-carbon quaternary stereocenters adjacent to

carbonyl groups. One example of an important target bearing this motif is the diuretic drug candidate indacrinone (**73**, Scheme 1.3.6).[62] Given the lack of efficient methods for synthesizing this structure, researchers at Merck envisaged an enantioselective phase-transfer alkylation method based on a quaternary ammonium salt derived from a naturally occurring cinchona alkaloid (e.g., **70**). In the event, readily prepared indanone **69** was methylated, producing ketone **72** with 95% yield and 92% enantiomeric excess, and **72** was then converted to indacrinone (**73**) in three additional steps.

Scheme 1.3.6. Phase-transfer alkylation toward indacrinone



Although successful in achieving enantioselective enolate alkylation, the mechanism for this process seems to be complex;[63] however, enantiofacial selectivity in the alkylation event may be rationalized through the hypothetical transition state **71** (Scheme 1.3.6). Three key interactions are thought to control selectivity: a hydrogen bond between the enolate oxygen and the catalyst hydroxyl group, and two π-system stacking interactions between the four aromatic rings. Perhaps as a consequence of the complex

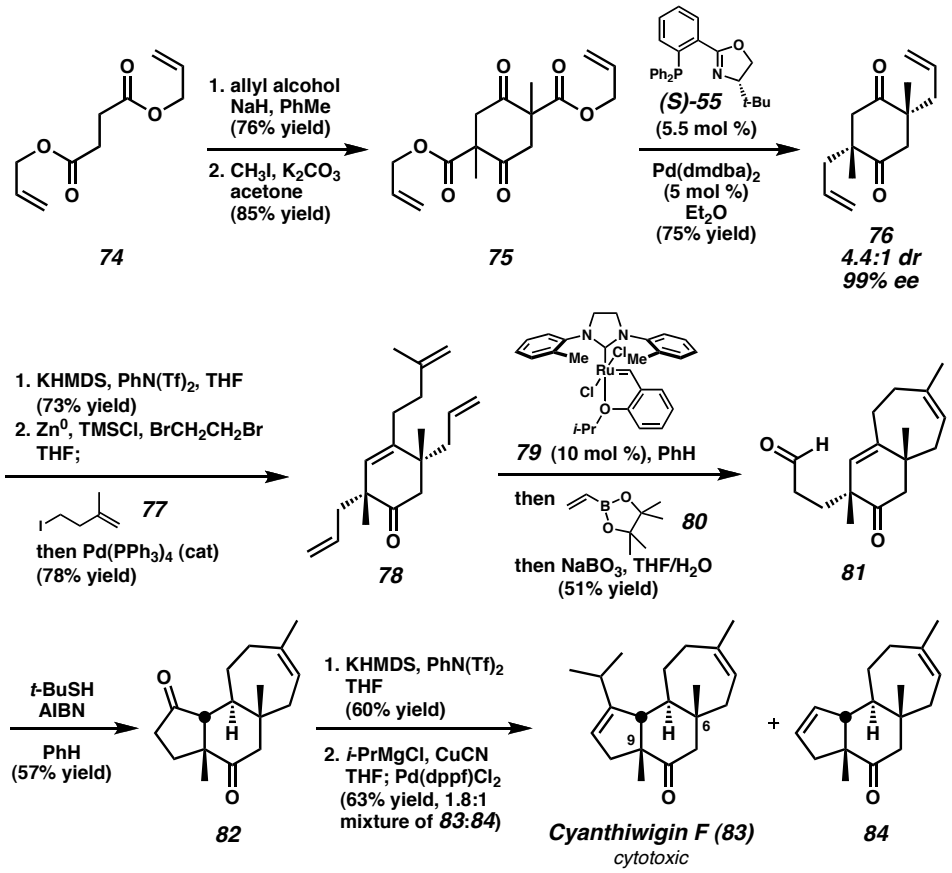
mechanism, the range of substrates for enolate alkylation is limited, and other solutions to this problem are still needed. However, these initial results have led to several related catalytic enantioselective reactions using cinchoninium salts or related organic ammonium complexes as catalysts.[64] The discovery of these useful catalysts has provided not only an alternative to related transformations using metal catalysts but also a means of accessing chiral environments that are simply not possible with metal-based catalysts. Moreover, eliminating metal waste materials is attractive from an industrial and environmental standpoint. Ultimately, the studies directed toward an enantioselective synthesis of indacrinone demonstrate the versatility of privileged catalysts developed for the synthesis of target molecules for a range of other applications.

1.3.7 Pd-CATALYZED ENOLATE ALKYLATION — CYANTHIWIGIN F

A recent case of enantioselective enolate alkylation is the synthesis of cyanthiwigin F (**83**, Scheme 1.3.7), a cytotoxic natural product from a sea sponge. The cyanthiwigin family is composed of more than 30 diterpenoids, most of which bear two quaternary stereocenters, at C(6) and C(9), and a syn relationship of the methyl groups in the central ring. These core stereochemical elements are a complicating factor for a convergent strategy that might seek to couple the five- and seven-membered ring portions and subsequently form the six-membered ring. To avoid this difficulty, Enquist and Stoltz chose instead to address these two central stereocenters at an early stage and append the five- and seven-membered rings to the assembled cyclohexane.[65] Accordingly, a synthetic strategy was devised that involved a one-pot double-enantioselective enolate alkylation reaction to form both quaternary stereocenters simultaneously. Although such

enantioselective alkylations have proved difficult, recent studies have identified palladium catalysts that might provide a solution to this problem and enable the synthesis of a variety of targets containing quaternary carbon stereocenters, including the cyanthiwigins.[66]

Scheme 1.3.7. Pd-catalyzed enolate alkylations toward cyanthiwigin F



The implementation of this retrosynthetic strategy began with a Claisen–Dieckmann sequence that converted diallyl succinate (**74**, Scheme 1.3.7) to bis(β-ketoester) **75** as a 1:1 mixture of racemic and meso diastereomers. On exposure to the catalyst derived from $Pd(dmdba)_2$ and phosphinooxazoline ligand (*S*)-**55**,[66] each stereoisomer of **75** was

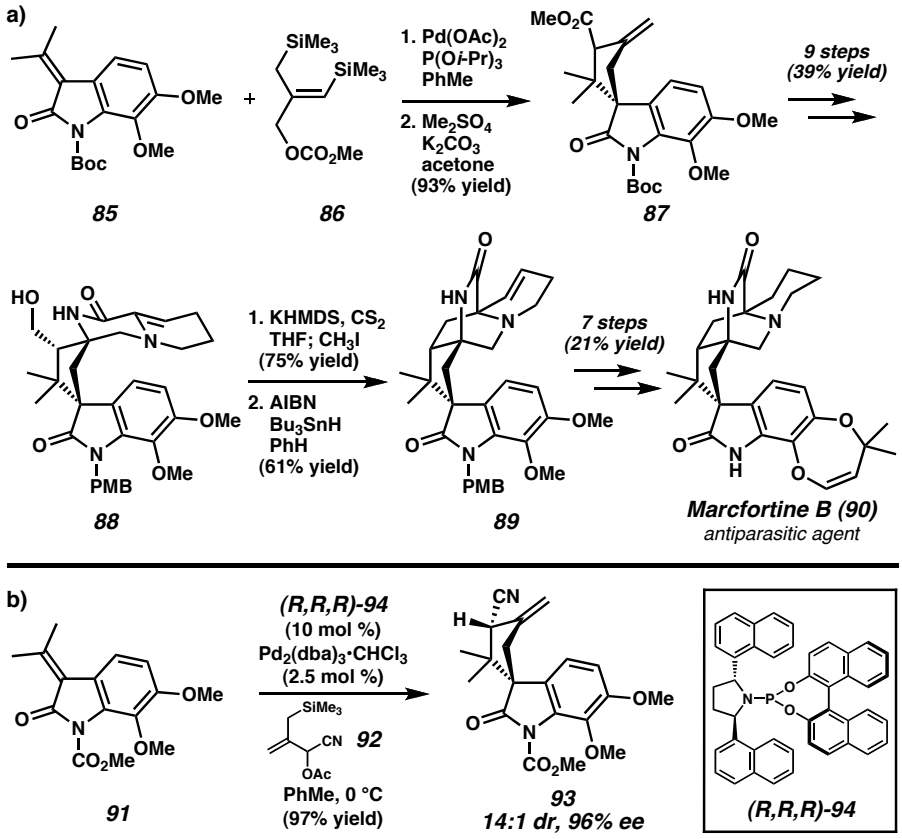
transformed to bis(allylated) ketone **76** with 75% yield and 99% enantiomeric excess as a 4.4:1 mixture of diastereomers. With both quaternary centers in place, elaboration of this stereochemically rich core structure to the natural product was achieved in six further steps. Enol triflate formation and Negishi coupling (**76** + **77** → **78**) preceded a tandem ring-closing metathesis–cross-metathesis sequence with Grubbs' ruthenium catalyst **79**.[67] Aldehyde–alkene radical cyclization generated the final ring of the cyanthiwigin core (**81** → **82**), and enol triflate formation and palladium-catalyzed cross-coupling formed (–)-cyanthiwigin F (**83**), together with reduction product **84**. Choosing to confront the difficult stereochemical elements of the cyanthiwigin structure at an early stage led to a direct synthetic route proceeding in nine steps from diallyl succinate. This strategy was made possible by the intriguing reaction mechanism of the enantioselective decarboxylative allylation, in which all three stereoisomers of bis(β-ketoester) **75** were converted to a specific stereoisomer of product (**76**) with high selectivity, through a stereoablative process.[68] In addition, of the nine steps required for the synthesis, seven form C–C bonds, and four form *multiple* C–C bonds. Directly addressing the carbon framework of the target molecule and the stereochemical challenges embedded within ultimately led to an efficient synthetic sequence for this important molecule.

Recently, the proposed chiral palladium enolate was shown to be intercepted by allyl or proton electrophiles.[66,69] Although the synthesis of cyanthiwigin F demonstrates the versatility of allyl moieties for further derivatization, the direct use of alternative electrophiles would provide a more general and direct method for transition metal-mediated enolate functionalization.[70]

1.3.8 TRIMETHYLENEMETHANE CYCLIZATIONS — MARCFORTINE B

Of the many fundamental approaches to the formation of five-membered rings from acyclic precursors, the [3 + 2] cycloaddition is among the most convergent strategies. A useful method of achieving such a cyclization is via a trimethylenemethane (TMM) intermediate.[71] This interesting non-Kekulé molecule was first prepared and studied through photolytic decomposition of a cyclic diazene precursor. However, the free diyl is prone to several undesired reaction pathways and does not lend itself to asymmetric catalysis. Despite this, intramolecular diyl-trapping reactions are valuable methods of cyclopentane formation.[71] Recognizing the synthetic utility of TMM, Trost and co-workers developed an array of 2-(trimethylsilyl)-2-propenyl acetate reagents that generate a metal•TMM complex when exposed to a palladium catalyst.[72] A recent application of this transformation in total synthesis is the approach to marcfortine B (**90**, Scheme 1.3.8a), a member of a family of antiparasitic agents.[73] The strategy used sought to forge the [2.2.2]bicycle via an intramolecular radical cyclization and install the spiro all-carbon quaternary stereocenter by the cycloaddition of oxindole **85** with TMM precursor **86**. In the event, an excellent yield was observed for the annulation reaction yielding spirooxindole **87** as a 1:1 mixture of diastereomers. Over the course of nine additional steps, spirocycle **87** was transformed into amide **88**. Preparation of the xanthate derivative of alcohol **88** allowed radical cyclization, generating the challenging [2.2.2]bicycle **89**. Seven further steps produced (±)-marcfortine B (**90**).

Scheme 1.3.8. a) Pd-catalyzed TMM-[3 + 2]-cycloaddition toward marcfortine B. b) Enantioselective TMM-cyclization



Although this strategy demonstrated several intriguing ring-forming reactions, an asymmetric synthesis of **90** would require an enantioselective variant of the key TMM-[3 + 2] cycloaddition, a goal that has remained elusive.[74] The first asymmetric palladium-catalyzed [3 + 2] cycloaddition with various bis(phosphine) ligands was reported by Ito and co-workers,[75] but with only moderate enantiomeric excess (up to 78%) and diastereomeric ratio (up to 4:1 trans:cis). Thereafter, Trost and co-workers explored bulky monodentate phosphoramidite ligands (e.g., (*R*,*R*,*R*)-**94**, Scheme 1.3.8b) for the transformation and observed very high enantioselectivity for the first time.[76] Of particular interest is the enantioselective addition of substituted TMM reagents to

functionalized oxindole derivatives.[76b] The use of oxindole **91** and TMM-precursor **92** in the palladium-catalyzed cyclization with ligand (*R*,*R*,*R*)-**94** yielded spirooxindole **93** with 14:1 diastereomeric ratio and 96% enantiomeric excess for the major diastereomer. Although a completed asymmetric synthesis of marcfortine B (**90**) from intermediate **93** has not been reported, many of the key functional groups are in place and the challenging spiroquaternary stereocenter has been installed (cf. **87** and **93**). The development of this valuable asymmetric transformation highlights the ongoing efforts to devise new and useful techniques for the construction of important molecules.

1.4 OUTLOOK

The representative synthetic efforts presented here demonstrate the crucial interplay between target-directed synthesis and the development of novel reaction methods. Although many useful asymmetric technologies are currently available, the specific challenges posed by important natural products and pharmaceutical compounds highlight deficiencies in the current technology. Envisaging strategies to construct these relevant molecules through means beyond the current arsenal of enantioselective transformations will aid the evolution of both synthetic planning and reaction development. The symbiotic relationship between total synthesis and method development can continue to expand the understanding of synthetic strategy and catalysis on both fundamental and practical levels.

Despite the substantial advances that have been made so far, significant challenges remain for both multistep synthesis and catalysis. In addition to improvements to efficiency and selectivity, better reactivity and handling stability are constantly required

to implement and improve industrial processes for existing methods. Exceptionally reliable methods will aid in the discovery of new biologically active compounds by using high-throughput combinatorial screening techniques that are well established in the pharmaceutical industry, although these techniques are limited by the number of readily accessible chiral building blocks. Existing methods may be improved by identifying systems with better functional-group tolerances that might obviate the need for protecting and masking groups. Similarly, known privileged chiral frameworks may be modified to control chiral space more effectively for especially challenging transformations, a technique conspicuously successful for Trost's TMM cyclizations (see subsection 1.3.8).

Overall, creative solutions are required to address specific organic transformations that remain significant impediments to efficient syntheses, namely forming multiple stereocenters and rings, forming multiple C–C bonds, generating vicinal quaternary stereocenters, and achieving C–H and C–C functionalization reactions. Cyclic structures often present particular challenges owing to the unique strain and steric elements imparted by their connectivity. As a result, many highly strained or complex polycyclic structures are daunting targets for synthesis. Finally, the discovery of new natural products will undoubtedly result in new challenges for synthetic chemistry and catalysis. In this thesis, examples of the development of useful enantioselective transformations for the synthesis of natural products will be presented. These reactions were initially conceived as solutions to synthetic problems in the context of total synthesis efforts and have led to various derivative applications and methodologies with broad utility.

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