

RECENT ADVANCES IN CATALYTIC ASYMMETRIC SYNTHESIS OF PYRAZOLINE AND PYRAZOLIDINE DERIVATIVES

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Abstract. *Pyrazolines and pyrazolidines represent two important classes of five-membered N-heterocycles found in many natural products, agrochemicals and biologically active molecules. Over the past decades, tremendous efforts have been devoted to the development of efficient methods for efficient construction of these scaffolds. However, the catalytic asymmetric synthesis of pyrazolines and pyrazolidines remains a challenging task for organic chemists. Recently, a wide range of catalytic asymmetric cycloaddition, cyclization and cascade reactions have been developed to access these enantioenriched heterocycles. Thus, this chapter will survey the main recent advances on the catalytic asymmetric synthesis of pyrazoline and pyrazolidine derivatives and working models.*

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1. Introduction

Pyrazolines and pyrazolidines are two classes of privileged five-membered nitrogen-containing heterocycles with wide existence in many natural products, biologically active compounds, engineering materials and pharmaceuticals.¹ They have also been often utilized as valuable synthetic building blocks and chiral ligands in asymmetric catalysis.² Not surprisingly, over the past few decades, considerable efforts have been devoted to the development of much more practical, efficient and step-economic approaches to these important architectures. In this context, however, the catalytic asymmetric synthesis of pyrazoline and

pyrazolidine derivatives has still been largely unexplored and remains a challenging and attractive task for organic chemists. Recently, catalytic asymmetric 1,3-dipolar cycloaddition reaction has received extensive attention within the synthetic organic community, and been established as a versatile platform for the efficient synthesis of optically active pyrazoline and pyrazolidine derivatives.³ In this regard, nitrile imines, diazoacetates and azomethine imines have served as three types of versatile 1,3-dipoles and found wide applications in 1,3-dipolar cycloaddition reactions for their synthesis through metal- or organocatalysis. In addition, catalytic asymmetric 6π electrocyclization and conjugate addition/cyclization cascade reactions also provided efficient methods to construct these heterocyclic scaffolds. Since the first report of the Kobayashi group in 2002,⁴ the asymmetric [3+2] cycloaddition reactions of hydrazones with alkenes have also proved to be another powerful approach to these *N*-heterocycles.⁵ Thus, the main recent advances on the catalytic asymmetric synthesis of pyrazoline and pyrazolidine derivatives and working models will be discussed in this chapter.

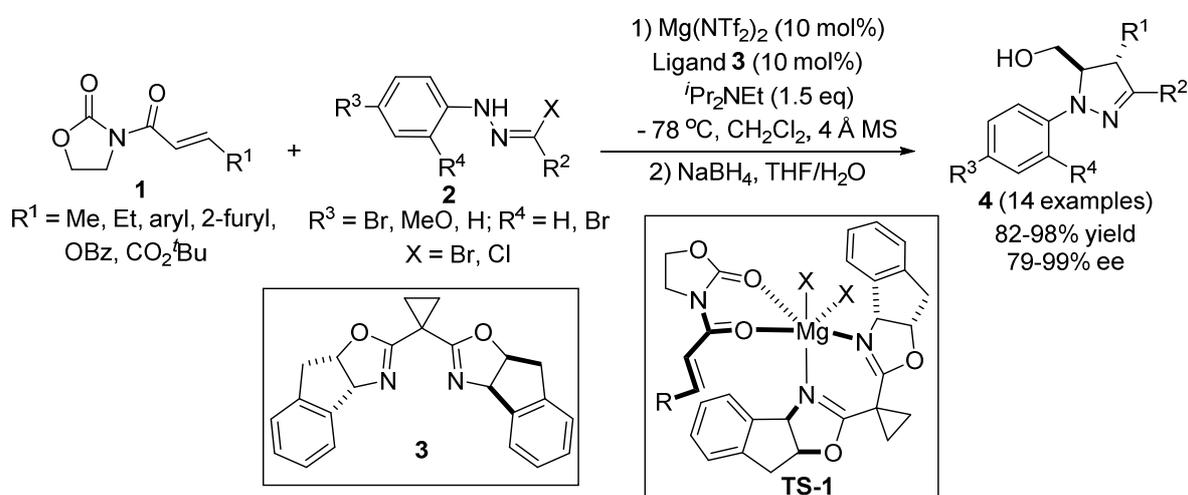
2. Catalytic asymmetric synthesis of pyrazolines

2.1. 1,3-Dipolar cycloaddition reactions

2.1.1. 1,3-Dipolar cycloaddition reactions of nitrile imines

Recently, the 1,3-dipolar cycloaddition reaction (1,3-DCR) has been established as one of the most powerful methods for the assembly of diversely functionalized five-membered nitrogen-containing heterocycles.³ In this context, nitrile imines represent a class of versatile 1,3-dipoles, generated *in situ* from the corresponding hydrazoneoyl chlorides or bromides under the alkaline condition, and have been successfully applied to the synthesis of biologically important pyrazoline derivatives. However, over the past decades, this field has been dominated by the racemic reactions. The development of catalytic asymmetric cycloadditions of nitrile imines for the synthesis of optically active pyrazolines remain a challenging task for synthetic chemists.

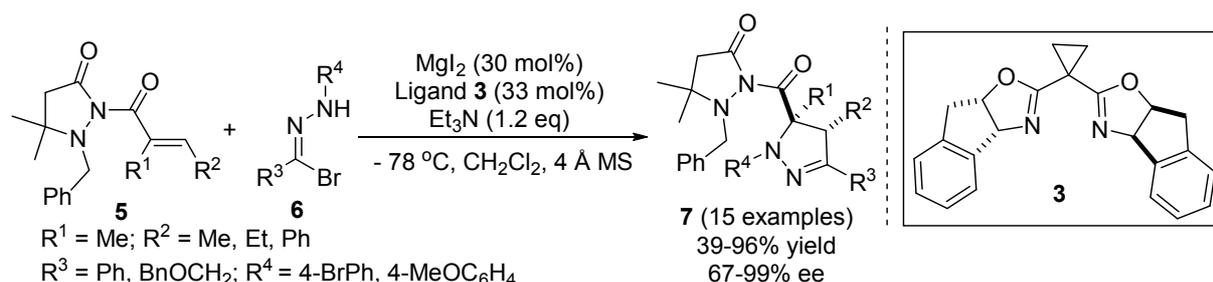
In this regard, the Sibi group in 2005 reported a pioneering example of catalytic asymmetric [3+2] cycloaddition of electron-deficient olefins **1** with nitrile imines **2** using a chiral Mg(II)-complex as catalyst (Scheme 1).⁶



Scheme 1. Mg(II)-complex catalyzed enantioselective [3+2] cycloaddition of nitrile imines.

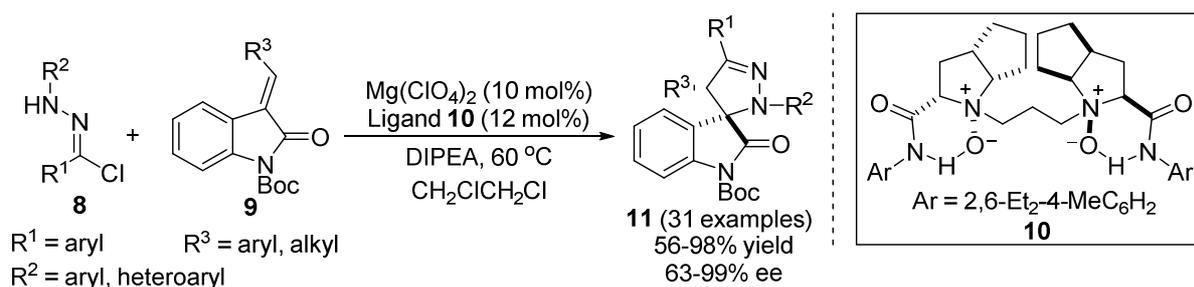
The achiral chelating auxiliary oxazolidinone moiety of **1** proved to be essential for high reaction efficiency. Compared with $\text{Mg}(\text{NTf}_2)_2$, other Lewis acids, such as $\text{Zn}(\text{II})$, $\text{Ni}(\text{II})$ and $\text{Cu}(\text{II})$, showed relatively lower catalytic activity. Under the optimized reaction conditions, the pyrazoline derivatives **4** could be obtained in generally good yields with excellent enantioselectivities (up to 98% yield, 99% ee). Based on the observed coherent absolute configuration of the products, a possible transition-state **TS-1** was also proposed to explain the stereochemical outcome of the reaction although the precise mechanism is unclear (Scheme 1). This work represented the first example of catalytic asymmetric 1,3-dipolar reaction of nitrile imines for the synthesis of optically active pyrazolines. However, the indispensable achiral chelating auxiliary of the substrates limited the potential practical application of this methodology to somewhat extent.

As part of their continuing work on pyrazolines synthesis via a [3+2] cycloaddition of nitrile imines, Sibi and co-workers in 2006 further developed a MgI_2 /bisoxazoline **3** complex catalyzed 1,3-dipolar cycloaddition reaction of α , β -unsaturated carbonyl substrates **5** with nitrile imines (Scheme 2). In contrast to their previous report,⁶ 1-benzyl-5,5-dimethylpyrazolidin-3-one was identified as the suitable achiral auxiliary in this reaction.⁷ Under the optimal conditions, various enantioenriched dihydropyrazoles **7** bearing a stereocenter at 5-position can be obtained in moderate to good yields with high enantioselectivities (up to 96% yield, 99% ee).



Scheme 2. MgI_2 /bisoxazoline complex catalyzed asymmetric [3+2] cycloaddition of nitrile imines.

Inspired by Sibi's pioneering works,^{6,7} Feng and co-workers recently reported an enantioselective cycloaddition reaction of nitrile imines **8** with 3-alkylidene oxindoles **9** by a chiral $\text{Mg}(\text{ClO}_4)_2$ / N,N' -dioxide ligand **10** complex as catalyst without using any auxiliary.⁸ Interestingly, it was found that higher reaction temperature ($60\text{ }^\circ\text{C}$) was crucial for good enantioselectivity. In addition, the HRMS experimental results indicated that the substrates and products could coordinate with the catalyst. Based on these results, the authors postulated that the substantial enhancement of the catalytic activity at slightly higher reaction temperature may overcome the uncatalyzed process.

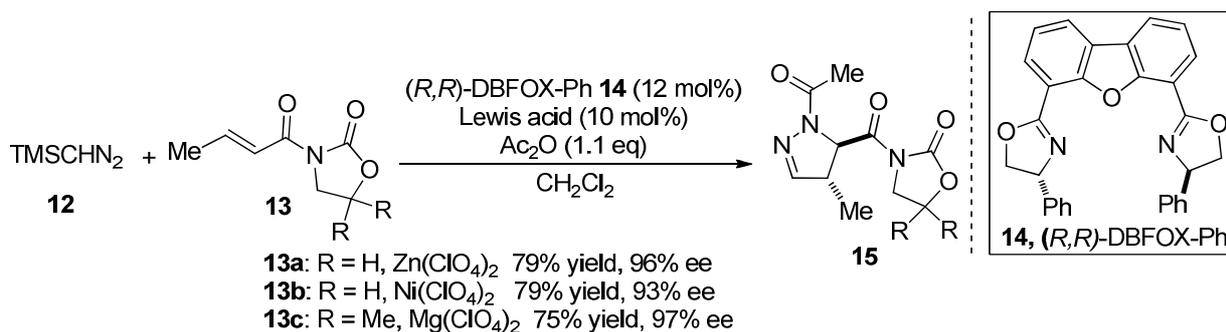


Scheme 3. Enantioselective [3+2] cycloaddition of nitrile imines with 3-alkenyl-oxindoles.

The reaction showed broad substrate scope and furnished the corresponding highly functionalized and biologically active spiro-pyrazoline-oxindole derivatives **11** in generally good yields with excellent enantioselectivities (Scheme 3).

2.1.2. 1,3-Dipolar cycloaddition reactions of diazoacetates

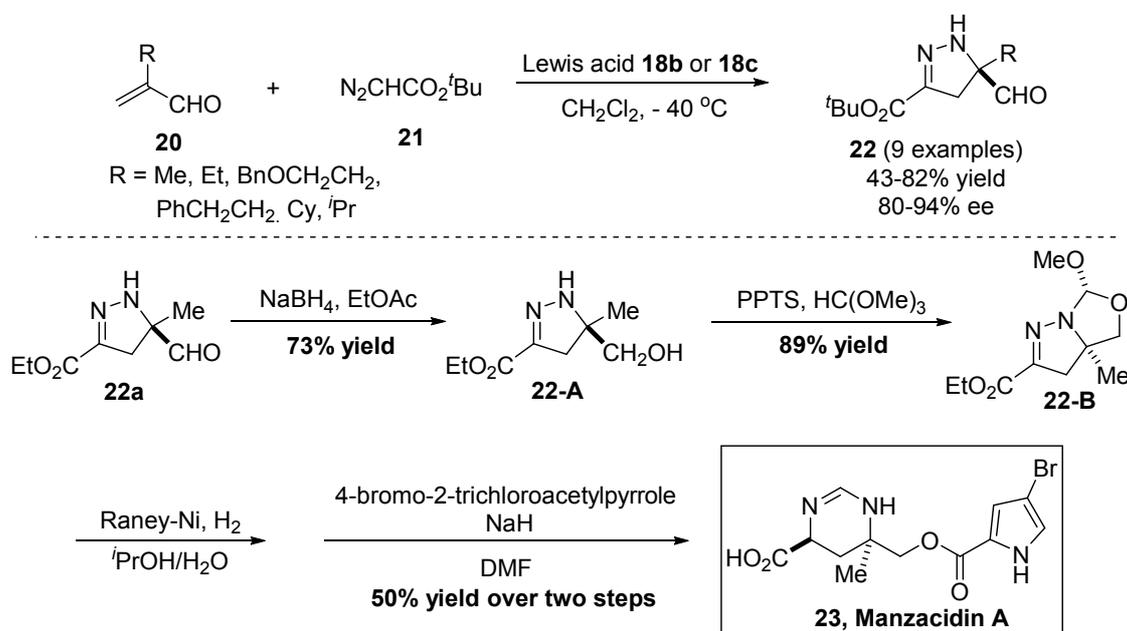
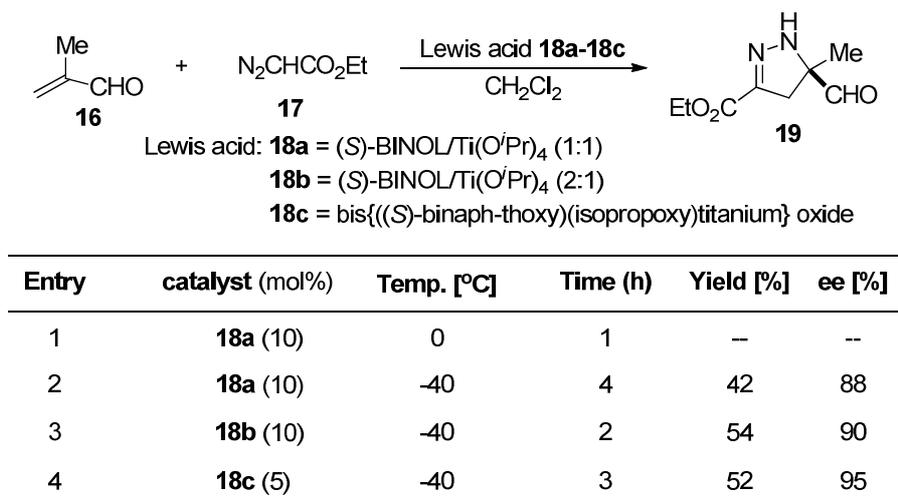
Diazoacetates could also serve as another class of powerful 1,3-dipoles and have been widely utilized in 1,3-dipolar cycloaddition reactions. Over the past decades, several asymmetric versions of these reactions have been successfully achieved by employing different chiral auxiliaries.⁹ In this regard, however, the catalytic asymmetric 1,3-dipolar cycloaddition of diazoacetates with olefins remains largely unexplored. In 2000, Kanemasa and Kanai reported the first example of catalytic asymmetric 1,3-dipolar cycloaddition reactions of trimethylsilyl-diazomethane **12** by using (*R,R*)-DBFOX-Ph **14**/metal perchlorate complexes as the chiral Lewis acid catalyst (Scheme 4).¹⁰ In the reaction, both of zinc(II) and nickel(II) complex showed high efficiency when using 3-crotonoyl-2-oxazolidinone (R = H) **13a** as the substrate, affording the corresponding product with 96% ee and 93% ee at -20 °C, respectively. However, in the case of 3-crotonoyl-4,4-dimethyl-2-oxazolidinone **13c**, both zinc(II) and nickel(II) complexes were less effective than Mg(II) complex. The corresponding cycloadduct **15c** was obtained with 75% yield and 97% ee by using Mg(II) complex at -78 °C.



Scheme 4. Catalytic enantioselective 1,3-dipolar cycloaddition of diazoacetate.

Inspired by Kanemasa's work, Maruoka and co-workers further extended the asymmetric 1,3-dipolar cycloaddition to the more readily available substrates, such as α -substituted acroleins and diazoacetates, which provided a practical access to enantioselective synthesis of densely functionalized pyrazoline derivatives.¹¹ It was found that both the reaction temperature and structure of titanium BINOLates are critical to the enantioselectivity of this transformation. As illustrated in Table 1, using titanium BINOLates **18a** as the catalyst, the reaction proceeded sluggishly, leading to a complex mixture at 0 °C. Fortunately, lowering the reaction temperature to -40 °C, the reaction proceeded well to give the desired product pyrazoline **19** with 42% yield and 88% ee. Further optimization of the reaction conditions identified titanium BINOLates **18b** and **18c** to be two optimal catalysts, delivering the corresponding product **19** with 90% ee and 95% ee, respectively. Thus, under the standard reaction conditions, various pyrazoline derivatives **22** were successfully synthesized in moderate to good yields with excellent enantioselectivities (Scheme 5). Importantly, the product **22a** can be conveniently applied to the total synthesis of Manzacidin **A** through simple four steps with good overall yield.

Table 1. Titanium complex catalyzed enantioselective 1,3-dipolar cycloaddition reaction between acrolein **16** and diazoacetate **17**.

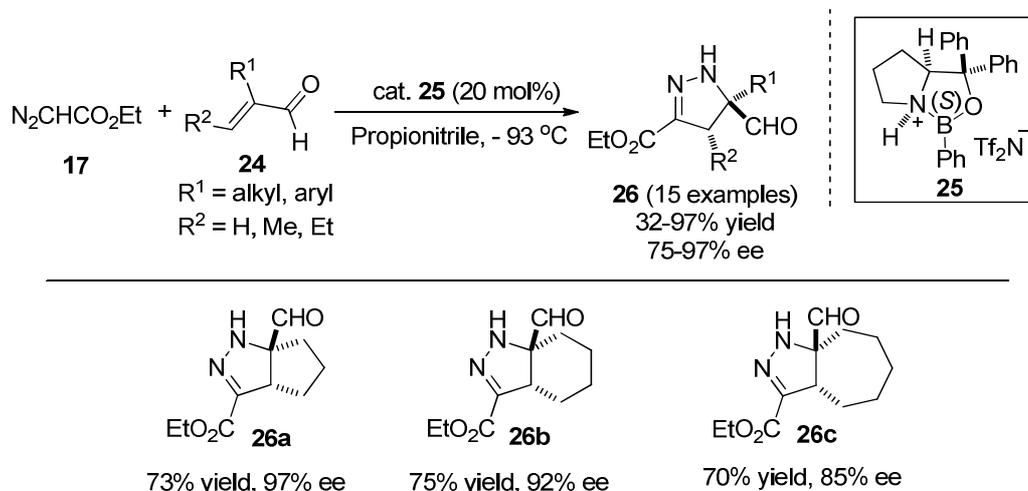


Scheme 5. Enantioselective 1,3-dipolar cycloaddition of diazoacetate and total synthesis of Manzacidin A.

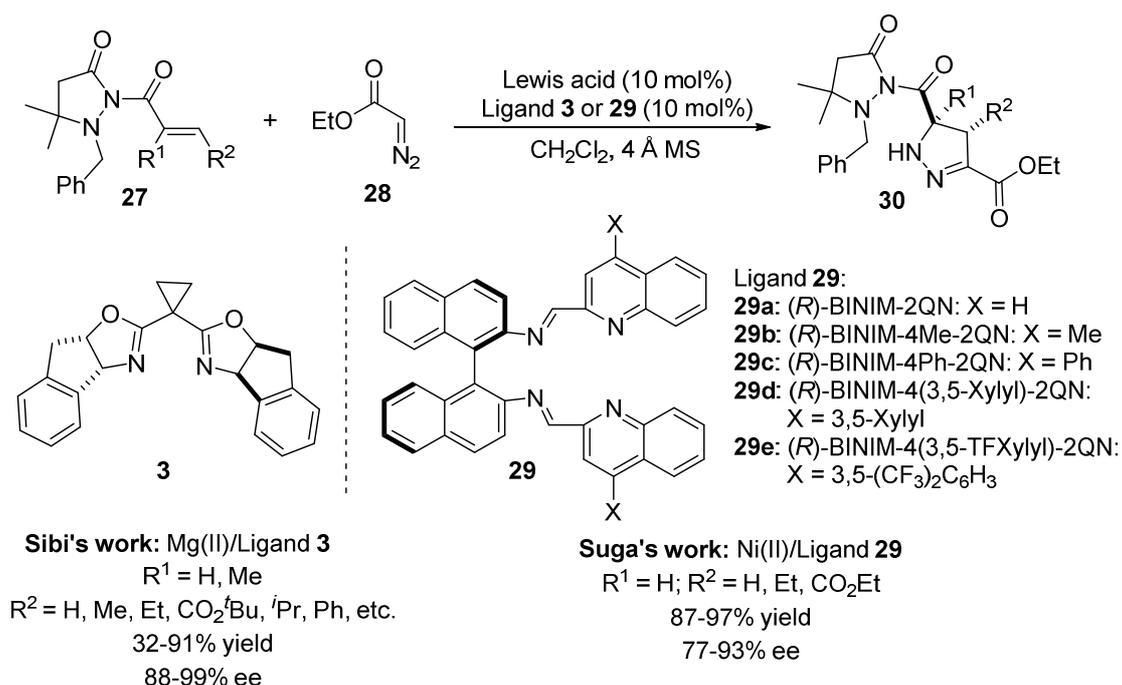
In 2009, the Ryu group reported that the (*S*)-oxazaborolidinium catalyst **25** could also catalyze a similar 1,3-dipolar cycloaddition between diazoacetate **17** and acroleins (Scheme 6).¹² It is noteworthy that the scope of acroleins could be successfully extended to various α,β -disubstituted unsaturated aldehydes **24**. For instance, the reaction with 1-cyclohexene, 1-cyclopentene, and 1-cycloheptene carboxaldehyde all proceeded smoothly to provide the corresponding densely functionalized chiral bicyclic 2-pyrazolines **26** in good yields with high enantioselectivities.

On the other hand, the group of Sibi in 2007 described a Mg(NTf₂)₂-catalyzed asymmetric [3+2] cycloaddition reaction of α or β -substituted α,β -unsaturated pyrazolidinone imides **27** with alkyl diazoacetates **28** (Scheme 7).¹³ A range of α,β -disubstituted dipolarophiles could also participate in the reaction smoothly to give the desired products with slightly low yields and excellent enantioselectivities, while at elevated reaction temperature. Recently, a similar methodology was independently developed by

Suga and co-workers using a Ni(II)/binaphthylidimine as a chiral Lewis acid for efficient synthesis of 2-pyrazoline derivatives in good yields with high levels of enantioselectivity.¹⁴



Scheme 6. Oxazaborolidinium catalyzed enantioselective 1,3-dipolar cycloaddition reaction between diazoacetates and α,β -unsaturated aldehydes.



Scheme 7. Mg(II) or Ni(II) complex catalyzed enantioselective [3+2] cycloaddition of pyrazolidinone imides.

2.1.3. 1,3-Dipolar cycloaddition reactions of azomethine imines to terminal alkynes

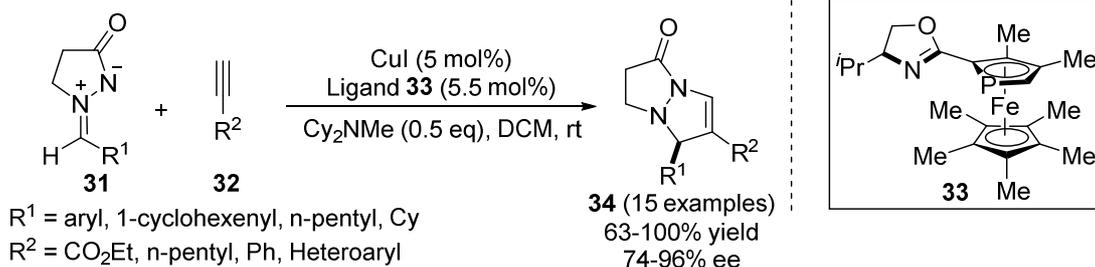
Catalytic asymmetric 1,3-dipolar cycloaddition reaction of azomethine imines with terminal alkynes has also been established as one of most practical and convenient methods for construction of various optically active five-membered *N*-heterocycles. However, though considerable attention has been devoted to this field over the past decades, there is still limited number of publications dealing with catalytic asymmetric version of such type of reaction. In this context, Fu's group in 2003 described the first example

of asymmetric Cu(I)-catalyzed [3+2] cycloaddition of azomethine imines **31** with terminal alkynes **32** (Scheme 8a).¹⁵ A bidentate *P,N*-ligand was finally determined as the best ligand after a careful optimization study. A significant wide variety of aryl and alkyl-derived azomethine imines and alkynes were well tolerated to allow for rapid synthesis of a wide variety of highly functionalized pyrazolidinone derivatives **34**.

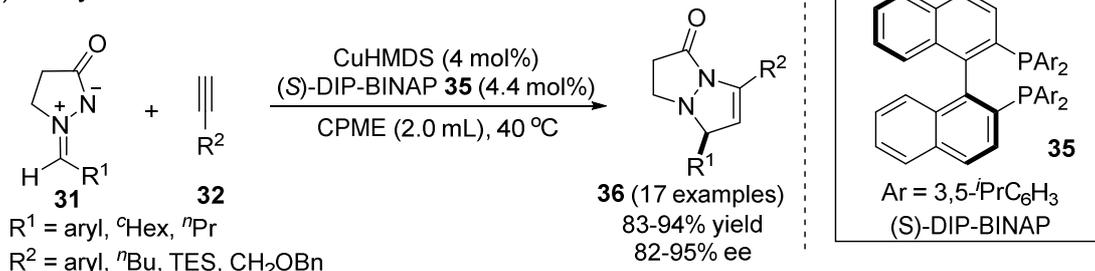
As for terminal alkynes, high reaction efficiency can be obtained when the alkynes contain electron-withdrawing groups (i.e. carbonyl group) or electron-deficient aromatic groups. In addition, the simple alkyl and phenyl substituents also proved to be suitable for this reaction, albeit with slightly diminished enantioselectivities. Subsequently, the authors further applied such Cu(I)-catalyzed [3+2] cycloaddition strategy to the kinetic resolution of racemic azomethine imines.¹⁶

On the contrary, Kobayashi and co-workers developed an unique 1,3-dipolar cycloaddition of azomethine imines with terminal alkynes catalyzed by group 11 metal amides, such as Ag (I) or Cu (I) amides with exclusive regioselectivity (Scheme 8b).¹⁷ For the racemic version, AgHMDS proved to be the best catalyst of choice. In contrast to Fu's work,¹⁵ the substrate scope can be successfully extended to electron-rich alkynes. More importantly, the asymmetric version of this process was achieved by the use of chiral Cu(I)/DIP-BINAP complex (Scheme 8b).

a) Fu's work:

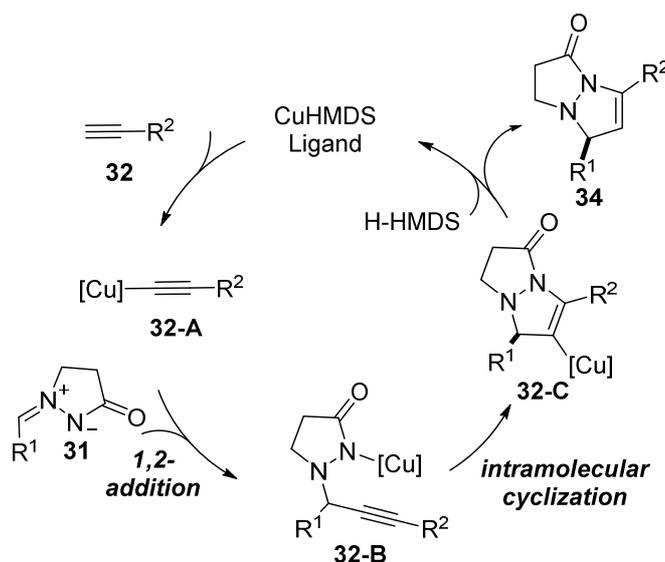


b) Kobayashi's work:



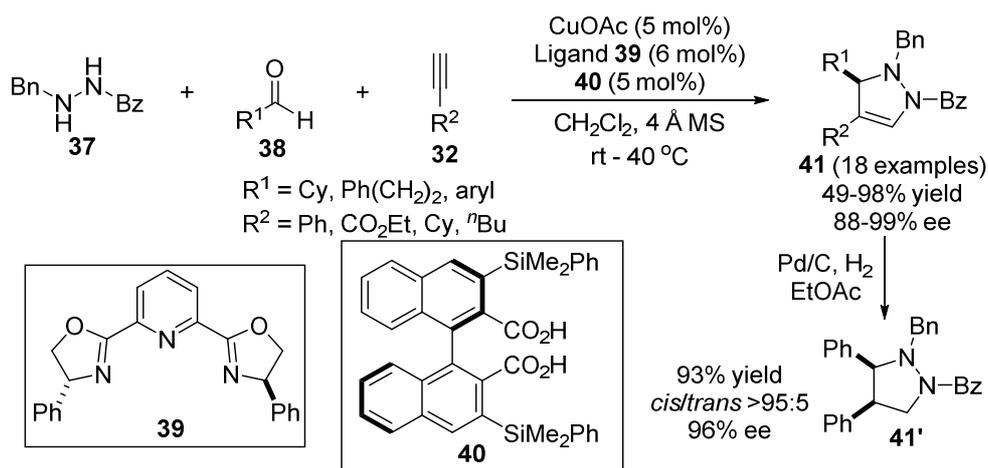
Scheme 8. Cu(I) complex-catalyzed enantioselective [3+2] cycloaddition of azomethine imines with alkynes.

Remarkably, the authors confirmed that the regioselectivity of this reaction was governed by the chiral ligands. In this reaction, employing 2,2'-bipyridine or bisoxazoline as ligands, an interesting complete reversal in regioselectivity was observed. On the basis of control experimental results, a stepwise reaction pathway was proposed to explain the unique regioselectivity of this reaction. As outlined in Scheme 9, the reactive intermediate Cu(I) acetylide **32-A** was firstly formed in the presence of Cu(I) catalyst, and then underwent an addition to azomethine imines to give the intermediate **32-B**. Finally, a Lewis acid promoted intramolecular cyclization process occurred to give the desired cycloadduct **34** through intermediate **32-C**.



Scheme 9. Proposed mechanism - a stepwise reaction pathway.

Inspired by these works, a catalytic asymmetric one-pot three-component 1,3-dipolar cycloaddition reaction of aldehydes, hydrazides and terminal alkynes was recently developed by Maruoka's group (Scheme 10).¹⁸ In this process, the key reactive intermediates acyclic azomethine imines were initially generated *in situ* from hydrazides **37** and aldehydes **38** through a condensation process. A combination of a chiral Cu(I)/Ph-pybox Lewis acid with a (*R*)-BINOL-derived dicarboxylic acid **40** was identified as the best catalytic system for the reaction, and the corresponding enantioenriched pyrazolines **41** obtained in good yields with excellent chemo- and enantioselectivities. Moreover, the chiral pyrazoline **41** could also be conveniently transformed into pyrazolidines such as **41'** with excellent diastereo- and enantioselectivity upon hydrogenation at mild conditions.

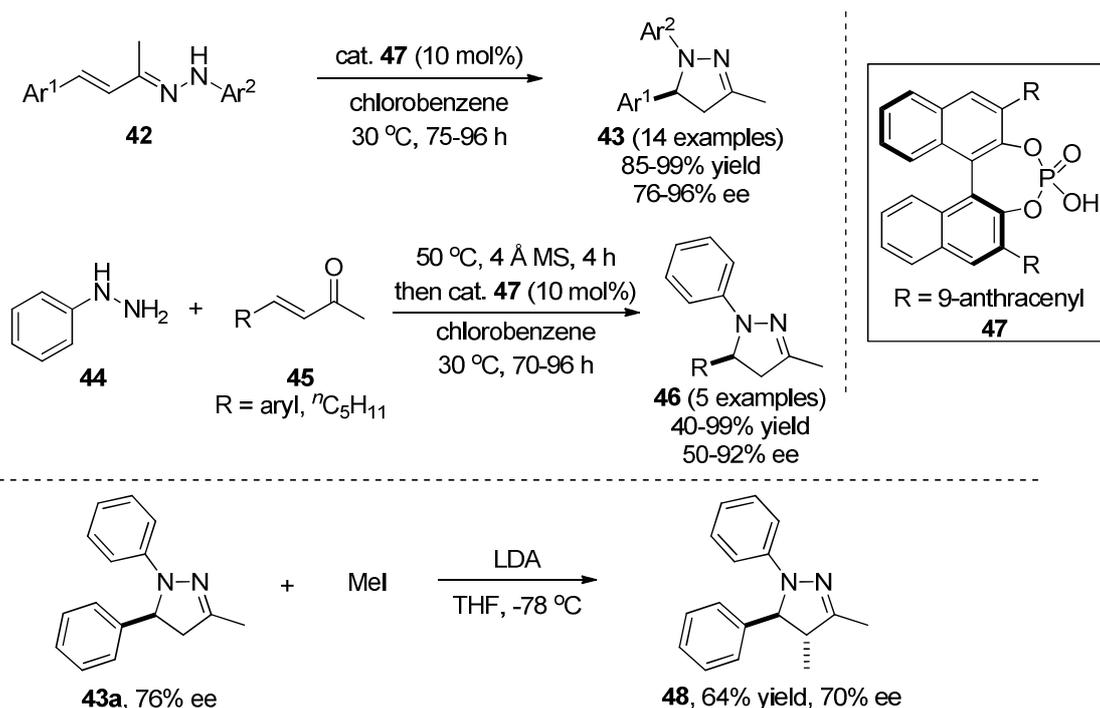


Scheme 10. Cu(I) complex/dicarboxylic acid cocatalyzed one-pot three-component 1,3-dipolar cycloaddition.

2.2. Asymmetric 6 π electrocyclicization and conjugate addition/cyclization cascade reactions

Pericyclic reaction represents one of the most powerful and efficient methods for synthesis of various carbo- and heterocycles in organic synthesis. In this context, the cycloaddition reactions, sigmatropic

rearrangements and electrocyclizations have been extensively investigated. However, the catalytic asymmetric 6π electrocyclization remains largely elusive but an attractive task for organic scientists. Inspired by the elegant work of Lewis acid-catalyzed 6π electrocyclizations of 2-substituted hexatriene systems by Bergman and Trauner,¹⁹ List and co-workers developed a catalytic enantioselective 6π electrocyclization reaction of α,β -unsaturated hydrazones **42** employing (*S*)-BINOL-derived phosphoric acid as catalysts, providing an efficient entry to synthesis of optically active 2-pyrazolines **43** (Scheme 11).²⁰ Under the standard reaction conditions, various electron-withdrawing groups substituted aryl hydrazones **42** reacted very well to give the corresponding 2-pyrazolines **43** in good yields with high enantioselectivities (up to 99% yield, 96% ee). The α,β -unsaturated hydrazones bearing an electron-donating groups (i.e. 4-MeO) at aryl moiety can also be well-tolerated in this transformation, albeit with slightly lower enantioselectivity. More importantly, the one-pot reaction of the corresponding enones **45** and hydrazines **44** can also proceed very well in chlorobenzene with the same catalyst (up to 99% yield, 96% ee), providing a more practical and facile access to the biologically active 4,5-dihydropyrazole derivatives **46**. This one-pot protocol also proved to be suitable for aliphatic enones under somewhat more acidic conditions, albeit with slightly low reaction efficiency. The 4,5-dihydropyrazole derivatives, such as **43a**, could also undergo alkylation to furnish structurally more complex 2-pyrazolines **48** with high diastereoselectivity.

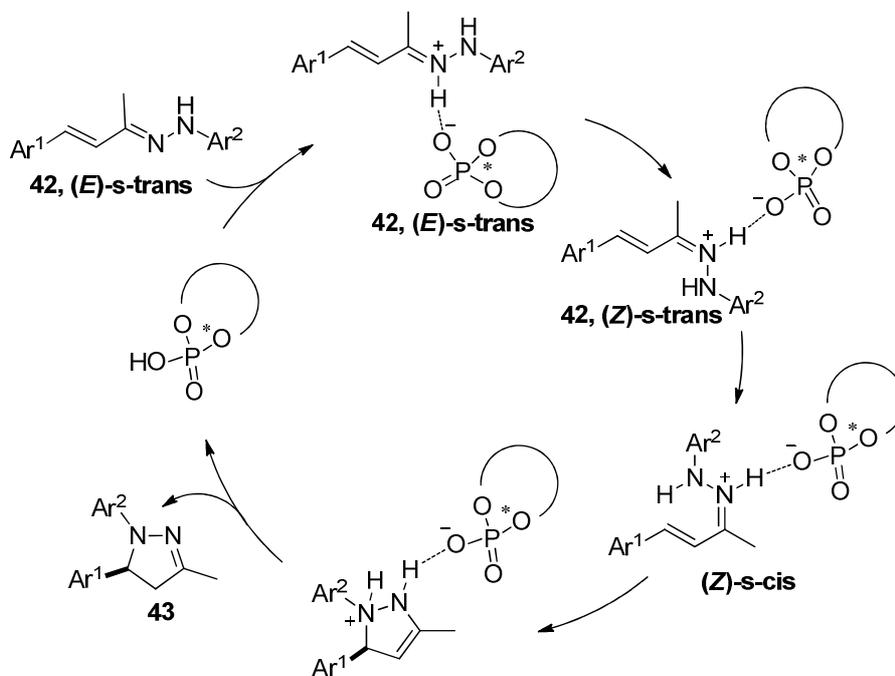


Scheme 11. Phosphoric acids catalyzed 6π electrocyclization of hydrazones.

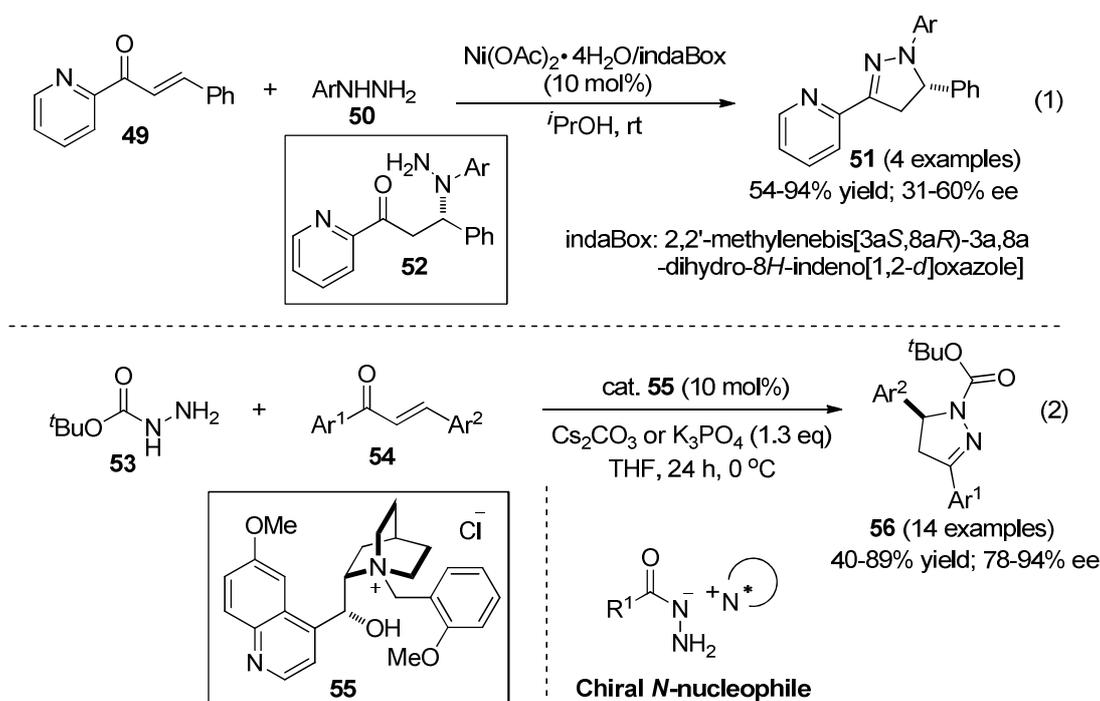
On the basis of the mechanistic studies, the authors proposed a possible pathway for the reaction as outlined in Scheme 12. Firstly, through a N-N single bond rotation and C=N double bond isomerization sequence in the presence of phosphoric acid catalyst, the substrate (*E*)-**42** can be converted into (*Z*)-**42**. Then, (*Z*)-*S-cis*-**42** underwent an intramolecular 6π electrocyclization reaction in a highly enantioselective manner to give the corresponding chiral pyrazolines **43** and release the phosphoric acid catalyst.

In contrast to the 6π electrocyclization process, a sequential intermolecular aza-Michael addition/cyclocondensation reaction of hydrazine with α,β -unsaturated ketones provides an alternative

approach for the synthesis of structurally diverse pyrazolines. For example, in 2007, the Kanemasa group reported a Ni(II)-catalyzed asymmetric aza-Michael addition/cyclocondensation cascade reaction of α,β -unsaturated ketones **49** and hydrazines **50**, giving the 3,5-diaryl pyrazolines **51** with moderate enantioselectivities (up to 60% ee) (Scheme 13, eq.1).²¹ In this process, the authors postulated that the intermediate **52**, generated *in situ* by an aza-Michael addition of hydrazine to electron deficient C=C double bond, might be involved in this transformation.



Scheme 12. Plausible reaction mechanism.



Scheme 13. Enantioselective aza-Michael addition/cyclization cascade reaction for the synthesis of pyrazolines.

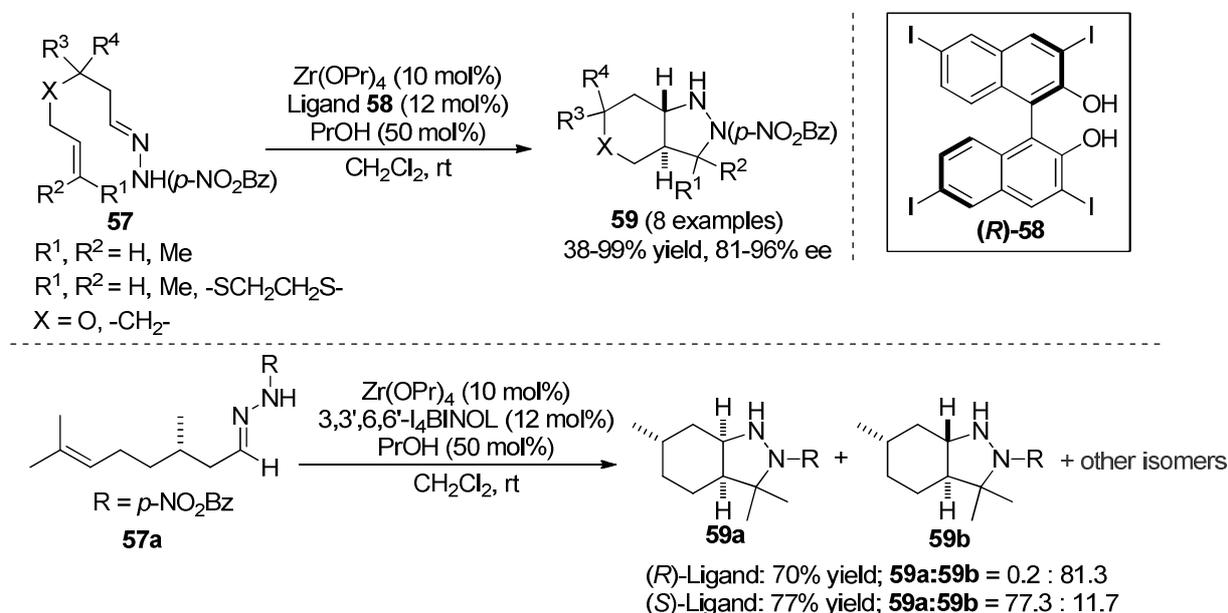
Inspired by this work, in 2010, Briere and co-workers developed a similar transformation between *N*-tert-butyloxycarbonyl hydrazine **53** and chalcone **54** catalyzed by chiral phase-transfer catalyst (PTC) **55** through a chiral ammonium/amide ion pair (Scheme 13, eq.2).²² It was found that the protecting group of hydrazines has significant influence on the reaction efficiency. For instance, the *N*-benzoyl hydrazine was not suitable for this reaction, while the hydrazine bearing *N*-acetyl substituent could react smoothly to give the desired product with only 9% ee. The best result could be achieved by employing *N*-Boc hydrazine as the substrate.

It was also found that the addition of chiral *N*-anionic nucleophile to chalcones is critical to the high enantioselectivity and quininium catalyst **55** was proved to be the best catalyst for this process. As a result, a wide range of 3,5-diaryl pyrazolines **56** can be successfully synthesized in moderate yields with excellent enantioselectivities (up to 89% yield, 94% ee). It should be noted that the Boc protecting group of products could be easily converted into 4-toluenesulfonyl, benzoyl and acetyl groups with no loss of enantiopurity via a simple one-pot process, further highlighting the synthetic potential of this methodology.

3. Catalytic asymmetric synthesis of pyrazolidines

3.1. [3 + 2] Cycloaddition reactions of hydrazones

The catalytic asymmetric [3+2] cycloaddition reaction of hydrazones with alkenes provides one of the most powerful and efficient strategies for construction of optically active pyrazolidines. In 2002, the group of Kobayashi disclosed the first example of catalytic asymmetric intramolecular [3+2] cycloaddition reaction of acylhydrazones with olefins by the use of a chiral Zirconium/BINOL **58** complex in CH₂Cl₂ at room temperature (Scheme 14).²³

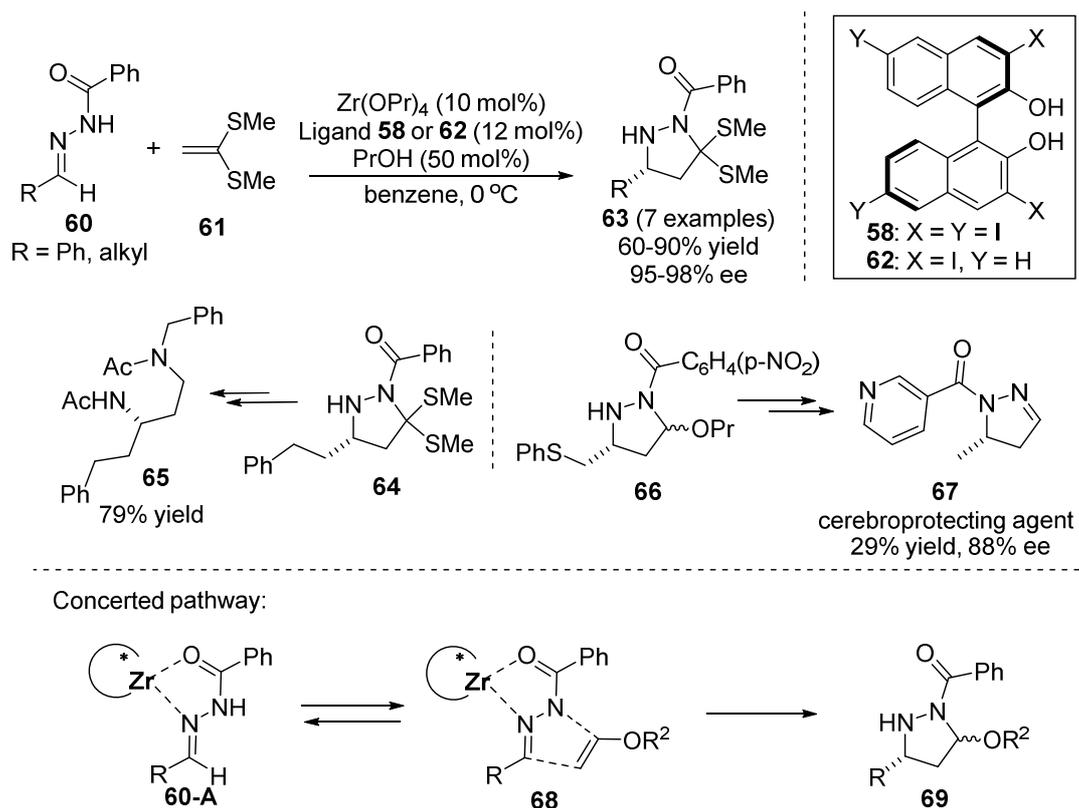


Scheme 14. Zr(IV) complex-catalyzed intramolecular [3+2] cycloaddition of hydrazones.

Under standard reaction conditions, various medicinally important bicyclic pyrazolidines **59** can be obtained in good yields with excellent enantioselectivities (up to 99% yield, 96% ee). Interestingly, control experimental results with respect to the correlation between the chiral catalysts and substrates suggested that *cis/trans* selectivity was dominated by the absolute configuration of the chiral catalyst. For example, using

57a as the substrate prepared from (*S*)-citronellal, the *trans*-pyrazolidine **59b** can be successfully obtained as a major product (81% yield) in the presence of Zr(OPr)₄/(*R*)-**58** complex. On the other hand, with the use of Zr(OPr)₄/(*S*)-**58** complex as the catalyst, the reaction also proceeds very smoothly to give the *cis*-adduct as **59a** the major product in 77% yield.

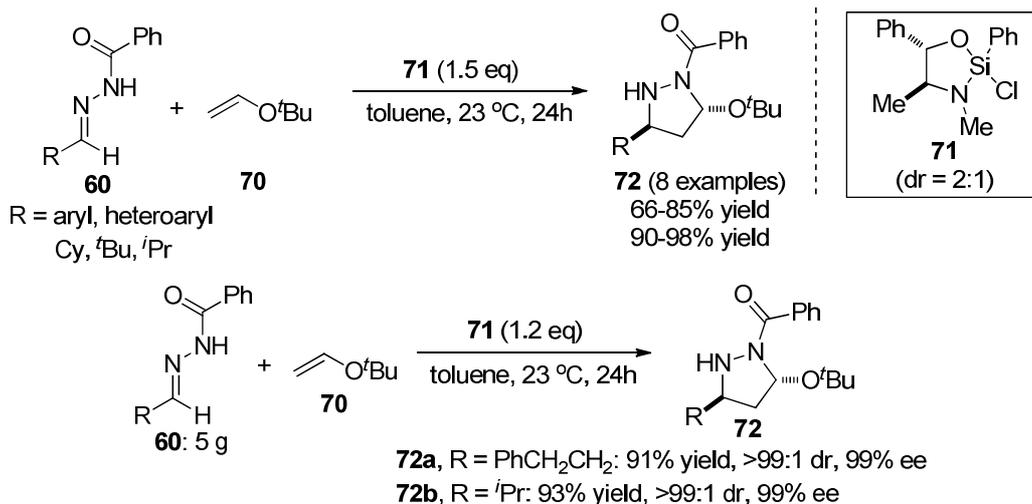
Shortly thereafter, the Kobayashi group also developed the first intermolecular [3+2] cycloaddition reaction of hydrazones with olefins by using the similar catalytic system (Scheme 15).²⁴ Under optimal conditions, the ketene dimethyl dithioacetal **61** reacted very well with various alkyl group substituted hydrazones **60**, leading to the formation of the desired adducts **63** with good yields and enantioselectivities (up to 90% yield, up to 98% ee). By using vinyl ethers as substrate, the reaction can also proceed well with moderate diastereoselectivities and high enantioselectivities. Moreover, several successful transformations of pyrazolidines into valuable compounds also further demonstrate the synthetic potential of this methodology. For example, the pyrazolidines can be easily converted into 1,3-diamines with good yield through an N-N bond cleavage in the presence of SmI₂. Significantly, this methodology can be further applied as the key step to the synthesis of biologically important compound **67** with 29% overall yield and 88% ee for the first time. In addition, a concerted mechanism was proposed based on the control experiments.



Scheme 15. Zr(IV) Complex-catalyzed enantioselective intermolecular [3+2] cycloaddition of hydrazones.

The limitations of the Kobayashi's work with respect to enantioselectivity in some cases and substrate scope prompted further exploration in this area. In 2005, Leighton and co-workers described a novel [3+2] cycloaddition of hydrazones **60** with vinyl ethers **70** promoted by a chiral silicon catalyst **71** (Scheme 16).²⁵ The chiral silicon catalyst **71** was prepared from the corresponding pseudoephedrine and phenyl-

trichlorosilane via a simple one-step reaction in a 2:1 mixture. Examination of hydrazones demonstrated that this catalytic system displayed a significant improvement in both substrate scope and enantioselectivity compared to Kobayashi's work.²⁴ Both aromatic and aliphatic hydrazones were all well tolerated under the standard reaction conditions. It should be noted that the reaction could also proceed very well on a gram-scale and the desired products **72a** and **72b** can be obtained in 91% and 93% yields, respectively. After a simple recrystallization, the enantioselectivity of two cycloadducts can be increased to 99%. However, the main drawback of this methodology involving the use of stoichiometric amount of the chiral silicon catalyst awaits further exploration.

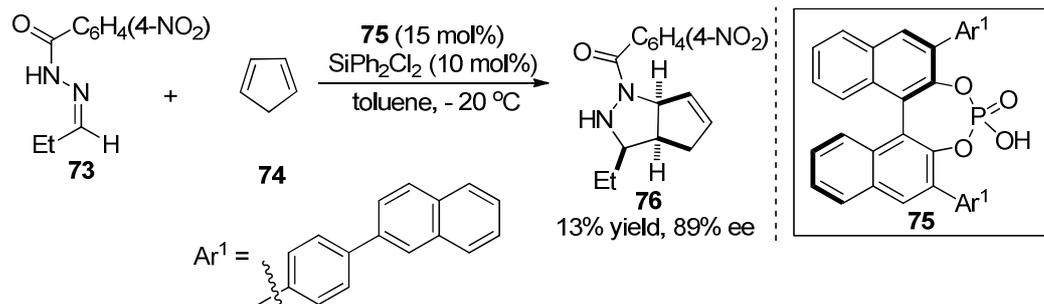


Scheme 16. Chiral silicon-promoted intermolecular [3+2] cycloaddition reaction of hydrazones.

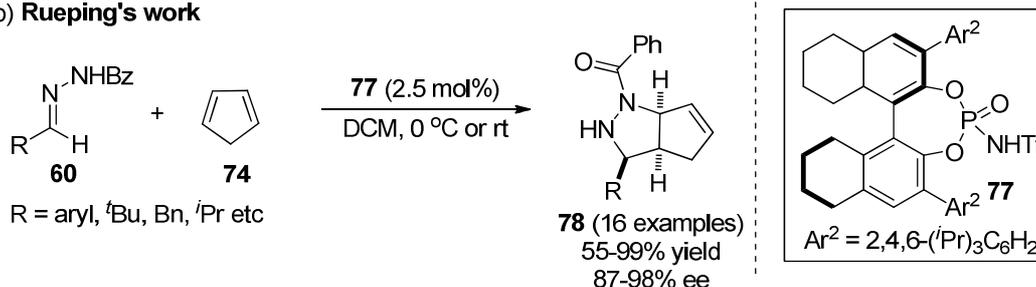
As an extension of this work, the group of Tsogoeva in 2011 developed an interesting chiral silicon catalyst, generated *in situ* from the corresponding binol-phosphate and SiPh₂Cl₂, and successfully applied it to the catalytic asymmetric [3+2] cycloaddition of hydrazone **73** with cyclopentadiene **74** with good enantioselectivity (89%), albeit with low yield (13%) (Scheme 17a).²⁶ It should be noted that only 47% ee was achieved by using a sole chiral phosphoric acid catalyst due to the low acidity of the catalyst. Shortly after, the Rueping group identified a more acidic *N*-triflyl-phosphoramides catalyst **77** for this reaction, and achieved a dramatic improvement of the reaction efficiency (Scheme 17b).²⁷ The scope of this reaction was successfully extended to aliphatic and aromatic hydrazones. Generally, the reaction proceeded well to give pyrazolidine derivatives **78** with good yields and excellent enantioselectivities (up to 99% yield, 98% ee).

Very recently, the authors further extended the substrate scope of alkenes to thioethers by using a new SPINOL-derived phosphoric acid catalyst.²⁸ More importantly, the mechanism and origin of selectivity of this transformation have been investigated through DFT calculations and related control experiments. Based on these results, they suggested that the chiral ion-pair complex was firstly generated as reactive intermediate through a protonation of hydrazone in the presence of strong phosphoric acid catalysts (Scheme 18). In the case of less acidic phosphoric acids, the ion-pair complex is difficult to form, and a H-bond complex was formed instead. Moreover, it was found that the alternative [3+2] cycloaddition pathway is less favorable because of the endergonic isomerization from hydrazone to azomethine imine.

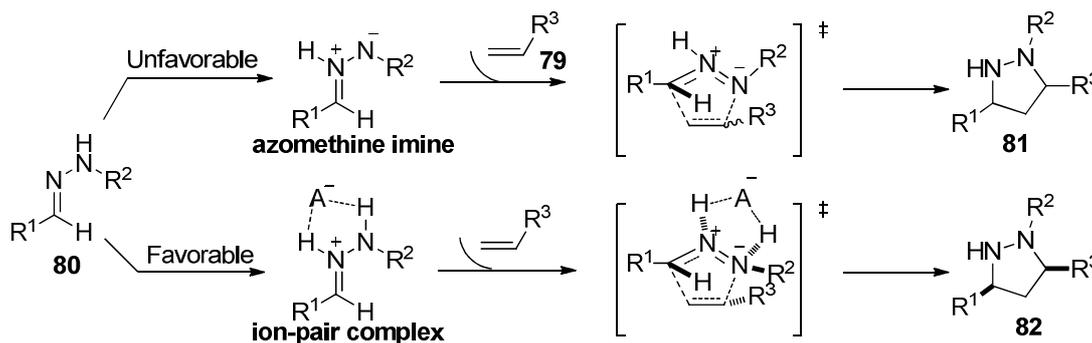
(a) Tsogoeva's work



(b) Rueping's work



Scheme 17. Catalytic asymmetric intermolecular [3+2] cycloaddition reaction of hydrazones.

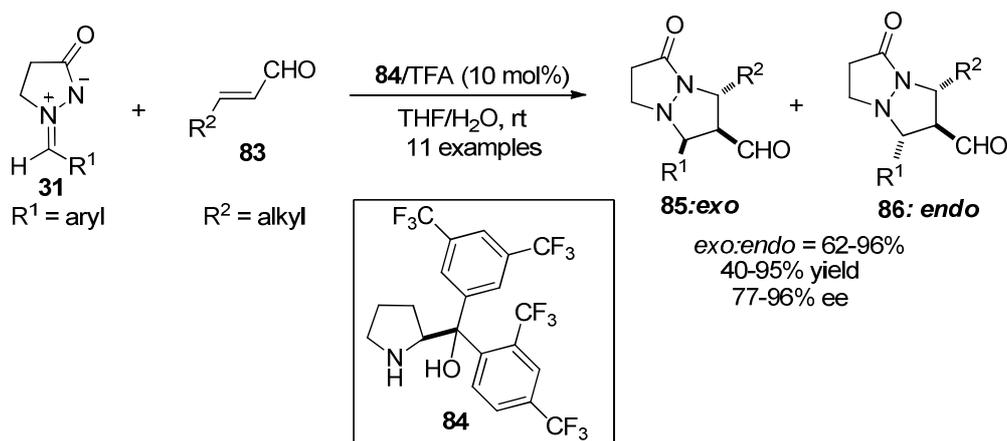


Scheme 18. Plausible mechanism for phosphoric acid catalyzed [3+2] cycloaddition reaction of hydrazones.

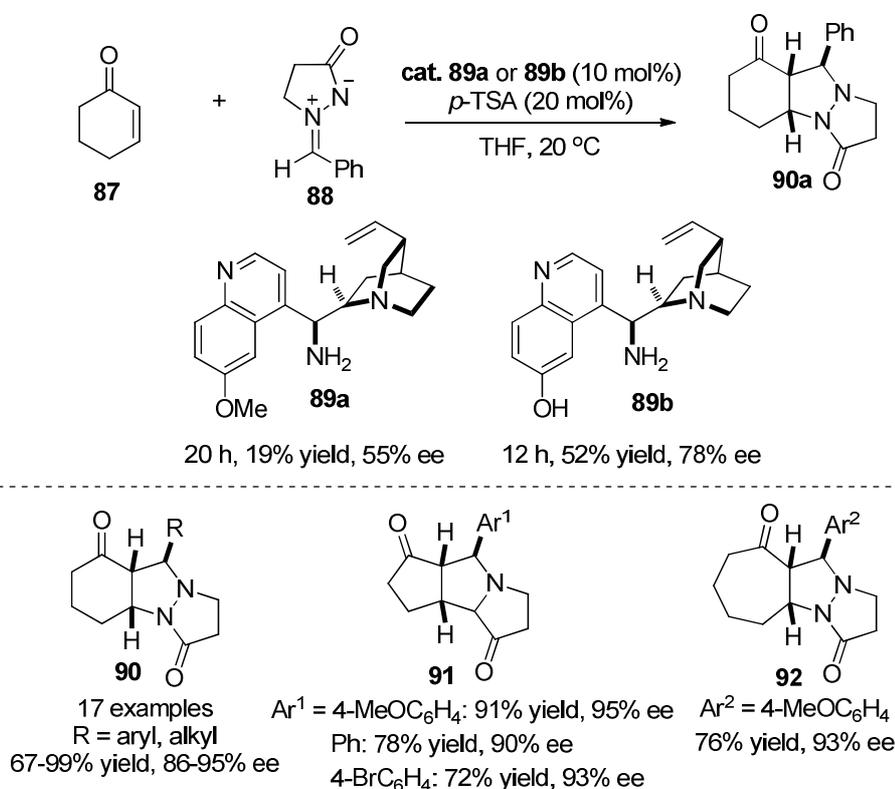
3.2. 1,3-Dipolar cycloaddition reactions of azomethine imines with alkenes

Azomethine imines, including N,N' -cyclic azomethines and C,N -cyclic azomethine imines, have also been widely utilized in 1,3-dipolar cycloaddition reactions for the construction of various highly functionalized N -containing heterocycles. Based on Inomata's work on asymmetric 1,3-dipolar cycloadditions of azomethine imines with allyl alcohol,²⁹ the group of Chen reported the first example of organocatalytic asymmetric [3+2] cycloaddition between N,N' -cyclic azomethine imines **31** with α,β -unsaturated aldehydes **83** by an iminium catalysis strategy (Scheme 19).³⁰ Screening of a range of chiral secondary amine catalysts demonstrated that a combination of catalyst **84** with TFA proved to be the best catalytic system. Under the optimized reaction conditions, the desired products were obtained with generally high yields and enantioselectivities, albeit with moderate diastereoselectivities.

However, the N,N' -cyclic azomethines imine with alkyl substituents (R^1) and aryl group substituted aldehydes proved to be not suitable under the standard reaction conditions. Shortly after, Chen and co-workers extended this catalytic strategy to an asymmetric [3+2] cycloaddition between cyclic enones **87** and N,N' -cyclic azomethine imines **88** (Scheme 20).³¹



Scheme 19. Organocatalytic asymmetric [3+2] cycloaddition of *N,N'*-azomethine imines with α,β -unsaturated aldehydes.

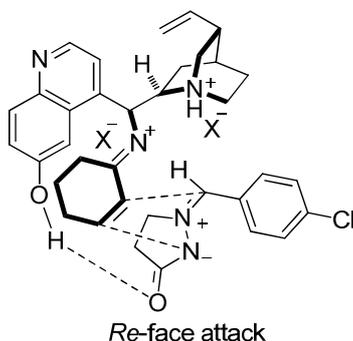


Scheme 20. The effect of organocatalysts and the scope of this reaction.

It was found that the hydroxyl group of catalyst has played an important role on both reaction efficiency and enantioselectivity. For examples, the use of **89a** as the catalyst furnished the cycloadduct **90a** only in 19% yield with 55% ee, while the catalyst **89b** with a H-bonding donor furnished gave rise to superior results (52% yield, 78% ee). The scope of this transformation is significantly broad. Various aryl-, alkyl-, and heteroaryl-substituted *N,N'*-cyclic azomethine imines could react with cyclic enones smoothly, furnishing the desired products with good yields and excellent enantioselectivities. More importantly, the five- and seven-membered cyclic enones were also well tolerated in this reaction, affording the corresponding products **91** and **92** in a highly enantioselective manner.

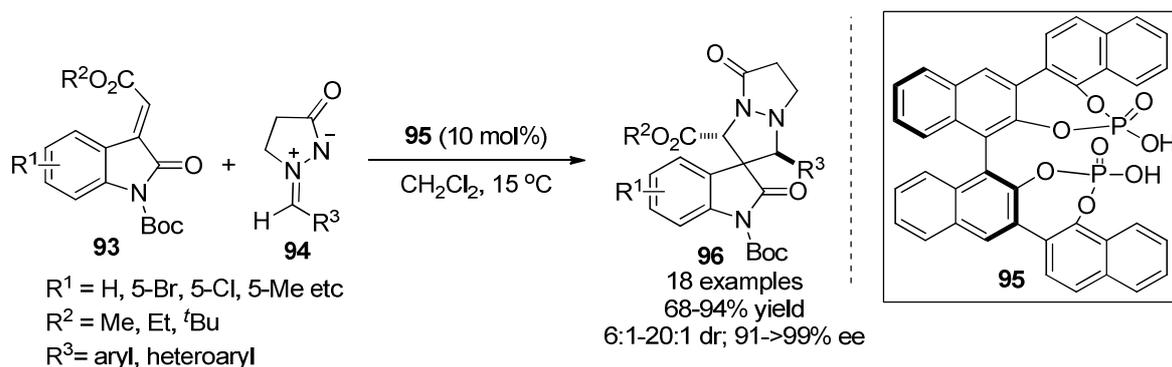
It was also proposed that the success of the reaction was due to the possible simultaneous activation of both reactants by a multifunctional primary amine catalyst through an iminium activation and H-bond

activation (Scheme 21). In the transition state, the iminium activation of cyclic enones, steric hindrance of tertiary amine moiety and the hydrogen bond interaction of azomethine imine could better account for the observed *endo*-selectivity of this transformation.



Scheme 21. Proposed transition state for the organocatalytic [3+2] cycloaddition between cyclic enones and *N,N'*-cyclic azomethine imines.

Recently, the Wang group designed a new chiral bis-phosphoric acid catalyst **95** for the asymmetric 1,3-dipolar cycloaddition of methyleneindolinones **93** with *N,N'*-azomethine imines **94** to efficiently synthesize the optically active spiro[pyrazolidin-3,3'-oxindoles] (Scheme 22).³²

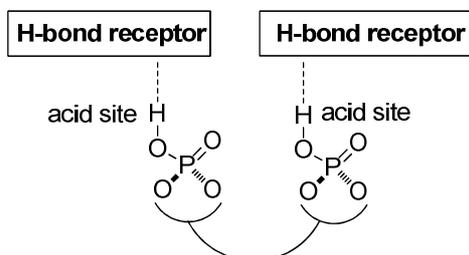


Scheme 22. Chiral bis-phosphoric acid catalyzed [3+2] cycloaddition of *N,N'*-azomethine imines.

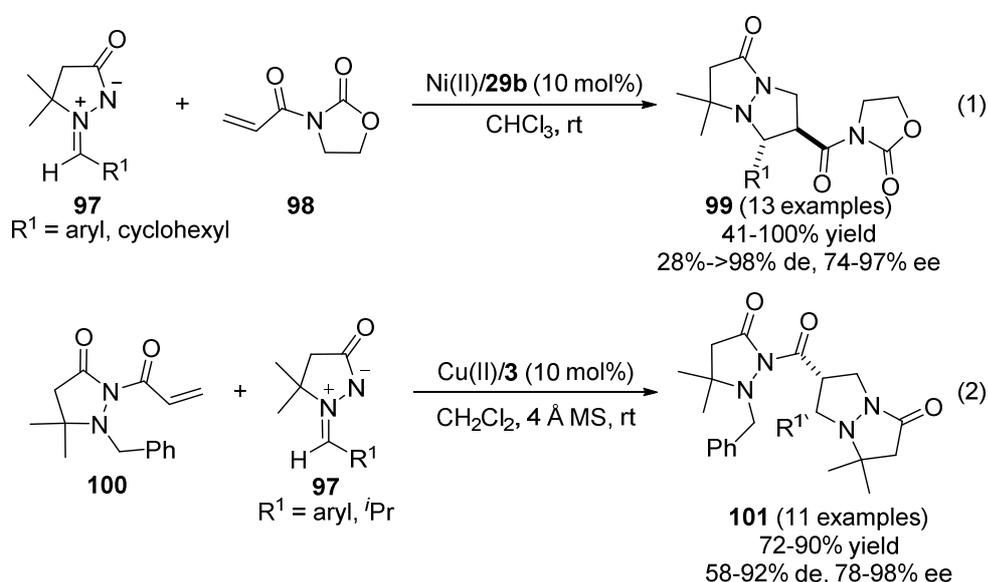
The reaction with commonly used mono-phosphoric acid catalysts only afforded moderate results, which was probably due to the fact that both reactants are H-bond receptors. A dual H-bond activation strategy was proposed to solve this problem (Scheme 23). Based on this concept, several chiral bis-phosphoric acid catalysts of type **95** have been synthesized and applied to this reaction. Generally, both the chemical yield and enantioselectivity have been obviously improved with the use of such bis-phosphoric acid catalysts, and catalyst **95** proved to be the best of choice to give the desired product **96a** with 93% yield and 98% ee. Under the standard conditions, a wide variety of highly functionalized spiro[pyrazolidin-3,3'-oxindoles] **96** were obtained in generally good yields with excellent diastereo- and enantioselectivities. A dual H-bond activation mode was also proposed for the observed stereochemical outcome based on control experiments and DFT calculation experiments.

Over the past decades, metal-catalyzed asymmetric cycloaddition reactions of azomethine imines have also attracted much attention from synthetic scientists. In this regard, the Suga group developed a highly catalytic asymmetric [3+2] cycloaddition of *N,N'*-azomethine imines **97** by use of chiral BINIM-Ni (II)

complex as the catalyst (Scheme 24, eq. 1).³³ Shortly after, a similar reaction was reported by Sibi and co-workers (Scheme 24, eq. 2).³⁴ In contrast to Suga's work, an *exo*-selectivity was observed employing chiral Cu(II) complex as the Lewis acid catalyst. In most cases, the reaction proceeded well in the presence of 10 mol% Cu(II)/**3** catalyst, giving the *exo*-adducts **101** with good yields and enantioselectivities.

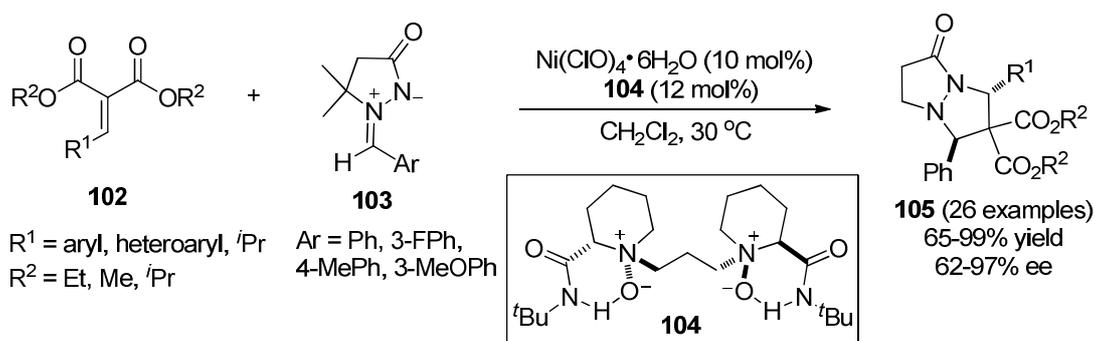


Scheme 23. Dual H-bond activation strategy.



Scheme 24. Ni(II) or Cu(II) complex catalyzed asymmetric [3+2] cycloaddition of *N,N'*-azomethine imines.

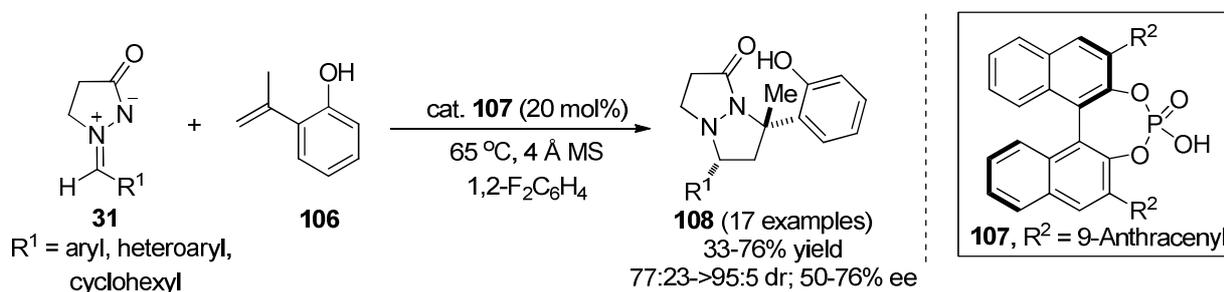
Recently, Feng and co-workers reported an asymmetric 1,3-dipolar cycloaddition of alkylidene malonates **102** with *N,N'*-azomethine imines **103** catalyzed by a chiral *N,N'*-dioxide Ni(II)/**104** complex (Scheme 25).³⁵



Scheme 25. Ni(II)-catalyzed enantioselective [3+2] cycloaddition of alkylidene malonates with *N,N'*-azomethines.

It was found that the metal salts played a critical role in the process. The reaction proceeded very sluggishly when employing Sc(III), Mg(II) and Co(II)-complexes as the chiral Lewis acids. The best results can be obtained with the use of Ni(II)/**104** complex in CH₂Cl₂. This methodology showed quite broad scope with respect to both components. A variety of alkylidene malonates and *N,N'*-azomethine imines were well tolerated under the standard reaction conditions, furnishing the corresponding products with generally good yields and excellent stereoselectivities. Notably, the gram-scale reaction also proceeded very well to give the desired cycloadduct with 85% yield and 92% ee.

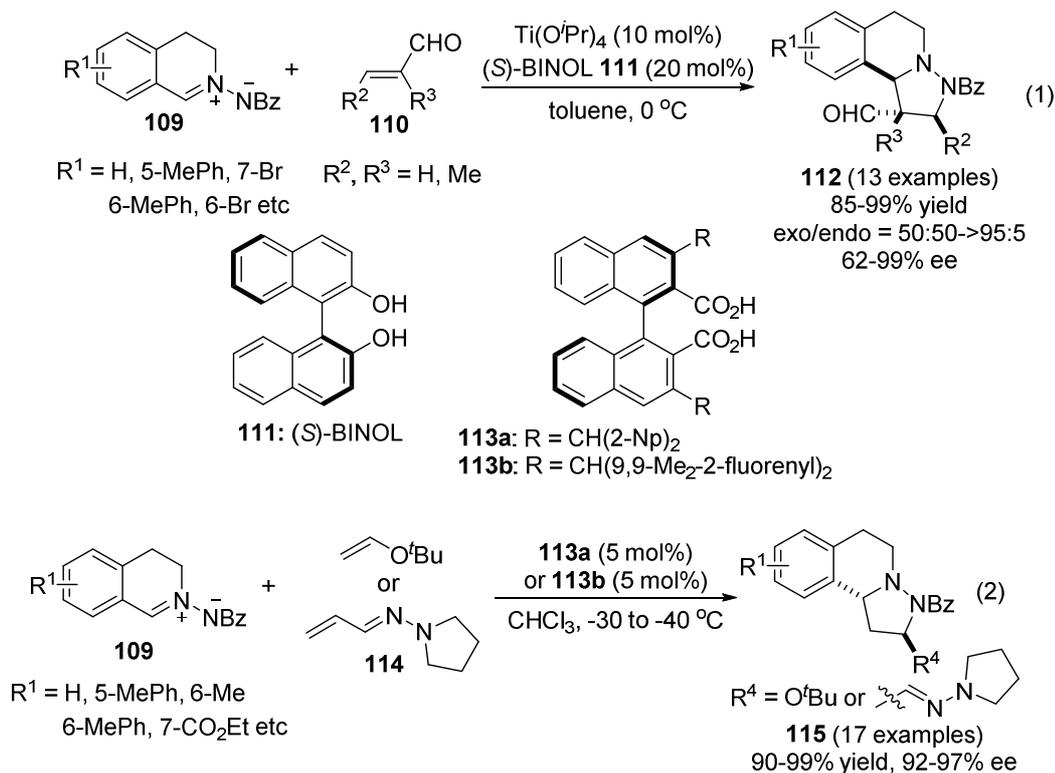
Unlike the traditional normal-electron-demand (NED) 1,3-dipolar cycloaddition, the electron-rich olefins are always employed as the dipolarophile in the IED 1,3-dipolar cycloaddition reactions. Very recently, Shi and co-workers disclosed an interesting inverse-electron-demand (IED) 1,3-dipolar cycloaddition of various *N,N'*-azomethine imines **31** with *o*-hydroxystyrenes **106** catalyzed by chiral phosphoric acid **107** (Scheme 26).³⁶ Several control experiments were performed to investigate the specific role of *o*-hydroxyl group of styrene, which established that the *o*-hydroxyl moiety proved to be very important for reaction efficiency and enantioselectivities. For example, the reactions with styrenes bearing *o*-methoxy- or *m*-hydroxyl groups resulted in no formation of any desired products under the standard reaction conditions. Therefore, it was postulated that the reaction was likely due to both dual H-bonding activation and the conjugative effect of *o*-hydroxyl group. However, the scope of styrene was still very limited.



Scheme 26. Phosphoric acid catalyzed IED 1,3-dipolar cycloaddition of electron-rich alkenes.

In addition, *C,N*-cyclic azomethine imines could also serve as another class of useful 1,3-dipoles and have found wide applications in synthesis of various carbo- and heterocycles.³⁷ In this regard, however, the catalytic asymmetric cycloadditions of such reagents remains largely unexploited. A major breakthrough in this field was achieved by the group of Maruoka in 2010. They developed an efficient catalytic asymmetric [3+2] cycloaddition of *C,N*-cyclic azomethine imines **109** with α,β -unsaturated aldehydes **110** by using a chiral Ti-BINOLate complex as the Lewis acid catalyst (Scheme 27, eq. 1).³⁸

In the reaction, the steric hindrance at the β -position of aldehydes played an important role on enantioselectivity. Those β -methyl, phenyl and propyl substituted α,β -unsaturated aldehydes could react smoothly to give the desired products in good diastereoselectivities and enantioselectivities (up to 95:5 dr, 99% ee). In the case of the β -unsubstituted substrates, only moderate results were obtained. It is worth mentioning that those structurally distinct and unstable *C,N*-cyclic azomethine imines, generated *in situ* under the alkaline conditions from corresponding salts, could also participate in the reaction very well. This study represented the first example of highly enantioselective [3+2] cycloaddition reaction of *C,N*-cyclic azomethine imines, providing an rapid access to the highly functionalized tetrahydroisoquinoline derivatives.



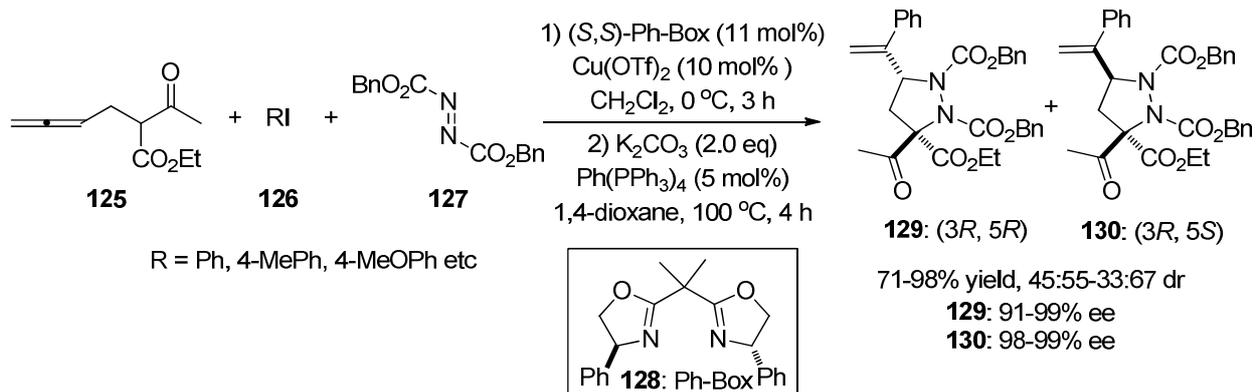
Scheme 27. Catalytic enantioselective [3+2] cycloaddition of *C,N*-cyclic azomethine imines.

Shortly after, Maruoka and co-workers further extended the reaction scope to the catalytic asymmetric inverse-electron-demand 1,3-dipolar cycloaddition of *C,N*-cyclic azomethine imines **109** with vinyl ether in the presence of their own chiral dicarboxylic acids **113** (Scheme 27, eq. 2).³⁹ In this process, both vinyl ether and aza-enamines were well tolerated and generally good yields and enantioselectivities were obtained for the corresponding cycloadducts **115**. Quite recently, Togni and co-workers reported a Ni(II) complex-catalyzed 1,3-dipolar cycloaddition of *C,N*-cyclic azomethine imines with crotonitriles to synthesize the pyrazolidine derivatives with good yields and enantioselectivities, albeit with slightly low diastereoselectivities.⁴⁰

3.3. Asymmetric conjugate addition/cyclization cascade reactions

Over the past few years, the asymmetric conjugate addition/cyclization cascade reaction of hydrazines has also been established as an efficient approach to the synthesis of biologically important optically active pyrazolidinones. In this context, the chemoselectivity and enantioselectivity remain two main challenges for organic chemists. In 2007, Sibi's group developed a highly efficient Mg(II)-catalyzed catalytic enantioselective conjugate addition/intramolecular cyclization cascade of α,β -unsaturated imides **116** with hydrazines **117** (Scheme 28).⁴¹ It was found that the achiral template of imides was critical to both regioselectivity and stereoselectivity, and the benzimide was finally proved to be the best of choice. Moreover, the lower temperature is beneficial for the chemoselectivity. Generally, the pyrazolidinones **118** can be obtained in good yields, excellent diastereoselectivities and moderate to good enantioselectivities.

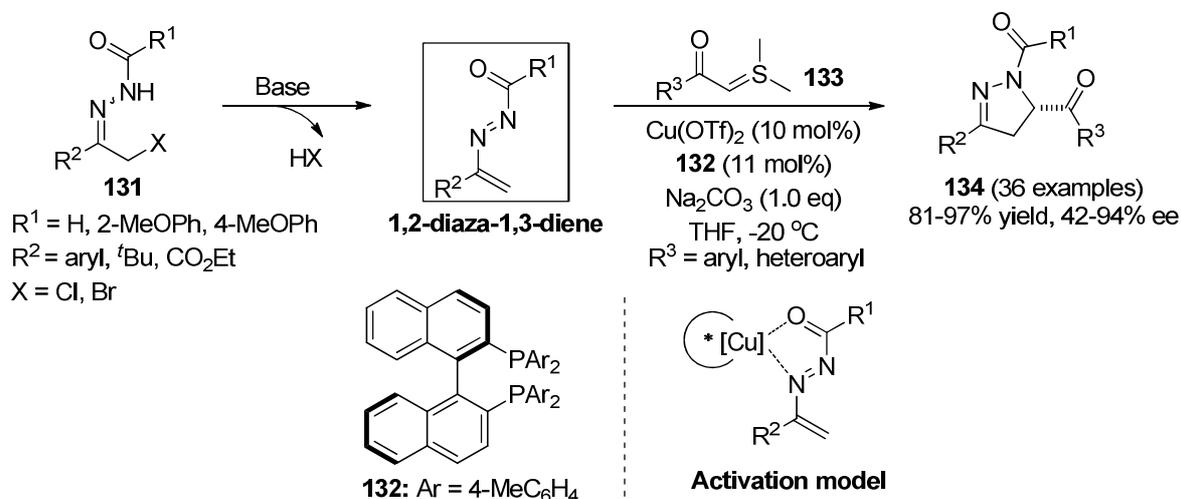
In 2012, a highly enantioselective aza-Michael/hemiaminal cascade reaction of enals **119** with hydrazines **120** was developed by the Vicario group through aminocatalysis (Scheme 29).⁴² In this reaction, *N,N'*-disubstituted hydrazines were used to avoid the direct formation of hydrazones through condensation reaction with enals.



Scheme 30. Tandem Cu- and Pd-catalyzed one-pot three-component addition/cyclization reaction.

4. Miscellaneous

The 1,2-diaza-1,3-dienes represent a unique class of versatile agents and synthetic building blocks, and have found wide applications in cycloaddition reactions for assembly of various *N*-heterocyclic ring systems. Typically, these highly reactive intermediates could be easily generated *in situ* from the corresponding α -halo hydrazones under the alkaline conditions. In 2012, the group of Bolm described the first example of highly enantioselective formal [4+1] annulation between *in situ*-derived 1,2-diaza-1,3-dienes and sulfur ylides **133** catalyzed by Cu(II)/(*R*)-Tol-BINAP complex (Scheme 31).⁴⁶

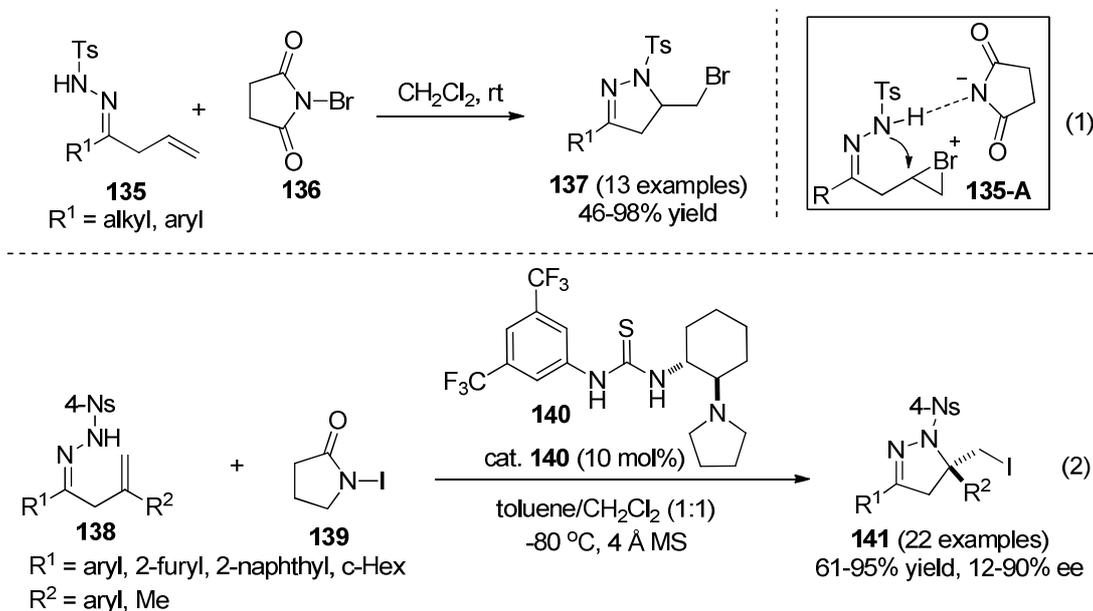


Scheme 31. Cu(II)-catalyzed formal [4+1] cycloaddition of 1,2-diaza-1,3-dienes.

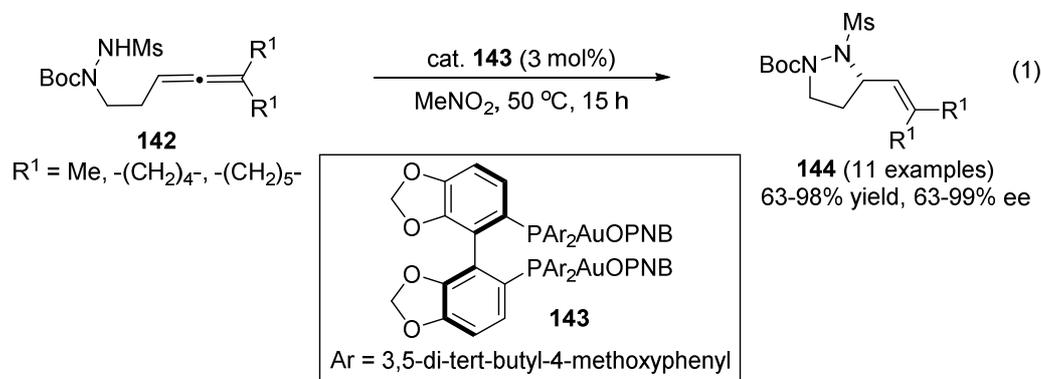
In this reaction, it has been found that both the protecting group of hydrazones and the structure of chiral ligands played an important role on the reaction efficiency and stereoselectivities. The transformation provided a straightforward access to the biologically important and optically active dihydropyrazole derivatives **134** in generally good yields with high enantioselectivities under mild conditions (up to 96% yield, 94% ee).

In 2014, Xiao and co-workers reported the first example of catalyst-free halocyclization of β,γ -unsaturated hydrazones **135** with NBS, and various dihydropyrazole derivatives can be obtained in good yields (Scheme 32, eq.1).⁴⁷ Unfortunately, the asymmetric version of this transformation remains challenging due to the strong uncatalyzed process. Based on their previous organocatalytic enantioselective

iodoetherification β,γ -unsaturated ketoximes,⁴⁸ the Mukherjee group recently achieved a catalytic asymmetric iodoaminocyclization of β,γ -unsaturated hydrazones **138** with the use of a bifunctional thiourea catalyst **140** to give the dihydropyrazole derivatives **141** with good yields and enantioselectivities (Scheme 32, eq.2).⁴⁹ In this process, the uncatalyzed process can be suppressed by using relatively low reactive [I⁺] source **139** and lowering the reaction temperature to -80 °C.



Scheme 32. Catalytic asymmetric iodoaminocyclization of a, b-unsaturated hydrazones.

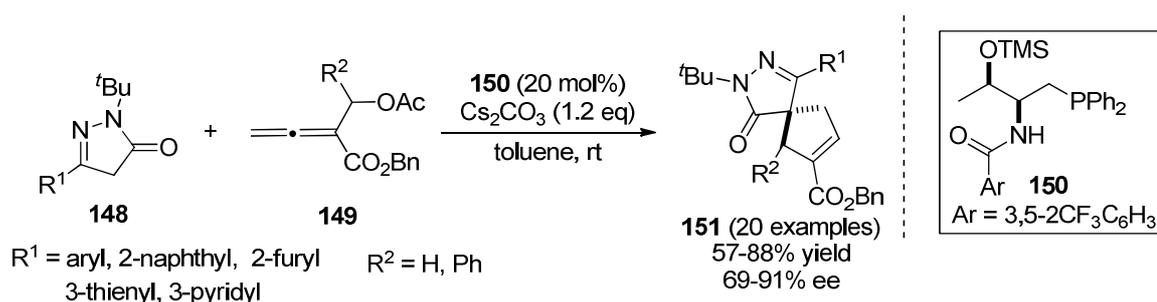


Scheme 33. Gold-catalyzed asymmetric cyclization of allenes.

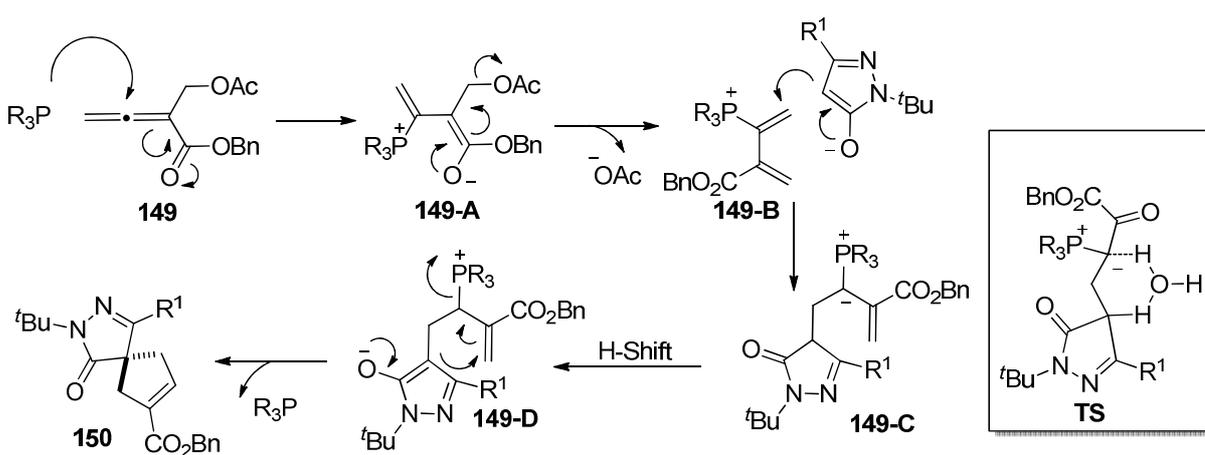
In addition, Toste and co-workers in 2009 reported a gold(I)-catalyzed enantioselective intramolecular hydroamination of allenes with hydrazine, affording the corresponding pyrazolidine derivatives **144** in good yields with high enantioselectivities (up to 99% ee) (Scheme 33, eq.1).⁵⁰ Recently, the same group also developed an highly enantioselective bromocyclization reaction of allenes **145** by use of the same gold

catalyst (Scheme 33, eq. 2). This reaction showed a quite broad substrate scope with respect to allenes **145**. Moreover, various nucleophiles such as hydrazine, amine, hydroxylamine, alcohol, and acid are all proved to be suitable for this process.⁵¹

Recently, Lu and co-workers reported a phosphine-catalyzed formal [4+1] cyclization of pyrazolones **148** with 2,3-butadienoates **149** for the synthesis of biologically potential spiropyrazolones **151** in a highly enantioselective manner (Scheme 34).⁵² Furthermore, the effect of H₂O on this reaction has been carefully investigated, and the results indicated that hydrogen-bonding interaction between such nucleophilic phosphine catalyst and pyrazolones also played an important role on the enantioselectivity of this transformation.

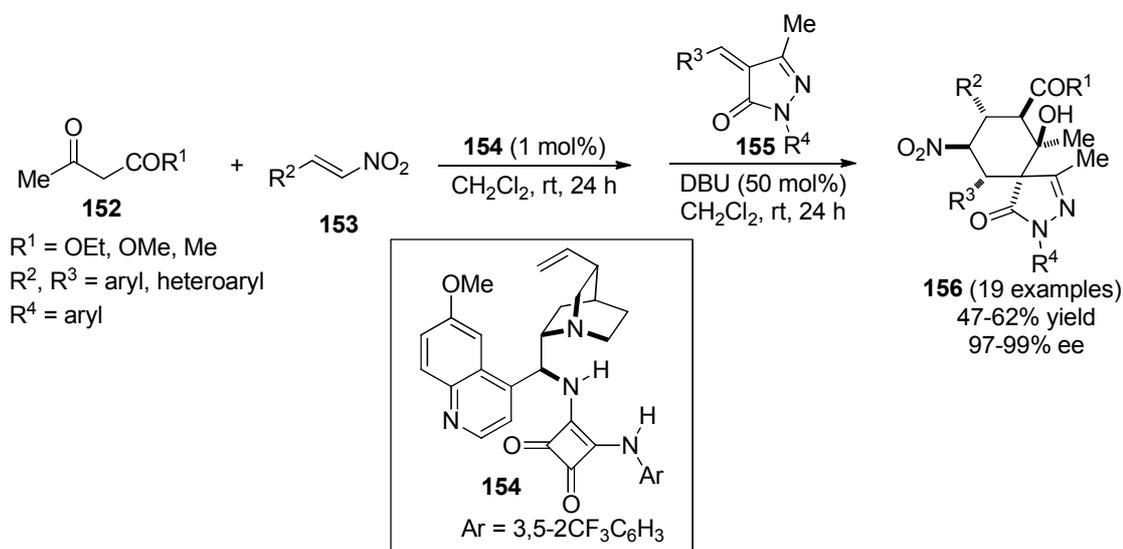


A possible mechanism was then postulated as depicted in Scheme 35. Firstly, a nucleophilic attack of phosphine moiety to 2,3-butadienoate **149** to give the active intermediate **149-A**. Then, upon elimination an acetate, **149-A** can be converted into intermediate **149-B**, which can react with the enolate of pyrazolones **148** to furnish phosphonium ylide **149-C**. Finally, a sequential 1,3-proton transfer/intramolecular Michael addition resulted in the formation of the desired product **150**.



Quite recently the group of Enders developed an organocatalytic one-pot sequential Michael/Michael/1,2-addition reaction of β -dicarbonyl compounds **152**, nitroalkenes **153** and unsaturated pyrazolones **155** by combination of a chiral cinchona-derived aminosquaramide catalyst **154** and organic base DBU (Scheme 36).⁵³ This methodology provided an efficient access to rapid assembly of optically active spiropyrazolones

156. Notably, the reaction can still work very well at gram-scale with no loss of efficiency and enantioselectivity. The opposite enantiomer of the products can also be obtained with good yields and enantioselectivities by the use of a pseudoenantiomeric catalyst.



Scheme 36. Chiral aminosquaramide-catalyzed one-pot procedure for the synthesis of spiropyrazolones.

Acknowledgments

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