Chapter 1

Asymmetric Dearomatization via Cycloaddition Reaction⁺

1.1 INTRODUCTION

The ability to rapidly generate structural complexity remains one of the foremost challenges in synthetic organic chemistry. As such, cycloaddition reactions are highly valued for their ability to efficiently construct complex architectures in a single step. In a typical reaction, two or more unsaturated substrates are joined to form a cyclic product in which there is a net reduction of the bond multiplicity.¹ The strong enthalpic benefit of exchanging π -bonds or non-bonded electron pairs for σ -bonds is the predominant driving force for these transformations, and it typically compensates for the unfavorable entropic cost of a highly ordered transition state. Catalytic asymmetric, dearomative cycloaddition reactions are an important subclass of these transformations, as they provide rapid access to a variety of cyclic or polycyclic scaffolds in a single step and often in high

[†] Part of this chapter is submitted as a book chapter and co-written with Dr. Madeleine E. Kieffer (a graduate student in the Reisman laboratory).

enantiomeric excess. Due in part to the potential pharmaceutical properties of heterocyclic compounds, much of the research in this field has focused on the reactions of furans, pyrroles, indoles and other heteroaromatic compounds using transition metals, Lewis acids, Brønsted acids and organo-catalysts. This chapter will cover recent advances in catalytic, asymmetric dearomatization reactions that proceed by cycloaddition.

1.2 (2 + 1) CYCLOADDITION

1.2.1 Asymmetric Büchner Reaction

One of the most ubiquitous aromatic motifs in organic chemistry is the benzene ring. Despite its high stability, which renders it challenging to dearomatize via cycloaddition, Büchner and co-workers discovered the cyclopropanation of benzene in $1896.^2$ They reported that at elevated temperatures in benzene, ethyldiazoacetate underwent thermolytic dediazotization and subsequent cyclopropanation of solvent to afford a norcaradiene product. Doering and co-workers later used nuclear magnetic resonance spectroscopy to determine that the products of the Büchner reaction were actually a mixture of cycloheptatrienes, which result from facile 6π -disrotatory ring opening of the norcaradiene followed by a series of [1,5]-hydride shift events.³ Modern efforts to further develop this reaction and render it enantioselective have focused on transition metal-catalyzed intramolecular variants.



Scheme 1.1. Early investigations of the asymmetric Büchner reaction

In 1990, McKervey and co-workers reported the first catalytic, asymmetric Büchner reaction.⁴ Subjection of α -diazoketone **1** to catalytic rhodium (II) carboxylate **4** provided cycloheptatriene **3** in 80% yield and 33% ee, presumably via 6π -disrotatory electrocyclic ring opening of nocaradiene product **2** (Scheme 1.1a). In a similar system, Maguire and co-workers discovered that the complex generated from CuPF₆ and bis(oxazoline) **8** catalyzed the cyclopropanation of α -diazoketone **5** in improved enantioselectivity (up to 95% ee, Scheme 1.1b).⁵ Unfortunately, the selectivity of this transformation depends heavily on the substrate substitution pattern, and does not provide a general solution for arene cyclopropantion. In 2009, follow-up work by the same group found that addition of NaBARF further improves the ee,⁶ which they suggest reveals a beneficial role of the sodium cation⁷ (Scheme 1.1c). However, more detailed studies are required to elucidate the origin of this effect.

Scheme 1.2. Asymmetric Büchner reactions in naphthyl and diaryl systems



Doyle and coworkers found that $Rh_2(4S-IBAZ)_4$ catalyst (14) could promote the intramolecular cyclopropanation of naphthyl substrate 12 in 80% yield and 81% ee (Scheme 1.2a).⁸ Recently, the same group also disclosed the desymmetrization of diaryl α -diazoacetates 15 using catalytic $Rh_2[(S)-TFPTTL]_4$ (17, Scheme 1.2b).⁹ Good to excellent enantioselectivities and high diastereoselectivity for the *trans* products were observed using *ortho*-methyl or *para*-halogenated arenes.

1.2.2 Cyclopropanation of Heterocyclic Compounds

Metal catalyzed carbenoid cyclopropanation has also been explored in heterocyclic arenes. Reiser and co-workers reported Cu/chiral bis(oxazoline)-catalyzed (2 + 1) enantioselective cycloadditions between acceptor-substituted carbenoids (diazoacetate **19** and **23**) and furans **18** or *N*-Boc-pyrrole **22** (Scheme 1.3).¹⁰ While unsubstituted furan **18a** only provided moderate ee (<50% ee, <20% yield), good enantioselectivity (91% ee) and exclusive *exo* selectivities were observed when placing a

Scheme 1.3. Copper-catalyzed asymmetric cyclopropanation of heteroarenes with acceptor-substituted carbenoids



methyl ester at the C2 position (**18b**, Scheme 1.3a). This superior selectivity was proposed to derive from a secondary H-bonding interaction between the methyl ester and the side chain of the chiral ligand. Interestingly, the opposite facial selectivity, in moderate ee, was observed when *N*-Boc-pyrrole **22** was employed (Scheme 1.3b). Boysen and co-workers were able to further extend this cyclopropanation to *N*-acyl indole scaffolds (**26**, Scheme 1.3c).¹¹ Using novel carbohydrate-derived bis(oxazoline) ligand **28**, *N*-Boc-3-methylindole **26** undergoes smooth cyclopropanation to give *exo* indoline **27** in 96% ee, while moderate enantioselectivities were observed in other substrates. This methodology was successfully applied to the total synthesis of (–)-desoxyeseroline.

Cyclopropanation between donor-acceptor-substituted carbenoids and heterocycles has also been reported. Davies and co-workers extensively studied the **Scheme 1.4.** Rhodium-catalyzed asymmetric cyclopropanation of heteroarenes with donor-acceptor-substituted carbenoids



ability and propensity of diazoacetate **30** to cyclopropanate a variety of aromatic heterocycles (Scheme 1.4).¹² In contrast to the Cu-catalyzed reactions of acceptorsubstituted carbenoids discussed previously, double cyclopropanation of the heteroarenes was observed with these carbenoids (Scheme 1.4b). The monocyclopropanation product could be only isolated as the major product when an excess of the heterocyclic starting material was employed (Scheme 1.4a). Rh₂(*S*-DOSP)₄(**32**) was identified as the catalyst of choice to promote enantioselective cyclopropanation of furan, *N*-Boc-pyrrole, and 3methylbenzofuran. Interestingly, double cyclopropanation on the benzenoid ring was observed with substituted indole and 2-methylbenzofuran substrates (**34a–34d**), while unsubstituted *N*-Boc indole was less reactive and resulted in carbene dimerization.

1.3 (3 + 2) CYCLOADDITION

The unique chemistry of indoles, which possess reactivity analogous to enamines but are hydrolytically stable, has resulted in their extensive use in the development of cycloaddition and formal cycloaddition reactions. Although these types of transformations have been known for decades, it was only recently that catalytic, asymmetric variants were developed.





In 2009, Davies and co-workers reported that treatment of indoles with vinyl diazoacetate **38** in the presence of rhodium catalyst **32** results in formal (3 + 2)

cycloaddition to provide fused tricyclic products (Scheme 1.5a).¹³ Interestingly, the substitution pattern of the indole starting material greatly affects the product of this reaction. Whereas 1,3-dimethylindole (**36**) gives rise to indoline **40**, the isomeric 1,2-dimethylindole (**37**) delivers indoline **42**; both reactions occur with good to excellent diastereo- and enantioselectivity. The authors rationalize these divergent reactivities by the steric encumberance of the C2- or C3-methyl substituent, which forces the initial nucleophilic attack to occur at the unsubstituted position of the indole. The same group later disclosed that in the presence of rhodium catalyst **48**, 1-phenylsulfonyl triazoles **44** can be used to generate α -iminocarbenoids *in situ*, which react with 1,3-dimethyl indoles (**43**) to furnish pyrroloindolines (**47**) in good yields and high enantioselectivities (Scheme 1.5b).¹⁴ In the contrast to the zwitterionic mechanism proposed in the previous reaction, the authors suggest that this reaction might proceed through initial cyclopropanation to form **45**, followed by cyclopropane opening and iminium trapping to afford the formal (3 + 2) cycloaddition product **47**.

Hashimoto and co-workers have investigated the Rh-catalyzed (3 + 2) cycloaddition reactions between *N*-methylindoles and 2-diazo-3,6-diketoesters **49** to prepare tetracyclic products (**51**), presumably via Rh-bound carbonyl ylide **50** (Scheme 1.6).¹⁵ Polychlorinated dirhodium complex **52** was found to catalyze the formation of *exo*-tetracycle **51** in good yields and high enantioselectivities. Whereas the reaction tolerates substitution of the indole backbone, use of the analogous 2-diazo-3,5-diketoesters results in significantly lower enantioinduction. This is the only report of an asymmetric dearomatization reaction that proceeds by cycloaddition with a carbonyl ylide.

Scheme 1.6. Rhodium-catalyzed (3 + 2) cycloaddition between indoles and diazodiketoesters



Scheme 1.7. Asymmetric (3 + 2) cycloaddition of indoles and donor-acceptor cyclopropanes



Donor-acceptor cyclopropanes have also been explored as dipoles in asymmetric (3 + 2) cycloaddition reactions (Scheme 1.7). Tang and co-workers found that these substrates participate in highly diastereo- and enantioseletive annulations of indoles when chiral Cu(II)-BOX complexes are used as catalysts.¹⁶ When di-benzyl linked BOX ligand **56** is employed, a variety of substituted indoles (**53**) and aryl-substituted cyclopropanes (**54**) react to produce enantioenriched indoline products (**55**). Whereas cyclopropanes bearing electron-rich arenes react through a mechanism in which both enantiomers converge to a single diastereomer of highly enantioenriched product (e.g. **57**),

cyclopropanes bearing less electron-rich arenes undergo kinetic resolution, with only the (R)-configured cyclopropane proceeding to product (e.g. **58**). This methodology was successfully applied to prepare the core of the natural product borreverine (**59**).

Scheme 1.8. Formal enantioselective (3 + 2) cycloadditions of indoles



Reisman and coworkers developed a formal (3 + 2) cycloaddition between methyl 2-trifluoroacetamidoacrylate (**61**, Scheme 1.8a) and 3-substituted indoles (**60**).^{17,18} Although the reaction requires stoichiometric SnCl₄, the chiral diol (*R*)-3,3'-dichloro-BINOL (**65**) is employed catalytically. A variety of indole substrates undergo cycloaddition with acrylate **61** to provide highly functionalized pyrroloindolines (**62**) in excellent enantioselectivities, favoring the *exo* diastereomer. Mechanistically, the reaction is proposed to proceed through cooperative Lewis acid–Brønsted acid activation. Activation of acrylate **61** by SnCl₄ results in nucleophilic attack of the indole to generate a tin enolate (63). A catalyst-controlled protonation of the enolate by $SnCl_4$ ·65 followed by cyclization affords the enantioenriched pyrroloindoline (62) in good yield with high diastereoselection and excellent ee.

Quinone monoimines (**67**, Scheme 1.8b) have also been found to engage in asymmetric cycloaddition reactions with indoles. Zhang and co-workers reported that chiral phosphoric acid **69** catalyzes the conjugate addition of indoles (**66**) to quinone monoimine **67**.¹⁹ Subsequent rearomatization of enamide intermediate **70** followed by phenol cyclization furnishes benzofuroindoline products (**68**). This method tolerates a wide range of substitution on the indoles and generally proceeds with excellent enantioselectivities.

Scheme 1.9. Formal enantioselective (3 + 2) cycloadditions between 3-nitroindoles and iminoesters



The aforementioned (3 + 2) cycloaddition reactions generally rely on the intrinsic nucleophilicity of the C3 site of indole to initiate reactivity. Alternatively, Arai and coworkers discovered a cascade reaction between 3-nitroindoles and iminoesters that proceeds by initial Cu-catalyzed attack of an iminoenolate at C2 of the indole to generate nitronate **76** (Scheme 1.9).²⁰ Subsequent intramolecular nitro-Mannich addition provides indoline **74** in a highly enantio- and diastereoselective fashion. The authors suggest that the presence of electron-withdrawing substituents at the N1 and C3 positions of indole are required to render these substrates sufficiently electrophilic at C2.

1.4 (3 + 3) CYCLOADDITION

Few examples of asymmetric dearomatization via (3 + 3) cycloaddition reactions have been reported in the literature. In 2013, Tang and co-workers reported a highly enantioselective cycloaddition between isoquinoline-derived dipole **77** and donoracceptor cyclopropanes **78** (Scheme 1.10a).²¹ Lewis acid activation of cyclopropane **78**, presumably through bidentate coordination to chiral Ni(II)-TOX catalyst (generated from **80**), results in nucleophilic attack by azomethine imine **77**. Control experiments reveal that the reaction proceeds by a kinetic resolution of the cyclopropane, in which the (*S*)enantiomer reacts more quickly. In order to obtain high yields of product, two equivalents of cyclopropane **78** are employed under standard conditions.

The Doyle group developed a highly enantioselective formal (3 + 3) cycloaddition between isoquinolinium or pyridinium methylides (**81**) and enol diazoacetate **82** (Scheme 1.10b).²² Chiral dirhodium complex **84**, in conjunction with enol diazoacetate **82**, is proposed to form a chiral metallo-1,3-dipole, which can then undergo (3 + 3)cycloaddition to form a variety of quinolizidines (**82**) with good enantioinduction. Recently, the Guo group demonstrated an enantioselective (3 + 3) cycloaddition reaction between phthalazinium dicyanomethanides (**85**) and iminoesters (**86**), catalyzed by a Cu(I)/[†]Pr-Phosferrox complex (**88**, Scheme 1.10c).²³ The authors propose that iminoester **86** is activated by the chiral Cu(I) complex to generate a metallo-1,3-dipole, which undergoes cycloaddition with phthalazinium dicyanomethanide **85**. This mild method **Scheme 1.10.** Catalytic, asymmetric (3 + 3) dearomatizing cycloaddition reactions



tolerates a wide range of aryl groups on the iminoester, as well as cinnamyl and isobutyl groups, and provides tricyclic compounds (87) in high yields with excellent diastereoand enantioselectivities.

1.5 (4 + 2) CYCLOADDITION

Despite the large number of catalytic asymmetric Diels–Alder reactions developed to date, relatively few examples involve dearomatization. In 2008, Bernardi, Ricci, and co-workers reported the first catalytic, asymmetric Diels–Alder reaction of 3-vinyl indoles (**89**) with assorted dienophiles (e.g. **90**, Scheme 1.11a).²⁴ Utilizing hydrogen-bonding catalyst **92**, a variety of tetrahydrocarbazole products (**91**) could be formed in good yields and excellent enantioselectivities. The authors hypothesize that the reaction proceeds through a cooperative mechanism involving Brønsted base

activation of the 3-vinyl indole and hydrogen bond activation of the dieneophile. When a mixture of (E)- and (Z)-3-(prop-1-en-1-yl)-1*H*-indole is subjected to the reaction conditions, only the *E*-diene proceeds to product; the *Z*-diene, in which the required *S*-*cis* conformation is disfavored, is recovered unchanged. These findings provide empirical support for a concerted mechanism.

Scheme 1.11. Organocatalytic asymmetric Diels–Alder reactions of 3-vinyl indoles



A similar approach was successfully employed by Barbas and co-workers (Scheme 1.11b).²⁵ Bisthiourea **96** was found to catalyze an exceedingly mild Diels–Alder reaction between 3-vinyl indoles (**93**) and 3-methyleneindolinones (**94**) for the direct synthesis of complex carbazolespirooxindoles (**95**). The products were isolated in nearly quantitative yield and with excellent enantio- and diastereoselection.

In 2009, MacMillan and co-workers disclosed a nine-step total synthesis of (+)minfiensine (103, Scheme 1.12).²⁶ Key to their synthesis was the development of an **Scheme 1.12.** Organocatalytic asymmetric Diels–Alder/cyclization cascade reaction



organocatalytic Diels-Alder/cyclization cascade reaction to construct the pyrroloindoline core of the molecule. The reaction is proposed to proceed via condensation of organocatalyst **100** with propynal (**98**) to generate an activated iminium ion, which enables an asymmetric, *endo*-selective Diels–Alder cycloaddition with diene **97** to give **101** and set the stereochemistry of the all-carbon quaternary center. Isomerization to iminium **102** followed by cyclization of the pendant amine and hydrolytic release of the catalyst provides the pyrroloindoline core. A reductive quench reduces the aldehyde to alcohol **99**, which can be further advanced to (+)-minfiensine (**103**) in only five steps. Using a similar cascade sequence, MacMillan and co-workers were also able to synthesize vincorine (**104**) in only nine steps, setting three of the four stereogenic centers in a single cascade reaction.²⁷

This catalytic asymmetric dearomative cascade strategy was further applied to members of the strychnos, aspidosperma, and kopsia alkaloids.²⁸ In the key cascade reaction, the asymmetric (4 + 2) is followed by β -elimination of methyl selenide and

Scheme 1.13. Organocatalytic asymmetric Diels–Alder/elimination/conjugate addition cascade reaction



conjugate addition of the pendant amine to access tetracycle **107** (Scheme 1.13). From this common intermediate, MacMillan and co-workers successfully synthesized six structurally distinct alkaloid natural products. An analogous sequence employing an ynone instead of an ynal was used to produce (–)-minovincine.²⁹

You and co-workers have developed formal (4 + 2) cycloadditions to prepare enantioenriched polycycles, which proceed by a tandem Michael addition/Mannich reaction sequence. In 2011, they reported that cinchona alkaloid **111** catalyzes the intramolecular, dearomative cycloaddition of indolyl enones (**108**) to provide tricycles (**110**) bearing three stereogenic centers (Scheme 1.14a).³⁰ The reaction exhibits a broad substrate scope and delivers products under mild conditions and in excellent enantioselectivities. Using similar conditions, they subsequently developed an intermolecular formal (4 + 2) cycloaddition between 2,3-disubstituted indoles (**112**) and methylvinylketone (**113**, Scheme 1.14b).³¹ The tetrahydrocarbazole products **114** are produced in good yields and excellent selectivities. **Scheme 1.14.** Organocatalytic asymmetric Michael addition/Mannich cyclization cascade reactions



In 2014, Chen and co-workers also utilized alkaloid **111** to catalyze (4 + 2) cycloaddition reactions of heteroaryl enones (**115**, Scheme 1.15).³² The reaction proceeds through the *in situ* generation of a trienamine species, which is proposed to result in a HOMO-activated diene. Subsequent selective (4 + 2) cycloaddition with electron deficient dienophiles delivers the observed product (**117**, **119**). C2- and C3-linked heteroaryl enones (**115** and **118**, respectively) are competent in the transformation; however, the C2-linked substrates exhibit a broader substrate scope. The polycyclic products are isolated in good yields and selectivities.





Organocatalysis has also been utilized to effect dearomative Diels–Alder reactions of anthracenylacetaldehydes (Scheme 1.16, **120** and **124**). In 2012, Jørgenson and co-workers reported the first asymmetric example of this transformation, which like the previously discussed reaction developed by Chen, utilizes a HOMO-raising strategy.³³ Good selectivity is achieved with bifunctional catalyst **123**, which is proposed to operate through a cooperative mechanism involving enamine formation with the aldehyde (**120**) and H-bond activation of the nitroalkene (**121**). A variety of (4 + 2) adducts are isolated in good yields and excellent enantioselectivities. Follow-up studies identified C2-symmetric catalyst **126**, which enabled the use of maleimides as dienophiles (**124**).³⁴ With this symmetric dienophile, the use of a bifunctional catalyst did not provide improved results.

Scheme 1.16. Organocatalytic dearomative Diels-Alder reactions with anthracenylacetaldehydes



As an alternative to organocatalysis, Nishida and co-workers disclosed the use of a novel, chiral holmium(III) complex to catalyze an enantioselective Diels–Alder reaction of 3-enoxy-indoles (**127**, Scheme 1.17).³⁵ Using only 5 mol % of Ho(NTf₂)₃·**130**, carbazole products (**129**) are isolated in excellent yields and with good enantioinduction.



Scheme 1.17. Holmium(III)-catalyzed enantioselective Diels-Alder reactions

Additionally, the silylenol ether functionality was found to preclude deleterious air oxidation and 1,3-hydride shifts that can result in rearomatization of the indole ring and loss of chiral information. The silylenol ether products (**129**) could be further functionalized to afford polycycles with four contiguous stereocenters in only two steps.

Bandini and co-workers employed a chiral gold catalyst to effect the dearomatization of indoles through an intramolecular, step-wise (4 + 2) cycloaddition (Scheme 1.18).³⁶ Subjection of alkynyl indole precursors (131) to chiral dinuclear gold catalyst (AuBF₄)₂·134 resulted in 5-*exo*-dig hydroindolination of the alkyne followed by iminium trapping to afford tetracyclic products (133) in good yields and moderate selectivities. When the corresponding tryptamine-dervied substrates were employed, 7-*endo*-dig selectivity was observed.





Furans have also been found to undergo catalytic asymmetric (4 + 2) cycloaddition reactions. In 2012, Shibatomi and co-workers utilized a Lewis acid-

activated oxazaborolidine catalyst (**138**, Scheme 1.19) to promote an asymmetric Diels– Alder cycloaddition between furans (**136**) and β -trifluoromethylacrylates.³⁷ The fluorinecontaining bicycles **137** were produced in good yield with moderate diastereoselection and excellent enantioselection. Substituents are tolerated at the C2- and C3-position of the furan; β -difluoromethylacrylates are also suitable dienophiles. The cycloaddition products could be further elaborated to fluorinated bioactive compounds.

Scheme 1.19. Asymmetric Diels-Alder cycloaddition reactions of furans and β -trifluoromethylacrylates



Recently, Larinov and co-workers disclosed the first example of a catalytic, enantioselective (4 + 2) annulation with highly reactive nitrosoalkenes (Scheme 1.20).³⁸ These alkenes were generated in-situ from 2-chlorooxime precursors (**140**), which then underwent Cu-catalyzed, asymmetric, inverse demand hetero-Diels–Alder reactions with 1,3-disubstituted indoles (**139**). The use of stoichiometric silver salts enabled catalysis through the sequestration of chloride ion. These (4 + 2) cycloadditions provide structurally unique heterocycles (**141**) in highly enantioenriched form.

Scheme 1.20. Enantioselective (4 + 2) cycloaddition reactions of indoles and nitrosoalkenes



A similar reaction was disclosed by Wang and co-workers in which copper catalyzes the asymmetric hetero-Diels–Alder reaction between indoles and α -halogenated hydrazones (Scheme 1.21).³⁹ In analogy to the generation of nitrosoalkenes from α -halooximes, it is proposed that coordination of hydrazone **143** to the chiral catalyst **145** followed by base-induced elimination of chloride generates the catalyst-bound azoalkene *in situ*, which undergoes (4 + 2) cycloaddition with a variety of indoles to furnish the 2,3-fused indoline products (**144**) in excellent yields and selectivities. The selectivities observed in this transformation are remarkable given the extremely facile un-catalyzed background reaction.

Scheme 1.21. Enantioselective (4 + 2) cycloaddition reactions of indoles and α -halogenated hydrazones



1.6 (4 + 3) CYCLOADDITION

In 1996, Davies and co-workers disclosed their efforts to develop a Rh-catalyzed asymmetric formal (4 + 3) cycloaddition between furan (146) and vinyldiazoester 147.⁴⁰ They hypothesized this reaction could proceed via an initial enantioselective cyclopropanation followed by a Cope rearrangement to give bicyclic product 149 (Scheme 1.22). Using Rh₂(*S*-TBSP)₄ (152) as the catalyst, they were able to isolate the desired product in moderate yields and 80% ee. Although these conditions were limited in scope, they identified a more general solution through the use of chiral esters. Similar

reactivity and selectivity issues were encountered when employing pyrroles, providing tropane products in low enantiomeric excess (Scheme 1.22b).⁴¹

Scheme 1.22. Preliminary studies of asymmetric Rhodium-catalyzed (4 + 3) cycloaddition reactions of heteroarenes and vinyldiazoesters



Ten years later, Davies and co-workers reported that the use of 2-(siloxy)vinyldiazoacetate **154** as a Rh-carbenoid precursor enables highly enantioselective formal (4 + 3) cycloaddition reactions of *N*-Boc-pyrroles (**153**, Scheme 1.23). The best selectivities were obtained using $Rh_2(S-PTAD)_4$ (**48**) as the catalyst.⁴² This catalyst system was compatible with a variety of substituted *N*-Boc-pyrroles, providing functionalized tropanes (**155**) in good yields and excellent enantioselectivities.

Scheme 1.23. Asymmetric Rh-catalyzed (4 + 3) cycloaddition reactions of pyrroles and siloxyvinyldiazoacetates



Inspired by MacMillan's work on secondary amine-catalyzed (4 + 2) cycloadditions, Harmata and co-workers described the first organocatalytic asymmetric (4 + 3) cycloaddition (Scheme 1.24a).⁴³ Imidazolidinone **160** was found to catalyze the cycloaddition between disubstituted furans (e.g. **157**) and siloxydienals (e.g. **156**) to produce oxa-bicycl[3.2.1]octanones (e.g. **158**) in modest to good yields and enantioselectivities. The major side products of this reaction were alkylated furan derivatives, suggesting a step-wise cycloaddition mechanism. This methodology was subsequently employed by Lin and co-workers in their synthesis of core of englerin A (**164**).⁴⁴ Although the regioselectivity of the cycloaddition with differentially-substituted furan **162** was poor, providing a mixture of **163a** and **163b**, the desired product was produced in promising enantioselectivity (Scheme 1.24b).

Scheme 1.24. Organocatalytic (4 + 3) cycloaddition reactions of furans



In 2004, a chiral Lewis acid-catalyzed (4 + 3) cycloaddition between furans and alleneamides was reported by Hsung and co-workers (Scheme 1.25).⁴⁵ The reaction occurs by *in situ* oxidative generation of a nitrogen-stabilized oxyallyl cation from

alleneamide **165**. Following (4 + 3) cycloaddition with furan **166**, the tricyclic products were isolated in moderate to good yields and enantioselectivities. The level of regioselectivity for the *syn* versus *anti* isomer of the product varied, and depended on the substitution pattern. It is proposed that enantioinduction occurs via coordination of the oxyallyl cation to Cu(OTf)₂·**168**, providing facial differentiation for the incoming diene. The scope of this reaction is complementary to that of Harmata (see above), as 2,5*un*substituted furans provide the best yields and selectivities.





1.7 CONCLUDING REMARKS

Over the past three decades, significant progress has been made in the development of new, catalytic asymmetric cyloaddition reactions of arenes. Yet, most of the progress to date has focused on the cycloadditions of heteroarenes, and indoles in particular. These systems benefit from a lower aromatic stabilization energy, relative to benzene, and thus a lower enthalpic cost to dearomatization. In essence, heteroarenes represent the "low hanging fruit." Moving forward, the discovery of novel modalities for enantioselective dearomatization reactions will be an important area of research, particularly as we seek to develop synthetically useful transformations for the dearomatization of non-hetero arenes.

Nevertheless, recently development of catalytic dearomatization transformation has introduced new and powerful synthetic tools to quickly assemble complex natural products. Chapters 2 and 3 will focus on the direct application of enantioselective formal (3 + 2) cycloaddition reaction developed in our lab (Scheme 1.8a) to access pyrroloindoline-containing diketopiperazine natural products.

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