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# Recent Developments in Enantioselective Metal-Catalyzed Domino Reactions

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**Abstract:** This review collects the very recent developments in enantioselective metal-catalyzed domino reactions published since the beginning of 2016. It illustrates that many types of enantioselective metal-catalyzed domino processes continue to be developed, allowing an easy one-pot access to complex molecular architectures from simple starting materials taking economic advantages, such as avoiding costly protecting groups and time-consuming purification procedures after each step.

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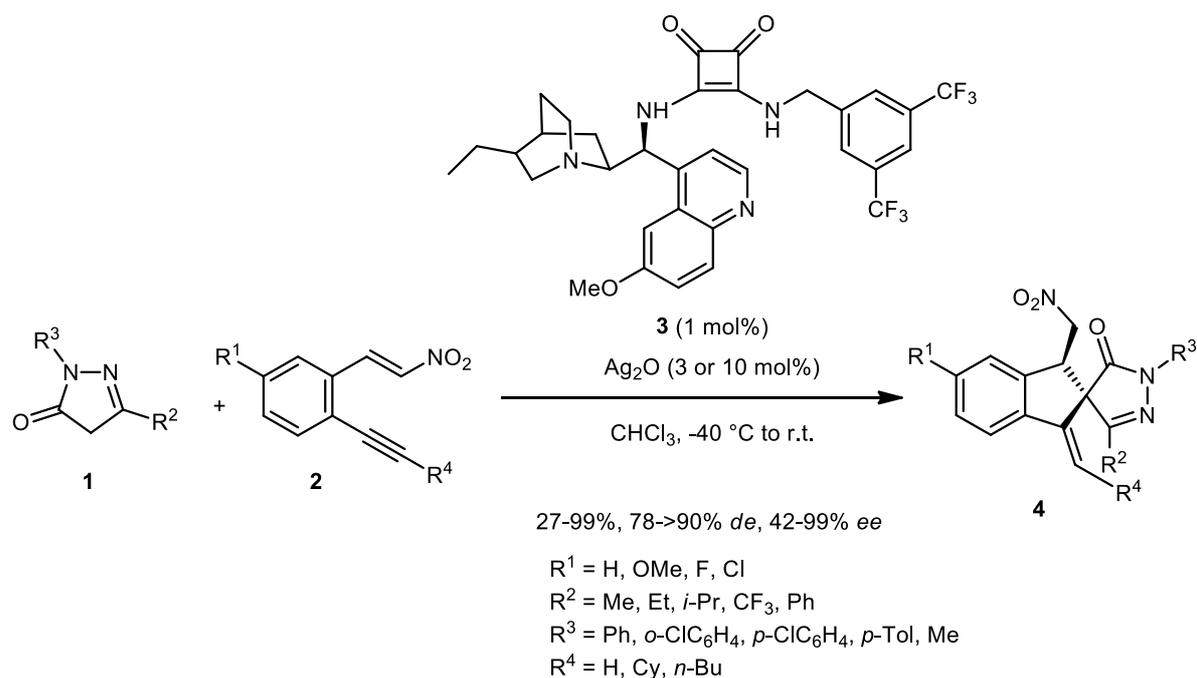
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## 1 Introduction

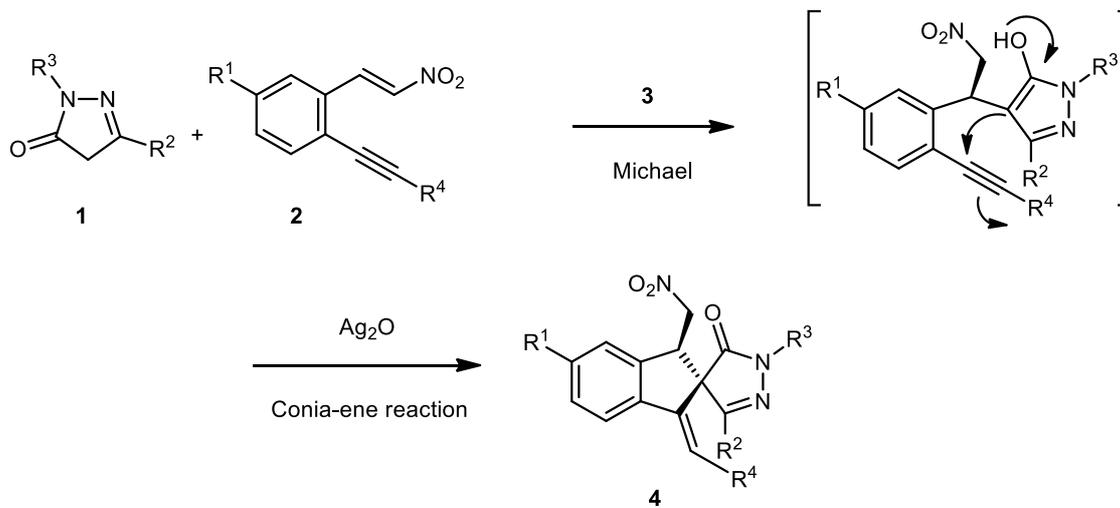
Asymmetric metal catalysis constitutes a powerful tool to highly enantioselectively perform many types of reactions.<sup>[1]</sup> In particular, the combination of asymmetric metal catalysis with the concept of domino reactions has allowed high molecular complexity to be easily achieved with remarkable levels of stereocontrol on the basis of simple economic one-pot procedures. In the last decade, many types of enantioselective domino processes, including multicomponent ones,<sup>[2]</sup> have been successfully catalyzed by a wide variety of chiral metal complexes.<sup>[3]</sup> Introduced by Tietze, the concept of domino reactions consists in one-step two or more bond-forming transformations occurring under the same reaction conditions.<sup>[4]</sup> A range of complex densely functionalized chiral molecules, including natural and/or biologically important products, have already been synthesized through these processes without requiring the purification of intermediates.<sup>[5]</sup> The goal of this review is to collect the very recent advances in enantioselective metal-catalyzed domino reactions published since the beginning of 2016 since this field was most recently updated this year, covering the literature until the end of 2015 (including only 2 references from 2016).<sup>[6]</sup> It is divided into ten parts, dealing successively with enantioselective silver-catalyzed domino reactions, scandium- and yttrium-catalyzed domino reactions, iron-catalyzed domino reactions, cobalt-catalyzed domino reactions, magnesium-catalyzed domino reactions, zirconium-catalyzed domino reactions, rhodium-catalyzed domino reactions, palladium-catalyzed domino reactions, copper-catalyzed domino reactions and enantioselective domino reactions catalyzed by other metals.

## 2 Enantioselective Silver-Catalyzed Domino Reactions

Related to its moderate Lewis acidity, silver has long been neglected in catalysis. However, many highly efficient transformations,<sup>[7]</sup> including enantioselective domino reactions,<sup>[8]</sup> are today available by using various types of chiral silver complexes. The first example of asymmetric silver-catalyzed domino reaction was reported in 1990 by Ito et al., dealing with a domino aldol/cyclization reaction of aldehydes with tosylmethyl isocyanide promoted by chiral ferrocenylphosphine/silver complexes with high enantioselectivity (86% *ee*).<sup>[9]</sup> Ever since, many other types of enantioselective silver-catalyzed domino reactions have been reported. For example in 2016, Enders et al. reported enantioselective silver-catalyzed domino Michael/Conia-ene reactions of 5-pyrazolones **1** with alkyne-tethered nitroalkenes **2** in chloroform as solvent.<sup>[10]</sup> The process was catalyzed at -40 °C to room temperature by a combination of 1 mol% of a cinchona-derived squaramide **3** as chiral organocatalyst with 3/10 mol% of Ag<sub>2</sub>O, providing the corresponding chiral spiropyrazolones **4**. As shown in Scheme 1, the first key of the sequence was promoted by the organocatalyst while the second step by Ag<sub>2</sub>O, according to a relay catalysis concept. The domino products were obtained in low to quantitative yields (27-99%) combined with moderate to excellent enantioselectivities (42-99% *ee*) and high diastereoselectivities (78->90% *de*) starting from variously substituted pyrazolones and terminal alkynes. It was found that sterically hindered nitroolefins provided the lowest yields (27-54%). Moreover, nitroalkenes with internal alkynes bearing aliphatic substituents (R<sup>4</sup> = Cy, *n*-Bu) were compatible, although requiring higher catalyst loadings in Ag<sub>2</sub>O (10 mol% instead of 3 mol%).



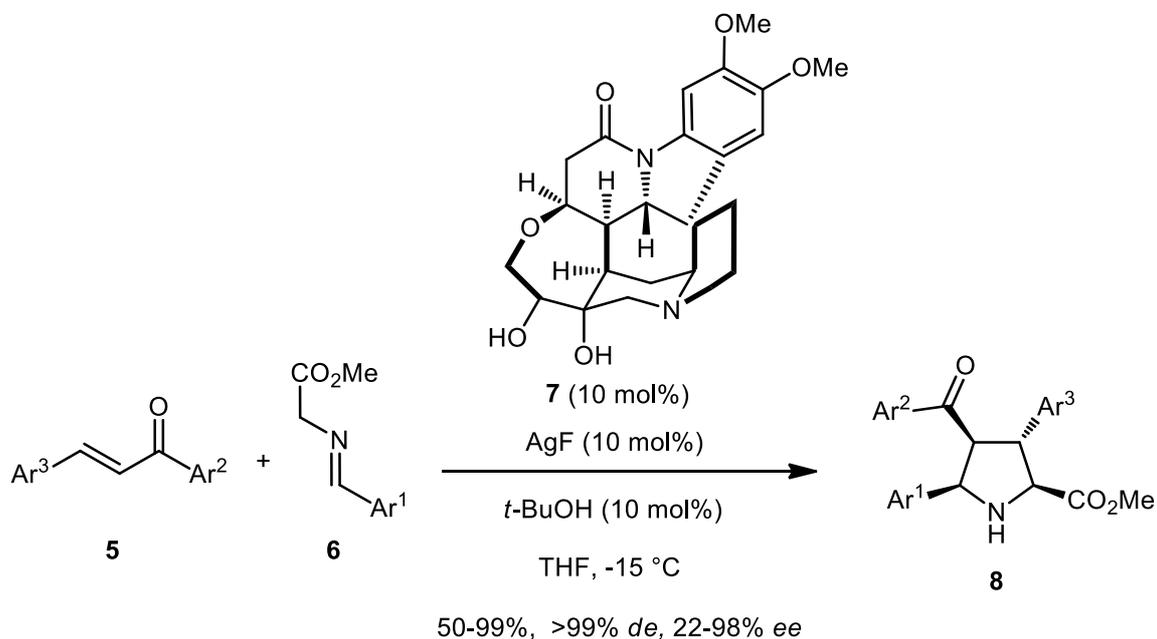
mechanism:



**Scheme 1.** Domino Michael/Conia-ene reaction of alkyne-tethered nitroalkenes with 5-pyrazolones.

The same year, Oh et al. developed another type of silver-catalyzed domino transformations, such as the enantioselective silver-catalyzed Michael/Mannich reaction of chalcones **5** with glycine imino esters **6** catalyzed by a combination of 10 mol% of AgF and the same quantity of brucine-derived diol **7** as a chiral ligand.<sup>[11]</sup> The process was performed at  $-15^\circ\text{C}$  in THF as solvent and in the presence of *tert*-butanol as an additive, leading to the corresponding chiral *endo*-cycloadducts **8** as single diastereomers in moderate to quantitative yields (50-99%) and low to excellent enantioselectivities (22-98% *ee*), as illustrated in Scheme 2. It was found that the electronic nature of the chalcone's  $\beta$ -aryl substituent ( $\text{Ar}^3$ ) had a negative impact on the enantioselectivity of the reaction while the nature of the aryl substituent on the imino esters ( $\text{Ar}^1$ ) had no effect on the enantioselectivity. For example, the lowest enantioselectivities (22-55% *ee*) were obtained in the reaction of chalcones bearing a *para*-tolyl group or a 1-, 3-, or 4-chloro-substituted phenyl group at the  $\beta$ -position. The authors proposed the

transition state depicted in Scheme 2 in which the silver atom was coordinated to two ligands through the N-19 tertiary amine.

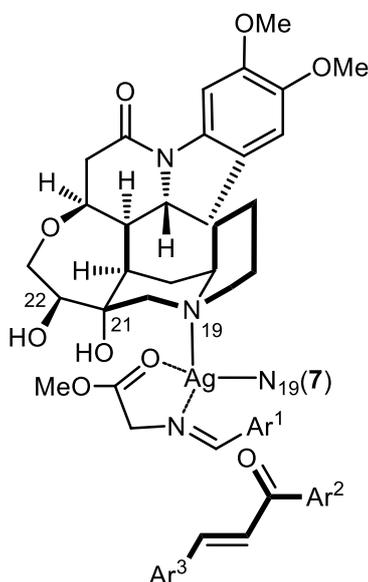


Ar<sup>1</sup> = Ph, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-Tol, *p*-FC<sub>6</sub>H<sub>4</sub>, *m*-BrC<sub>6</sub>H<sub>4</sub>, 2-thienyl

Ar<sup>2</sup> = Ph, *p*-ClC<sub>6</sub>H<sub>4</sub>

Ar<sup>3</sup> = Ph, *p*-Tol, *p*-ClC<sub>6</sub>H<sub>4</sub>, *o*-ClC<sub>6</sub>H<sub>4</sub>, *m*-ClC<sub>6</sub>H<sub>4</sub>

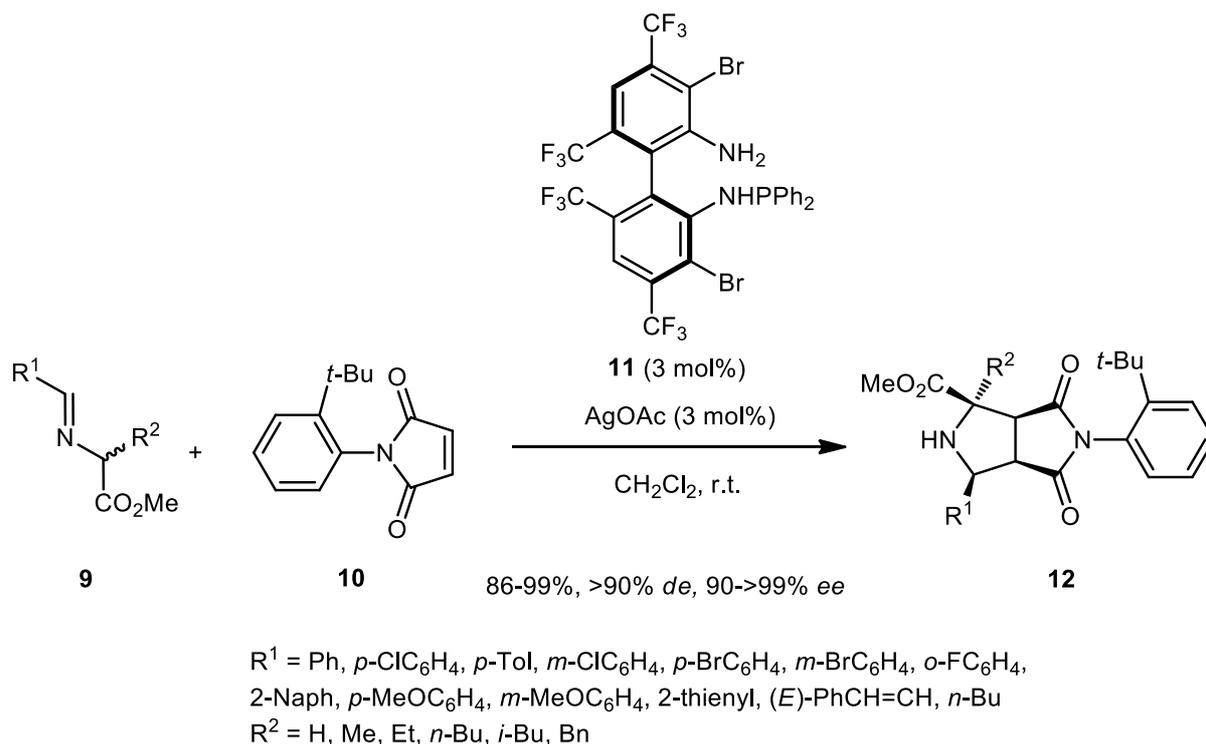
proposed transition state:



**Scheme 2.** Domino Michael/Mannich reaction of chalcones with glycine imino esters.

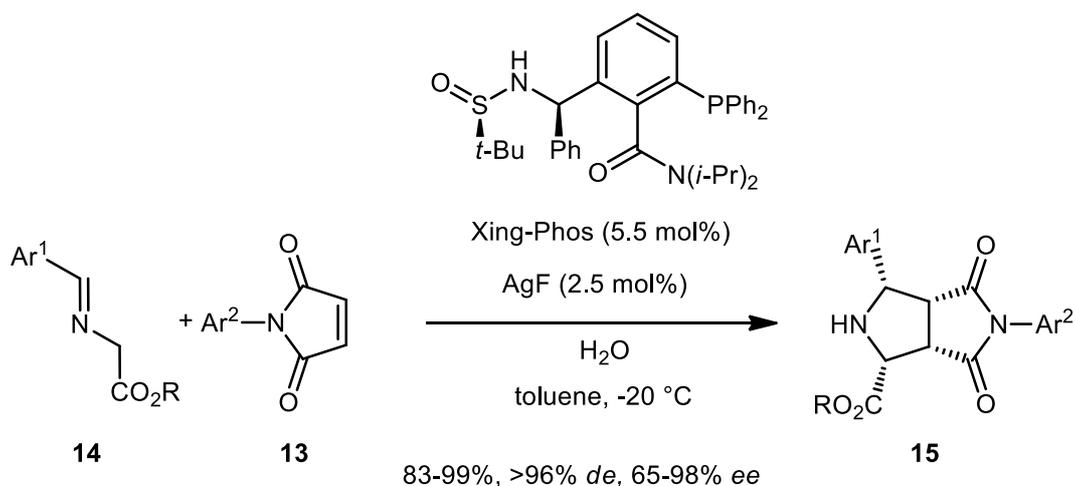
In the same area, enantioselective silver-catalyzed domino Michael/Mannich reactions of glycine imino esters **9** with *N*-(2-*t*-butylphenyl)maleimide **10** have been developed by Wang et al. in the presence of 3 mol% of a silver catalyst *in situ* generated from AgOAc and (*S*)-TF-BiphamPhos-derived ligand **11** (Scheme 3).<sup>[12]</sup> The reaction occurred in dichloromethane at room temperature to provide the corresponding chiral domino products **12** exhibiting four contiguous stereogenic centers as

almost single diastereomers (>90% *de*) in both high yields (86-99%) and enantioselectivities (90->99% *ee*). It was found that  $\alpha$ -non-substituted imino esters ( $R^2 = H$ ) could be substituted ( $R^1$ ) by aromatic, heteroaromatic or aliphatic groups, providing uniformly excellent results (86-99% yield, 90->99% *ee*). Moreover, more sterically hindered imino esters derived from  $\alpha$ -substituted- $\alpha$ -amino acids ( $R^2 \neq H$ ) were also tolerated. For example, alanine-derived imino esters ( $R^2 = Me$ ) were tolerated, providing the corresponding products in 99% yield and 98% *ee*. Excellent results (97-98% yield and 97->99% *ee*) were also achieved in the reaction of sterically hindered substrates ( $R^2 = Et, n\text{-Bu}, i\text{-Bu}$ , or *Bn*). The utility of this methodology was demonstrated by converting product into various important structures, such as chiral *2H*-pyrroles and highly functionalized pyrrole derivatives.



**Scheme 3.** Domino Michael/Mannich reaction of *N*-(2-*t*-butylphenyl)maleimide with glycine imino esters.

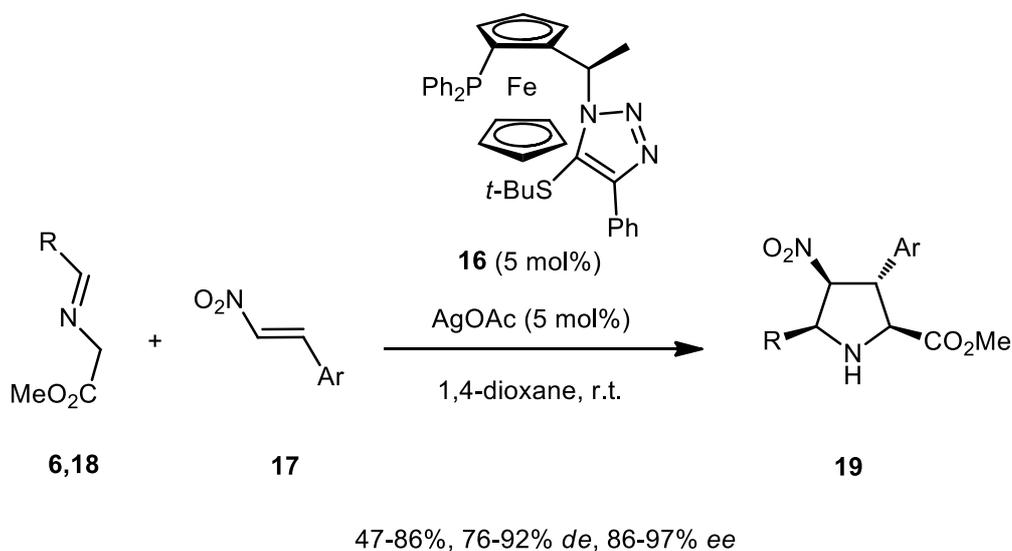
This type of reactions was also investigated by Xia and Xu in the presence of a combination of 5.5 mol% of Xing-Phos ligand with 2.5 mol% of AgF.<sup>[13]</sup> The reaction of a range of *N*-aryl-substituted maleimides **13** with various aromatic imino esters **14** was performed in toluene at -20 °C in the presence of water as traces, affording the corresponding chiral pyrrolidines **15** exhibiting four contiguous stereogenic centers as single *endo*-diastereomers (>96% *de*) in good to excellent yields (83-99%) and moderate to excellent enantioselectivities (65-98% *ee*), as illustrated in Scheme 4. The enantioselectivity of the reaction was found to be sensitive to the electronic nature of the substituents beared by the aryl rings ( $Ar^1$ ) of the imino esters. Indeed, tolyl-substituted imino methyl ester yielded the corresponding product in only 65% *ee*, while the corresponding 4-halogen-substituted-phenyl imino methyl esters provided much better enantioselectivities (90-91% *ee*).



$\text{Ar}^1 = \text{Ph, } o\text{-MeOC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, p\text{-Tol, } p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4,$   
 $p\text{-PhC}_6\text{H}_4, p\text{-MeSC}_6\text{H}_4, 3,5\text{-(F}_3\text{C)}_2\text{C}_6\text{H}_3$   
 $\text{Ar}^2 = \text{Ph, } m\text{-ClC}_6\text{H}_4, m\text{-Tol, } m\text{-BrC}_6\text{H}_4, p\text{-EtOC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, 3,5\text{-Me}_2\text{C}_6\text{H}_3$   
 $\text{R} = \text{Me, Et}$

**Scheme 4.** Domino Michael/Mannich reaction of *N*-aryl-substituted maleimides with glycine imino esters.

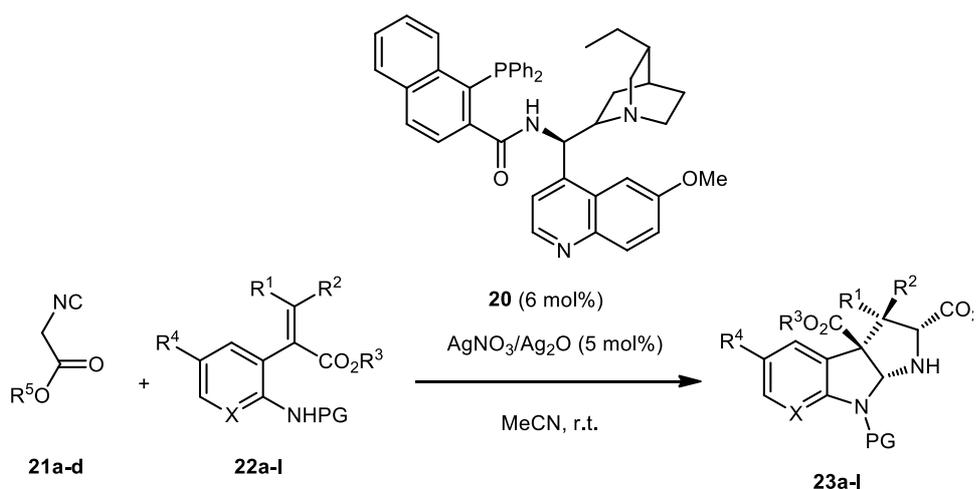
In 2016, Fukuzawa et al. reported enantioselective silver-catalyzed domino Michael/aza-Henry reactions of nitroalkenes with glycine imino esters.<sup>[14]</sup> The processes were catalyzed at room temperature in 1,4-dioxane as solvent by a combination of 5 mol% of AgOAc with the same quantity of ThioClickFerrophos ligand **16**. As shown in Scheme 5, various (hetero)aromatic nitroalkenes **17** reacted with a range of (hetero)aromatic imino esters **6/18** to give the corresponding chiral pyrrolidines **19** as almost single *endo*-cycloadducts in moderate to good yields (51-86%), good to high diastereoselectivities (82-92% *de*) and enantioselectivities (86-97% *ee*). The scope of the methodology was also extended to an alkyl imino ester (R = Cy) with a high enantioselectivity (93% *ee*) albeit combined with lower yield (47%) and diastereoselectivity (76% *de*).



$\text{R} = \text{Ph, } o\text{-Tol, } m\text{-Tol, } p\text{-Tol, } p\text{-MeOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, 1\text{-Naph, } 2\text{-thienyl, Cy}$   
 $\text{Ar} = \text{Ph, } o\text{-Tol, } p\text{-Tol, } p\text{-MeOC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, 2\text{-furyl, ferrocenyl}$

**Scheme 5.** Domino Michael/aza-Henry reaction of nitroalkenes with glycine imino esters.

In another context, enantioselective silver-catalyzed domino Michael/double cyclization reactions between 2-(2-aminophenyl)acrylates and isocyanoacetates were described by Xie et al., in 2016.<sup>[15]</sup> The processes were cooperatively promoted at room temperature by a combination of 5 mol% of AgNO<sub>3</sub>/Ag<sub>2</sub>O and 6 mol% of chiral cinchona alkaloid **20** in acetonitrile as solvent. They evolved through the sequential Michael addition of metallated isocyanoacetates **21a-d** to acrylates **22a-l**, the intramolecular nucleophilic addition of the thus-formed enolates to the isocyano group, and the intramolecular attack of the nucleophilic amido to the thus-produced 2*H*-pyrrolidine intermediates, leading to the corresponding functionalized chiral *cis*-3*a*,8*a*-hexahydropyrrolo[2,3-*b*]indoles **23a-l** exhibiting up to four contiguous stereogenic centers in good to quantitative yields (73-99%) and moderate to high enantioselectivities (59-90% *ee*), as illustrated in Scheme 6. Concerning the diastereoselectivity of the reaction, it was generally low except for  $\beta$ -substituted 2-(2-amidophenyl)acrylates, which afforded the corresponding products **23d-e** as single diastereomers (>90% *de*). The reaction conditions were compatible with the presence of various functional groups on the phenyl and alkene moieties, amino protecting groups in acrylates and ester groups in both acrylates and isocyanoacetates.



**23a:**  $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$ ,  $\text{R}^3 = \text{R}^5 = \text{Et}$ ,  $\text{PG} = \text{Piv}$ ,  $\text{X} = \text{CH}$ :

93%, 1.6:1 *dr*, 85% *ee*/88% *ee*

**23b:**  $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{R}^5 = \text{Et}$ ,  $\text{R}^4 = \text{Me}$ ,  $\text{PG} = \text{Piv}$ ,  $\text{X} = \text{CH}$ :

89%, 1.4:1 *dr*, 80% *ee*/85% *ee*

**23c:**  $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{R}^5 = \text{Et}$ ,  $\text{R}^4 = \text{Cl}$ ,  $\text{PG} = \text{Piv}$ ,  $\text{X} = \text{CH}$ :

86%, 2.3:1 *dr*, 59% *ee*/65% *ee*

**23d:**  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Ph}$ ,  $\text{R}^4 = \text{Cl}$ ,  $\text{R}^3 = \text{R}^5 = \text{Et}$ ,  $\text{PG} = \text{Piv}$ ,  $\text{X} = \text{CH}$ :

87%, >19:1 *dr*, 80% *ee*

**23e:**  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = n\text{-Pr}$ ,  $\text{R}^3 = \text{R}^5 = \text{Et}$ ,  $\text{R}^4 = \text{Cl}$ ,  $\text{PG} = \text{Piv}$ ,  $\text{X} = \text{CH}$ :

85%, >19:1 *dr*, 71% *ee*/82% *ee*

**23f:**  $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$ ,  $\text{R}^3 = \text{R}^5 = \text{Et}$ ,  $\text{PG} = \text{Piv}$ ,  $\text{X} = \text{N}$ :

84%, 2.4:1 *dr*, 78% *ee*/77% *ee*

**23g:**  $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$ ,  $\text{R}^3 = \text{R}^5 = \text{Bn}$ ,  $\text{PG} = \text{Piv}$ ,  $\text{X} = \text{CH}$ :

97%, 1.4:1 *dr*, 77% *ee*/82% *ee*

**23h:**  $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$ ,  $\text{R}^3 = t\text{-Bu}$ ,  $\text{R}^5 = \text{Et}$ ,  $\text{PG} = \text{Piv}$ ,  $\text{X} = \text{CH}$ :

75%, 2.4:1 *dr*, 88% *ee*/90% *ee*

**23i:**  $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$ ,  $\text{R}^3 = t\text{-Bu}$ ,  $\text{R}^5 = 1\text{-adamantyl}$ ,  $\text{PG} = \text{Piv}$ ,  $\text{X} = \text{CH}$ :

99%, 4:1 *dr*, 0% *ee*/18% *ee*

**23j:**  $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$ ,  $\text{R}^3 = t\text{-Bu}$ ,  $\text{R}^5 = \text{Et}$ ,  $\text{PG} = \text{Tos}$ ,  $\text{X} = \text{CH}$ :

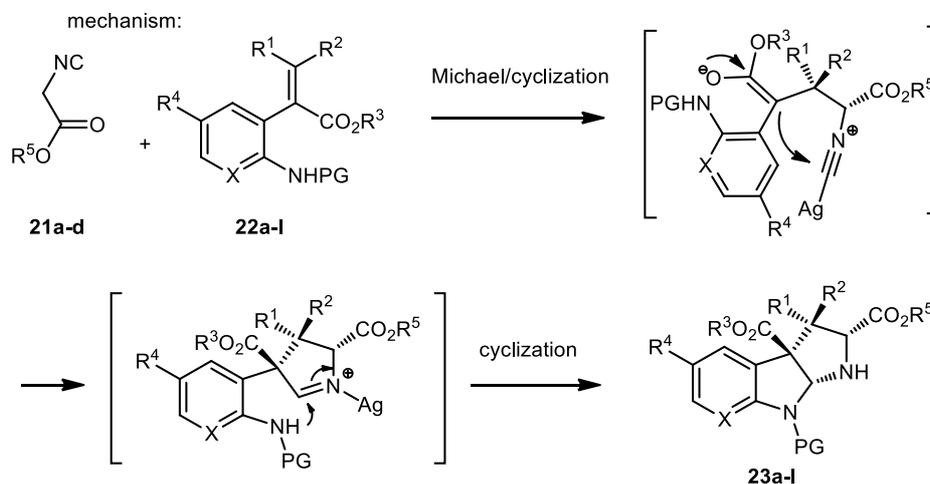
83%, 3:1 *dr*, 12% *ee*/41% *ee*

**23k:**  $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$ ,  $\text{R}^3 = t\text{-Bu}$ ,  $\text{R}^5 = \text{Et}$ ,  $\text{PG} = \text{Ac}$ ,  $\text{X} = \text{CH}$ :

73%, 2:1 *dr*, 7% *ee*/11% *ee*

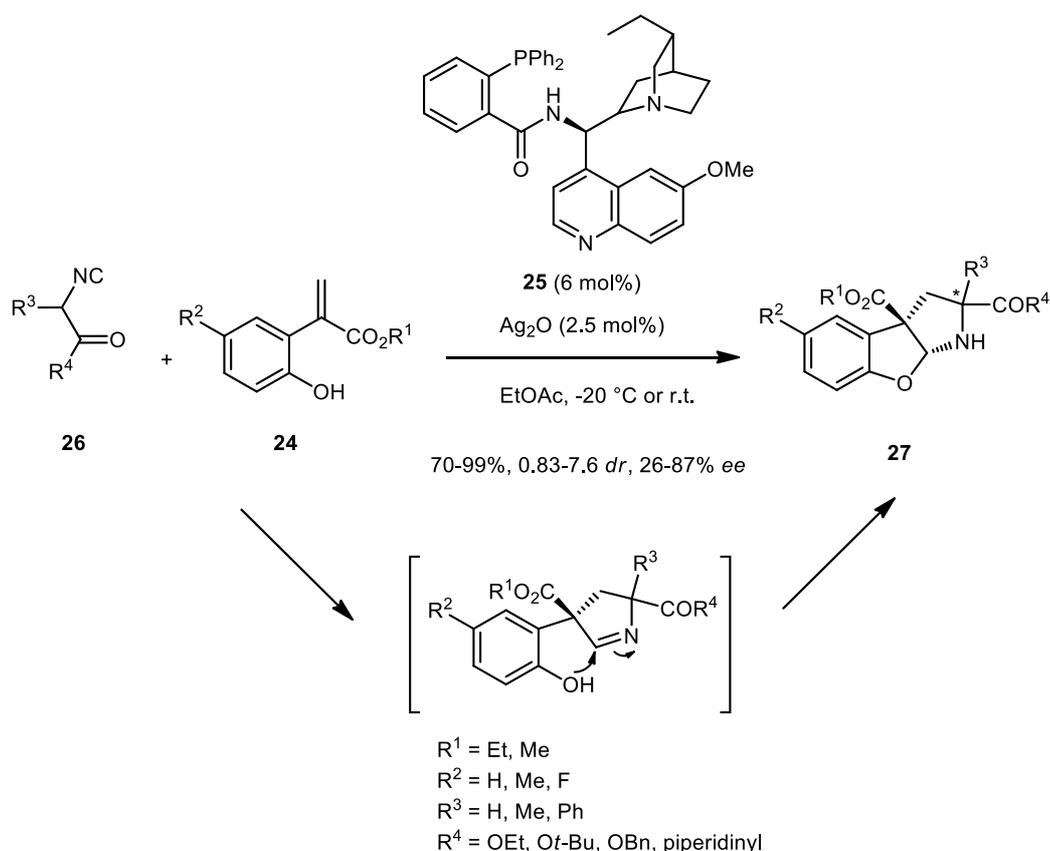
**23l:**  $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$ ,  $\text{R}^3 = \text{R}^5 = t\text{-Bu}$ ,  $\text{PG} = \text{Boc}$ ,  $\text{X} = \text{CH}$ :

82%, 2:1 *dr*, 6% *ee*/6% *ee*



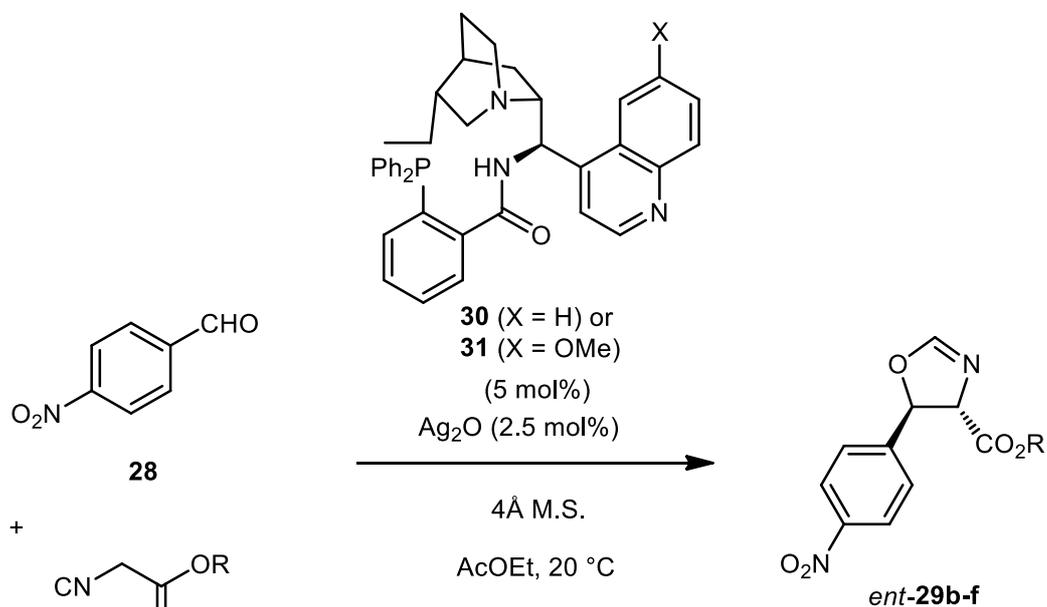
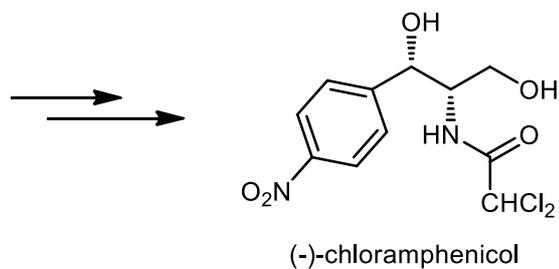
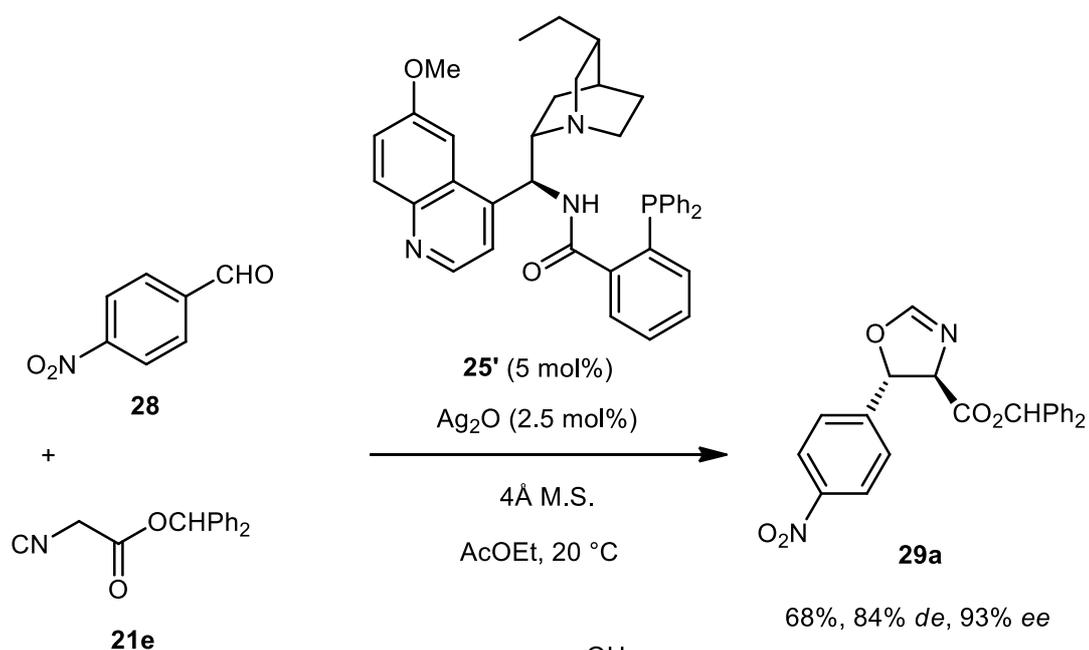
**Scheme 6.** Domino Michael/double cyclization reaction of 2-(2-aminophenyl)acrylates with isocyanoacetates.

In 2018, the same authors developed related reactions involving another type of substrates, such as 2-(2-hydroxyphenyl)acrylates **24**.<sup>[16]</sup> In this case, the active catalyst was *in situ* generated from 2.5 mol% of Ag<sub>2</sub>O and 6 mol% of a related cinchona alkaloid ligand **25**. The domino Michael/double cyclization reaction of 2-(2-hydroxyphenyl)acrylates **24** with isocyanoacetates **26** performed at -20 °C or room temperature in ethyl acetate as solvent led to the corresponding chiral tetrahydrobenzofuro[2,3-*b*]pyrroles **27** as mixtures of two diastereomers with low to moderate diastereomeric ratios (0.83-7.6 *dr*) in generally excellent yields (92-99%) and low to excellent enantioselectivities (26-87% *ee*), as shown in Scheme 7. A lower yield (70%) was observed in the reaction of an isocyanoacetamide (R<sup>4</sup> = piperidinyl). The lowest enantioselectivities (26-55% *ee*) were obtained in the reaction of an acrylate exhibiting a fluorine atom on the phenyl ring (R<sup>2</sup> = F).



**Scheme 7.** Domino Michael/double cyclization reaction of 2-(2-hydroxyphenyl)acrylates with isocyanoacetates.

Enantioselective silver-catalyzed domino reactions not initiated by a Michael addition have also been recently disclosed. For example, in 2016 Dixon et al. developed a silver-catalyzed enantioselective domino aldol/cyclization reaction, allowing a novel total synthesis of antibiotic (-)-chloramphenicol.<sup>[17]</sup> As shown in Scheme 8, *p*-nitrobenzaldehyde **28** reacted with isocyanoacetate **21e** to give the corresponding *trans*-oxazoline **29a** in moderate yield (68%), good diastereoselectivity (84% *de*) and high enantioselectivity (93% *ee*). The reaction was catalyzed at room temperature in ethyl acetate as solvent with a combination of 2.5 mol% of Ag<sub>2</sub>O and 5 mol% of chiral cinchona alkaloid **25'**. The chiral domino product **29a** was further converted into (-)-chloramphenicol through three supplementary steps. The scope of this methodology was extended to various alkyl isocyanoacetates **21b-f** by using chiral silver complexes derived from other chiral cinchona alkaloid ligands, such as **30** and **31**, which allowed the corresponding chiral oxazolines *ent*-**29b-f** to be obtained in moderate to good yields (56-80%) combined with good diastereo- and enantioselectivities (76-82% *de* and 78-87% *ee*, respectively), as shown in Scheme 8.



with L\* = **30**:

*ent-29b*: R = *t*-Bu: 70%, 82% *de*, 78% *ee*

*ent-29c*: R = Me: 80%, 76% *de*, 82% *ee*

*ent-29d*: R = Bn: 61%, 80% *de*, 87% *ee*

with L\* = **31**:

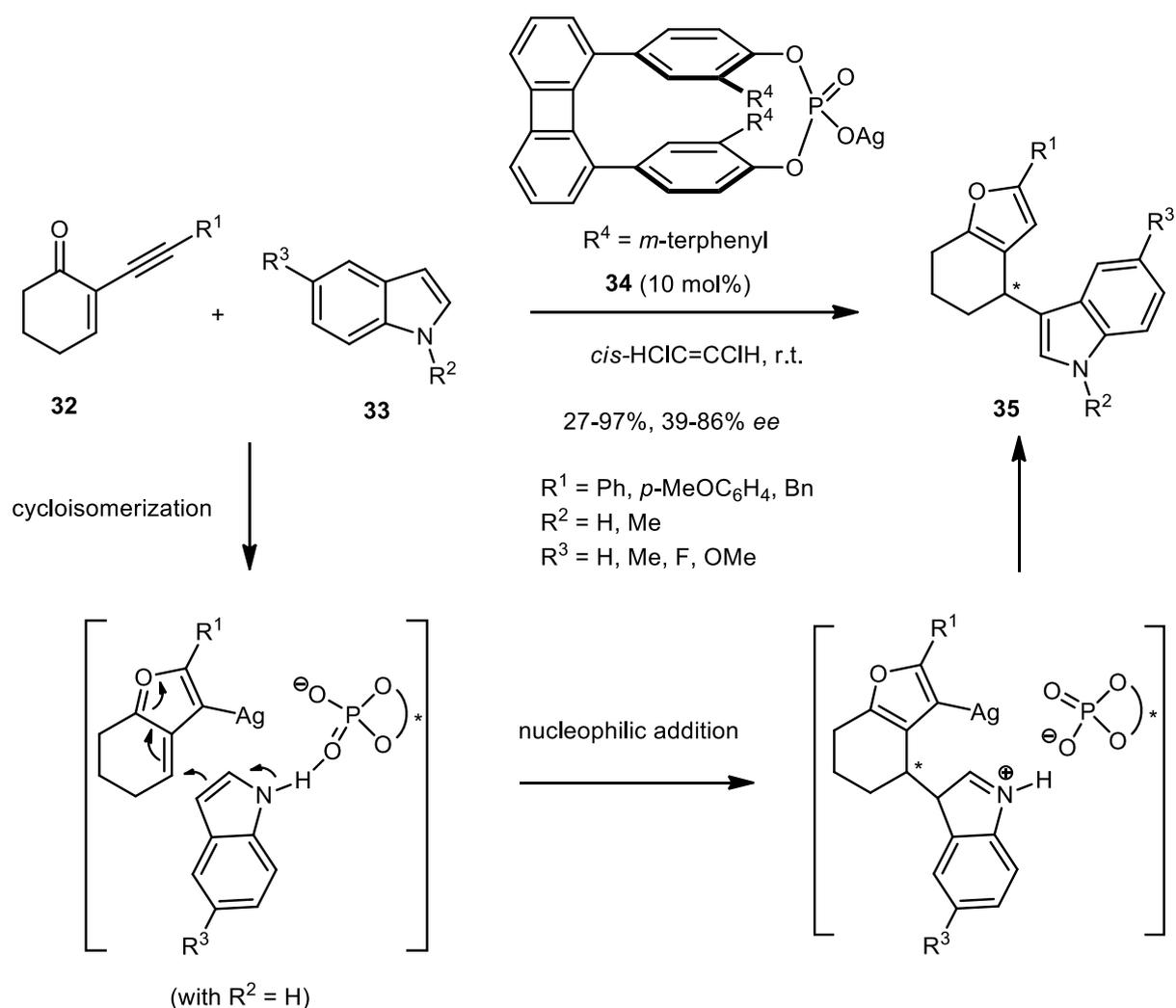
*ent-29d*: R = Bn: 64%, 80% *de*, 87% *ee*

*ent-29e*: R = *p*-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>: 63%, 78% *de*, 86% *ee*

*ent-29f*: R = 3,5-(F<sub>3</sub>C)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>: 56%, 80% *de*, 84% *ee*

**Scheme 8.** Domino aldol/cyclization reactions of *p*-nitrobenzaldehyde with isocyanoacetates and synthesis of (-)-chloramphenicol.

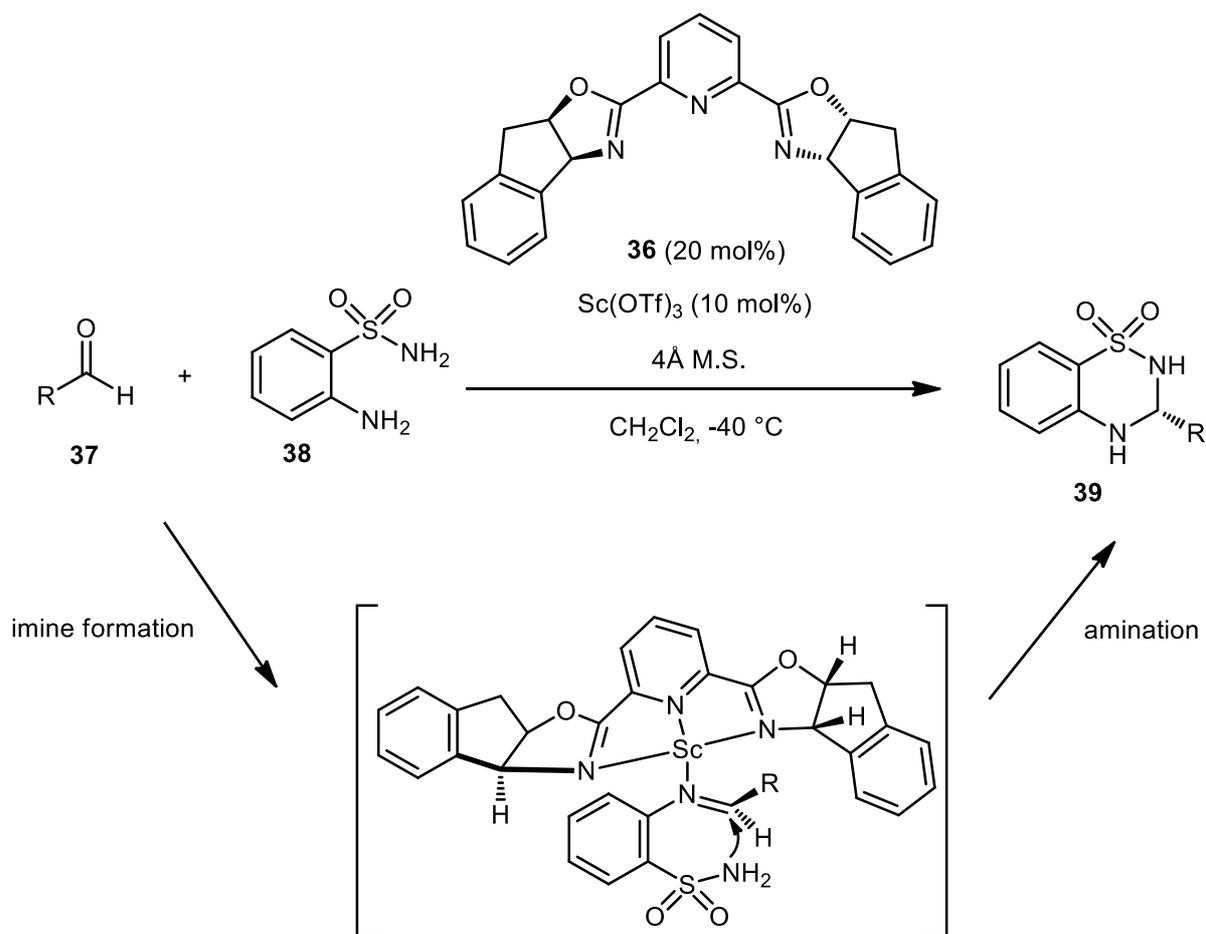
In 2018, Marinetti and Betzer reported a novel route to chiral bicyclic furans which was based on an enantioselective silver-catalyzed domino cycloisomerization/addition reaction of 2-(1-alkynyl)-2-cyclohexenone **32** with 5-substituted indoles **33**.<sup>[18]</sup> The process employed 10 mol% of preformed chiral paracyclophane-based silver phosphate **34** as catalyst in *cis*-1,2-dichloroethylene as solvent. As shown in Scheme 9, the reaction afforded at room temperature the corresponding chiral domino products **35** in low to quantitative yields (27-97%) and moderate to high enantioselectivities (39-86% *ee*). Both electron-withdrawing and electron-donating substituents on the 5-position ( $R^3$ ) of the indoles were tolerated. However, a significant drop of the enantioselectivity (39% *ee*) was observed in the reaction of *N*-methylindole ( $R^2 = \text{Me}$ ) as the nucleophile, which highlighted a probable role of the NH function of the indole in the stereoselectivity of the process. Indeed, the NH group of *N*-unsubstituted indoles could enable hydrogen bonding with the phosphoryl moiety of the silver phosphate in the enantiodetermining addition step depicted in Scheme 9. The H-bonding, combined with a tight ion pairing of the phosphate with the cationic intermediate, generated a better-defined relative orientation of the substrates in the transition state and consequently contributed to chiral induction. Generally, the best enantioselectivities (82-86% *ee*) were achieved in the reaction of 2-(phenylethynyl)cyclohex-2-enone ( $R^1 = \text{Ph}$ ). Notably, these results constituted the first use of chiral phosphates based on C2-symmetric paracyclophane scaffolds as chiral counterions in transition metal catalysis.



**Scheme 9.** Domino cycloisomerization/addition reaction of 2-(1-alkynyl)-2-cyclohexenones with 5-substituted indoles.

### 3 Enantioselective Scandium- and Yttrium-Catalyzed Domino Reactions

While chiral catalysts based on p-block or d-block metal elements have been widely investigated in asymmetric catalysis, the use of f-block elements, such as scandium and yttrium, has been much less studied.<sup>[19]</sup> Meanwhile in the last decade, chiral scandium catalysts have been successfully applied to promote various asymmetric domino reactions.<sup>[20]</sup> For example in 2016, Zhou et al. reported the use of a combination of 10 mol% of  $\text{Sc}(\text{OTf})_3$  and 20 mol% of a chiral Pybox ligand **36** to catalyze the enantioselective domino imine formation/intramolecular amination reaction of aldehydes **37** with 2-aminobenzenesulfonamide **38** to give the corresponding chiral 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1-dioxides **39**.<sup>[21]</sup> These scaffolds are widespread in medicinal chemistry. As shown in Scheme 10, when the domino reaction was performed in dichloromethane at  $-40\text{ }^\circ\text{C}$ , a range of 3-alkyl-/3-aryl-substituted chiral 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1-dioxides **39** were synthesized in both moderate to good yields (60-88%) and enantioselectivities (36-93% *ee*). It must be noted that the best enantioselectivities (73-93% *ee*) were generally achieved in the reaction of aliphatic aldehydes while aromatic substrates provided low to high enantioselectivities (36-75% *ee*).



with R = *i*-Bu, *i*-Pr, *t*-BuCH<sub>2</sub>, Cy, *c*-Pent, *c*-Pr, Bn, BnCH<sub>2</sub>:

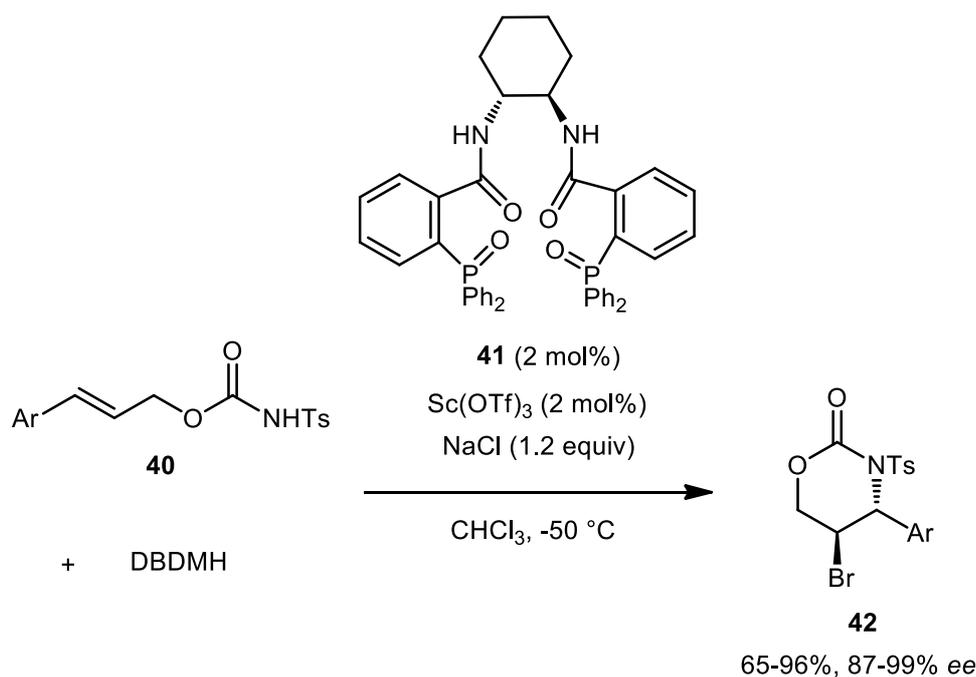
60-75%, 73-93% *ee*

with R = Ph, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-BrC<sub>6</sub>H<sub>4</sub>, *m*-BrC<sub>6</sub>H<sub>4</sub>, *o*-BrC<sub>6</sub>H<sub>4</sub>, 3-Br-4-MeOC<sub>6</sub>H<sub>3</sub>, 1-furyl:

60-88%, 36-75% *ee*

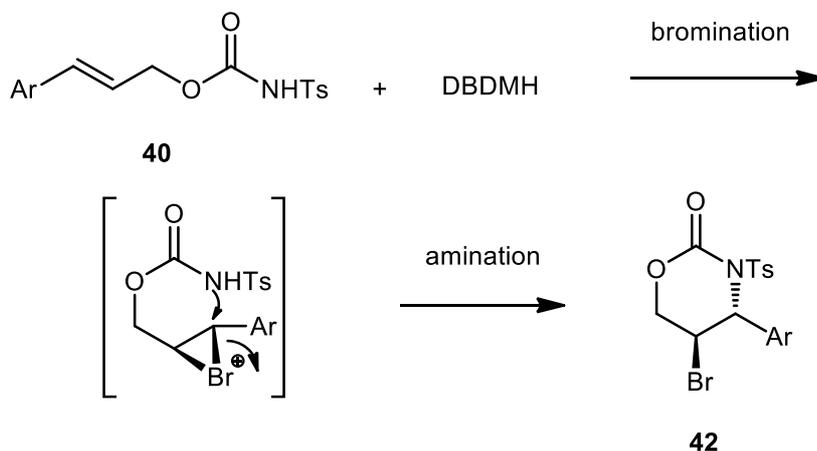
**Scheme 10.** Scandium-catalyzed domino imine formation/intramolecular amination reaction of aldehydes with 2-aminobenzenesulfonamide.

Highly regio- and enantioselective scandium-catalyzed domino bromination/amination reactions of (*E*)-cinnamyl tosylcarbamates **40** with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the bromine source were developed by Shi et al., in 2016 (Scheme 11).<sup>[22]</sup> Performed in chloroform at  $-50\text{ }^\circ\text{C}$  in the presence of NaCl as a superstoichiometric additive and a chiral scandium catalyst *in situ* generated from only 2 mol% of  $\text{Sc}(\text{OTf})_3$  and the same quantity of chiral diphosphine oxide ligand **41**, the domino reaction led to the corresponding chiral aryl 5-bromo-1,3-oxazinan-2-ones **42** in moderate to high yields (65-96%) and excellent enantioselectivities (87-99% *ee*). It was found that these good results were obtained regardless of the nature of the aryl group of the substrates.



Ar = Ph, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *m*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-BrC<sub>6</sub>H<sub>4</sub>, *m*-BrC<sub>6</sub>H<sub>4</sub>,  
*p*-ClC<sub>6</sub>H<sub>4</sub>, *m*-FC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, 2,4,6-F<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, *o*-Tol, *p*-Tol,  
 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, 1-Naph, 2-Naph, 2-thienyl

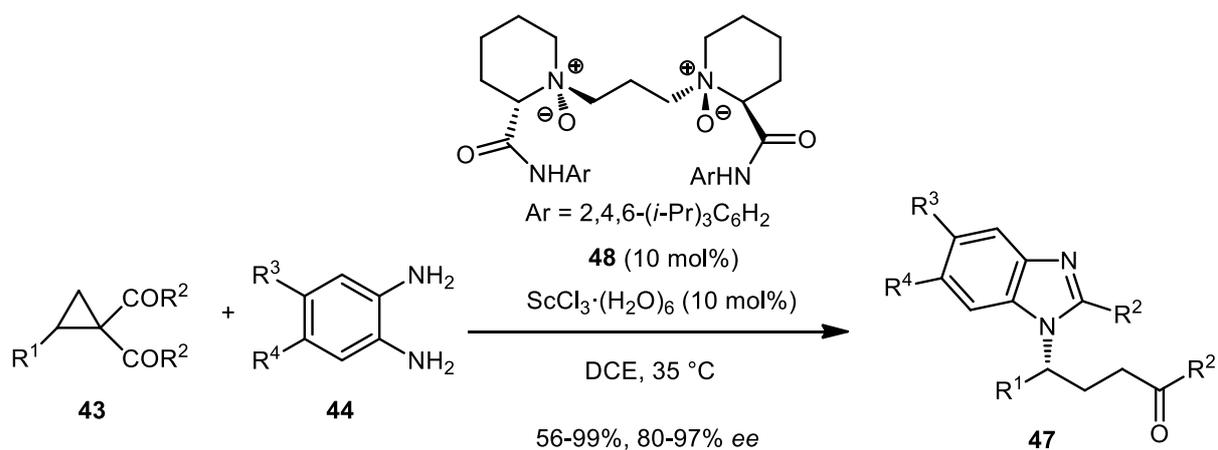
mechanism:



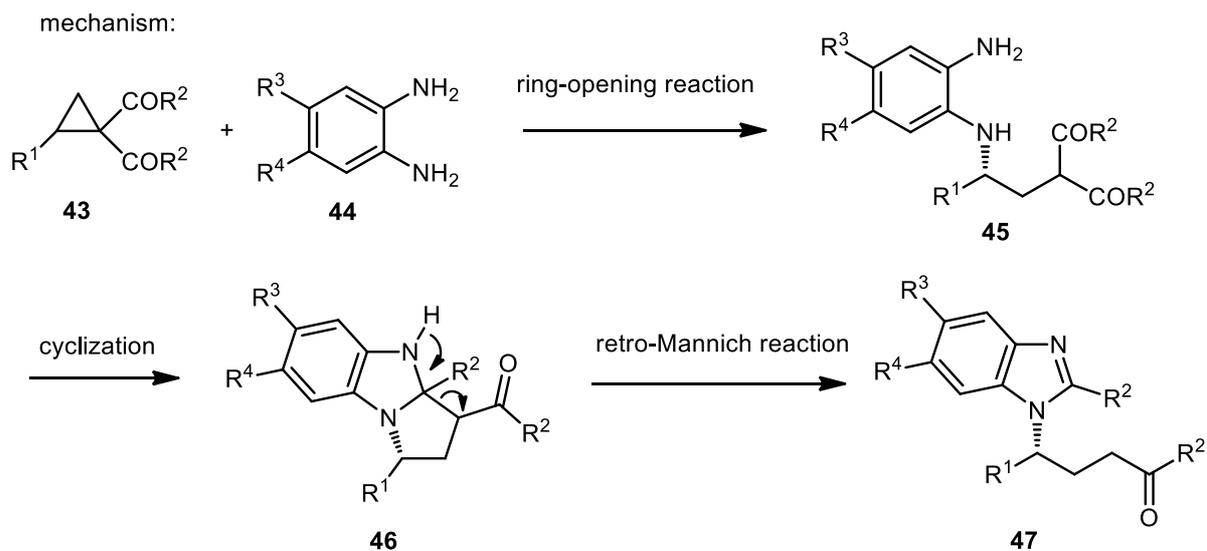
**Scheme 11.** Scandium-catalyzed domino bromination/amination reaction of (*E*)-cinnamyl tosylcarbamates with DBDMH.

Benzimidazole scaffolds are present in many natural products and bioactive compounds. In 2016, Liu and Feng described the first asymmetric route to these products based on an enantioselective scandium-catalyzed domino ring-opening/cyclization/retro-Mannich reaction between cyclopropyl ketones **43** and aromatic 1,2-diamines **44**.<sup>[23]</sup> As illustrated in Scheme 12, the process began with the ring-opening of the cyclopropane substrate **43** by the diamine **44** to give intermediate **45** which subsequently underwent a cyclization to form tricyclic intermediate **46**. The latter was further

submitted to a retro-Mannich reaction to afford the final benzimidazole **47** bearing a chiral side chain. When the reaction was catalyzed at 35 °C in DCE as solvent with a combination of 10 mol% of  $\text{ScCl}_3 \cdot (\text{H}_2\text{O})_6$  and the same quantity of chiral  $N,N'$ -dioxide ligand **48**, the domino products **47** were obtained in moderate to quantitative yields (56-99%) and high enantioselectivities (80-97% *ee*). The reaction was suitable to a variety of cyclopropyl ketones with either electron-withdrawing- or electron-donating-substituted aryl groups (80-95% *ee*) as well as naphthyl-substituted substrates (92-93% *ee*). Notably, even a vinyl-substituted cyclopropane was tolerated, thus producing the corresponding product in 90% *ee* and 86% yield.

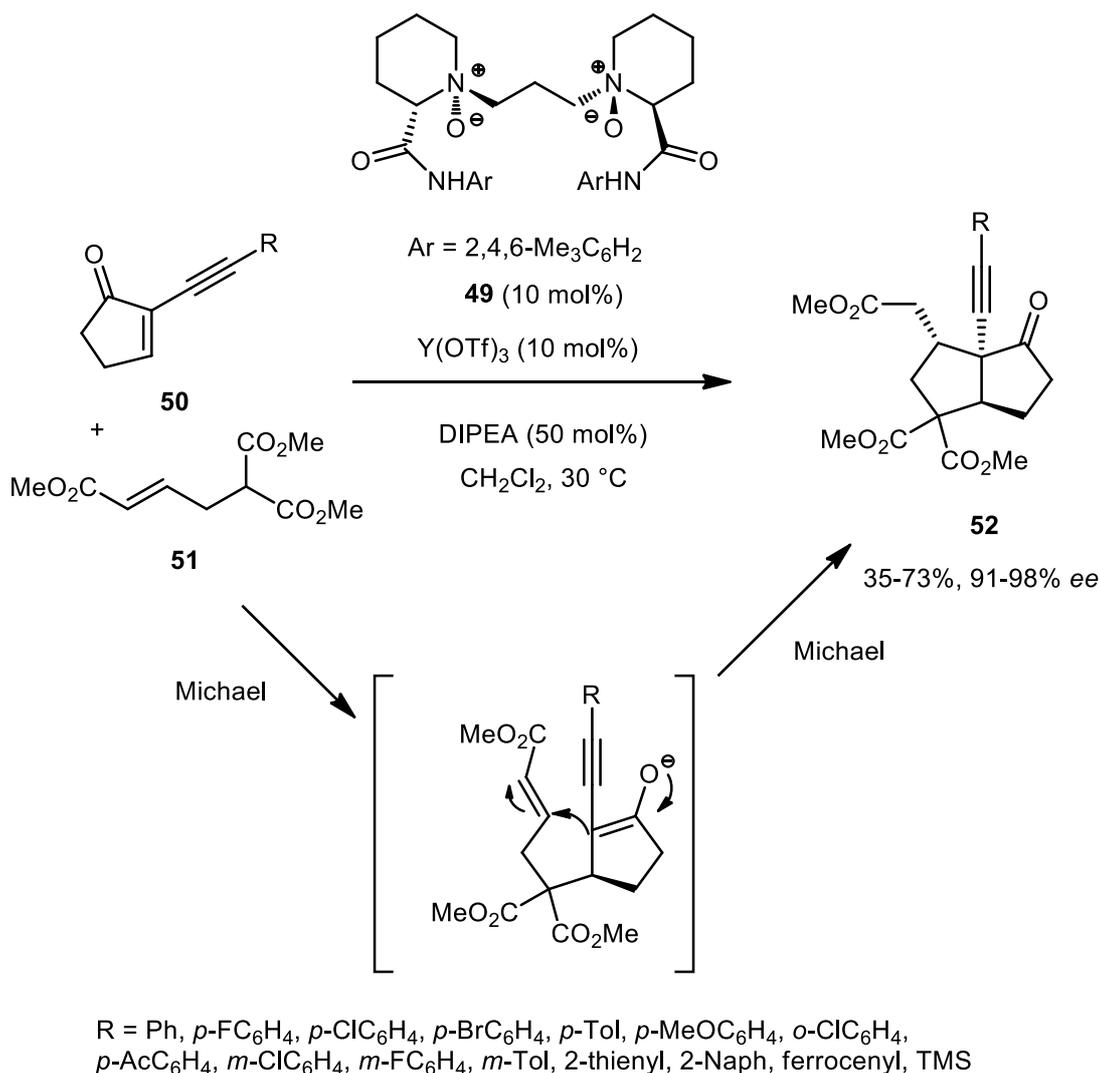


$\text{R}^1 = \text{Ph}, p\text{-MeOC}_6\text{H}_4, p\text{-Tol}, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, m\text{-Tol},$   
 $m\text{-ClC}_6\text{H}_4, o\text{-Tol}, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, 1\text{-Naph}, 2\text{-Naph}, \text{vinyl}, \text{Me}$   
 $\text{R}^2 = \text{Ph}, p\text{-Tol}, p\text{-FC}_6\text{H}_4$   
 $\text{R}^3 = \text{H}, \text{Me}, \text{OMe}, \text{F}, \text{Cl}, \text{Br}, \text{NO}_2$   
 $\text{R}^4 = \text{H}, \text{Me}, \text{OMe}, \text{F}, \text{Cl}, \text{Br}, \text{NO}_2$



**Scheme 12.** Scandium-catalyzed domino ring-opening/cyclization/retro-Mannich reaction of cyclopropyl ketones with aromatic 1,2-diamines.

In 2017, 10 mol% of another chiral *N,N'*-dioxide ligand **49** was combined by Feng et al. with the same quantity of  $Y(OTf)_3$  to *in situ* generate an active chiral yttrium catalyst which was used to promote the asymmetric synthesis of multisubstituted diquinanes through enantioselective domino double Michael reaction occurring between electron-deficient enynes **50** and a malonate-derived  $\alpha,\beta$ -unsaturated ester **51**.<sup>[24]</sup> This reaction was performed in dichloromethane at 30 °C in the presence of 50 mol% of DIPEA, as shown in Scheme 13. It provided a range of chiral multisubstituted diquinanes **52** in low to good yields (35-73%) and uniformly excellent enantioselectivities (91-98% *ee*). Moreover, some of these products could be easily converted into various enantiopure [3.3.0]bicyclic compounds constituting skeletons of many biologically interesting products.

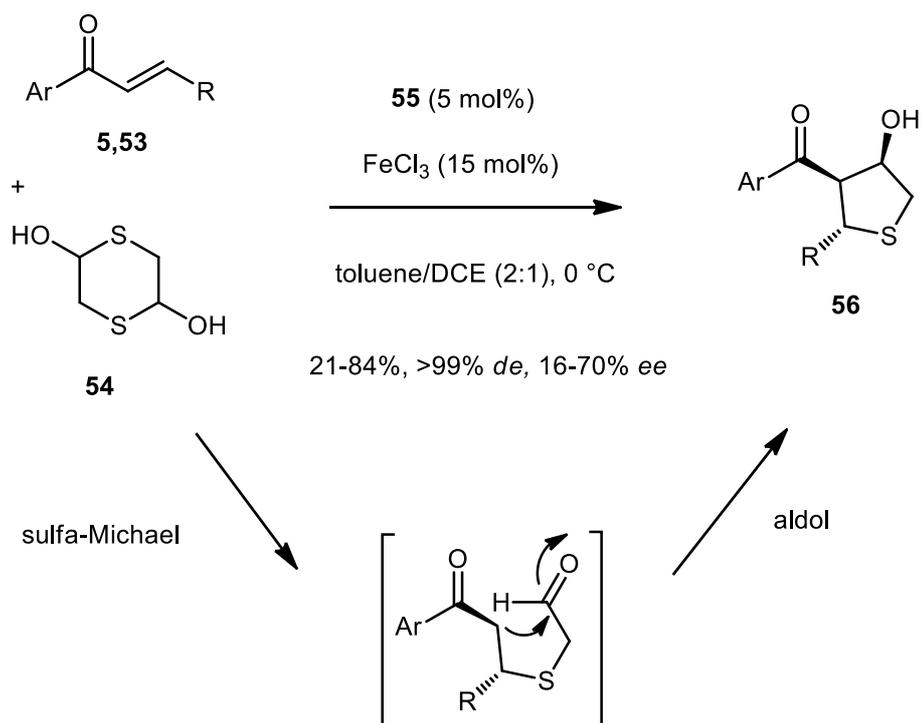


**Scheme 13.** Yttrium-catalyzed domino double Michael reaction of electron-deficient enynes with a malonate-derived  $\alpha,\beta$ -unsaturated ester.

## 4 Enantioselective Iron-Catalyzed Domino Reactions

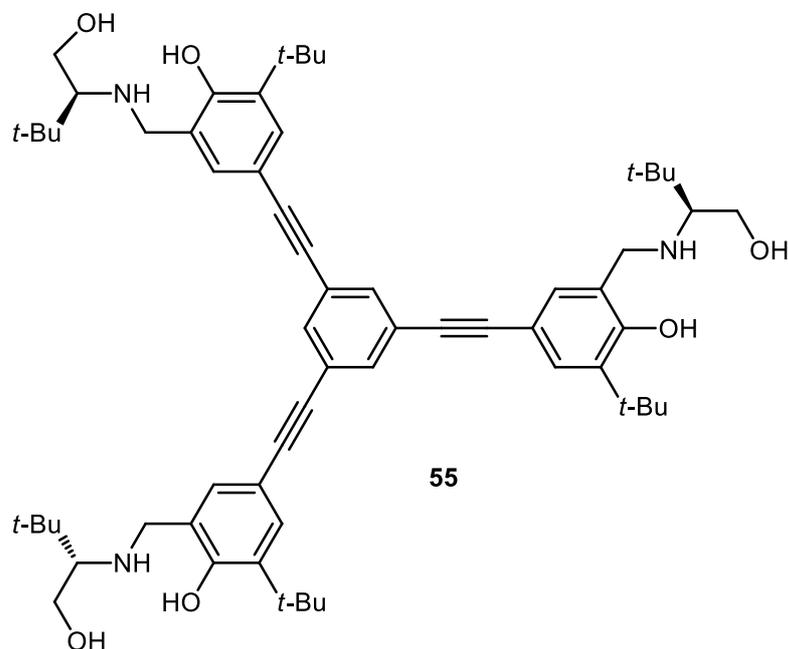
Related to the higher abundance and lower cost and toxicity of iron catalysts in comparison with other transition metals, more economic and ecologic iron-catalyzed domino transformations represent a wide potential for future organic synthesis.<sup>[25]</sup> However, only few asymmetric versions of these reactions mediated by chiral iron catalysts have been described so far. Among them, enantioselective iron-catalyzed domino sulfa-Michael/aldol reactions were reported by Punniyamurthy et al., in 2018.<sup>[26]</sup> These reactions occurred between aromatic  $\alpha,\beta$ -unsaturated ketones **553** and 1,4-dithiane-

2,5-diol **54** by using a combination of 15 mol% of FeCl<sub>3</sub> and 5 mol% of a novel chiral dendrimer ligand **55** as catalyst system in a 2:1 mixture of toluene and dichloroethane as solvent. It afforded a series of chiral tetrahydrothiophenes **56** as single diastereomers in low to good yields (21-84%) and low to moderate enantioselectivities (16-70% *ee*), as shown in Scheme 14. Notably, the catalyst was easily recovered and reused for three runs without loss of activity and selectivity. Interestingly, this work represented the first example of a metal-catalyzed domino sulfa-Michael/aldol reaction between chalcones and 1,4-dithiane-2,5-diol.



Ar = Ph, *p*-EtOC<sub>6</sub>H<sub>4</sub>, *p*-EtC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>

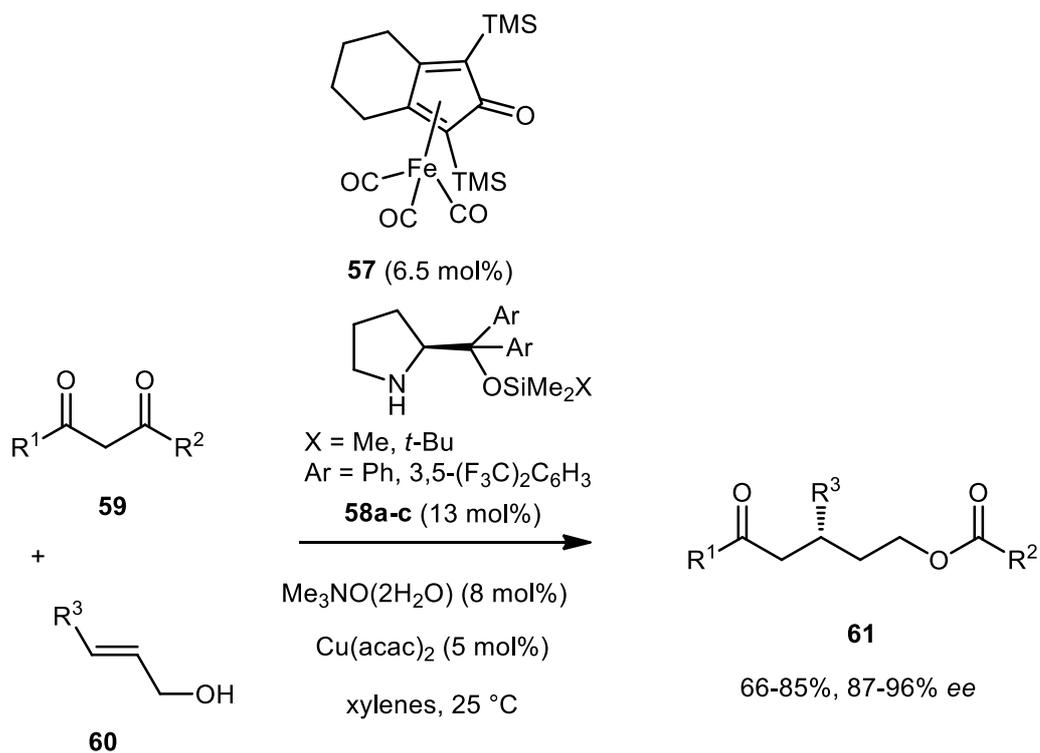
R = *o*-Tol, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, *p*-Tol, *p*-NCC<sub>6</sub>H<sub>4</sub>, 2-furyl, 2-thienyl, Cy, *i*-Pr, 2-Naph



**Scheme 14.** Domino sulfa-Michael/aldol reaction of aromatic  $\alpha,\beta$ -unsaturated ketones with 1,4-dithiane-2,5-diol.

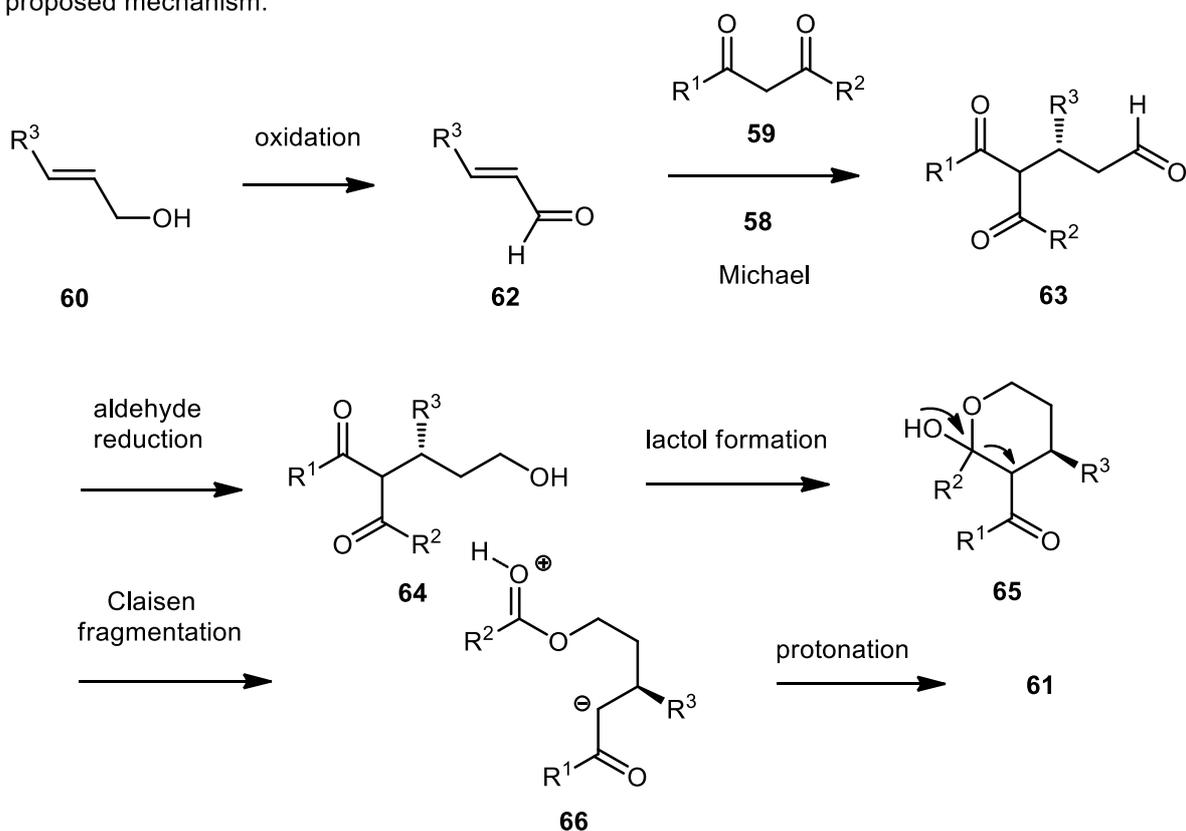
In 2016, Quintard and Rodriguez combined 6.5 mol% of achiral iron tricarbonyl complex **57** with 13 mol% of chiral proline-derived organocatalysts **58a-c** in the presence of 5 mol% of  $\text{Cu}(\text{acac})_2$  as additive to promote enantioselective domino oxidation/Michael/reduction/Claisen fragmentation reactions of 1,3-diketones **59** with allylic alcohols **60** (Scheme 15).<sup>[27]</sup> The multicatalyst system

employed at 25 °C in xylenes as solvent allowed the corresponding chiral 3-alkylpentanols **63** to be achieved in moderate to good yields (66-85%) and uniformly high enantioselectivities (87-96% *ee*). The mechanism of the domino reaction depicted in Scheme 14 began with the iron-catalyzed oxidation of the allylic alcohol **60** into the corresponding  $\alpha,\beta$ -unsaturated aldehyde **62** which subsequently underwent a Michael addition with the 1,3-diketone **59** through iminium catalysis from chiral organocatalyst **58** to afford chiral intermediate **63**. A chemoselective aldehyde reduction of the latter led to alcohol intermediate **64** which further cyclized into lactol **65**. Then, intermediate **65** was submitted to a Claisen fragmentation to give novel intermediate **66** which led after protonation to the final chiral domino product **61**.



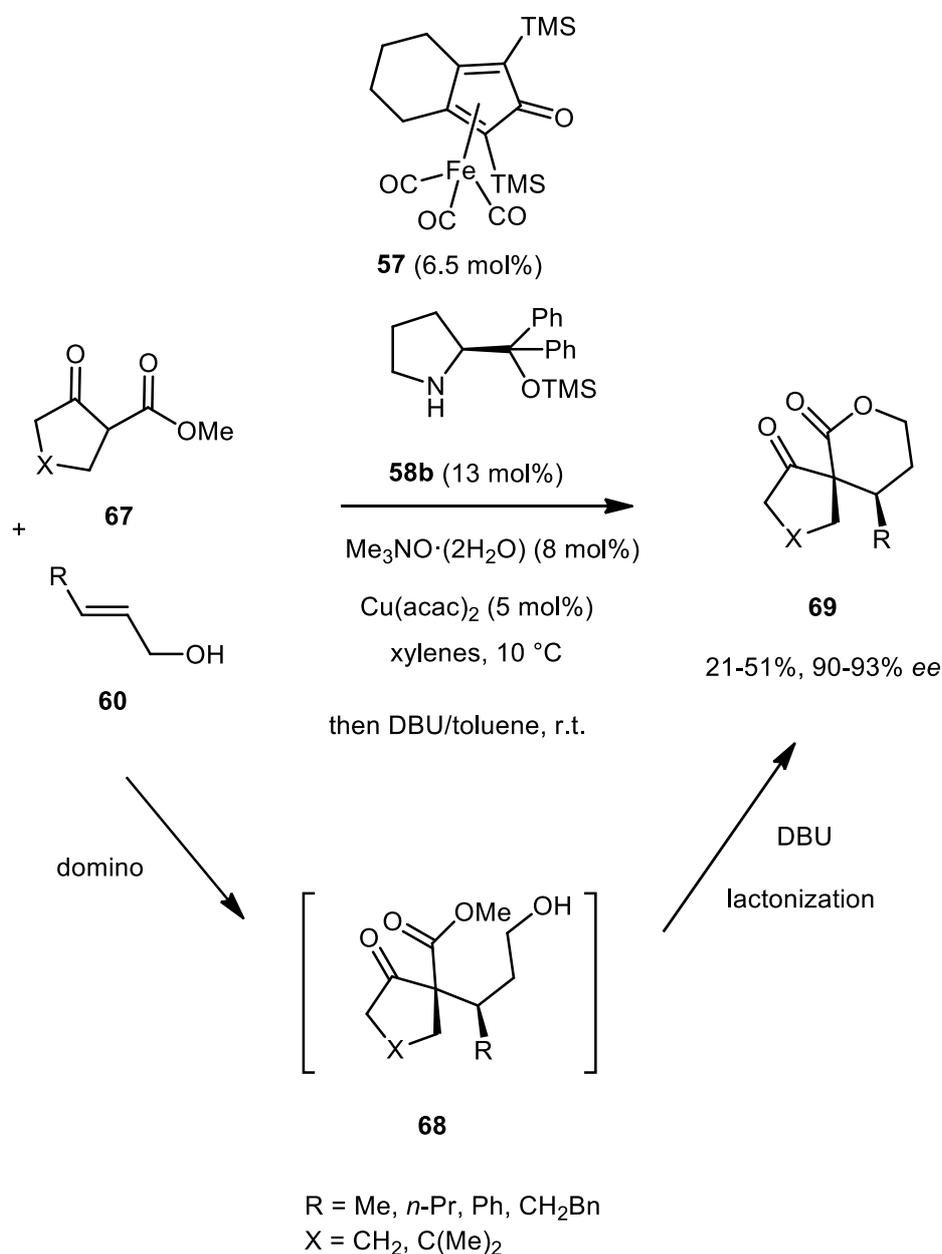
R<sup>1</sup> = Me, Et, Ph  
 R<sup>2</sup> = Me, Ph, Et  
 R<sup>3</sup> = Me, *n*-Hex, CH<sub>2</sub>Bn, (CH<sub>2</sub>)<sub>2</sub>OMOM

proposed mechanism:



**Scheme 15.** Multicatalytic domino oxidation/Michael/reduction/Claisen fragmentation reaction of 1,3-diketones with allylic alcohols.

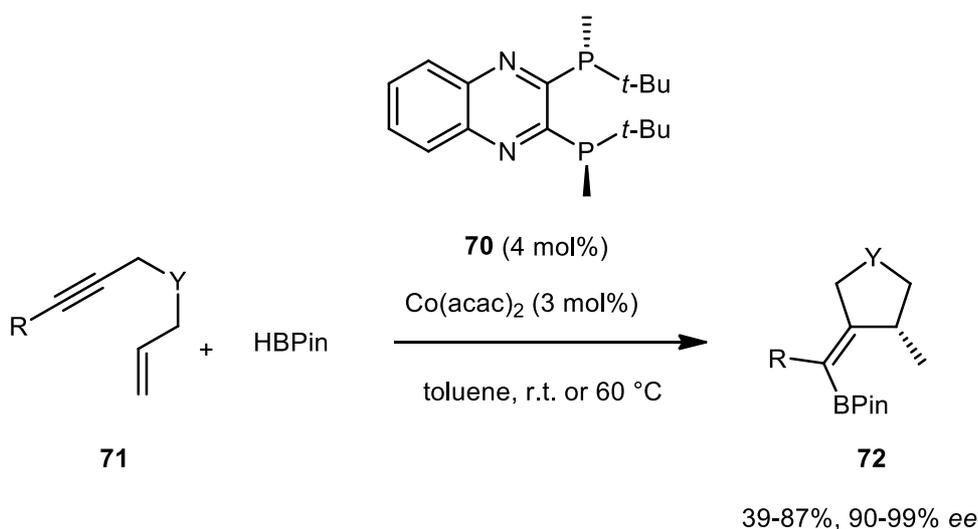
In 2018, the same authors applied a closely related multicatalyst system to develop another type of enantioselective domino reactions.<sup>[28]</sup> As shown in Scheme 16, the use of a multicatalytic system composed of 6.5 mol% of the same achiral iron tricarbonyl complex **57**, 13 mol% of chiral proline-derived organocatalyst **58b** and 5 mol% of Cu(acac)<sub>2</sub> allowed enantioselective domino oxidation/Michael/reduction reactions between cyclic  $\beta$ -keto esters **67** and allylic alcohols **60** to occur in xylenes at 10 °C. The domino products **68** were not isolated but subsequently submitted to lactonization by treatment with DBU at room temperature in toluene to give the corresponding chiral  $\delta$ -lactones **69** in low to moderate yields (21-51%) combined with high enantioselectivities (90-93% *ee*).



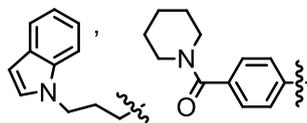
**Scheme 16.** Multicatalytic domino oxidation/Michael/reduction reaction of cyclic  $\beta$ -keto esters with allylic alcohols followed by lactonization.

## 5 Enantioselective Cobalt-Catalyzed Domino Reactions

In the field of enantioselective cobalt-catalyzed reactions, novel domino methodologies have been recently described on the basis of the ability of cobalt catalysts to adopt various reaction pathways, and taking advantages of the lower cost and toxicity of cobalt catalysts in comparison with other transition metals.<sup>[29]</sup> In 2017, Ge et al. reported the first enantioselective cobalt-catalyzed domino hydroboration/cyclization reaction of 1,6-enynes with pinacolborane.<sup>[30]</sup> It was promoted at room temperature or 60 °C by a cobalt catalyst *in situ* generated from 3 mol% of  $\text{Co}(\text{acac})_2$  and 4 mol% of chiral biphosphine ligand **70** in toluene as solvent. A variety of oxygen-, carbon-, and nitrogen-tethered 1,6-enynes **71** reacted with pinacolborane to afford the corresponding chiral vinyl-substituted boronate esters **72**. These domino products were obtained in moderate to high yields (39-87%) and excellent enantioselectivities (90-99% *ee*), as illustrated in Scheme 17.



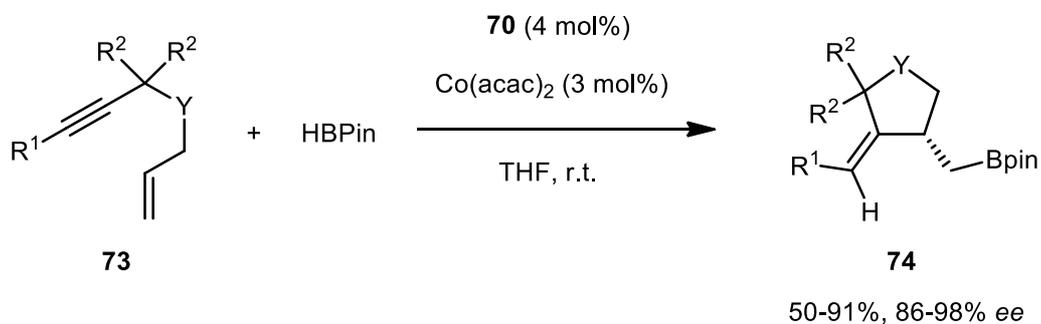
$\text{Y} = \text{O}, \text{C}(\text{CO}_2i\text{-Pr})_2, \text{C}(\text{CO}_2\text{Me})_2, \text{NTs}$   
 $\text{R} = \text{Ph}, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-Tol}, p\text{-}t\text{-BuC}_6\text{H}_4, p\text{-TMSOC}_6\text{H}_4,$   
 $p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, m\text{-Tol}, p\text{-AcC}_6\text{H}_4, p\text{-OHCC}_6\text{H}_4,$   
 $p\text{-MeO}_2\text{CC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, p\text{-TBSOC}_6\text{H}_4, 2\text{-thienyl}, \text{BnO}(\text{CH}_2)_3,$   
 $(2\text{-Naph})(\text{O})\text{CO}(\text{CH}_2)_3, 3\text{-pyridyl},$



**Scheme 17.** Domino hydroboration/cyclization reaction of 1,6-enynes with pinacolborane.

Furthermore, the use of another type of substrates, such as enynes **73** bearing an *ortho*-substituted aryl group ( $\text{R}^1 = o\text{-Tol}, 2\text{-Naph}$ ) in THF as solvent, provided by reaction with pinacolborane the corresponding chiral alkyl boronate esters **74** in both high yields (86-88%) and enantioselectivities (88-90% *ee*), as illustrated in Scheme 18.<sup>[30]</sup> The scope of this *anti*-Markovnikov hydroboration/cyclization reaction was extended to O-tethered 1,6-enynes ( $\text{Y} = \text{O}$ ) bearing two substituents ( $\text{R}^2$ ) at the propargylic position as well as N- and C-tethered 1,6-enynes which afforded

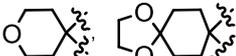
the corresponding products in moderate to high yields (50-91%) and uniformly high enantioselectivities (86-98% *ee*), as shown in Scheme 18.



Y = O, C(CO<sub>2</sub>*i*-Pr)<sub>2</sub>, C(CO<sub>2</sub>Me)<sub>2</sub>, NTs

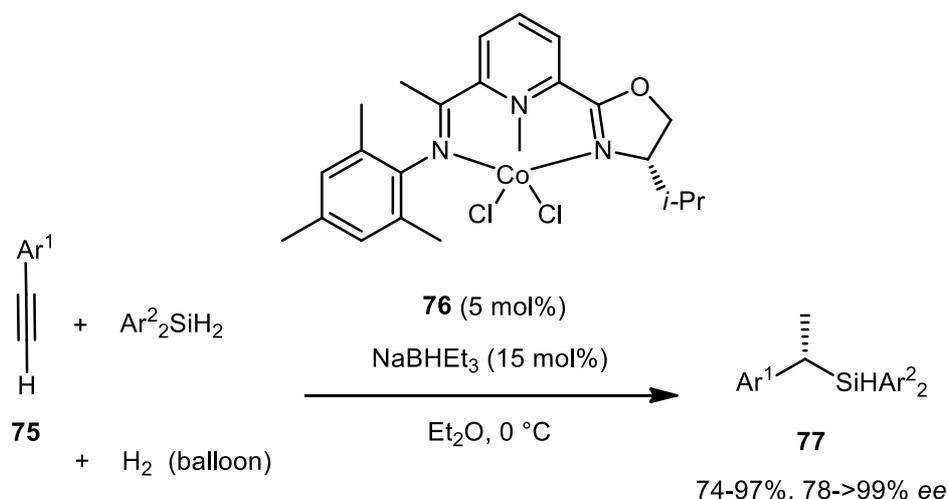
R<sup>1</sup> = *o*-Tol, 2-Naph, Ph, *p*-Tol, *p*-*t*-BuC<sub>6</sub>H<sub>4</sub>, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *m*-Tol

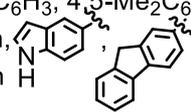
R<sup>2</sup> = H, Me, Ph

R<sup>2</sup>, R<sup>2</sup> = (CH<sub>2</sub>)<sub>3</sub>, (CH<sub>2</sub>)<sub>4</sub>, (CH<sub>2</sub>)<sub>5</sub>, (CH<sub>2</sub>)<sub>6</sub>, (CH<sub>2</sub>)<sub>7</sub>, 

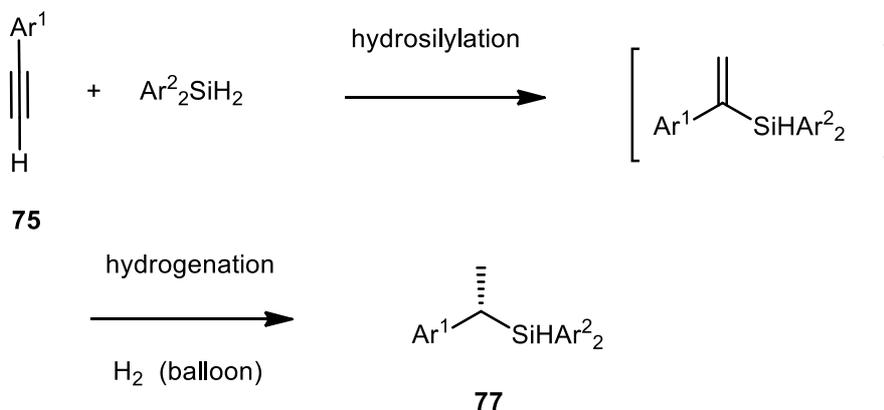
**Scheme 18.** Domino hydroboration/cyclization reaction of other 1,6-enynes with pinacolborane.

In 2017, Lu et al. reported an asymmetric three-component domino hydrosilylation/hydrogenation reaction of terminal aromatic alkynes **75** with Ar<sub>2</sub>SiH<sub>2</sub> and hydrogen.<sup>[31]</sup> The reaction was promoted at 0 °C by 5 mol% of a chiral preformed cobalt catalyst **76** derived from a Pybox ligand in the presence of NaBHET<sub>3</sub> as the reducing agent in diethylether as solvent, affording the corresponding chiral silanes **77** in both good to excellent yields (74-97%) and enantioselectivities (78->99% *ee*), as shown in Scheme 19.



Ar<sup>1</sup> = Ph, *p*-Tol, *m*-Tol, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-PhC<sub>6</sub>H<sub>4</sub>, *p*-(TBSOCH<sub>2</sub>)C<sub>6</sub>H<sub>4</sub>, *p*-(BnOCH<sub>2</sub>)C<sub>6</sub>H<sub>4</sub>,  
*m*-ClC<sub>6</sub>H<sub>4</sub>, *m*-BrC<sub>6</sub>H<sub>4</sub>, 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 4,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2-Naph, 3-CO<sub>2</sub>Me-4-MeC<sub>6</sub>H<sub>3</sub>,  
 3-Cl-4-MeC<sub>6</sub>H<sub>3</sub>, 7-OMe-2-Naph,   
 Ar<sup>2</sup> = Ph, 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2-Naph H

mechanism:

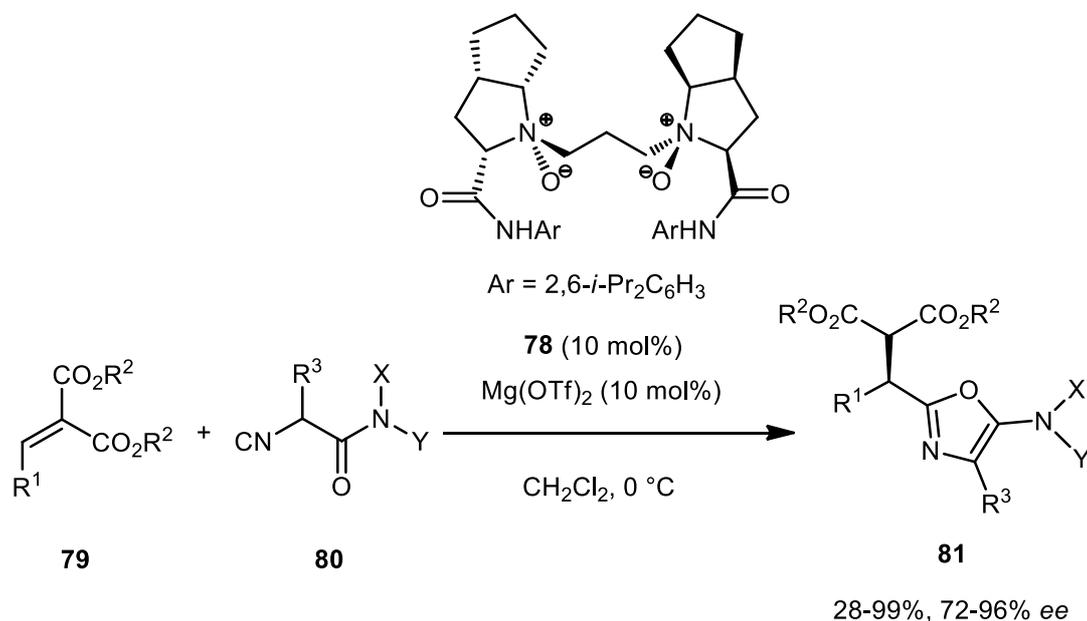


**Scheme 19.** Three-component domino hydrosilylation/hydrogenation reaction of terminal aromatic alkynes with Ar<sub>2</sub>SiH<sub>2</sub> and hydrogen.

## 6 Enantioselective Magnesium-Catalyzed Domino Reactions

Unlike transition metals, alkaline earth metals, such as magnesium, are abundant, inexpensive and environmentally benign. In addition, due to their milder Lewis acidity in comparison to other transition metals, they exhibit a promising ability in the field of catalytic organic synthesis.<sup>[32]</sup> In 2016, Feng et al. reported the use of a chiral magnesium catalyst *in situ* generated from 10 mol% of Mg(OTf)<sub>2</sub> and the same quantity of chiral *N,N'*-dioxide ligand **78** to promote the enantioselective domino Michael/cyclization reaction of alkylidene malonates **79** with  $\alpha$ -isocyanoacetamides **80**.<sup>[33]</sup> It afforded the corresponding chiral 2-alkyl-5-aminooxazoles **81** in low to quantitative yields (28-99%) and moderate to excellent enantioselectivities (72-96% *ee*), as illustrated in Scheme 20. The best enantioselectivities (80-96% *ee*) were achieved in the reaction of (hetero)aromatic alkylidene malonates while aliphatic substrates provided lower enantioselectivities (72-86% *ee*). On the other

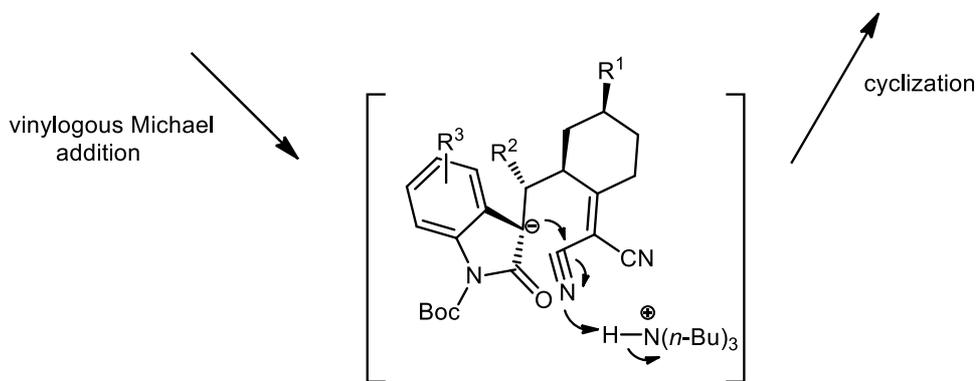
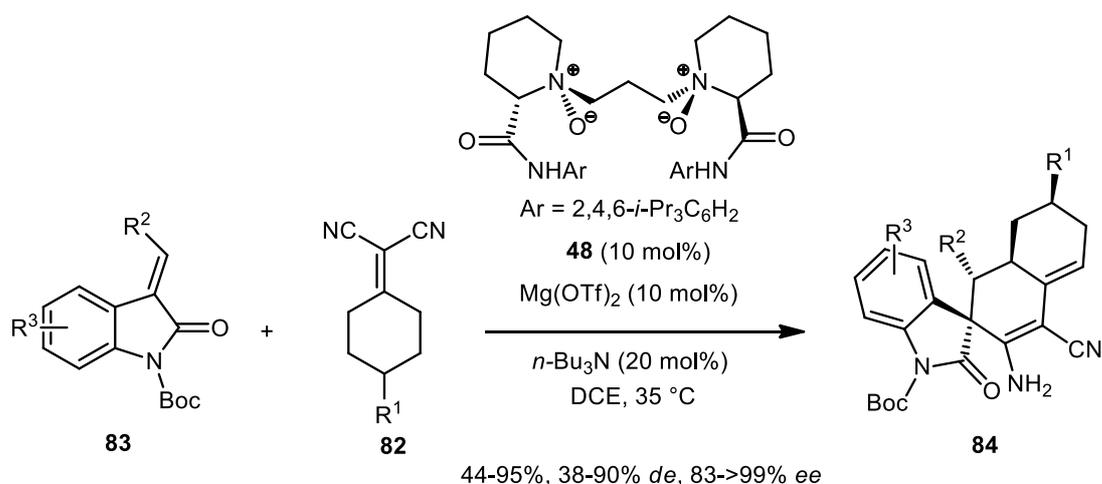
hand, uniformly high enantioselectivities were obtained regardless the aliphatic or aromatic nature of the substituent ( $R^3$ ) on the  $\alpha$ -isocyanoacetamide partner.



$R^1 = \text{Ph}, o\text{-FC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, m\text{-Tol}, m\text{-MeOC}_6\text{H}_4, m\text{-PhOC}_6\text{H}_4,$   
 $p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, p\text{-O}_2\text{NC}_6\text{H}_4, p\text{-Tol}, p\text{-PhC}_6\text{H}_4,$   
 $p\text{-MeOC}_6\text{H}_4, p\text{-PhOC}_6\text{H}_4, p\text{-BnOC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, 2\text{-Naph}, 2\text{-thienyl}, 3\text{-furyl}, \text{Cy}, \text{Me}$   
 $R^2 = \text{Me}, \text{Et}, i\text{-Pr}$   
 $R^3 = t\text{-Bu}, \text{Bn}, \text{Ph}, \text{Me}, i\text{-Pr}, \text{H}$   
 $X, Y = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2, (\text{CH}_2)_5, (\text{CH}_2)_4$

**Scheme 20.** Domino Michael/cyclization reaction of alkylidene malonates with  $\alpha$ -isocyanoacetamides.

In 2018, Feng and Lin reported a highly enantioselective desymmetrization of prochiral  $\alpha,\alpha$ -dicyanoalkenes **82** through asymmetric magnesium-catalyzed domino vinylogous Michael/cyclization reaction with *N*-protected 3-arylideneoxindoles **83**.<sup>[34]</sup> As shown in Scheme 21, the reaction of the latter with 4-substituted cyclic  $\alpha,\alpha$ -dicyanoalkenes promoted at 35 °C by a magnesium catalyst *in situ* generated from 10 mol% of  $\text{Mg}(\text{OTf})_2$  and the same quantity of chiral *N,N'*-dioxide ligand **48** in DCE as solvent led to the corresponding chiral spiroindolinones **84** bearing four stereogenic centers. These tetracyclic products were achieved in moderate to excellent yields (44-95%), good to excellent enantioselectivities (73->99% ee) and moderate to excellent diastereoselectivities (38-90% de) by using tributyl amine as base.



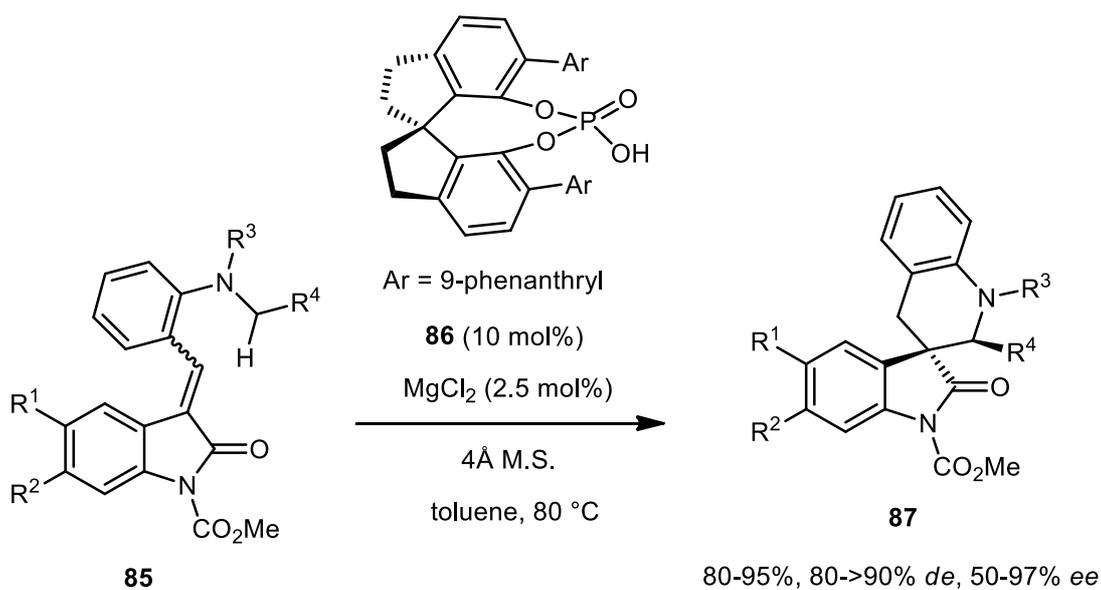
$R^1 = \text{Ph}, m\text{-Tol}, p\text{-Tol}, m\text{-MeOC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, 2\text{-Naph}, t\text{-Bu}$

$R^2 = \text{Ph}, m\text{-Tol}, p\text{-Tol}, o\text{-MeOC}_6\text{H}_4, p\text{-PhC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, o\text{-BrC}_6\text{H}_4, m\text{-F}_3\text{CC}_6\text{H}_4, 1\text{-Naph}, t\text{-Bu},$  

$R^3 = \text{H}, 5\text{-F}, 6\text{-F}, 7\text{-F}$

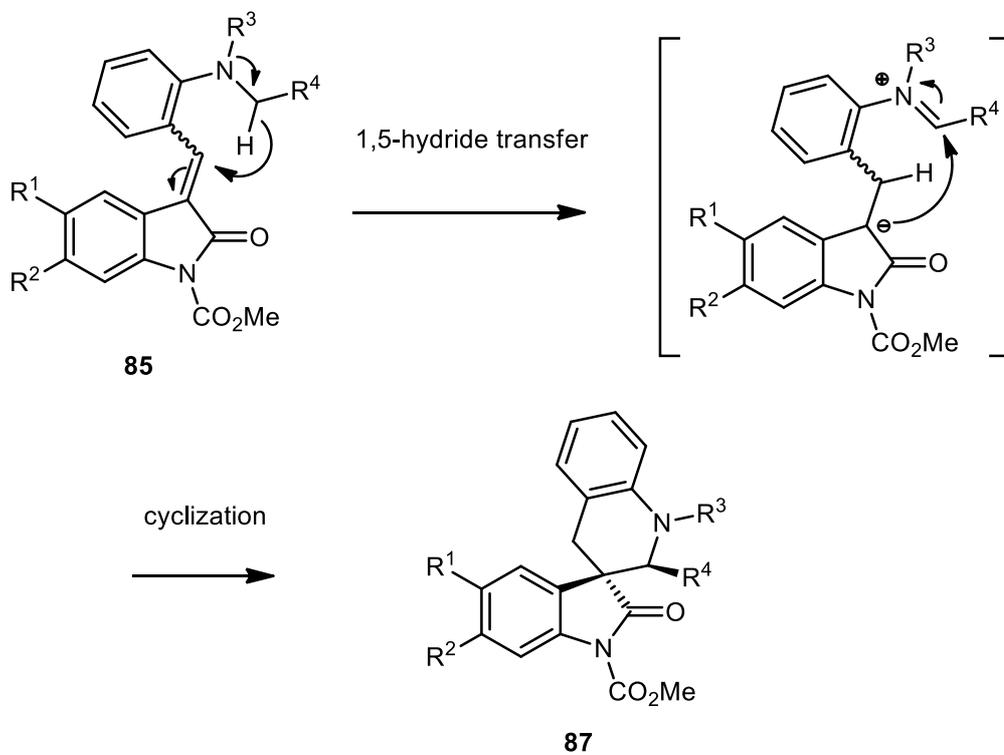
**Scheme 21.** Domino vinylogous Michael/cyclization reaction of *N*-protected 3-arylideneoxindoles with  $\alpha,\alpha$ -dicyanoalkenes.

In 2016, Lin et al. reported an enantioselective intramolecular domino 1,5-hydride transfer/cyclization reaction of oxindole derivatives **85** promoted by a chiral magnesium catalyst *in situ* generated from 2.5 mol% of  $\text{MgCl}_2$  and 10 mol% of chiral phosphoric acid **86**.<sup>[35]</sup> Performed in toluene at 80 °C, the reaction afforded the corresponding chiral spirooxindole tetrahydroquinolines **87** in both high yields (80-95%) and diastereoselectivities (80->90% *de*) combined with moderate to excellent enantioselectivities (50-97% *ee*), as illustrated in Scheme 22. The best enantioselectivities (93-97% *ee*) were achieved in the reaction of substrates bearing a strong electron-withdrawing group on the oxindole aromatic ring, such as  $\text{NO}_2$ , ( $R^1 = \text{NO}_2$ ) while the lowest enantioselectivity (50% *ee*) was observed in the reaction of a substrate bearing an electron-rich substituent ( $R^1 = \text{Me}$ ).



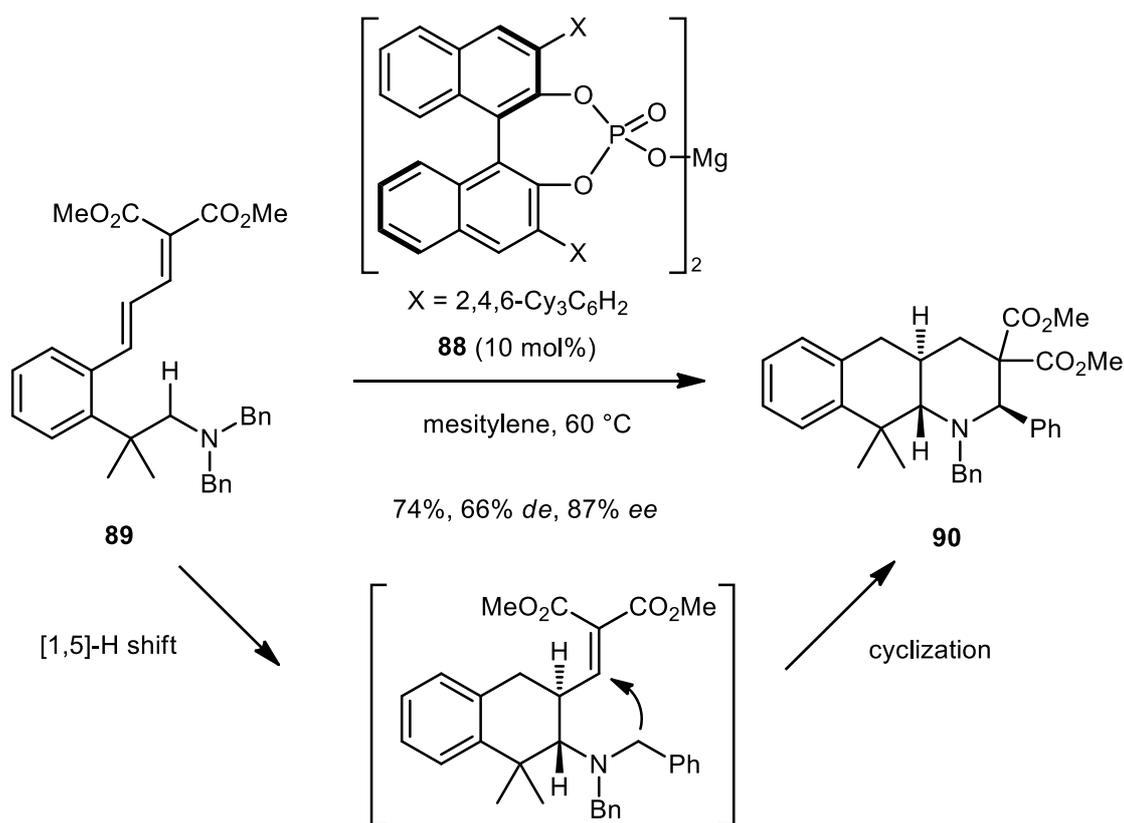
R<sup>1</sup> = H, NO<sub>2</sub>, F, Br, Me  
R<sup>2</sup> = H, Cl  
R<sup>3</sup>, R<sup>4</sup> = (CH<sub>2</sub>)<sub>3</sub>, (CH<sub>2</sub>)<sub>4</sub>  
R<sup>3</sup> = Bn, R<sup>4</sup> = Ph

mechanism:



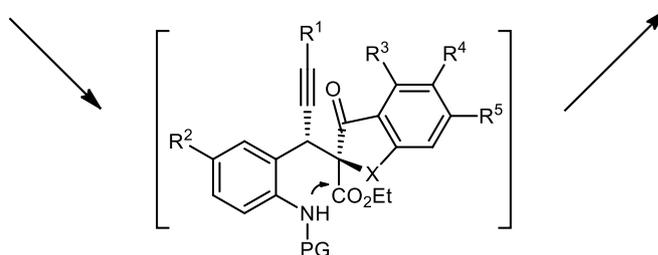
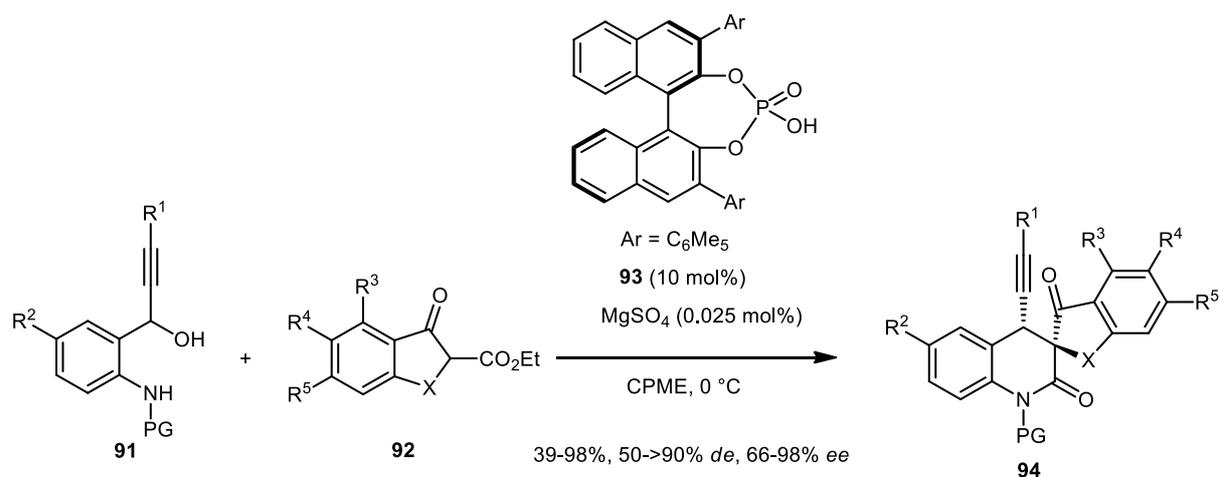
**Scheme 22.** Domino intramolecular 1,5-hydride transfer/cyclization reaction of oxindole derivatives.

In 2018, Mori and Akiyama employed a chiral bisphosphate magnesium complex **88** to promote the asymmetric domino [1,5]-hydride shift/cyclization reaction of cinnamylidene malonate **89**.<sup>[36]</sup> When catalyzed at 60 °C with 10 mol% of this chiral bisphosphate magnesium complex in mesitylene as solvent, the intramolecular reaction afforded the corresponding chiral tricyclic piperidine **90** in good yield (74%), moderate diastereoselectivity (66% *de*) and high enantioselectivity (87% *ee*), as shown in Scheme 23.



**Scheme 23.** Domino intramolecular 1,5-hydride transfer/cyclization reaction of a cinnamylidene malonate.

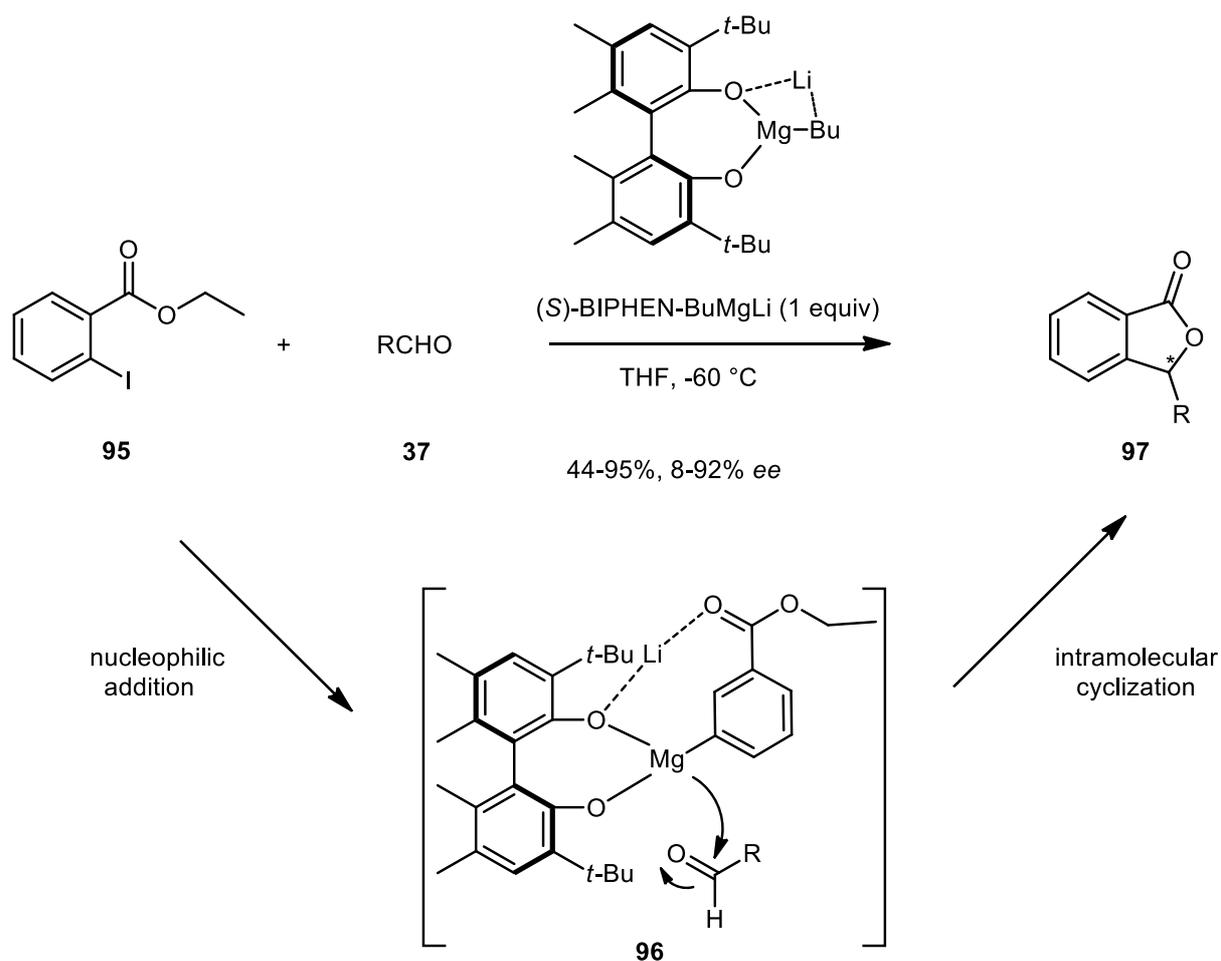
Recently, Schneider and Hodik developed asymmetric domino addition/lactamization reactions between *ortho*-quinone methide imines **91** and cyclic  $\beta$ -oxo esters **92**.<sup>[37]</sup> The reactions were performed at 0 °C in CPME as solvent in the presence of a chiral magnesium catalyst *in situ* generated from  $\text{MgSO}_4$  and 10 mol% of chiral phosphoric acid ligand **93**. They afforded the corresponding chiral spirocyclic dihydroquinolones **94** bearing two contiguous stereogenic centers with moderate to quantitative yields (39-98%) and both moderate to excellent diastereo- (50->90% *de*) and enantioselectivities (66-98% *ee*), as illustrated in Scheme 24. The substrate scope was wide since a range of *ortho*-amino benzyl alcohols exhibiting alkyl, cycloalkyl, silyl, aryl and heteroaryl groups ( $\text{R}^1$ ), different *N*-protecting alkyl groups (PG) and both electron-withdrawing and electron-donating substituents ( $\text{R}^2$ ) were compatible. Uniformly high enantioselectivities (76-98% *ee*) were obtained with a single exception (66% *ee*) in the reaction of a 4-methoxy-substituted coumaran-3-one-2-carboxylate ( $\text{X} = \text{O}$ ,  $\text{R}^3 = \text{OMe}$ ,  $\text{R}^4 = \text{R}^5 = \text{H}$ ). Mechanistic studies demonstrated that the *in situ* generated chiral magnesium phosphate salt was more reactive to promote the reaction than the free phosphoric acid.

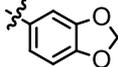


R<sup>1</sup> = *p*-MeOC<sub>6</sub>H<sub>4</sub>, TMS, *t*-Bu, decyl, *c*-Pr, Cy, cyclohexenyl, Ph, *p*-(*t*-Bu)C<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *m*-MeOC<sub>6</sub>H<sub>4</sub>, 2-thienyl  
R<sup>2</sup> = H, Me, Cl  
R<sup>3</sup> = H, OMe  
R<sup>4</sup> = H, Me, OMe, NO<sub>2</sub>, Br  
R<sup>5</sup> = H, Cl  
X = O, S  
PG = Me, Et, Bu, allyl

**Scheme 24.** Domino addition/lactamization reaction of *ortho*-quinone methide imines with cyclic  $\beta$ -oxo esters.

In 2018, Gros et al. developed a novel route to chiral 3-substituted isobenzofuranones based on a domino addition/cyclization reaction of 2-ethylidobenzoate **95** with aldehydes **37**.<sup>[38]</sup> Actually, the process required the preparation of a bimetallic organomagnesiante complex (*S*)-BIPHEN-BuMgLi from *n*-BuLi, *n*-BuMgCl and (*S*)-BIPHEN as ligand. The latter then reacted with 2-ethylidobenzoate **97** to give intermediate arylmagnesiante **96** quantitatively which subsequently added to aldehyde **37** to afford the corresponding chiral lactone **97** after a final intramolecular cyclization. As shown in Scheme 25, a range of chiral 3-substituted isobenzofuranones **97** were synthesized under these conditions with moderate to excellent yields (44-95%) and low to high enantioselectivities (8-92% *ee*). Moreover, (*S*)-BIPHEN ligand was found recyclable and reusable.

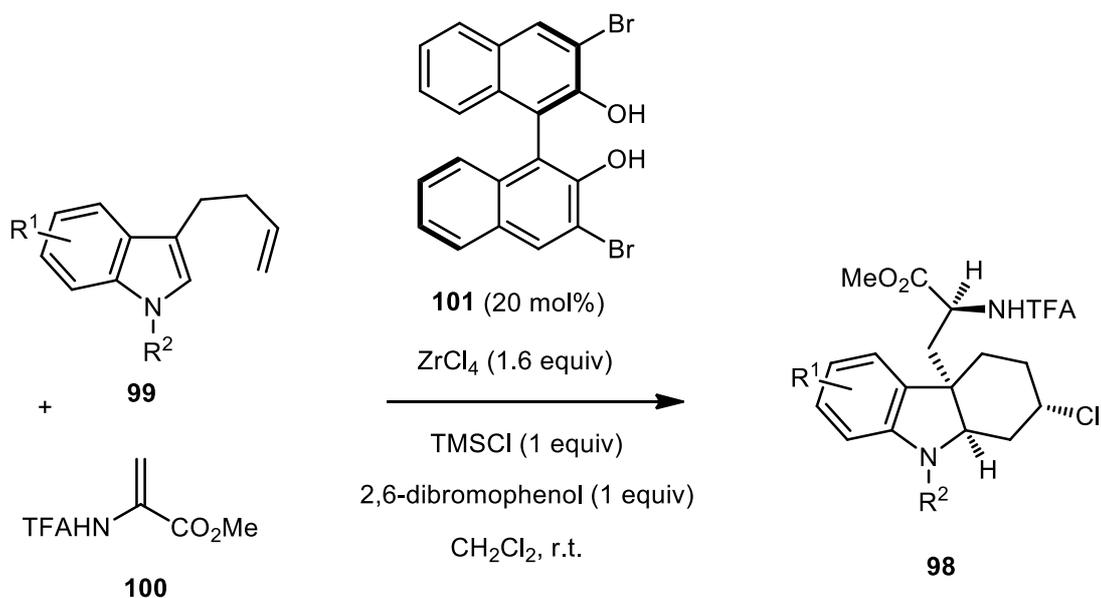


R = *p*-MeOC<sub>6</sub>H<sub>4</sub>, *m*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-MeOC<sub>6</sub>H<sub>4</sub>, 2,4,6-(MeO)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, 3,4,5-(MeO)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *m*-ClC<sub>6</sub>H<sub>4</sub>, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, *p*-(*t*-Bu)C<sub>6</sub>H<sub>4</sub>, 2-Naph, 2-thienyl, 2-pyridyl, *n*-Pent, piperidyl, 

**Scheme 25.** Domino addition/cyclization reaction of 2-ethyliodobenzoate with aldehydes.

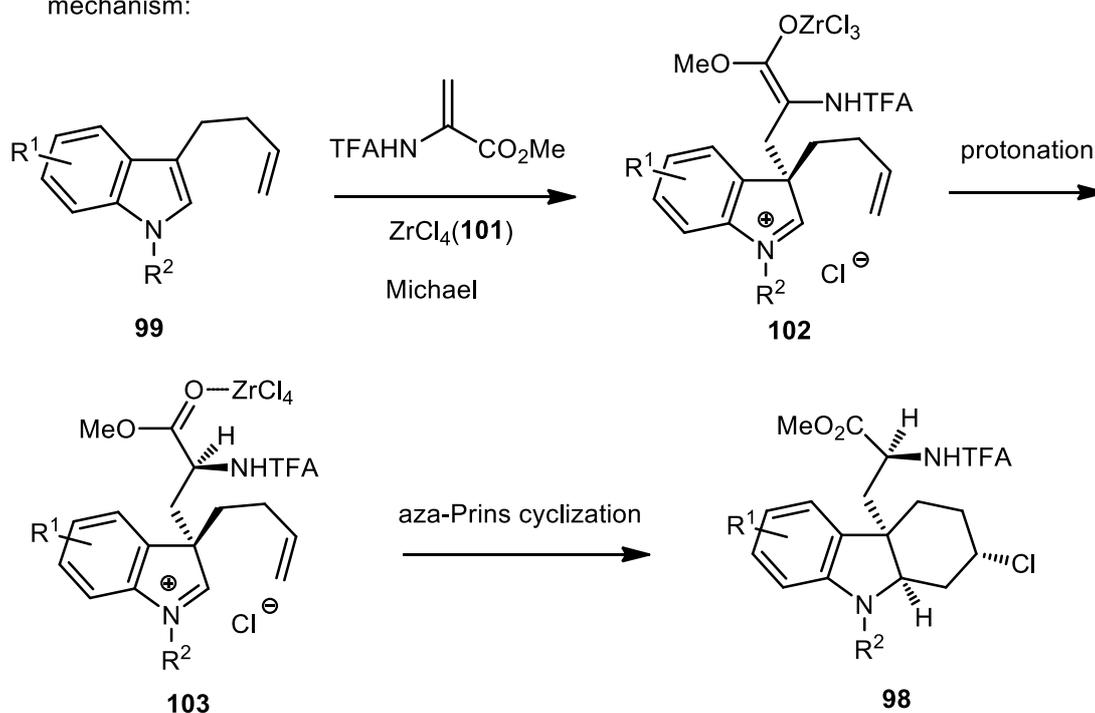
## 7 Enantioselective Zirconium-Catalyzed Domino Reactions

In 2016, Reisman et al. reported an asymmetric zirconium-mediated domino Michael/protonation/aza-Prins reaction of C3-substituted indoles **99** with amidoacrylate **100**, leading to the corresponding chiral fused tricyclic indolines **98**.<sup>[39]</sup> As shown in Scheme 26, the reaction was promoted by a chiral zirconium catalyst *in situ* generated from 1.6 equivalent of ZrCl<sub>4</sub> and 20 mol% of chiral BINOL-derived ligand **101**. Performed in the presence of 2,6-dibromophenol and TMSCl as stoichiometric additives, the domino reaction began with the Michael addition of the indole to the amidoacrylate, leading to intermediate **102** which then underwent protonation to give novel intermediate **103**. Then, the latter underwent an aza-Prins cyclization to afford the final domino product (Scheme 26). Therefore, a range of variously substituted chiral indoles **98** were synthesized in moderate to quantitative yields (70-99%), moderate diastereoselectivities (50-72% *de*) and uniformly high enantioselectivities (85-93% *ee*).



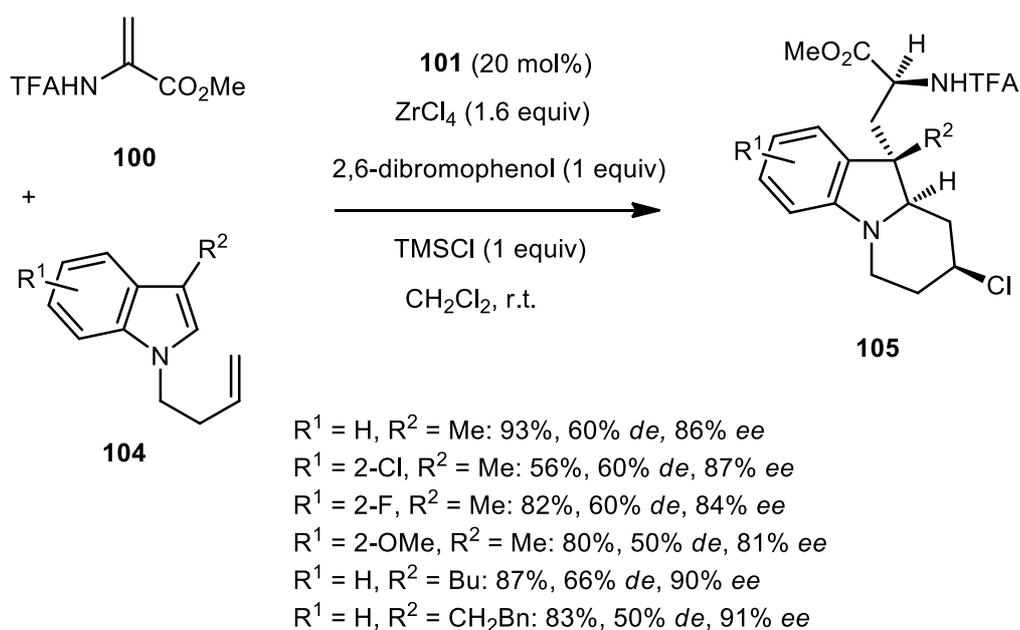
$\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}$ : 84%, 60% *de*, 87% *ee*  
 $\text{R}^1 = \text{H}, \text{R}^2 = \text{allyl}$ : 70%, 60% *de*, 89% *ee*  
 $\text{R}^1 = \text{H}, \text{R}^2 = \text{Bn}$ : 82%, 66% *de*, 86% *ee*  
 $\text{R}^1 = 1\text{-Me}, \text{R}^2 = \text{Bn}$ : 90%, 60% *de*, 88% *ee*  
 $\text{R}^1 = 2\text{-Me}, \text{R}^2 = \text{Bn}$ : 99%, 72% *de*, 92% *ee*  
 $\text{R}^1 = 3\text{-Me}, \text{R}^2 = \text{Bn}$ : 74%, 50% *de*, 93% *ee*  
 $\text{R}^1 = 4\text{-Me}, \text{R}^2 = \text{Bn}$ : 89%, 72% *de*, 89% *ee*  
 $\text{R}^1 = 2\text{-OMe}, \text{R}^2 = \text{Bn}$ : 93%, 72% *de*, 91% *ee*  
 $\text{R}^1 = 2\text{-Br}, \text{R}^2 = \text{Bn}$ : 70%, 60% *de*, 85% *ee*

mechanism:



**Scheme 26.** Domino Michael/protonation/aza-Prins reaction of C3-alkene-linked indoles with an amidoacrylate.

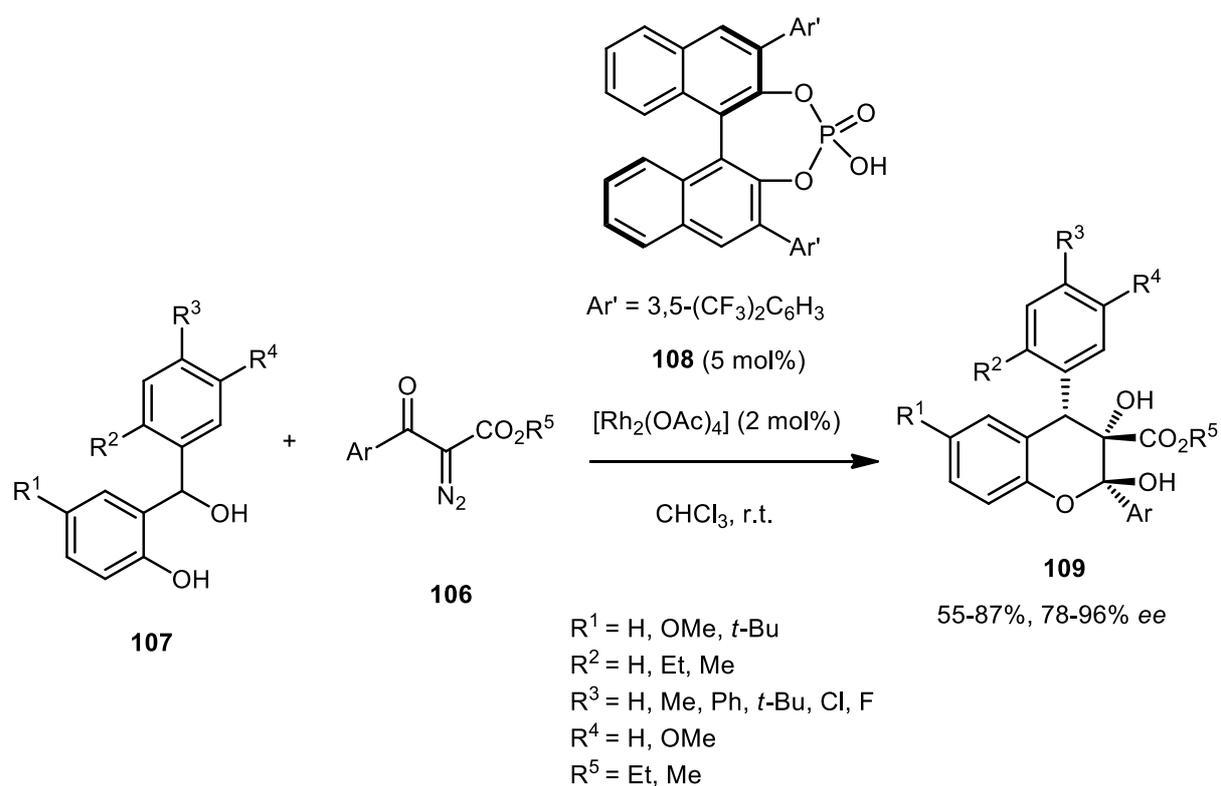
Another type of substrates, such as indoles **104** in which the pendant alkene was linked through the indole nitrogen atom, were also submitted to the same reaction conditions.<sup>[39]</sup> As depicted in Scheme 27, they led to the corresponding functionalized tricyclic chiral indolines **105** in moderate to high yields (56-93%), moderate diastereoselectivities (50-66% *de*) combined with good to high enantioselectivities (81-91% *ee*).



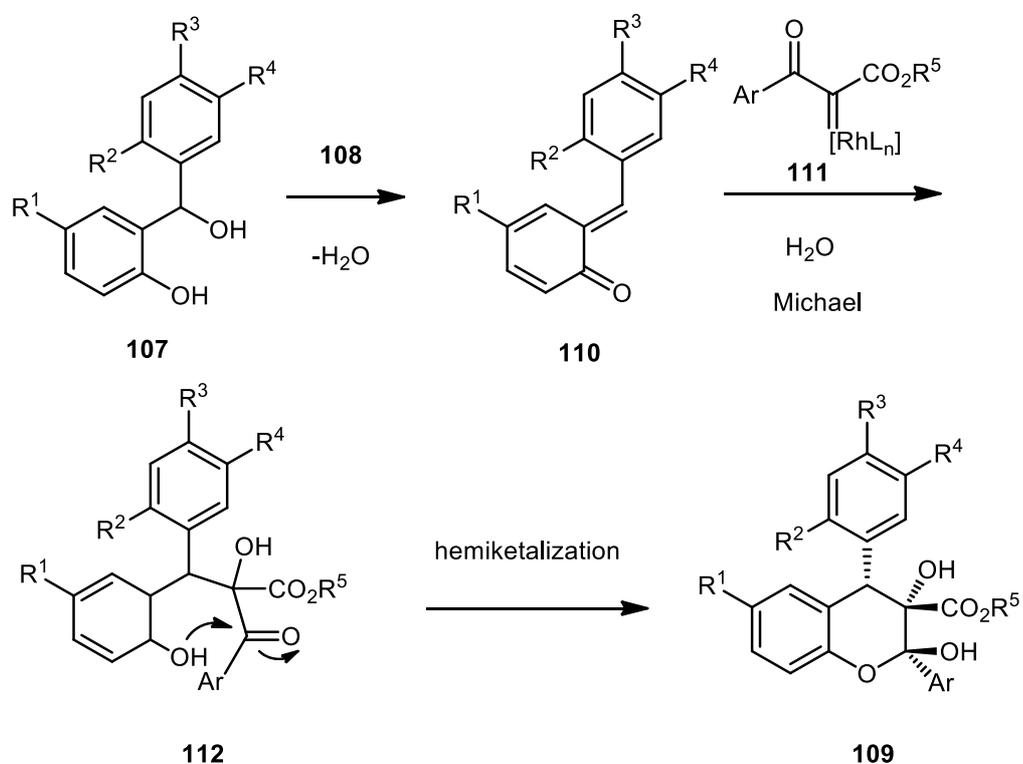
**Scheme 27.** Domino Michael/protonation/aza-Prins reaction of N-alkene-linked indoles with an amidoacrylate.

## 8 Enantioselective Rhodium-Catalyzed Domino Reactions

In 2016, Schneider et al. described an enantioselective domino Michael/hemiketalization reaction between diazoesters **106** and *ortho*-hydroxy benzhydryl alcohols **107**, evolving through synergistic rhodium/phosphoric acid catalysis.<sup>[40]</sup> As shown in Scheme 28, the multicatalytic process was performed in the presence of a combination of 2 mol% of  $[\text{Rh}_2(\text{OAc})_4]$  and 5 mol% of chiral phosphoric acid **108** in chloroform at room temperature, providing the corresponding densely functionalized chiral chromans **109** bearing three contiguous stereogenic centers as single diastereomers in moderate to high yields (55-87%) and good to excellent enantioselectivities (78-96% *ee*). The process involved the *in situ* generation of *ortho*-quinone methides **110** from the corresponding starting *ortho*-hydroxy benzhydryl alcohols **107** in the presence of the chiral phosphoric acid that trapped the rhodium carbene **111** generated from the reaction of the diazoester **106** with  $[\text{Rh}_2(\text{OAc})_4]$ , resulting in the formation of intermediate **112**. The latter then cyclized through hemiketalization to give the final domino product **109**.

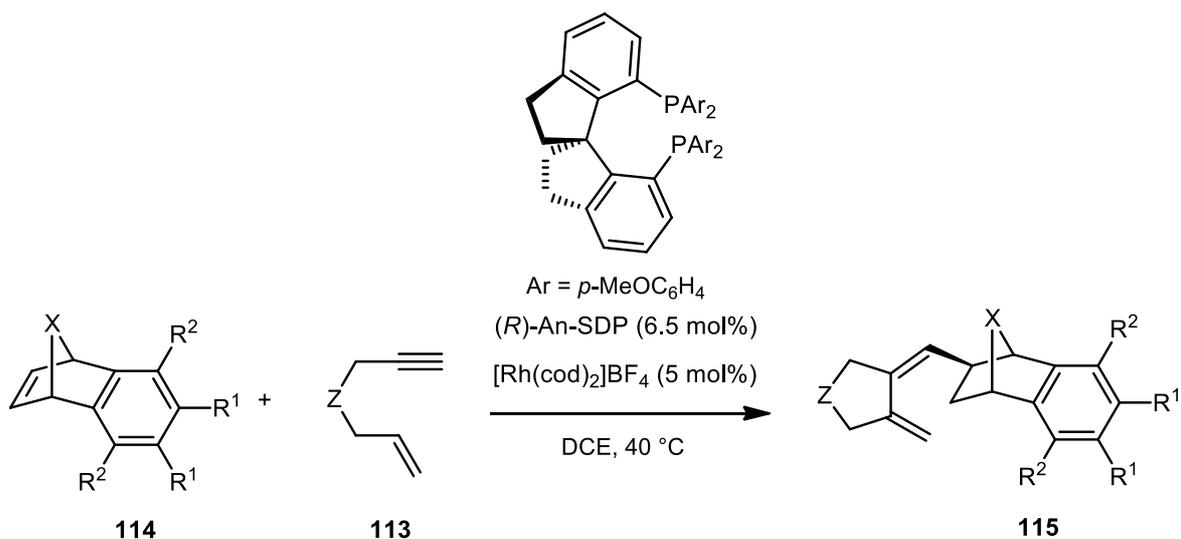


proposed mechanism:



**Scheme 28.** Domino Michael/hemiketalization reaction of *ortho*-hydroxy benzhydryl alcohols with diazoesters in the presence of a chiral phosphoric acid.

In 2018, Fan and coworkers reported a novel asymmetric domino cyclization/addition reaction of 1,6-enynes **113** with oxa/azabenzonorbornadienes **114** catalyzed by a chiral diphosphine rhodium complex.<sup>[41]</sup> The latter was *in situ* generated from 5 mol% of [Rh(cod)<sub>2</sub>]BF<sub>4</sub> and 6.5 mol% of a chiral diphosphine ligand, such as (*R*)-An-SDP. The process was carried out at 40 °C in dichloroethane as solvent, leading to the corresponding chiral domino products **115** in moderate to high yields (38-89%) and uniformly high enantioselectivities (82-99% *ee*), as shown in Scheme 29. The absolute configurations of these products were identified by X-ray analysis. The mechanism of the domino process depicted in Scheme 29 began with the complexation of the *in situ* generated chiral catalyst with the 1,6-enyne **113** to give intermediate **116**. Then, a cyclo-isomerization of this intermediate led to a rhodacyclopentene intermediate **117** which underwent a β-hydride elimination of the allylic hydrogen to afford a rhodium hydride intermediate **118**. A coordination of the latter with the oxa/azabenzonorbornadiene **114** provided novel intermediate **119**. The alkene inserted into the Rh–C bond to generate intermediate **120** which finally led to the domino product **115** along with the regenerated catalyst. The catalyst system tolerated a range of substituents on the phenyl ring of the oxa/azabenzonorbornadiene including sterically hindered ones. Uniformly remarkable enantioselectivities were achieved in the reaction of azabenzonorbornadienes (97-99% *ee*) while oxabenzonorbornadienes generally provided lower enantioselectivities (82-93% *ee*).



$R^1 = \text{H, Me, OMe, Br}$

$R^1, R^1 = \text{OCH}_2\text{O, O}(\text{CH}_2)_2\text{O}$

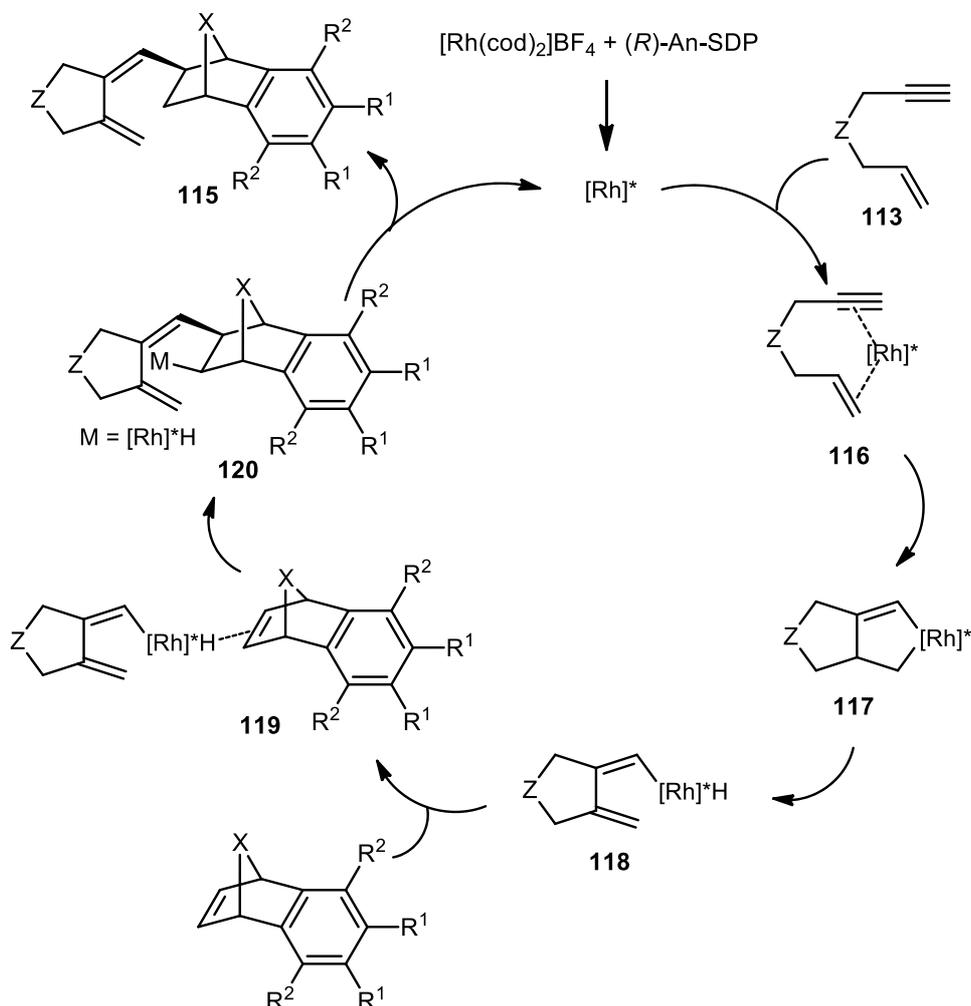
$R^2 = \text{H, OMe}$

$Z = \text{NTs, NNs, NSO}_2\text{Ph, NBoc, C}(\text{CO}_2\text{Et})_2, \text{C}(\text{CO}_2\text{Me})_2, \text{O}$

$X = \text{NBoc, NTs, O}$

38-89%, 82-99% ee

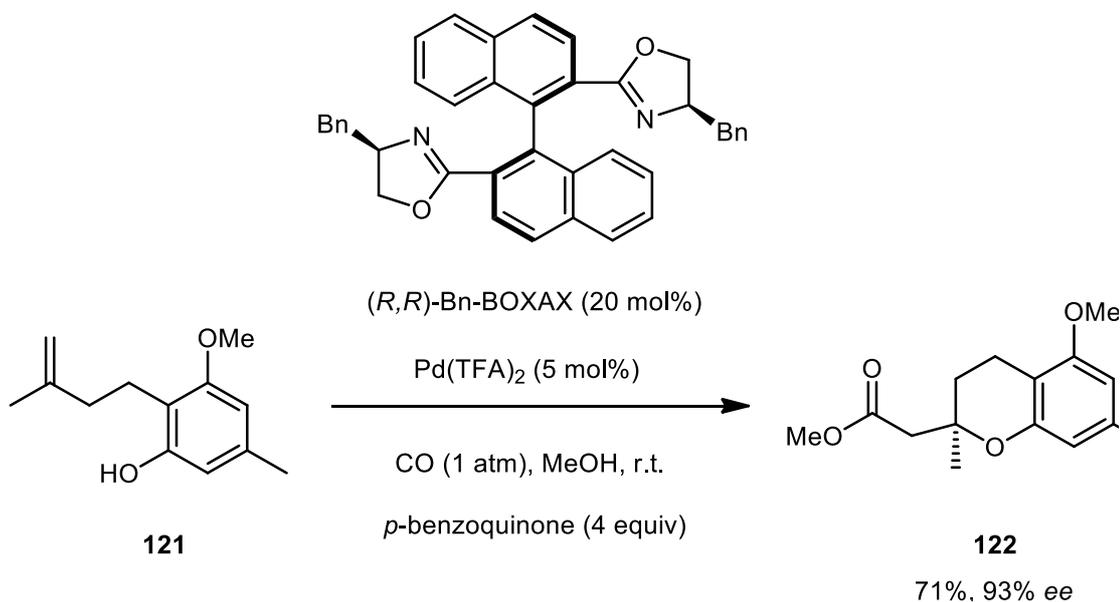
proposed mechanism:



**Scheme 29.** Domino cyclization/addition reaction of 1,6-enynes with oxa/azabenzonorbornadienes.

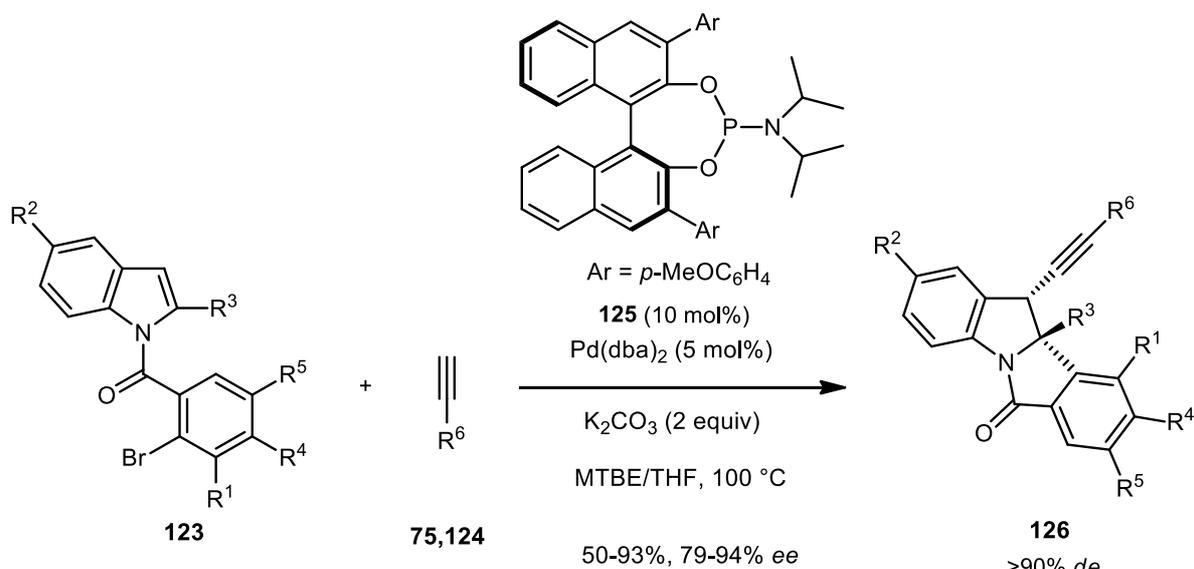
## 9 Enantioselective Palladium-Catalyzed Domino Reactions

A number of enantioselective palladium-catalyzed domino transformations have also been developed related to the fact that this transition metal presents the advantage to be compatible with many functional groups.<sup>[42]</sup> As a recent example, Tietze et al. reported an enantioselective palladium-catalyzed domino Wacker/carbonylation/methoxylation reaction that constituted the key step of a formal total synthesis of naturally occurring and bioactive product (-)-siccanin.<sup>[43]</sup> As depicted in Scheme 30, the treatment of alkenyl phenol **121** by a chiral palladium catalyst *in situ* generated from 5 mol% of Pd(TFA)<sub>2</sub> as precatalyst and 20 mol% of (*R,R*)-Bn-BOXAX as ligand in the presence of *p*-benzoquinone as reoxidant under an atmosphere of carbon monoxide in methanol as solvent led at room temperature to the corresponding chiral chroman **122** in 71% yield and 93% *ee*.



**Scheme 30.** Domino Wacker/carbonylation/methoxylation reaction of an alkenyl phenol.

In 2017, Jia et al. reported an enantioselective palladium-catalyzed dearomative arylalkynylation of *N*-substituted indoles **123** with alkynes **75,124** through a domino Heck/Sonogashira reaction.<sup>[44]</sup> As shown in Scheme 31, the process was promoted at 100 °C by a chiral palladium catalyst *in situ* generated from 5 mol% of Pd(dba)<sub>2</sub> and 10 mol% of chiral BINOL-derived phosphoramidite ligand **125** in a mixture of MTBE and THF as solvent. It afforded the corresponding chiral 2,3-disubstituted indolines **126** bearing vicinal quaternary and tertiary stereocenters at C2 and C3 positions with almost complete diastereoselectivity (>90% *de*) in all cases of substrates combined with moderate to high yields (50–93%) and uniformly high enantioselectivities (79–94% *ee*). It evolved through an intramolecular Heck arylation of the *N*-substituted indole followed by the intermolecular capture of a secondary benzyl-palladium species by the alkyne. The substrate scope was found very wide since an impressive range of aliphatic, aromatic and silylated alkynes was tolerated, all providing high enantioselectivities. Moreover, both electron-donating and electron-withdrawing substituents (R<sup>1</sup>-R<sup>5</sup>) on the indole moiety were compatible.



R<sup>1</sup> = H, Me

R<sup>2</sup> = H, *i*-Pr, Me, Cl, F

R<sup>3</sup> = Me, Ph, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, 2-furyl, Et, CO<sub>2</sub>Me

R<sup>4</sup> = H, OMe

R<sup>5</sup> = H, OMe, Me, F

R<sup>6</sup> = Ph, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-Tol, *p*-FC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-(Pent)C<sub>6</sub>H<sub>4</sub>, *p*-PhC<sub>6</sub>H<sub>4</sub>, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-(OPent)C<sub>6</sub>H<sub>4</sub>,

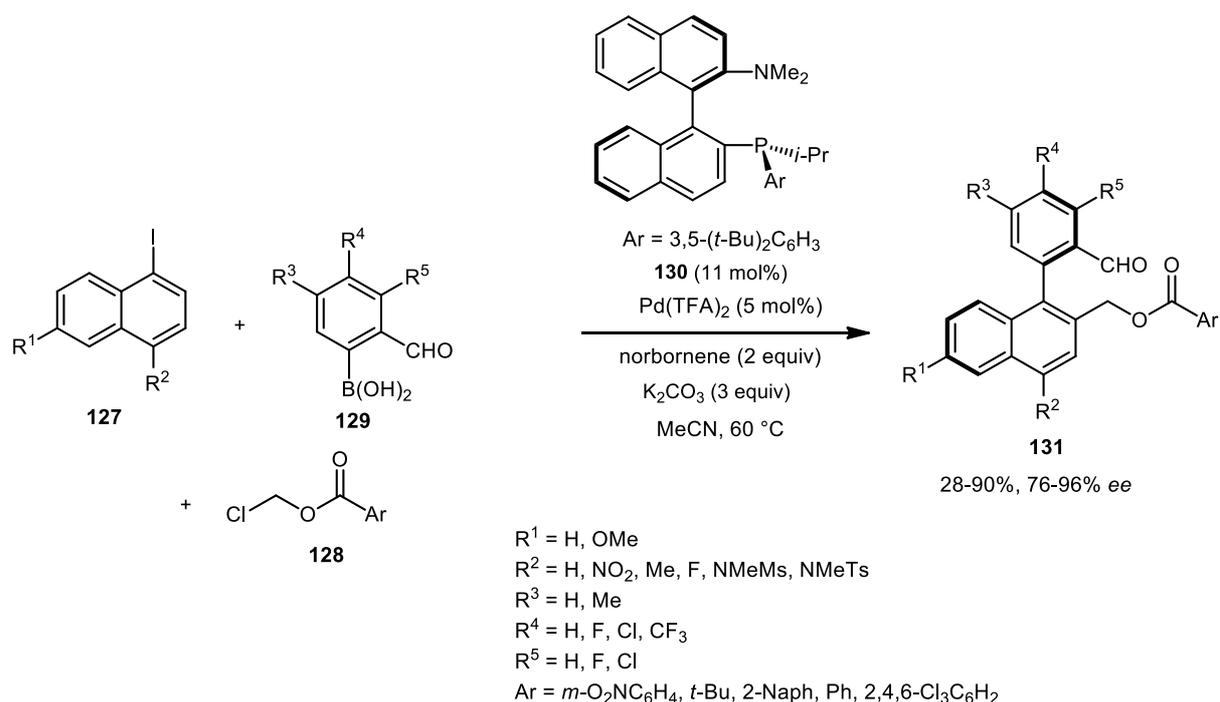
*p*-(*t*-Bu)C<sub>6</sub>H<sub>4</sub>, *p*-(MeO<sub>2</sub>C)C<sub>6</sub>H<sub>4</sub>, *p*-NCC<sub>6</sub>H<sub>4</sub>, *p*-NCCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, *p*-(F<sub>3</sub>CO)C<sub>6</sub>H<sub>4</sub>, *p*-(OCH)C<sub>6</sub>H<sub>4</sub>, *m*-Tol, *m*-MeOC<sub>6</sub>H<sub>4</sub>,

*m*-FC<sub>6</sub>H<sub>4</sub>, *m*-ClC<sub>6</sub>H<sub>4</sub>, *o*-Tol, *o*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *o*-ClC<sub>6</sub>H<sub>4</sub>, *o*-FC<sub>6</sub>H<sub>4</sub>, 2-Naph, 2-thienyl, 1-thienyl, 3-pyridyl, 2-ferrocenyl,

CH(OEt)<sub>2</sub>, *t*-Bu, PhthNCH<sub>2</sub>, Cl(CH<sub>2</sub>)<sub>4</sub>, HO(CH<sub>2</sub>)<sub>4</sub>, HO(CH<sub>2</sub>)<sub>2</sub>, TMS, (Me)C=CH<sub>2</sub>

**Scheme 31.** Domino Heck/Sonogashira reaction of *N*-substituted indoles with alkynes.

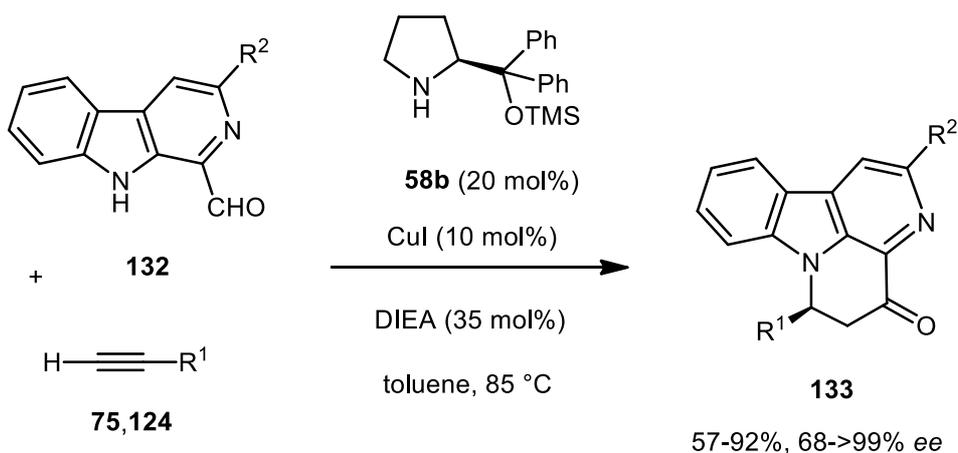
In 2018, Gu et al. developed an enantioselective three-component cross-coupling reaction cocatalyzed by a chiral palladium complex and norbornene, allowing the synthesis of chiral biaryl atropisomers.<sup>[45]</sup> The process involved 1-iodonaphthalenes **127**, chloromethyl benzoates **128** and aryl boronic acids **129** as three partners in acetonitrile as solvent. It was performed at 60 °C in the presence of K<sub>2</sub>CO<sub>3</sub> as base and two equivalents of norbornene as cocatalyst. The reaction was promoted by a chiral palladium catalyst *in situ* generated from Pd(TFA)<sub>2</sub> and chiral phosphine ligand **130** exhibiting axial and P center chirality, which led to the corresponding chiral biaryl atropisomers **131** in low to high yields (28-90%) and good to excellent enantioselectivities (76-96% *ee*), as shown in Scheme 32. This novel process presents advantages over traditional cross-couplings because of its step economy and its compatibility with readily available *ortho*-substituted aryl halides, which can be used instead of continuously trisubstituted aryl halides which are more complicated to synthesize.



**Scheme 32.** Three-component reaction of 1-iodonaphthalenes, chloromethyl benzoates and aryl boronic acids.

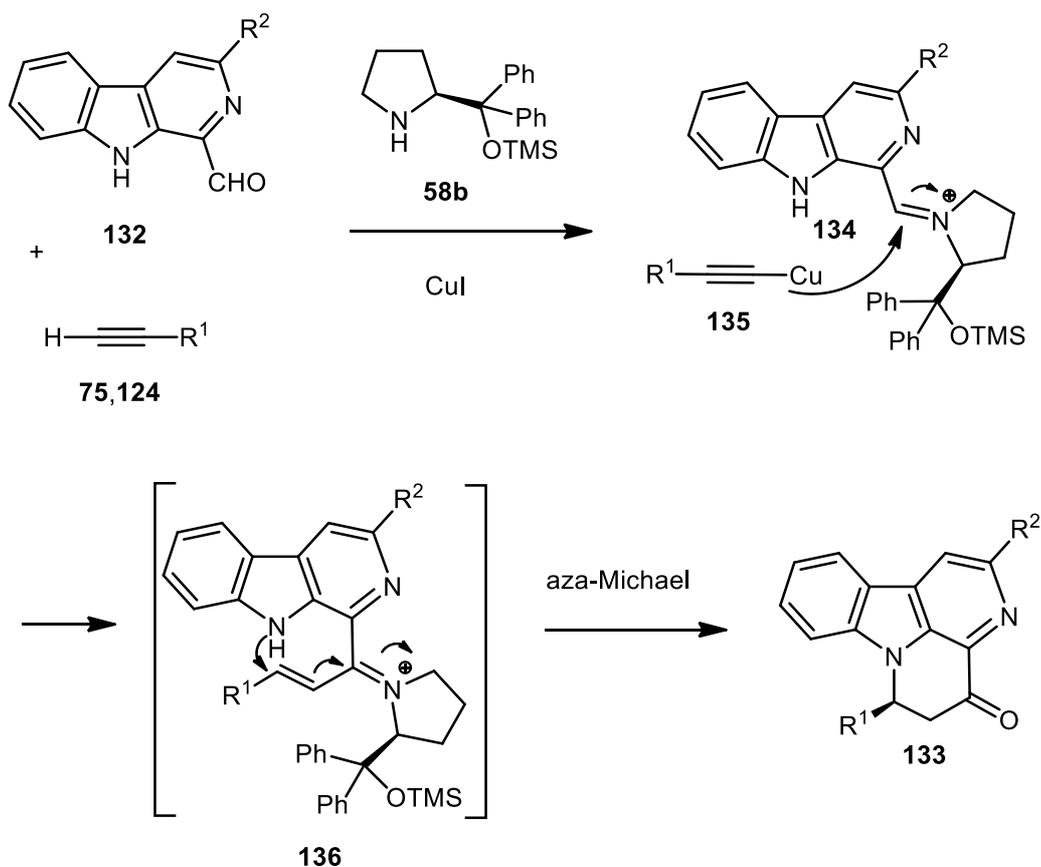
## 10 Enantioselective Copper-Catalyzed Domino Reactions

Chiral copper catalysts have also been recently employed to promote asymmetric domino reactions.<sup>[46]</sup> For example in 2016, 10 mol% of CuI was combined with 20 mol% of a chiral proline-derived organocatalyst **58b** to cooperatively catalyze enantioselective domino reactions between terminal alkynes **75/124** with 1-formyl-9*H*-β-carbolines **132**.<sup>[47]</sup> This efficient multcatalysis opened a novel route for achieving biologically interesting chiral 5,6-dihydroanthin-4-ones **133** in both moderate to high yields (57-92%) and enantioselectivities (68->99% *ee*), as shown in Scheme 33. A number of variously substituted alkynes were compatible with the highest enantioselectivities (84->99% *ee*) obtained with (hetero)aromatic alkynes (R<sup>1</sup> = (hetero)aryl). A possible mechanism is depicted in Scheme 33 which began with the reaction of the aldehyde substrate **132** with the chiral organocatalyst **58b** to give the corresponding iminium ion **134** which then reacted with the *in situ* generated Cu-coordinated alkyne **135** to give novel intermediate **136**. The latter subsequently underwent an intramolecular aza-Michael addition to provide the final domino product **133** after hydrolysis.



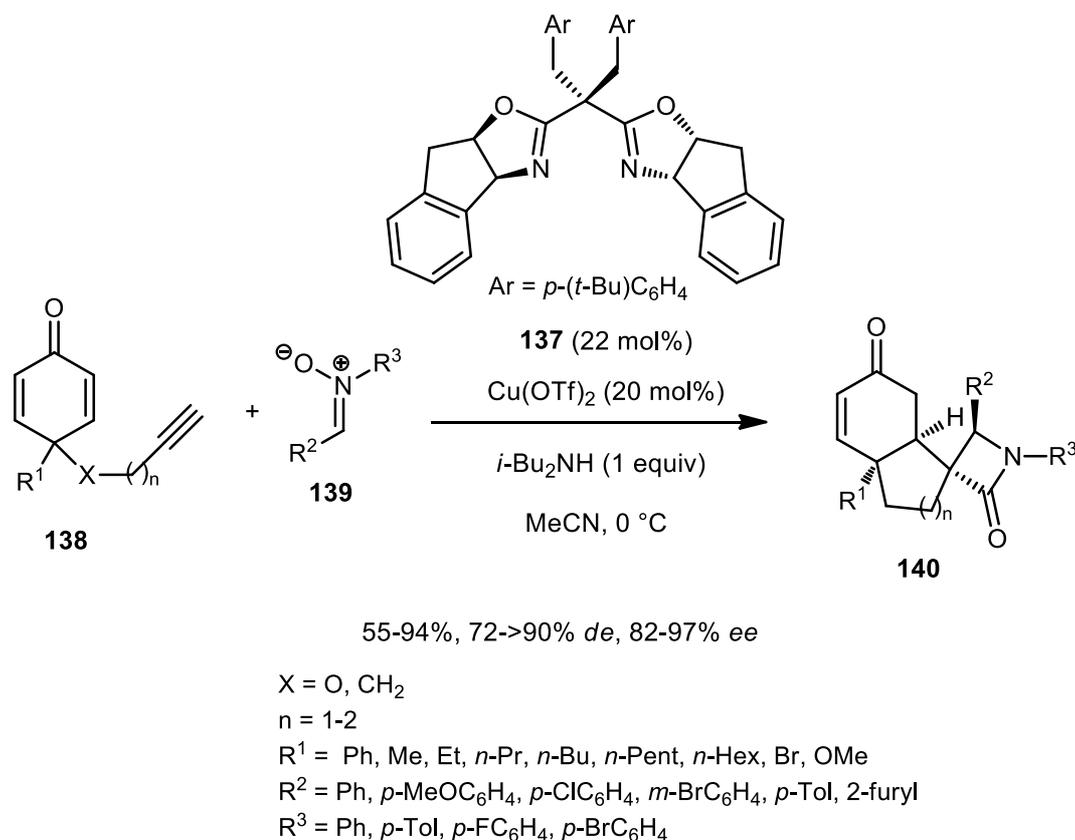
$\text{R}^1 = \text{Ph}, p\text{-}t\text{-BuC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, m\text{-Tol}, 2\text{-pyridyl}, 2\text{-cyclohexenyl}, n\text{-Bu}, \text{CO}_2\text{Me}, 2\text{-thienyl}, p\text{-}n\text{-BuC}_6\text{H}_4, p\text{-PhOC}_6\text{H}_4, p\text{-MeO}(2\text{-Naph}), 3,4\text{-Cl}_2\text{C}_6\text{H}_3$   
 $\text{R}^2 = \text{CO}_2\text{Me}, \text{H}$

proposed mechanism:



**Scheme 33.** Domino condensation/aza-Michael reaction of terminal alkynes with 1-formyl-9H- $\beta$ -carboline in the presence of a proline-derived organocatalyst.

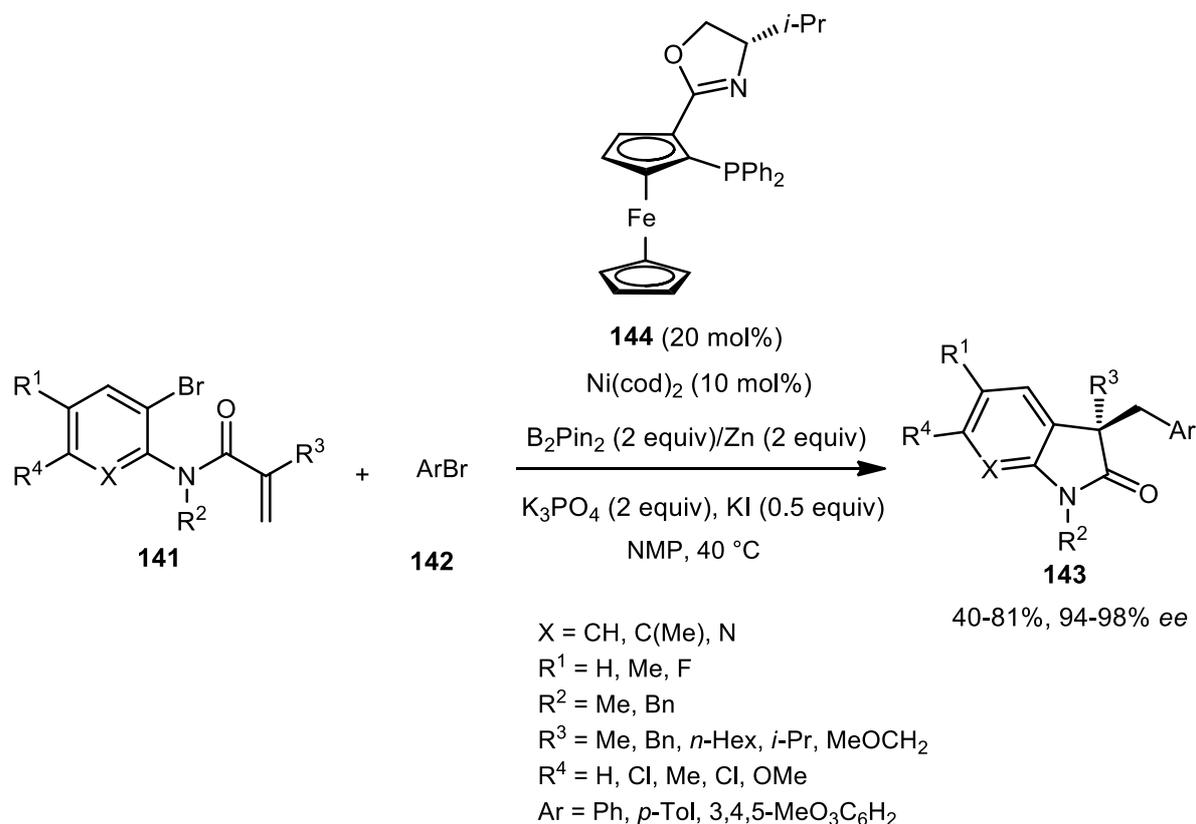
In 2018, Enders et al. reported the first copper-catalyzed highly chemo-, regio-, diastereo- and enantioselective domino Kinugasa/Michael reaction for the desymmetrization of prochiral cyclohexadienones.<sup>[48]</sup> As illustrated in Scheme 34, in the presence of a chiral copper catalyst *in situ* generated from Cu(OTf)<sub>2</sub> and chiral bisoxazoline ligand **137**, alkyne-tethered cyclohexadienones **138** reacted with nitrones **139** in the presence of a base, such as *i*-Bu<sub>2</sub>NH, in acetonitrile at 0 °C to give the corresponding chiral spirocyclic lactams **140**. These highly functionalized domino products exhibiting four contiguous stereocenters were obtained in moderate to high yields (55-94%), good to high diastereoselectivities (72->90% *de*) and uniformly high enantioselectivities (82-97% *ee*). The process exhibited high functional-group tolerance and a broad substrate scope with various substituents on the two substrates. Especially, the diastereoselectivity was almost complete (>90% *de*) in all cases of substrates with three exceptions for cyclohexadienones bearing a longer alkyl chain (R<sup>1</sup> = *n*-Bu, *n*-Pent, *n*-Hex) which reacted with lower diastereoselectivity levels (72-82% *de*).



**Scheme 34.** Domino Kinugasa/Michael reaction of alkyne-tethered cyclohexadienones with nitrones.

## 11 Enantioselective Domino Reactions Catalyzed with Other Metals

Reductive diarylation of alkenes based on the addition of two aryl electrophiles without requiring the use of prepared organometallic reagents remains unexploited. In this context, Kong et al. recently developed the first enantioselective reductive diarylation of activated alkenes **141** with aryl bromides **142** evolving through an asymmetric nickel-catalyzed domino cyclization/cross-coupling reaction.<sup>[49]</sup> As shown in Scheme 35, this highly enantioselective process afforded the corresponding chiral bis-heterocycles **143** bearing an all-carbon quaternary center in moderate to good yields (40-81%) and uniformly excellent enantioselectivities (94-98% *ee*). The reaction was performed at 40 °C in NMP as solvent in the presence of two equivalents of Zn/B<sub>2</sub>Pin<sub>2</sub> as reductant, K<sub>3</sub>PO<sub>4</sub> as base and KI as additive. It employed a chiral nickel catalyst *in situ* generated from 10 mol% of Ni(cod)<sub>2</sub> and 20 mol% of chiral PHOX-type ligand **144**. These mild reaction conditions were tolerant to a variety of functional groups.



**Scheme 35.** Domino cyclization/cross-coupling reaction of activated alkenes with aryl bromides.

## 12 Conclusions

This review updates the very recent progress in the field of enantioselective domino reactions promoted by chiral metal catalysts, covering the literature since the beginning of 2016. It shows that many types of enantioselective metal-catalyzed domino processes continue to be developed, allowing a one-pot access to complex functionalized molecules from simple starting materials. The increasing diversity of these fascinating one-pot processes well reflects that of metals employed to promote them. For example, various types of chiral silver complexes have been successfully employed to promote different types of enantioselective domino reactions including formal 1,3-dipolar cycloadditions. Some of these processes evolved through domino Michael/Mannich reactions between glycine imino esters and  $\alpha,\beta$ -unsaturated carbonyl compounds, such as chalcones or maleimides, providing highly functionalized chiral products in enantioselectivities of up to 98% *ee* and >99% *ee*, respectively, by using brucine-derived diol and aminophosphine ligands. Silver-catalyzed asymmetric 1,3-formal cycloadditions of glycine imino esters were also performed with nitroolefins as acceptors in the presence of ThioClickFerrophos ligand with up to 97% *ee*, evolving through domino Michael/aza-Henry processes. Among other enantioselective Michael-initiated silver-catalyzed domino reactions, domino Michael/Conia-ene reactions of 5-pyrazolones with alkyne-tethered nitroalkenes were promoted with squaramide silver chiral catalysts, leading to highly functionalized chiral spiropyrazolones with up to 99% *ee*. In addition, high enantioselectivities of up to 93% *ee* were obtained in domino aldol/cyclization reactions between isocyanoacetates and *p*-nitrobenzaldehyde promoted by cinchona silver complexes. In another area, scandium chiral complexes also provided excellent results in different types of asymmetric domino reactions, such as domino imine formation/intramolecular amination reactions of aldehydes with 2-aminobenzenesulfonamide performed with a chiral Pybox scandium complex with up to 93% *ee*; highly regioselective domino bromination/amination reactions of (*E*)-cinnamyl tosylcarbamates with DBDMH achieved with enantioselectivities of up to 99% *ee* when using a chiral phosphine oxide ligand; and asymmetric domino ring-opening/cyclization/retro-Mannich reactions between cyclopropyl ketones and aryl 1,2-

diamines performed with enantioselectivities of up to 97% *ee* in the presence of a chiral *N,N'*-dioxide ligand. On the other hand, enantioselective yttrium-catalyzed domino double Michael reactions of electron-deficient enynes with malonate-derived  $\alpha,\beta$ -unsaturated esters were achieved in up to 98% *ee* with the same type of chiral ligand. Related to the higher abundance and lower costs and toxicity of iron catalysts in comparison with other transition metals, the first iron-catalyzed enantioselective domino reactions have been developed. Among them, asymmetric domino oxidation/Michael/reduction/Claisen fragmentation reactions of 1,3-diketones with allylic alcohols performed in the presence of a combination of an achiral iron tricarbonyl complex and a chiral proline-derived organocatalyst provided enantioselectivities of up to 96% *ee*. The same levels of enantioselectivities were described in related domino oxidation/Michael/reduction reactions of cyclic  $\beta$ -keto esters with allylic alcohols followed by lactonization promoted by a comparable multicatalyst system. In another context, several novel enantioselective cobalt-catalyzed domino reactions were recently described on the basis of the ability of cobalt catalysts to adopt unexpected reaction pathways, and taking advantages of their lower costs and toxicity in comparison with other transition metals. Among them, are enantioselective cobalt-catalyzed domino hydroboration/cyclization reactions of 1,6-enynes with pinacolborane performed in the presence of a chiral biphosphine ligand with up to 99% *ee*. Remarkable enantioselectivities of up to >99% *ee* were also reported in asymmetric cobalt-catalyzed three-component domino hydrosilylation/hydrogenation reactions of terminal aryl alkynes with  $\text{Ar}_2\text{SiH}_2$  and hydrogen. Moreover, unlike transition metals, alkaline earth metals, such as magnesium, are abundant, inexpensive and environmentally benign. In this context, this metal was used in the presence of chiral *N,N'*-dioxide ligands to promote enantioselective domino Michael/cyclization reactions of isocyanides with alkylidene malonates with enantioselectivities of up to 96% *ee*. Magnesium was also combined with a chiral phosphoric acid to promote asymmetric domino 1,5-hydride transfer/cyclization reactions of oxindole derivatives to give a series of structurally diverse chiral spirooxindole tetrahydroquinolines with up to 97% *ee*. Chiral zirconium catalysts derived from BINOL have been applied to develop a novel direct approach to different types of chiral fused polycyclic indolines on the basis of domino Michael/protonation/aza-Prins reactions of C3- and N-alkene-linked indoles with an amidoacrylate achieved with up to 93% and 91% *ee*, respectively. Other metals, such as copper, rhodium and palladium, also provided excellent results. For example, enantioselectivities of up to >99% *ee* were described in the synthesis of biologically interesting chiral 5,6-dihydrocanthin-4-ones through enantioselective copper-catalyzed domino condensation/aza-Michael reactions performed in the presence of a chiral proline-derived organocatalyst. Moreover, asymmetric rhodium-catalyzed domino Michael/hemiketalization reactions afforded densely functionalized chiral chromans with 96% *ee* in the presence of a chiral phosphoric acid. In addition, an enantioselective palladium-catalyzed domino Wacker/carbonylation/methoxylation reaction performed in the presence of (*R,R*)-Bn-BOXAX as ligand with 93% *ee* constituted the key step of a formal total synthesis of (-)-siccanin. Undoubtedly, many other enantioselective metal-promoted asymmetric domino reactions will be discovered in the near future through the combination of different types of reactions, and the use of novel chiral more environmentally benign metal catalyst systems.

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