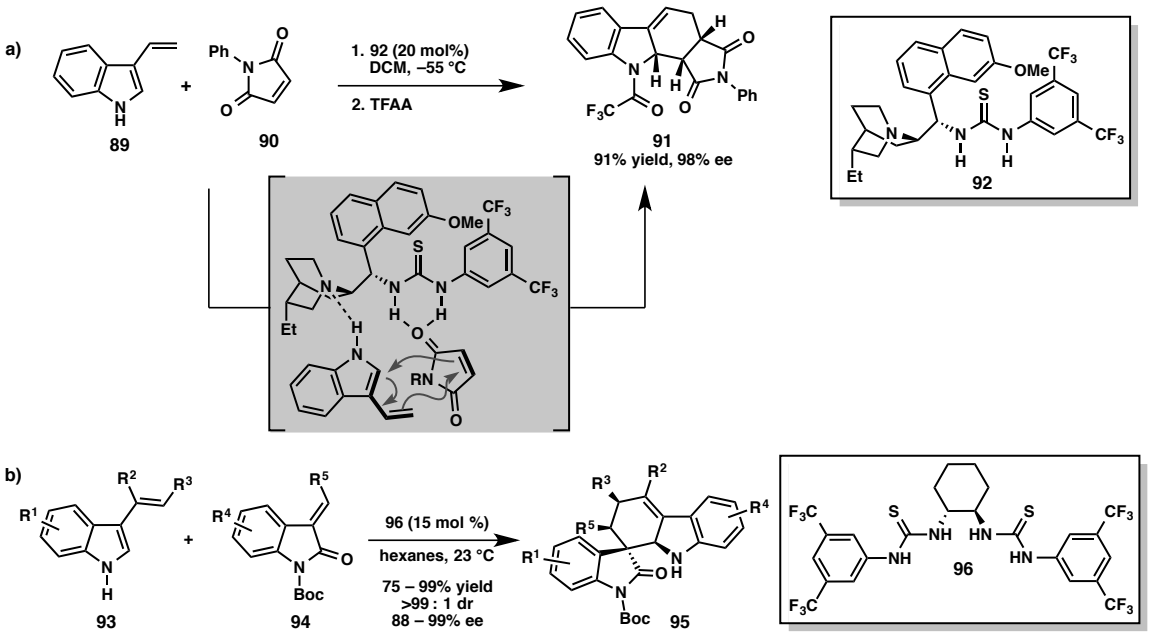
activation of the 3-vinyl indole and hydrogen bond activation of the dieneophile. When a mixture of (*E*)- and (*Z*)-3-(prop-1-en-1-yl)-1*H*-indole is subjected to the reaction conditions, only the *E*-diene proceeds to product; the *Z*-diene, in which the required *S-cis* conformation is disfavored,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

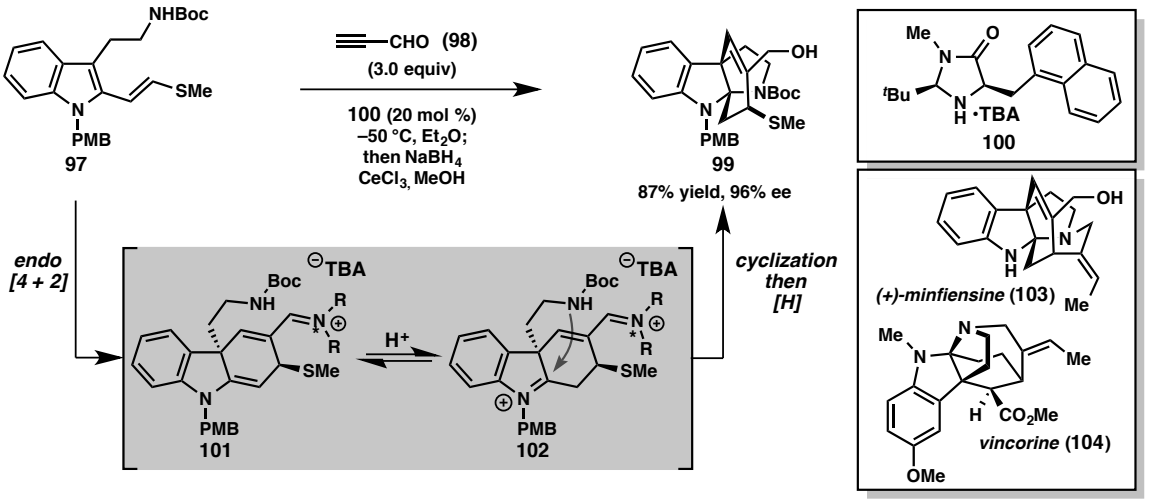
Scheme 1.11. *Organocatalytic asymmetric Diels–Alder reactions of 3-vinyl indoles*



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

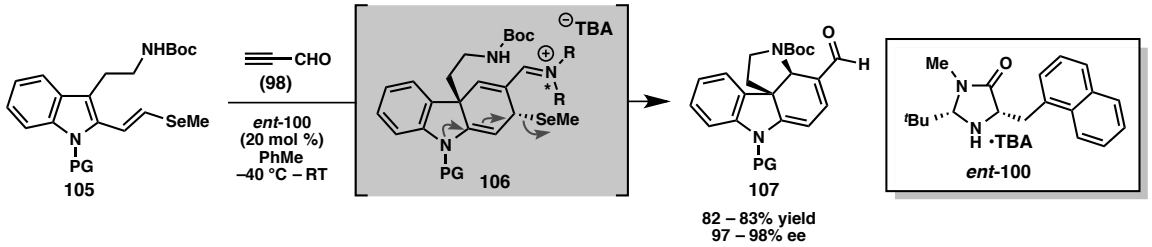
Scheme 1.12. *Organocatalytic asymmetric Diels–Alder/cyclization cascade reaction*



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

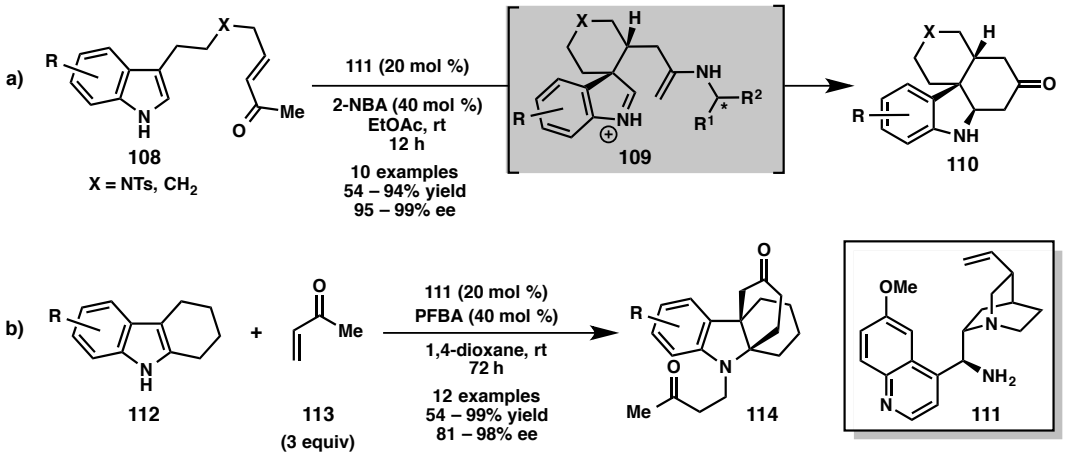
Scheme 1.13. *Organocatalytic asymmetric Diels–Alder/elimination/conjugate addition cascade reaction*



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]

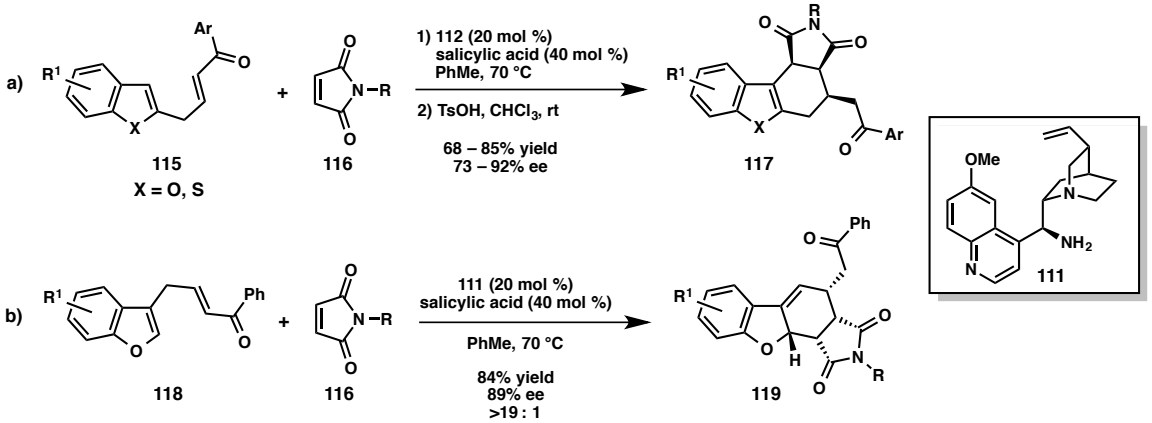
You and co-workers have developed formal (4 + 2) cycloadditions to prepare enantioenriched polycycles, which proceed by a tandem Michael addition/Mannich reaction sequence. In 2011, they reported that cinchona alkaloid **111** catalyzes the intramolecular, dearomative cycloaddition of indolyl enones (**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*



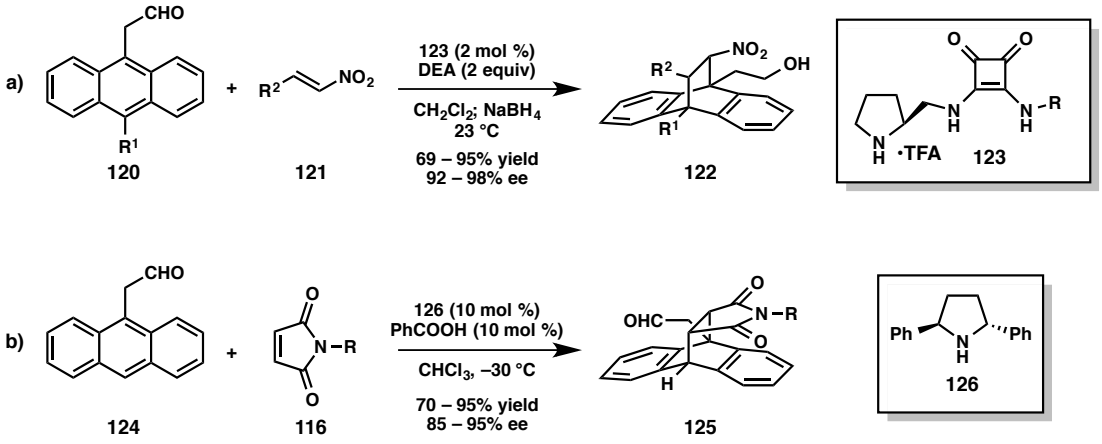
In 2014, Chen and co-workers also utilized alkaloid **111** to catalyze (4 + 2) cycloaddition reactions of heteroaryl enones (**115**, Scheme 1.15).[32] The reaction proceeds through the *in situ* generation of a trienamine species, which is proposed to result in a HOMO-activated diene. Subsequent selective (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.

Scheme 1.15. *Organocatalytic asymmetric intermolecular Diels-Alder reactions of heteroaryl enones*



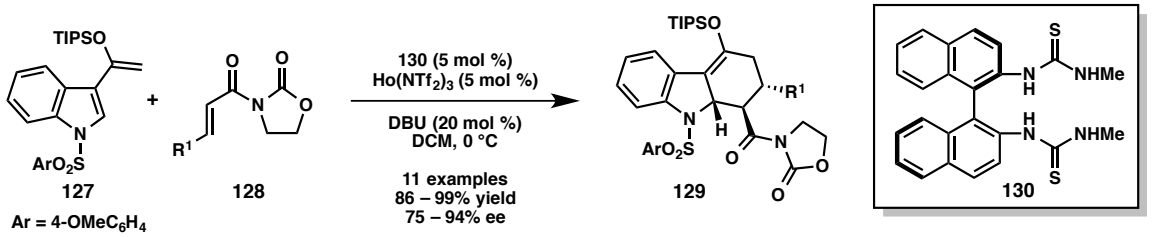
Organocatalysis has also been utilized to effect dearomative Diels–Alder reactions of anthracenylacetaldehydes (Scheme 1.16, **120** and **124**). In 2012, Jørgenson and co-workers reported the first asymmetric example of this transformation, which like the previously discussed reaction developed by 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 $Ho(NTf_2)_3$·**130**, carbazole products (**129**) are isolated in excellent yields and with good enantioinduction.

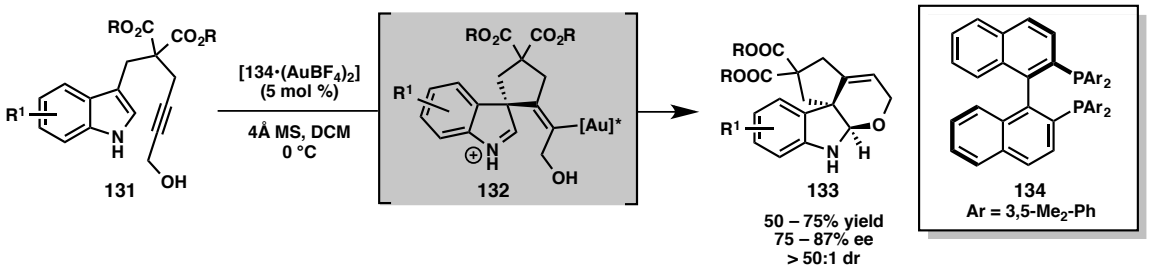
Scheme 1.17. *Holmium(III)-catalyzed enantioselective Diels-Alder reactions*



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 $(AuBF_4)_2 \cdot$**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.

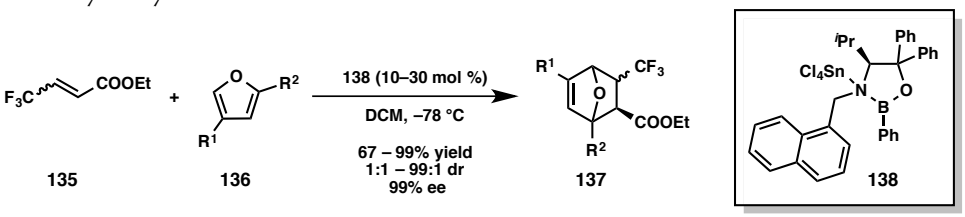
Scheme 1.18. *Gold-catalyzed intramolecular formal (4 + 2) cycloaddition reactions*



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

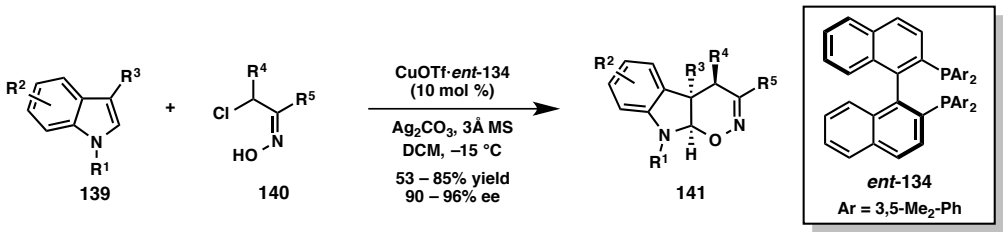
activated oxazaborolidine catalyst (**138**, Scheme 1.19) to promote an asymmetric Diels–Alder cycloaddition between furans (**136**) and β-trifluoromethylacrylates.[37] The fluorine-containing bicycles **137** were produced in good yield with moderate diastereoselection and excellent enantioselection. 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*



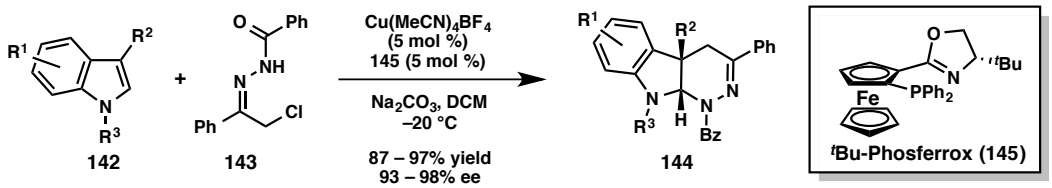
Recently, Larinov and co-workers disclosed the first example of a catalytic, enantioselective (4 + 2) annulation with highly reactive nitrosoalkenes (Scheme 1.20).[38] These alkenes were generated in-situ from 2-chlorooxime precursors (**140**), which then underwent Cu-catalyzed, asymmetric, inverse 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*

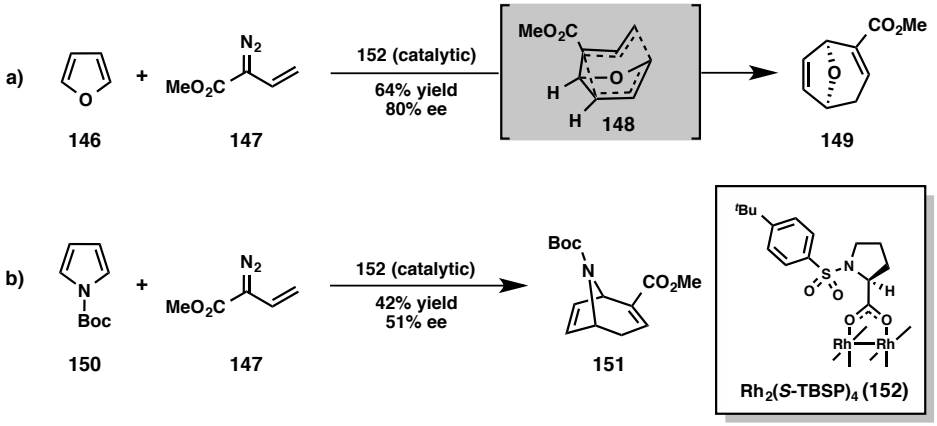


1.6 (4 + 3) CYCLOADDITION

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 Rh_2(*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

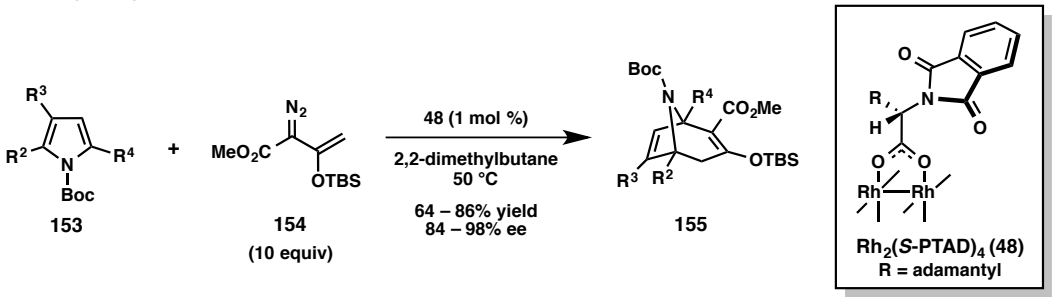
reactivity and selectivity issues were encountered when employing pyrroles, providing tropane products in low enantiomeric excess (Scheme 1.22b).[41]

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



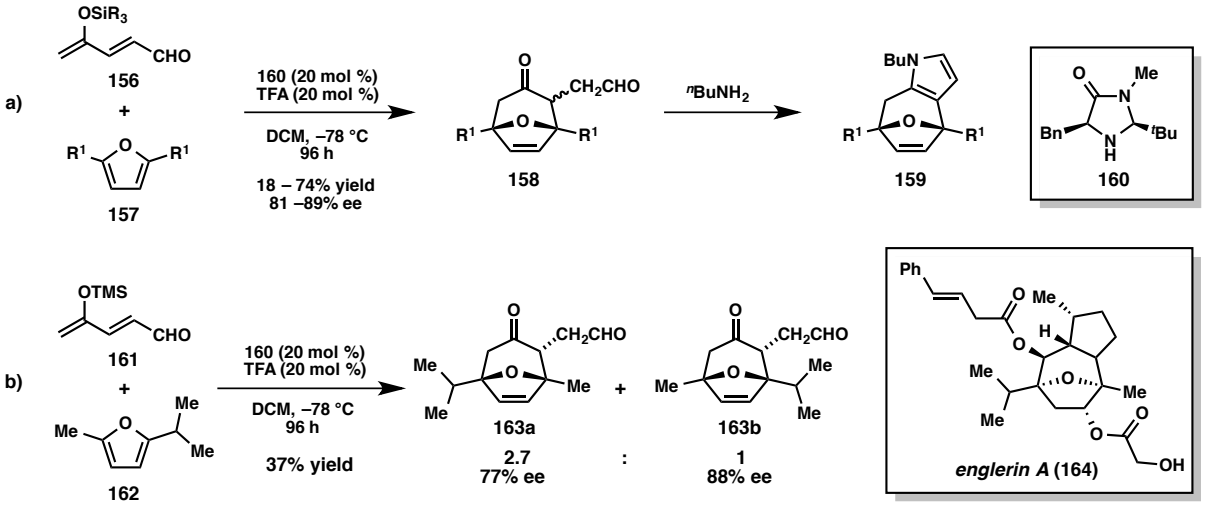
Ten years later, Davies and co-workers reported that the use of 2-(siloxy)vinyldiazoacetate **154** as a Rh-carbenoid precursor enables highly enantioselective formal (4 + 3) cycloaddition reactions of *N*-Boc-pyrroles (**153**, Scheme 1.23). The best selectivities were obtained using Rh_2(*S*-PTAD)$_4$ (**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).

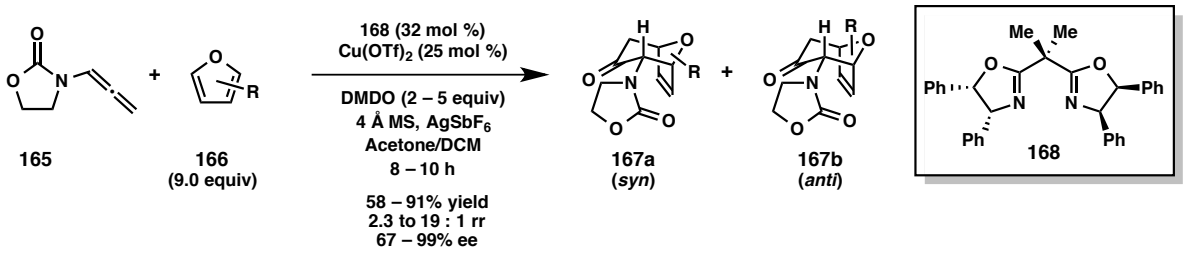
Scheme 1.24. *Organocatalytic (4 + 3) cycloaddition reactions of furans*



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.

Scheme 1.25. *Copper-catalyzed asymmetric (4 + 3) cycloaddition reactions of furans*



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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