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Review

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Asymmetric Catalysis for the Synthesis of Spirocyclic Compounds

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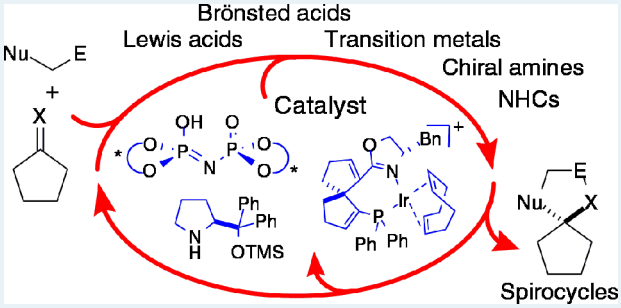
ABSTRACT: Spirocycles provide an exciting platform to develop and understand the reactivity and selectivity for a wide variety of catalysts while affording diverse strategies to access molecules with important applications. This review features recent examples in which a spirocenter is formed within the key step of a catalytic asymmetric process, in either an intramolecular or intermolecular fashion. Examples highlight notable spirocyclization strategies and compare the reactivity and selectivity for different classes of chiral organocatalysts and organometallic catalysts.



KEYWORDS: *spirooxindole, asymmetric, catalytic, spirocyclic, spirocenter, spiroketals, spirolactones*

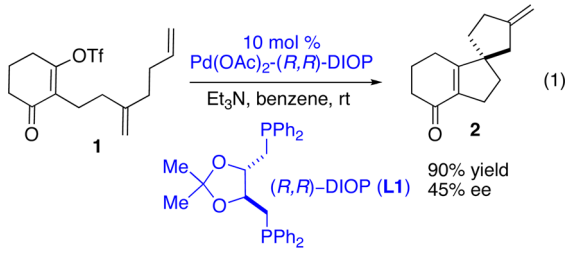
INTRODUCTION

The enantioselective construction of spirocyclic centers provides an exciting synthetic challenge that contributes to the discovery of new catalysts and complex molecules. In 1900, Baeyer introduced the first "spirocyclane" as a structure consisting of two perpendicular rings that are connected through one atom to form a rigid tetrahedral center.[1] Since 1900, compounds containing spirocyclic centers have been identified and utilized in broad applications, ranging from natural products,[2−5] chiral ligands,[6−9] and organometallic complexes[10] (Figure 1). The development of chiral catalysts for spirocyclization reactions requires a sufficiently active catalyst that induces asymmetry at the site of the spirocyclic center while tolerating diverse electronic and steric functional groups. Many spirocyclization reactions also present opportunities to develop a catalytic asymmetric process that establishes more than one stereocenter during the spirocycle construction.

This review features recent examples of catalysts and reactions in which a spirocenter is formed within the key step of a catalytic asymmetric process, in either an intramolecular or intermolecular fashion. Examples have been selected to highlight notable spirocyclization strategies and compare the reactivity and selectivity for different classes of chiral organocatalysts and organometallic catalysts. The reader is also referred to a recent tutorial review by Rios describing a more general overview for the synthesis of spirocyclic compounds.[11]

PIONEERING AND EARLY EXAMPLES FOR THE CATALYTIC ASYMMETRIC SYNTHESIS OF SPIROCYCLES

Pioneering examples for the catalytic asymmetric synthesis of spirocyclic molecules were reported by Overman and coworkers utilizing a Pd-catalyzed intramolecular Heck reaction.[12,13] The seminal report, in 1989, utilized the intramolecular bis-cyclization of trienyl triflate **1** with asymmetric induction from a chiral diphosphine ligand (DIOP, **L1**) (eq 1).



Despite the modest enantioselectivity (45% ee), this spirocyclization demonstrated the utility of the Heck reaction as a promising new method for the catalytic asymmetric synthesis of quaternary carbon centers and the development of asymmetric catalytic methods for the construction of spirocenters. The asymmetric Heck reaction has since been used as a powerful method for the construction of quaternary carbon centers and spirocycles, especially in the context of natural product synthesis.[14]

In 1992, Overman further demonstrated the utility of the intramolecular Heck reaction when this strategy was applied for the first catalytic asymmetric synthesis of a spirocyclic oxindole. This application represents a notable early case because of the importance of the spirooxindole as a biological core structure and also because of the mechanistic insight accounting for the unprecedented discovery of enantiocontrol based on the effect of the HI scavenger.[12,15,16] Using the same enantiomer of phosphine ligand with 5 mol % $Pd_2(dba)_3$ and 10 mol % (*R*)-BINAP ligand (**L2**), both enantiomers of spirooxindole **4** can be selectively obtained from acryloyl 2′-iodoanilide **3**, depend-

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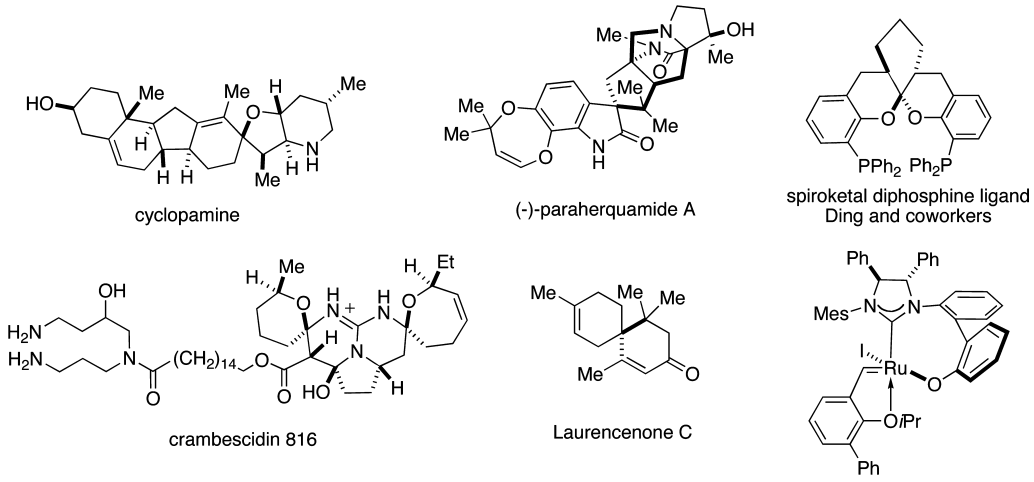
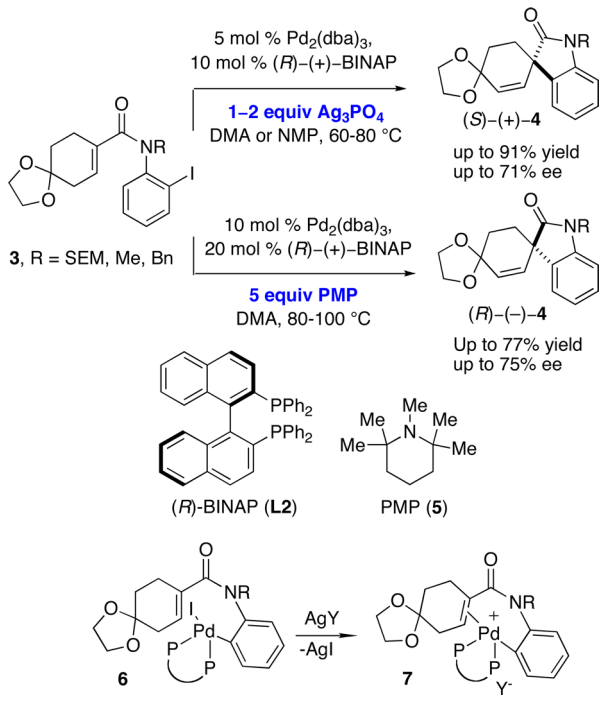


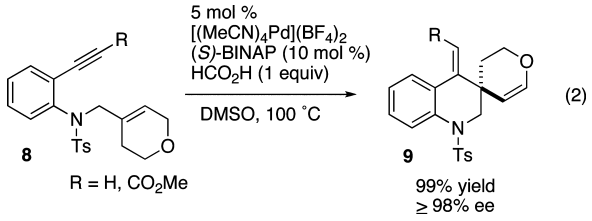
Figure 1. Natural products, chiral ligands, and organometallic complexes containing spirocenters.

ing on how the HI is scavenged (silver salt vs amine). In the presence of a silver salt as an HI acceptor (e.g., Ag_3PO_4 or Ag_2CO_3), the reaction produces (*S*)-spirooxindole **4** with high yield (76−91%) and up to 71% ee. In the presence of a basic tertiary amine, such as 1,2,2,6,6-pentamethylpiperidine (PMP, **5**), as an HI scavenger, the reaction affords (*R*)-spirooxindole **4**, also with high yields and enantioselectivity (up to 77% yield and 75% ee). The enantioselection is attributed to two distinct mechanistic pathways: a "cationic" vs "neutral" pathway based on the charge in the first-formed Pd(II)−alkene complex in each pathway. Silver salts with basic anions, such as Ag_2CO_3, Ag_2O, and Ag_3PO_4, act as HI scavengers to promote formation of cationic Pd(II) intermediate **7** for the olefin coordination (Scheme 1). In the absence of a Ag(I) additive as an HI acceptor, the Heck reaction proceeds through a neutral palladium−alkene complex.

Scheme 1. Intramolecular Heck Spirocyclization and Role of Silver Salt



More than 10 years after the pioneering reports with the asymmetric Heck reaction, Mikami reported a Pd-catalyzed ene-type cyclization strategy that has proved to be applicable as a general strategy for the enantioselective synthesis of various spirocyclic compounds.[17−19] The first report in 2003 utilizes a Pd(II)−BINAP complex for the synthesis of spirocyclic quinolines **9** (eq 2).[17] Subsequently, the authors demonstrate the success of this strategy for the synthesis of other spiroheterocycles, such as spiropyrrolidines and spirofurans.[17−19]



Several early examples for the catalytic asymmetric synthesis of spirocycles involve the use of Rh-catalyzed cyclizations. The first example of a Rh(I)-catalyzed spirocyclization was demonstrated by Tamao and co-workers in 1996 using an intramolecular bis-cyclization of silane **10** to afford spirosilane **13** (Scheme 2).[20] The reaction proceeds through a double hydrosilylation reaction that simultaneously generates chiral centers on silicon and carbon. It was not until 2001 that the first Rh-catalyzed enantioselective synthesis of an all-carbon spirocenter was reported: Hashimoto and co-workers demonstrated a double intramolecular bis-cyclization that proceeds through a double C−H insertion catalyzed by a chiral dirhodium(II) carboxylate (eq 3).[21] In addition to Pd- and Rh-catalysis, examples also include chiral molybdenum and zirconium catalysts for enantioselective spirocyclization reactions.[22,23]

Two additional interesting examples of Rh-catalyzed cycloaddition reactions are also highlighted here. In 2006, Shibata described an enantioselective Rh-catalyzed [2 + 2 + 2] cycloaddition for the synthesis of spirocycles, such as **19**, containing a quaternary carbon center (Scheme 3A).[24] This example involves an intermolecular variant using a diyne (**17**) with an exomethylene cyclic compound (**16**) and proceeds via achiral bicyclic metallacyclopentadiene intermediate **18**. The subsequent insertion of a 1,1-disubstituted alkene, followed by

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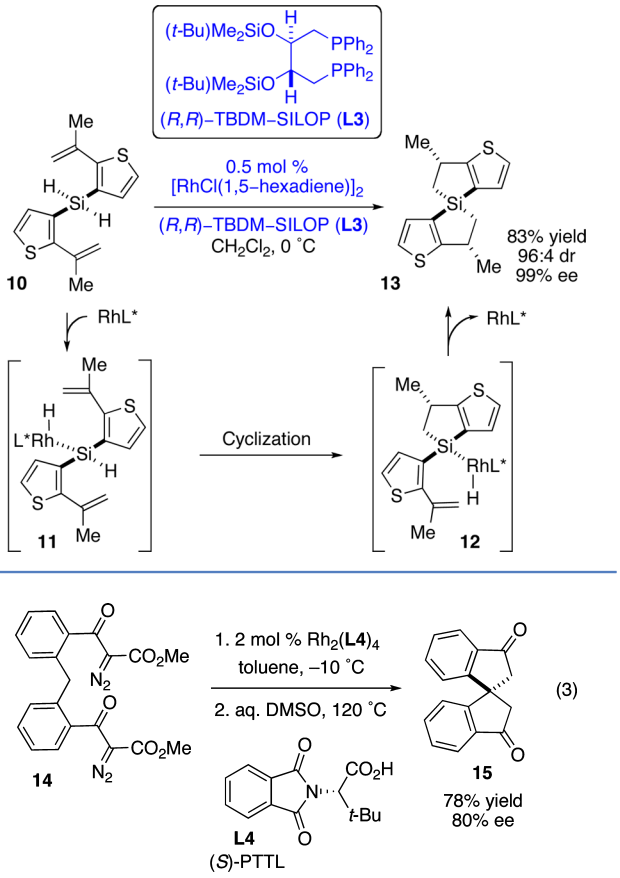
Scheme 2. Rh-Catalyzed Spirocyclic Silane Synthesis



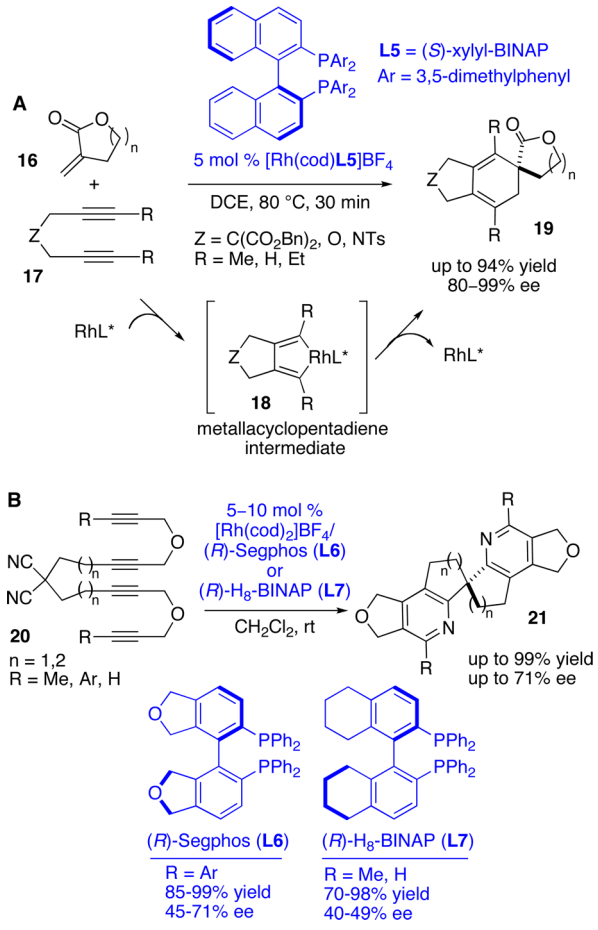
reductive elimination, induces formation of a chiral quaternary carbon spirocycle. Tanaka and co-workers have also reported an enantioselective Rh(I)-catalyzed intramolecular [2 + 2 + 2] cycloaddition with tetraynes **20** to access hexacyclic system **21** (Scheme 3B).[25] Two optimal ligands were identified for use on the basis of the R group (e.g., aryl or alkyl) of the substrate. The H8-BINAP ligand **L7** was identified as the most effective ligand for alkynes without aryl substitution, albeit with moderate enantioselectivity.

In 2008, Tanaka and co-workers also reported a Rh(I)-catalyzed intermolecular [4 + 2] spirocyclization reaction between acenapthenequinone **22** and 2-alkynylbenzaldehydes **23** to access spirocyclic benzopyranones such as **25**.[26] The reaction employs a cationic rhodium catalyst with (*R*,*R*)-walphos as the optimal chiral bisphosphine ligand (**L8**) to achieve excellent enantioselectivity (up to 99% ee) and yield (up to 97%) (Scheme 4). Other bisphosphine ligands were also investigated using benzaldehyde as a model system, but these showed lower yields and enantioselectivity. Various dicarbonyl substrates, including isatins, proceeded efficiently with high yields and enantioselectivity, although in some cases, a higher catalyst loading (e.g., 10 mol %) was utilized to maintain efficient conversion.

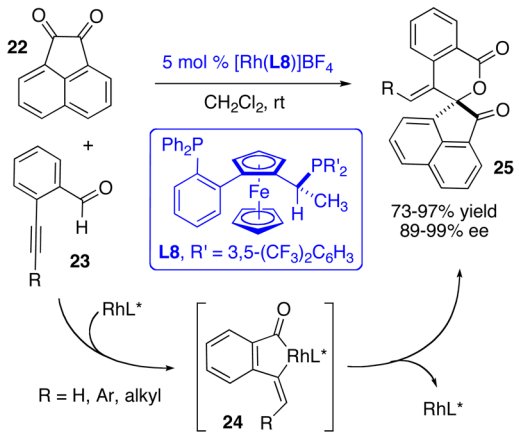
■ ENANTIOSELECTIVE SYNTHESIS OF SPIROKETALS

Spiroketal scaffolds are fascinating and synthetically challenging targets that are prevalent in natural products and have also been demonstrated as an important backbone for chiral ligands.[8,9] Many stepwise strategies have been employed for the formation of the spiroketal center, but here, we highlight two strategies

Scheme 3. Enantioselective Rh-Catalyzed [2 + 2 + 2] Cycloaddition Reactions: (A) Shibata and Co-workers. (B) Tanaka and Co-workers



Scheme 4. Rh(I)-Catalyzed Intermolecular [4 + 2] Spirocyclization



(metal-catalyzed and acid-catalyzed) in which the chiral catalyst is involved in the key spirocyclization step.

Wang, Ding, and co-workers reported the first asymmetric synthesis of aromatic spiroketals **28** using a one-pot Ir(I)-catalyzed hydrogenation and spiroketalization of α,α'-bis(2-hydroxyarylidene)ketones, such as **26** (eq 4).[6] The iridium complex (**27**) plays a dual catalytic role, acting as a catalyst for both the hydrogenation and the spiroketalization, and avoids racemization of the chiral α-carbon centers formed upon

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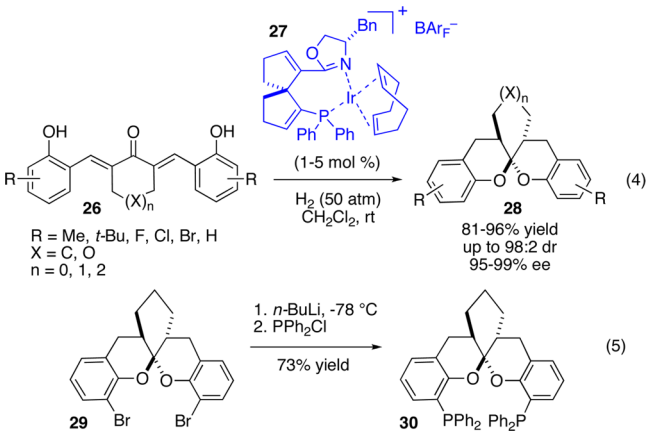
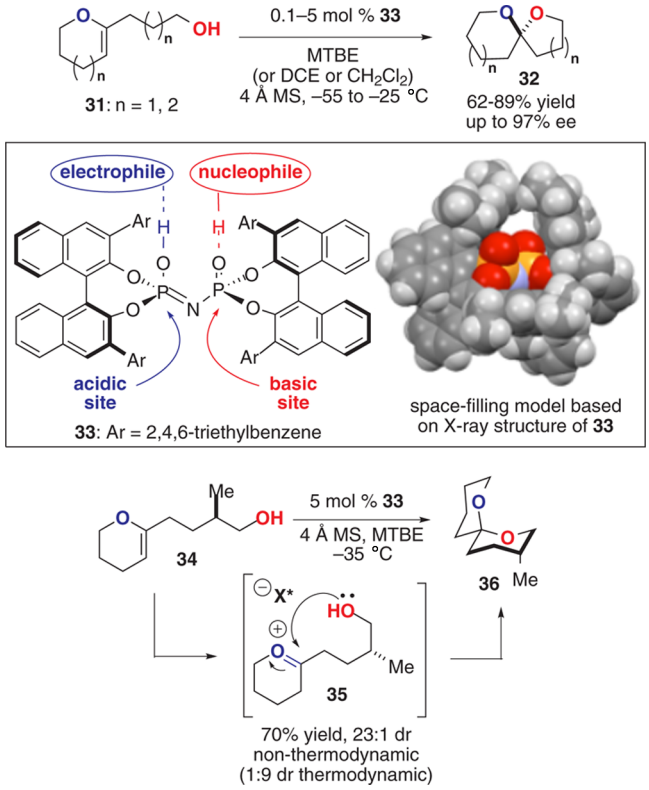


hydrogenation. Notably, the iridium catalyst complex uses a SpinPHOX spiroligand for the enantioselective synthesis of spiroketal scaffolds, for which the spiroketals (e.g., **29**) themselves have applications as the backbone for diphosphine spiroligands, such as **30**.[7] The reaction selectively produces the *trans*-spiroketal product with up to 98:2 diastereoselectivity in high yields (81−96%) and excellent enantioselectivity (95−99% ee), and the catalyst is effective with as low as 1 mol % catalyst loading. Investigations of the SpinPHOX ligand structure demonstrated that the chirality of the spiro backbone and the substituents on the oxazoline fragment play a dominant role in determining the levels of asymmetric induction and catalytic activity. Results of control experiments with different iridium complexes in the presence and absence of hydrogen indicate that the sequential reaction proceeds through an Ir(III) species generated by the oxidative insertion of H_2 into the chiral Ir(I) precatalyst. No spiroketalization was observed in the absence of H_2. The utility of the spiroketal backbone was demonstrated by transforming the *ortho*-brominated aromatic spiroketal to diphosphine ligand **30** in 73% yield (eq 5).

List and co-workers recently demonstrated the first catalytic enantioselective synthesis of unfunctionalized spiroketals via a spiroacetylation of hydroxyenol ethers **31** using a newly developed imidodiphosphoric acid catalyst **33** (Scheme 5).[27] Stereocontrol for the spirocyclization relies on the "confined" sterically compact chiral environment of the rigid bifunctional C_2-symmetric catalyst **33**, which possesses both a Brönsted acidic site and a Brönsted basic site. The *O*,*O*-syn isomer of the imidodiphosphate anion is conformationally locked with C_2-symmetry as a result of the bulky 3,3′-substituents. Previous chiral acid catalysts have been designed with an open active site, whereas this catalyst design features a sterically constrained active site inspired by enzymes and artificial enzyme mimics with deep active site pockets.[28,29] An extensive screen of chiral phosphoric acid catalysts revealed that the sterically compact environment, referred to as a "rigid chiral microenvironment," around the active site is essential to control the relative and absolute configuration of the spirocenter following the formation of the oxocarbenium ion intermediate. X-ray structure analysis of the catalyst and comparison with previous examples of phosphoric acid catalysts confirm that the chiral active site is deeply buried.

The design and activity of this catalyst utilizes as low as 0.1 mol % catalyst loading and is effective for the synthesis of spiroketal ring sizes from 5- to 7-membered rings in moderate to good yields (up to 88%) and excellent enantioselectivity (91−97% ee). It is also notable that this catalyst system allows

Scheme 5. Spiroacetylation of Hydroxyenol Ethers 31 and 34 Using Imidodiphosphoric Acid Catalyst 33



access to either the thermodynamically or kinetically favored spiroacetals. An optimized method affords the synthesis of the thermodynamically unfavored spiroketals in good yields (up to 89%), and in some cases, the diastereoselectivity for the nonthermodynamic spiroketal is higher than the diastereoselectivity for the thermodynamic spiroketal. The utility of the catalyst system was also demonstrated by a kinetic resolution in the presence of a substituted enol ether, such as **34**. The authors indicate that the catalyst design strategy based on a sterically constrained active site is one that is particularly effective for enantioselective reactions of small aliphatic substrates that do not possess sterically demanding substituents, large aromatic groups, or large protecting groups. As such, it is envisioned that this catalyst may have broad applications for traditionally difficult transformations. Of practical note, the imidodiphosphoric acid catalysts require only one additional synthetic step for preparation, as compared with the corresponding phosphoric acid catalysts.

■ ASYMMETRIC CATALYSIS FOR [3 + 2] DIPOLAR CYCLOADDITION REACTIONS

Among the strategies employed for the catalytic enantioselective synthesis of spirocyclic compounds, cycloaddition reactions have been identified as some of the most efficient and highly selective strategies. Several recent examples of catalysts and cycloaddition strategies are highlighted here.

NHC-Catalyzed Cycloaddition Reactions. Since Wanzlick reported the first synthesis of N-heterocyclic carbenes (NHCs) in the 1960s,[30,31] NHCs have found wide application as catalysts for enantioselective synthesis because of their umpolung-type reactivity.[32,33] In 2006, Nair reported the first NHC-catalyzed annulation of 1,2-diketones with enals for the

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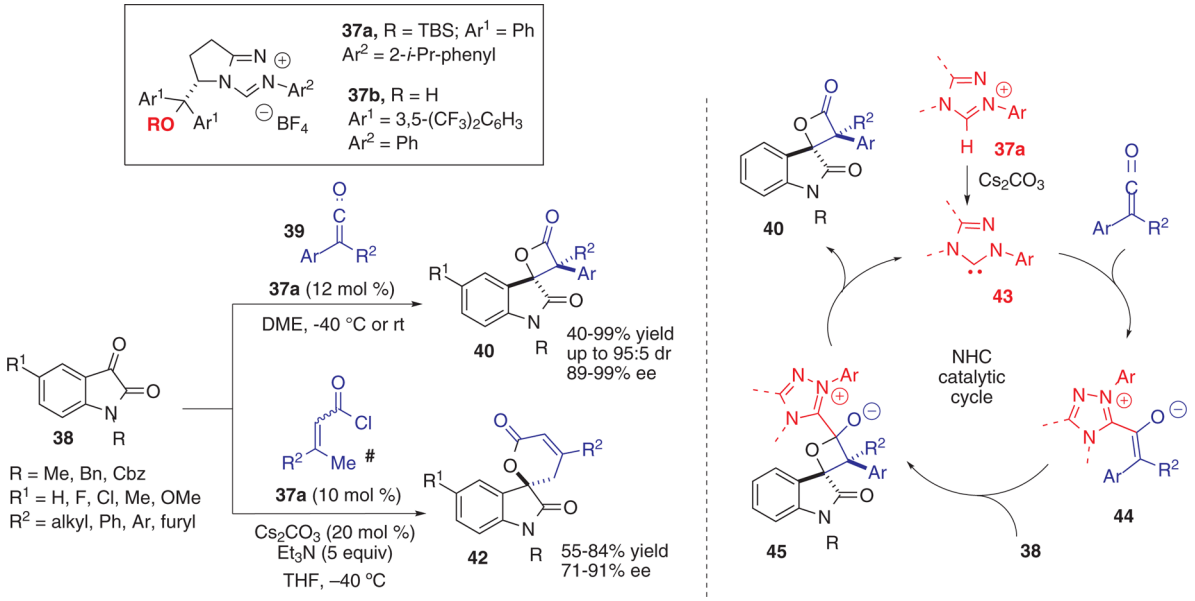
Scheme 6. (A) NHC-Catalyzed Cycloaddition/Annulation Reactions for the Synthesis of Spirocyclic Oxindoles Lactones; (B) Example of NHC Catalytic Cycle

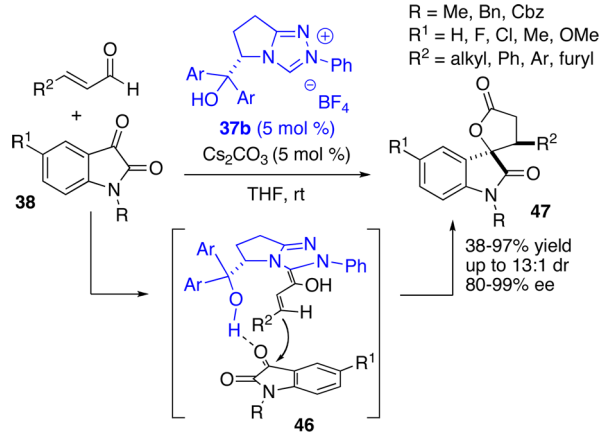


synthesis of racemic spirocyclic lactones with 1:1 diastereoselectivity.[34] The reports highlighted here showcase several of the applications for the enantioselective synthesis of spirocyclic compounds while comparing the reactivity and selectivity features for this class of catalyst.

Ye and co-workers have reported several examples of NHC-catalyzed cycloaddition/annulation reactions for the synthesis of spirocyclic oxindoles lactones, which also allows the opportunity to compare the reactivity and selectivity for these catalysts. Ye first reported that NHC catalyst **37a** is effective for the enantioselective synthesis of spirocyclic oxindole-β-lactones in a [2 + 2] cycloaddition between ketenes and isatins (Scheme 6A).[35] This strategy employs umpolung reactivity formed by the addition of the NHC catalyst to ketenes, as shown in the representative catalytic cycle for this class of reactions (Scheme 6B). The scaffold of carbene catalyst **37b** contains a distal alcohol, and the authors compared the reactivity and selectivity for the free hydroxy (**37b**) with the silyl ether (**37a**) catalyst variant. When the free hydroxyl group was capped with a sterically bulky TBS group, the catalytic activity was greatly increased. The authors also demonstrate that silyl ether NHC catalyst **37a** is optimal with acyl chlorides **41** to provide access to spirocyclic oxindole dihydropyranones **42**.[36] Here, the reaction requires the addition of triethylamine and also likely proceeds through a ketene intermediate.

Subsequently, Ye reported a related NHC-catalyzed [3 + 2] annulation strategy for the synthesis of spirocyclic oxindole-γ-butyrolactones **47** (Scheme 7).[37] This strategy employs umpolung reactivity of the homoenolate formed by the addition of the NHC catalyst to enals. The hydroxy (**37b**) and silyl ether (**37a**) variants of NHC catalysts were evaluated, and it was determined that the hydroxy NHC catalyst **37b** is optimal. Silyl ether catalyst **37a** demonstrated no reactivity, indicating that the hydrogen-bonding capability of free hydroxy catalyst is important for catalytic activity. Thus, the stereochemical outcome was rationalized on the basis of an essential hydrogen-bonding interaction between the catalyst and isatin, which activates the isatin and directs the homoenolate for addition (Scheme 7). The conditions used to generate the

Scheme 7. NHC-Catalyzed [3 + 2] Annulation Strategy for the Synthesis of Spirocyclic Oxindole–γ-Butyrolactones



NHC catalyst were also important, and it was found that 5–10 mol % of Cs_2CO_3 in toluene afforded the highest consistent diastereo- and enantioselectivity. Although high enantioselectivity was generally observed for various combinations of base and solvent, the diastereoselectivity was more directly affected by the selection of base and solvent. Under optimal conditions, catalyst loading could be reduced to 5 mol % with no loss in reactivity.

Scheidt and co-workers have recently featured a cooperative carbene catalysis strategy[38] with NHC and Lewis acid catalysts utilizing the same umpolung strategy of enals with isatins for the synthesis of spirocyclic oxindole-γ-butyrolactones **47** (Scheme 8).[39] Because these NHC catalysts (**48** and **49**) do not possess a proximal hydroxy capable of hydrogen bonding, as seen with the example from Ye and co-workers,[37] the authors demonstrate that a cooperative catalysis strategy can employ a Lewis acid to activate the chelating isatin electrophile. This strategy affords the same major diastereomer as observed above with Ye's system, albeit generally with a lower diastereoselectivity. Evaluation of various Lewis acids and additives

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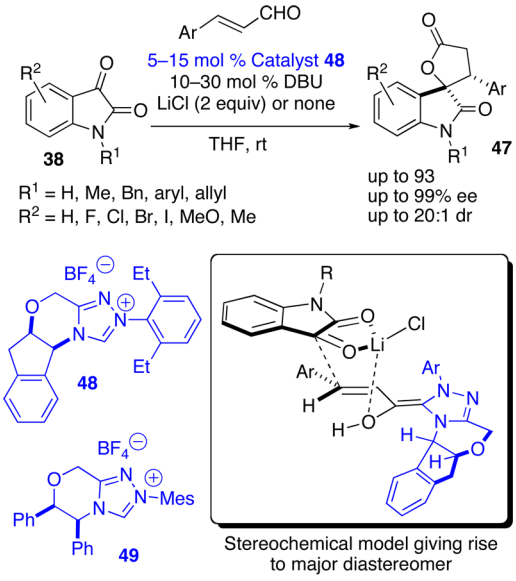
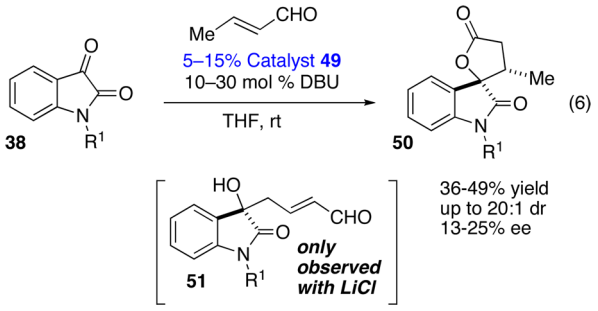
Scheme 8. Cooperative Carbene Catalysis Strategy for the Synthesis of Spirocyclic Oxindole−γ-Butyrolactones



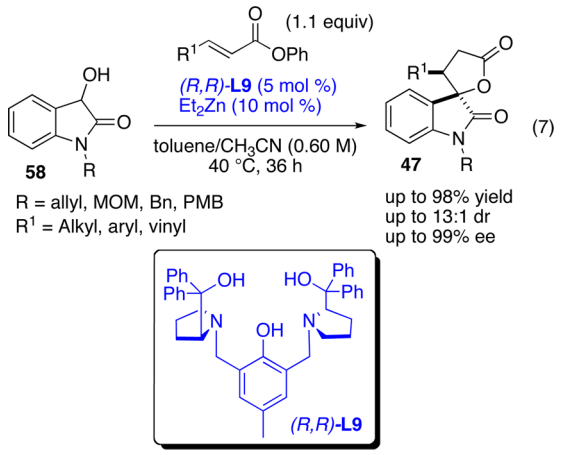
demonstrated that the lithium chloride was integral to achieve high selectivity; addition of 12-crown-4 to sequester the lithium cation afforded lower diastereo- and enantioselectivity. The enantioselectivity trend observed among cations (Li > Mg > Na) was attributed to the oxophilicity and coordination states, in which the high enantioselectivity observed with the lithium cation is attributed to an organized transition state through coordination of the enol oxygen of the NHC-bound homoenolate and the dicarbonyl of the isatin. To apply this methodology to alkyl enal substrates, the use of an alternate azolium catalyst had to be optimized without the use of LiCl because of the formation of enal **51** through a competing γ-alkylation pathway (eq 6).



(6)

In a complementary strategy to access spirolactones **47**, Melchiorre and co-workers have utilized the Jørgensen−Hayashi catalyst (**56**) in a Michael reaction strategy with an enediol intermediate **53** accessed from dioxindole **52** (Scheme 9).[40] The Michael reaction first produces spirohemiacetal **54**, which can be directly oxidized to the spirolactone. The authors note a "tremendous" rate acceleration using *o*-fluorobenzoic acid as an additive, which they attribute to minimizing the unproductive oxidative dimerization pathway that can produce an isatide byproduct (**57**).

Trost and co-workers have reported an alternate enantioselective synthesis of spirolactones **47** using a zinc−ProPhenol complex to catalyze the formal [3 + 2] cycloaddition of an α,β-unsaturated ester with 3-hydroxyoxindoles **58** (eq 7).[41] This



(7)

method utilizes the 3-hydroxyoxindole **58** to generate a nucleophilic isatinic anion equivalent for a tandem Michael addition-transesterification process. When evaluating the scope of Michael acceptors, the authors observed a significant dependency of diastereoselectivity on electronic and steric properties of the substrate. The reaction proceeds with excellent enantioselectivity for various electron-rich aryl groups; however, a decrease in diastereoselectivity was obtained with heteroaromatic rings, *ortho*-substituted rings, and disubstituted rings. In finding the optimal reaction conditions, reactions with cinnamoylpyrrole or cinnamoylindole gave excellent yields (91−92%) but moderate diastereo- and enantioselectivity (4.4:1 to 6:1). The highest diastereoselectivity and enantioselectivity were obtained with phenyl cinnamate (89% yield, 9.2:1 dr, 96% ee). A high concentration (0.6 M at 40 °C in toluene/CH_3CN) was determined to be optimal for the highest diastereoselectivity and yield of **47**. When Bu_2Mg was investigated in place of Et_2Zn to compare the activity of the corresponding dinuclear Mg complex, a precipitous drop was observed in the yield and selectivity. Trost and co-workers further investigated the zinc-catalyzed mechanism to demonstrate the role of the catalyst in the transesterification step. Upon subjecting a racemic hydroxyoxindole intermediate to reaction conditions, the spirolactone product was isolated with 11% ee, suggesting that the catalyst did not differentiate the stereochemistry upon cyclization. Without catalyst, no cyclized lactone product **47** was observed. Trost and co-workers propose that the mechanism proceeds through the deprotonation and coordination of the oxindole to the chiral catalyst complex, followed by coordination of the α,β-unsaturated ester to the least hindered Zn atom (Scheme 10). Subsequent Michael addition, followed by tautomerization and transesterification, affords spirolactone **47**.

Metal- and Acid-Catalyzed Cycloaddition Strategies for Spiroheterocycles. Several dipolar cycloaddition reactions using a chiral auxiliary to induce asymmetry have been reported,[42] but the first example of a catalytic asymmetric three-component dipolar cycloaddition reaction was reported for the synthesis of a spiro[pyrrolidine-3,3′-oxindole], such as **66** in 2009 by Gong and colleagues.[43] The spiro[pyrrolidine-3,3′-oxindole] core is an attractive synthetic target[44] because this heterocycle structure has been identified in various alkaloid natural products and is particularly significant for drug discovery efforts.[45−47] Gong reported BINOL-derived phosphoric acid catalyst **65** for the reaction between alkylidene oxindole **63** and azomethine ylides generated in situ from

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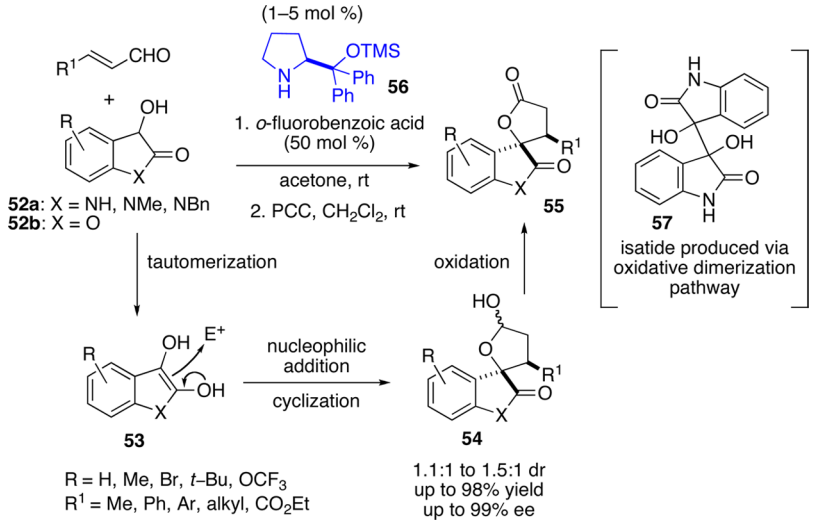
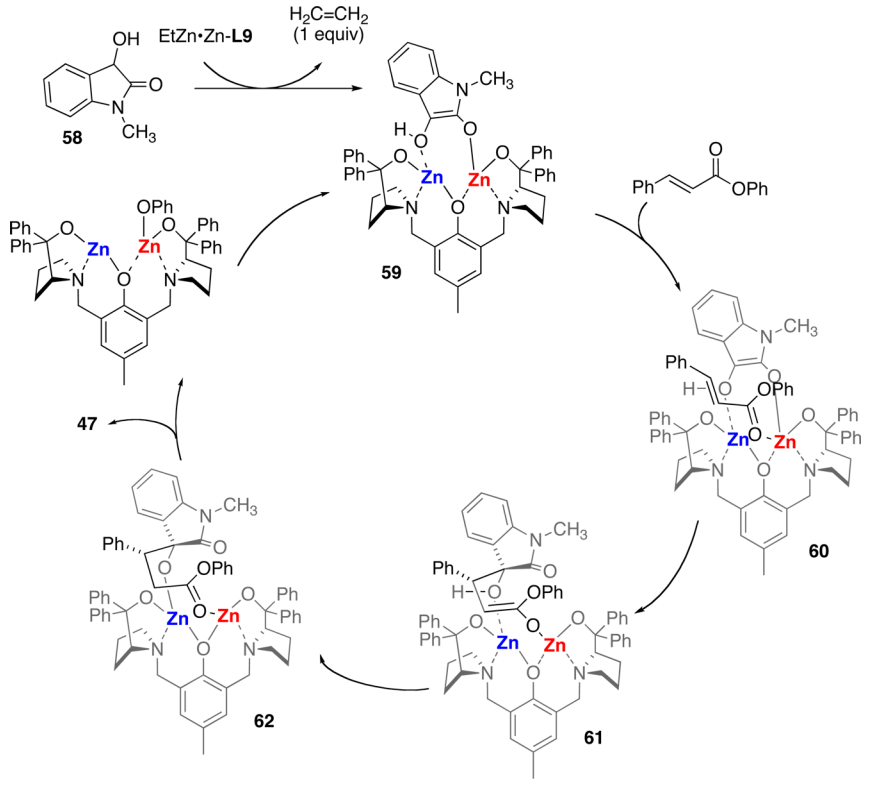
Scheme 9. Synthesis of Spirocyclic Oxindole−γ-Butyrolactones Using a Michael Reaction Strategy



Scheme 10. Proposed Mechanism for Zinc-ProPhenol-Catalyzed Spirolactone Synthesis



aldehydes with amino ester **64** (Scheme 11A). Using the *N*-acetate derivative of the alkylidene oxindole, the 1,3-dipolar cycloaddition proceeds with high yields, excellent enantioselectivity (up to 98% ee), and high regioselectivity. The regiochemistry of product **66** is rationalized on the basis of the stabilizing $\pi-\pi$ stacking interactions between the oxindole ring and the conjugated ester, which is opposite to what would be expected if directed by an electronic effect.[44] To account for the high enantio- and regioselectivity of the reaction, theoretical studies for the mechanism were performed, and transition state **TS-1** was proposed, in which both the azomethine ylide and the methyleneindolinone are hydrogen-bonded to chiral phosphoric acid catalyst **65**.

Both Waldmann[48] and Wang[49,50] have independently reported the enantioselective synthesis of spiropyrrolidine oxindoles **68** using a metal-catalyzed dipolar cycloaddition reaction (Scheme 11B). The metal-catalyzed reactions afford the regioisomeric products, in comparison with the products obtained from the acid-catalyzed reaction. This selectivity of the metal-catalyzed reaction is dependent on the ligand and metal combination. Waldmann reported high enantioselectivity (up to 98% ee) using copper with chiral ligand **L10**. A nonlinear relationship was observed for the ligand/Cu ratio in which a slight excess of ligand in a 1.1:1 ratio of ligand/Cu affords a 91:9 diastereomeric ratio with only 72% ee, whereas a 2:1 ratio affords a 94:6 diastereomeric ratio with 98% ee. Similar to the

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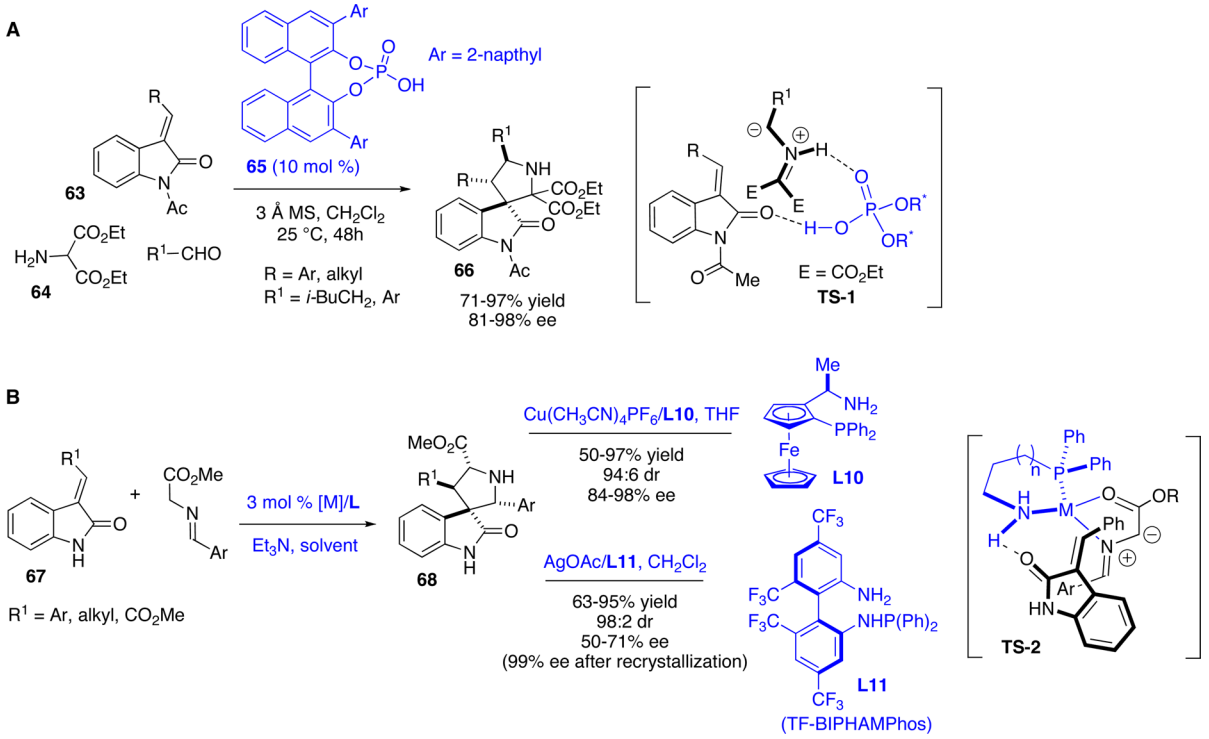
Scheme 11. Catalytic Asymmetric Three-Component Dipolar Cycloaddition Reactions for the Synthesis of Spiropyrrolidine Oxindoles with (A) a Chiral Phosphoric Acid Catalyst or (B) Metal Catalysts

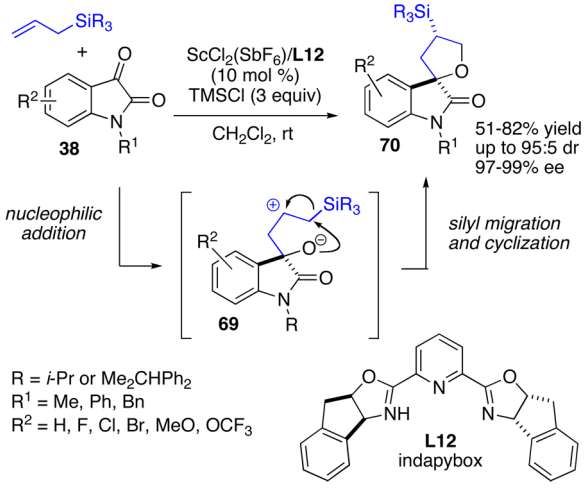


stereochemical rationale proposed for the Brönsted acid catalyst, the origin of enantioselectivity with the metal-catalyzed reaction is proposed to depend on hydrogen-bonding interactions of the ligand complex with oxindole **67** while chelating of copper to the imine. Waldmann also speculates that stabilizing $\pi-\pi$ stacking interactions contribute to the selectivity (Scheme 11B, **TS-2**). Using a Ag(I) complex as a catalyst, Wang and co-workers reported that TF-BIPHAMPhos (**L11**) is the optimal ligand. Using silver salts afforded consistently high diastereoselectivity (98:2 dr) and higher enantioselectivity (50−71% ee) compared with copper salts with this same ligand.

Franz and co-workers reported the first catalytic asymmetric [3 + 2] allylsilane annulation reaction, obtaining excellent enantioselectivity for tetrahydrofuranyl spirooxindoles, such as **70**, using a $ScCl_2(SbF_6)$-indapybox catalyst complex with TMSCl as an essential additive (Scheme 12).[51] Although allylsilanes have been demonstrated as mild nucleophiles effective for enantioselective allylation reactions, the formation of intermediate β-silyl carbocations (stabilized through hyperconjugation) can be used to access a spirocyclic annulation product, depending on the catalyst and silyl group employed.[52] Because of the competing allylation pathway (i.e., Hosomi−Sakurai addition), the reactivity of the catalyst was optimized to ensure high enantioselectivity as well as high selectivity for the annulation product. The role of the scandium salt (triflate vs chloride), counterion, and solvent were all important factors to optimize formation of the annulation product. The annulation products can be further transformed using Tamao−Fleming conditions to oxidize the C−Si bond and generate hydroxy-substituted tetrahydrofuranyl spirooxindoles.[53,54]

Cycloaddition strategies with phosphine-catalyzed Morita−Baylis−Hilman[55] (MBH) reactions have been extensively explored[56,57] and can be applied for the synthesis of

Scheme 12. Catalytic Asymmetric [3 + 2] Allylsilane Annulation Reaction Using a $ScCl_2(SbF_6)$-indapybox Catalyst



spirocyclopentenes, such as **74**. The first use of an asymmetric phosphine-catalyzed [3 + 2] annulation/cycloaddition reaction was reported by Zhang and co-workers,[58] and the first report of an asymmetric phosphine-catalyzed MBH reaction was reported by Wakatsuki and co-workers.[56] Marinetti and co-workers reported access to spirocyclopentenes, such as **74**, using chiral phosphine catalysts in a MBH reaction with allenes **71** and alkylidene oxindoles **63** (Scheme 13).[57] This reaction affords access to spirocyclic pentenes containing various substitution patterns based on the position of the alkene and the EWG. The authors investigated several phosphine catalysts to identify the appropriate balance of activity and selectivity in this reaction. Phosphine **75** was identified to give the highest

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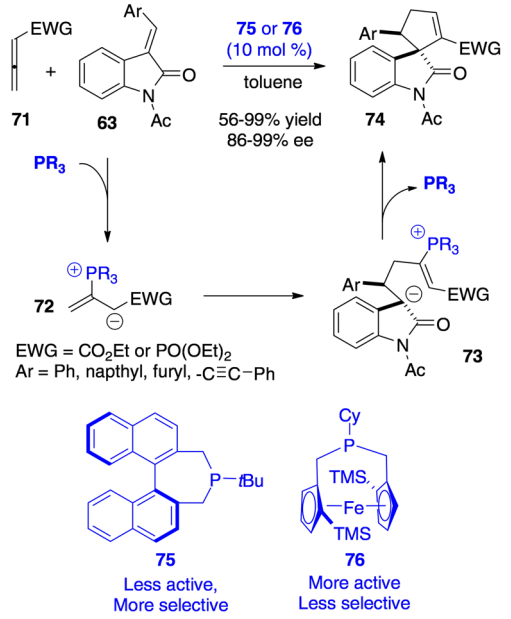
Scheme 13. Synthesis of Spirocyclopentenes Using Chiral Phosphine Catalysts in a MBH Reaction

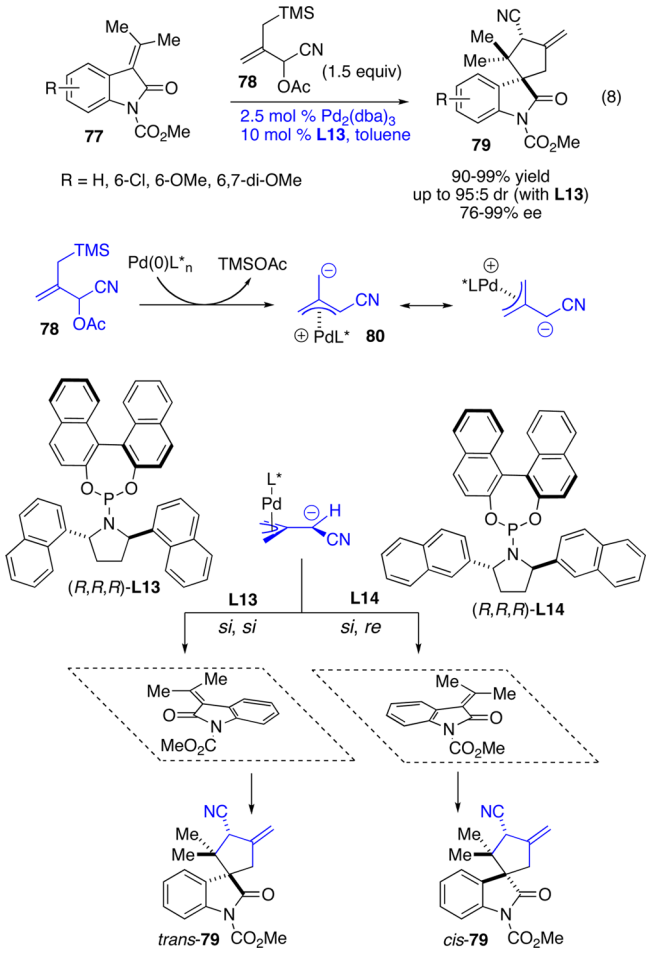


enantioselectivity (97% ee) and regioselectivity, but was less efficient and proceeded with lower yields with electron-rich alkylidene substrates. Phosphine **76** was identified as a more active catalyst for a broader scope of reactants, albeit affording products with slightly lower selectivity (e.g., 90% ee). Subsequently, Barbas and Lu independently reported the synthesis of related spirocycles with moderate to high yields and enantioselectivity using a similar Morita−Baylis−Hilman strategy with bifunctional phosphine catalysts.[59,60]

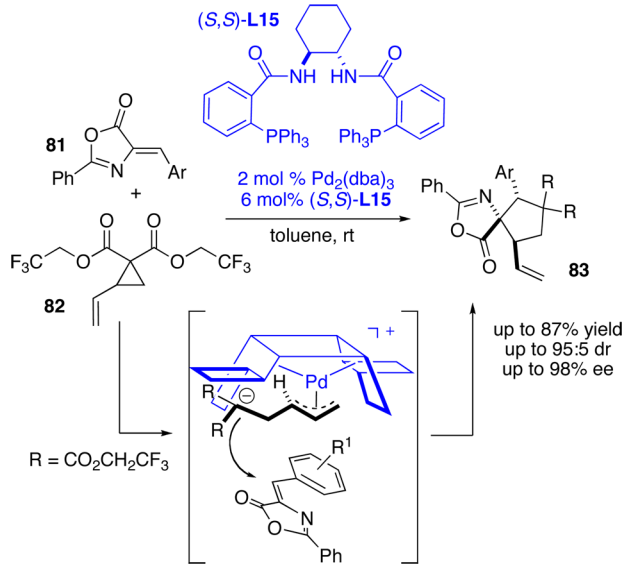
Several examples of Pd-catalyzed cycloaddition reactions that showcase applications of cycloaddition reactions for the synthesis of spirocyclic compounds have been reported. Trost and co-workers first reported the synthesis of spirocyclic cyclopentanes **79** in 2007 using a Pd-catalyzed [3 + 2]-cycloaddition reaction of trimethylenemethane **80** with alkylidine oxindole **77** (eq 8 in Scheme 14).[61] This reaction uses allylic silane **78** to access the nucleophilic Pd-allyl species **80**. Chiral phosphoramide ligands afford high diastereo- and enantioselectivity for this reaction (up to 95:5 dr and 99% ee). Remarkably, the selection of chiral ligand (**L13** or **L14**, which differ only by the position of the naphthyl substitution on the pyrrolidine ring), can control the formation of either the cis or trans product with high diastereoselectivity. Using the achiral hexamethylphosphoramide as a ligand only afforded a 2:1 mixture of trans/cis diastereomers of spirooxindole **79**. The authors identified that an ester substituent on the nitrogen of the alkylidene greatly enhanced reactivity, a trend that is consistent for many reactions of alkylidene oxindoles. The authors also demonstrate that an unsymmetrical disubstituted alkylidene oxindole can be employed to obtain an additional stereocenter, albeit with lower diastereo- and enantioselectivity.

Trost has also reported the use of palladium catalysts for the dynamic kinetic asymmetric formal [3 + 2]-cycloaddition of vinyl cyclopropanes **82** as a new class of 1,3-dipole donors and alkylidene azalactones (**81**) as prochiral Michael acceptors (Scheme 15).[62] This reaction sets three stereogenic centers with high diastereo- and enantioselectivity to provide functionalized chiral amino acid derivatives, such as **83**. The

Scheme 14. Pd-Catalyzed [3 + 2]-Cycloaddition Reaction of Trimethylenemethane for the Synthesis of Spirocyclic Cyclopentanes



Scheme 15. Pd-Catalyzed [3 + 2]-Cycloaddition of Vinyl Cyclopropanes with Alkylidene Azalactones



trifluoroethyl ester group was determined to be vital to enhance the stability and increase the lifetime of the dipole while still maintaining reactivity. Spirocycle **83** was identified as

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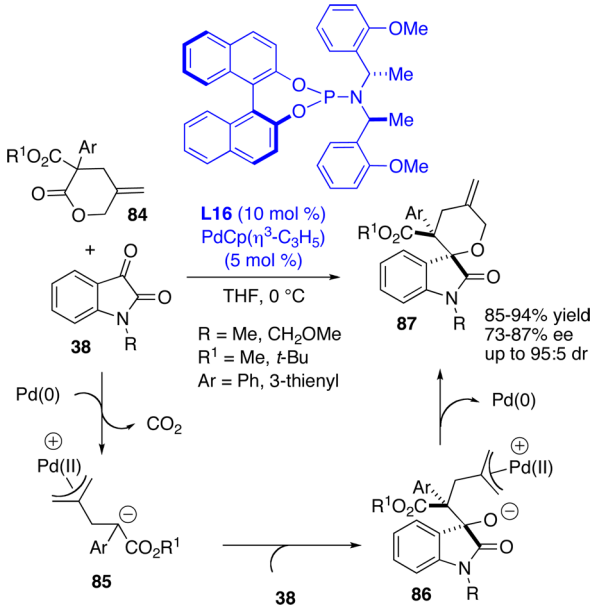
the trans isomer between the vinyl and aryl groups (although cis is more thermodynamically favorable). This was the first time that phosphine ligands such as **L15** have been used to induce asymmetry in a conjugate addition reaction. The observed stereoselectivity is rationalized on the basis of a modification of Trost's previously reported "wall and flap" model.[63,64] These phosphine ligands are able to control stereochemistry in the Michael reaction at a bond-forming event distal to the π-allyl Pd-complex, in addition to controlling the stereochemistry at the prochiral nucleophile and the allyl center.

Hayashi and co-workers have reported an asymmetric Pd-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactones **84** with isatins (**38**) to access spirocyclic oxindole pyrans **87** (Scheme 16).[65] The reaction affords the highest yield

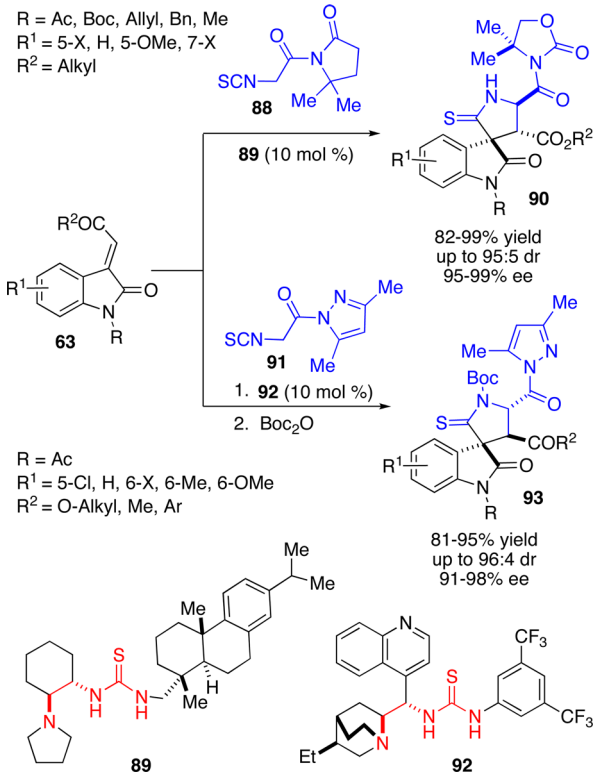
Scheme 16. Pd-Catalyzed Decarboxylative Spirocyclization



and enantioselectivity with phosphoramide ligands, such as ligand **L16**. The reaction proceeds with high diastereoselectivity for either a methyl or *tert*-butyl ester (88:12 and 95:5 dr, respectively) but the highest enantioselectivity was observed with the methyl ester (87% vs 73% ee for the *t*-Bu ester).

Thiourea-Catalyzed Cycloaddition Reactions. Several thiourea-catalyzed cycloaddition reactions have been reported for the enantioselective synthesis of spirocyclic compounds. Wang has reported a thiourea-catalyzed reaction of α-isothiocyanato amides **88** in an enantioselective 1,3-dipolar cycloaddition strategy with alkylidenes **63** to form spirooxindole **90** (Scheme 17).[66] Bifunctional rosin-derived thiourea catalyst **89** (10 mol %) containing an appended tertiary amine to promote asymmetric induction, afforded excellent yields (99%) and high enantio- and diastereoselectivities (99% ee, 95:5 dr). Barbas and Zhong have reported a similar strategy using bifunctional tertiary amine-thiourea **92** to catalyze the addition of diazole isothiocyanates **91** to alkylidene oxindoles.[67] The proximal diazole or amide appendage of the isocyanate was essential for high diastereo- and enantioselectivity, which is attributed to a bidentate mode of binding with the thiourea catalyst.

Scheme 17. Thiourea-Catalyzed Cycloaddition Reactions



Barbas and co-workers have also reported an expedient synthesis of pentacyclic spirooxindoles, such as **97**, using a Diels–Alder reaction with vinyl indoles **95** catalyzed by C_2-symmetric bis-thiourea catalyst **96** (Scheme 18).[68] The authors demonstrate that enantioselectivity is specific to the use of the *N*-Boc oxindole; no stereoinduction was observed with N–H or *N*-Bn oxindole derivatives. A control experiment demonstrated that the reaction of N–H oxindole substrates proceeds without a catalyst, providing a quantitative yield of the product in ≤2 h. An investigation of catalyst loading and concentration effects for the reaction demonstrated that a lower concentration of alkylidene **94** (0.025 vs 0.1 M) and a higher catalyst loading (15 vs 5 mol %) led to optimal enantioselectivity. A comparison with other thiourea catalysts demonstrated dramatically reduced selectivity. The authors comment on several practical aspects for this catalyst system because the product was insoluble and immediately precipitated, while the catalyst remained in solution. Therefore, catalyst recycling experiments were performed using a simple centrifugation and filtration procedure to recycle the soluble catalyst and demonstrate its continued efficacy up to five times, showing that the diastereoselectivity was retained, and only a mild effect on the enantioselectivity was observed.

Barbas and co-workers have designed and utilized a multifunctional organocatalyst **99** for the enantio- and diastereoselective synthesis of bispirooxindole **100** on the basis of a domino aldol–Michael strategy (eq 9).[69] Organocatalysts have been widely employed for domino aldol–Michael strategies,[70,71] and this is one example that specifically highlights the application of this strategy for the synthesis of spirocyclic compounds. The design of catalyst **99** involves the fusion of (*S*)-binaphthyl amine, thiourea, and cinchona alkaloid components. The asymmetric catalytic domino reaction of alkylidene oxindole **63** with β-oxindolyl ketone **98** produces

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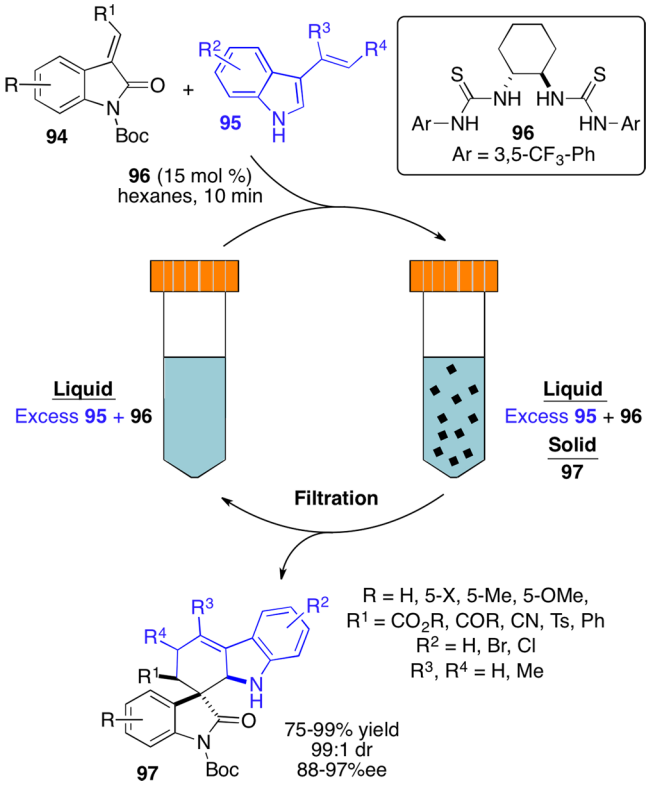
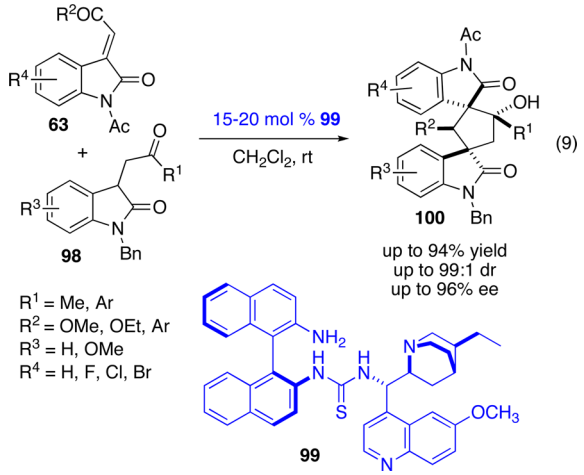
Scheme 18. Synthesis of Pentacyclic Spirooxindoles with Thiourea Catalyst Recycling





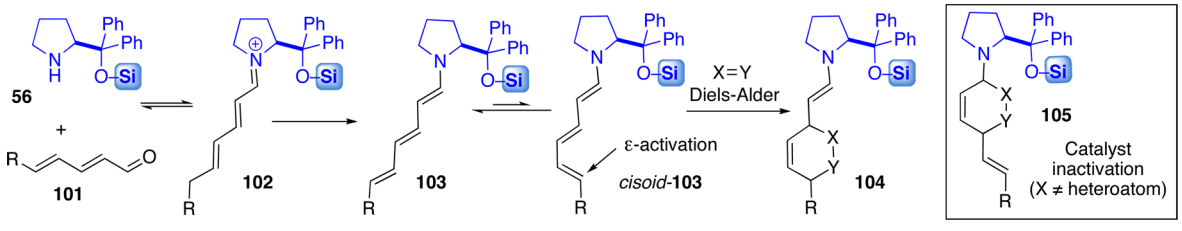
bispirooxindole **100** with four stereocenters in high yields (up to 94%), high enantioselectivity (up to 96% ee), and excellent diastereoselectivity (up to 99:1 dr) at room temperature. To investigate the significance of each component of the multifunctional catalyst system, several related cinchona alkaloid derivatives and thiourea−cinchona-type organocatalysts were compared. From this analysis, the (*S*)-binaphthyl primary amine, the tertiary nitrogen of the cinchona alkaloid, and the thiourea components were each demonstrated to be significant for optimal enantio- and diastereoselectivity. Although *β*-oxindolyl arylketones perform better than the methylketone variants (in terms of yield and diastereoselectivity), the enantioselectivity remains remarkably high for many functional groups.

Pyrrolidine Catalysts for Cycloaddition Reactions. Jørgensen and co-workers describe the first example of a pyrrolidine-catalyzed trienamine strategy and showcase this as a remarkably broad strategy for the enantioselective synthesis of complex spirocycles (Scheme 19). The first report described the use of a TES-variant of the Jørgensen-Hayashi catalyst (**56**) for the cyclization of *α*,*β*,*γ*-unsaturated aldehydes **101** combined with alkylidene oxindoles **94** to afford spirooxindoles **106** with high diastereo- and enantioselectivity (up to 93:7 dr and 99% ee) (Scheme 20).[72] Expanding on the electrophilic component, Jørgensen additionally reports the capture of the enamine intermediate using an ethyl 2-(diethoxyphosphoryl)-acrylate electrophile **107** to access spirocycle **108**. On the basis of analysis of ^{1}H NMR spectroscopy, the amount of trienamine generated under neutral conditions was <10%; however, using an acid additive, the amount of trienamine in solution was observed to increase up to 50%. In addition, only one isomer of the trienamine was observed (with no iminium ion observed), explaining the lack of dimerization products and the high selectivity.

Jørgensen and co-workers have additionally reported this trienamine strategy with alkylidene oxindoles **94** and *α*,*β*,*γ*-unsaturated aldehyde **109** (Scheme 20) to generate bridged pentacyclic spirocycles **112** in good yield with excellent diastereo- and enantioselectivity (up to 95:5 dr and 99% ee).[73] Although the addition of trienamines to *β*-aryl-substituted olefinic azalactones was previously investigated by Jørgensen and co-workers, this report expanded upon their earlier work.[74] Computational studies provided insight into the reaction mechanism and the energy barriers for the formation of several enamine intermediates. Initially, the "linear" trienamine **110** is formed (similar to **102**), which can be observed by ^{1}H NMR spectroscopy; however, "cross" trienamine **111** is proposed as the active species that leads to spirocycle **112**. The energy barrier for the reaction with linear trienamine **110** pathway was lower than that of the cross trienamine species (**111**), whereas the energy of the product (i.e., **112**) was lower for the cross trienamine pathway, thus indicating that the reaction is under thermodynamic control.

Melchiorre and co-workers have also reported an asymmetric Diels−Alder reaction using a trienamine strategy with the Jørgensen−Hayashi catalyst (**56**) and alkylidene oxindoles **94**

Scheme 19. Overview of Trienamine Strategy for Cycloaddition Reactions



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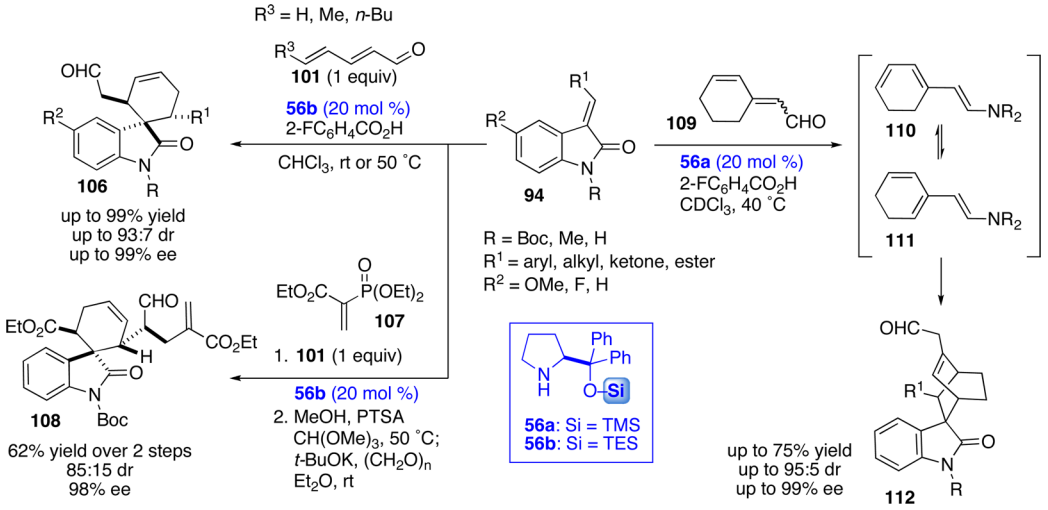
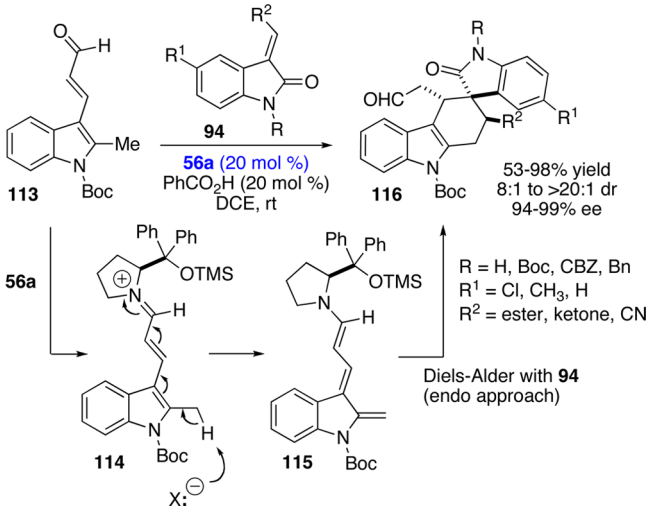
Scheme 20. Spirocycle Accessed Using a Trienamine Strategy with Catalyst 56



as dieneophiles (Scheme 21). The reaction harnesses transiently generated *ortho*-quinodimethane intermediates

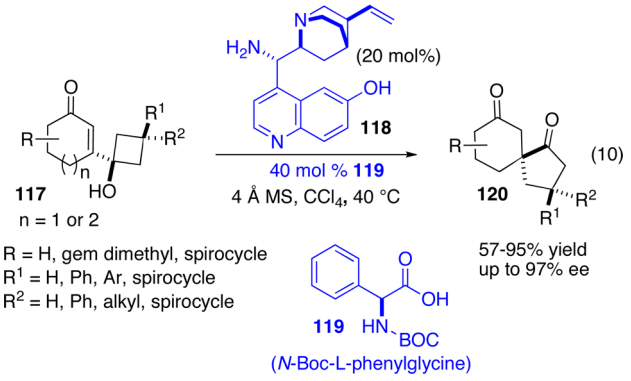
Scheme 21. Asymmetric Diels-Alder Reaction with Transient *ortho*-Quinodimethanes



(**115**) as reactive dienes to afford spirooxindoles such as **116** in high yields with selectivity up to 95:5 dr and 93% ee.[75] Upon formation of iminium ion **114** with catalyst **56a**, the formation of *ortho*-quinodimethane **115** is driven by the increased acidity of the proton of 2-methylindole. Initial investigations with proline or imidazolidinone aminocatalysts showed no reactivity under various conditions. The addition of catalytic amounts of benzoic acid provided an increase in diastereoselectivity from 80:20 to 92:8. A stereochemical model is proposed on the basis of both the steric interactions of the catalyst and the electronic interactions of the π-system. The steric effects of the chiral catalyst can effectively induce π-facial selectivity for approach to the *ortho*-quinodimethane intermediate with favorable π(C=O)−π(diene) orbital interactions in an endo approach. The scope of the Diels−Alder reaction also extends to pyrrole- and furan-based *ortho*-quinodimethanes, which also proceed with high yield and enantioselectivity.

ASYMMETRIC CATALYSIS FOR REARRANGEMENT/RING-EXPANSION REACTIONS

Rearrangements and ring-expansion reactions also provide a unique strategy to establish a spirocenter with interesting opportunities for asymmetric catalysis. The stereoselective construction of quaternary carbon stereocenters via a semipinacol rearrangement has been demonstrated.[76] Tu and co-workers developed the first enantioselective synthesis of a spirocyclic compound using a cinchona alkaloid catalyst (**118**) for a semipinacol rearrangement strategy (eq 10).[77] The



semipinacol reaction proceeded through a ring expansion to afford spirocyclic diketone **120** in 84% yield and 77% ee. The reaction required 20 mol % catalyst loading and also relies on the presence of *N*-boc-L-phenylglycine (**119**) as an acid additive (40 mol %). The method is successful for 5-, 6-, or 7-membered ring spirocycles fused onto the 3-position of a cyclobutane where the enone ring is substituted; however, a noticeable decrease in enantioselectivity was observed for *trans*-cyclobutane substrates (vs the cis-substituted cyclobutane). The reaction affords the highest enantioselectivity (77% ee) when multiple functional groups within the alkaloid catalyst are available, including the hydroxyl group of the alkaloid catalyst.

Subsequently, Tu and co-workers also demonstrated a related semipinacol rearrangement for the synthesis of chiral spiroethers **125** using a bulky chiral BINOL-derived phosphoric acid **122a** (Scheme 22).[78] Both the protonated form (**122a**) of the catalyst and the silver salt form (**122b**) were identified as active catalysts for this reaction. The steric bulk of the R group

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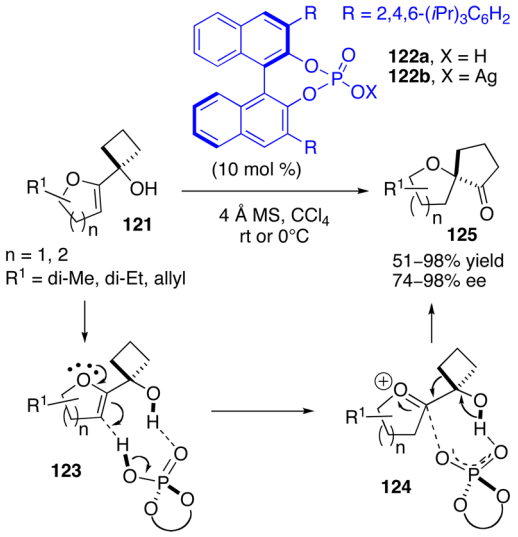
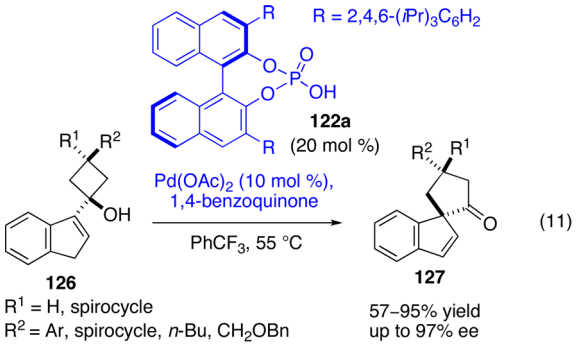
Scheme 22. Phosphoric Acid-Catalyzed Semipinacol Rearrangement



of the catalyst plays a significant role to increase the enantioselectivity and yield of the reaction (up to 98% yield and 98% ee), with the 2,4,6-(iPr)$_3$C$_6$H$_2$-substituted BINOL-phosphoric acid identified as the optimal catalyst. For this transformation, Tu and co-workers propose that an acidic proton is transferred to the enol ether (e.g., **123**) to induce the asymmetric semipinacol rearrangement.

Rainey and co-workers have subsequently reported an asymmetric semipinacol rearrangement for the synthesis of spirocycle **127** through the allylic C−H activation of indene **126** (eq 11).[79] This reaction employs a dual catalyst system



with Pd(OAc)$_2$ and chiral BINOL-derived phosphoric acid **122a**, affording moderate to high yields and high enantioselectivity (up to 98% ee) with various alkyl and aryl substituents at the 3 position of the cyclobutane. The electronic and steric effects of the BINOL−phosphoric acid play a competing role in the reactivity and enantioselectivity. Although the highest reactivity was achieved using BINOL−phosphoric acid derivatives containing electron-deficient aryl groups, the highest enantioselectivity was achieved using acid derivatives containing sterically bulky groups (e.g., 2,4,6-(iPr)$_3$C$_6$H$_2$−). The use of 1,4-benzoquinone was also determined to be essential for reactivity, which serves to oxidize the Pd(0) species to generate the Pd(II) catalytic species for effective turnover of the catalyst. Efforts to elucidate the mechanism of the reaction revealed that there is a primary kinetic isotope effect at the allylic C−H position and indicated that β-hydride elimination is the rate-determining step.

SUMMARY AND OUTLOOK

Spirocycles provide an exciting platform to develop and understand the reactivity and selectivity for a wide variety of catalysts while affording diverse strategies to access molecules with important applications. Although certain catalysts and strategies appear to have become "privileged" routes for the efficient construction of spirocenters, there are many new strategies being developed on the horizon. These strategies will continue to be developed and utilized, providing enhanced opportunities for asymmetric catalysis.

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Notes

The authors declare no competing financial interest.

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