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► **To cite this version:**

Hélène Pellissier. Recent Developments in Enantioselective Domino Reactions. Part B: First Row Metal Catalysts. *Advanced Synthesis and Catalysis*, In press, 10.1002/adsc.202300002. hal-04009686

HAL Id: hal-04009686

<https://hal.science/hal-04009686v1>

Submitted on 1 Mar 2023

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Recent Developments in Enantioselective Domino Reactions. Part B: First Row Metal Catalysts

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Abstract: This review updates the field of enantioselective domino reactions promoted by chiral catalysts derived from first row metals, such as zinc, iron, copper, scandium, nickel, cobalt, titanium, chromium and magnesium as special case, published since the beginning of 2019. It illustrates how much a diversity of these catalysts allow an impressive range of novel highly enantioselective domino reactions of many types to be achieved, providing a one-pot access to very complex and functionalized chiral molecules from simple starting materials.

Keywords: domino reactions; multicomponent reactions; transition metals; first row metals; asymmetric synthesis

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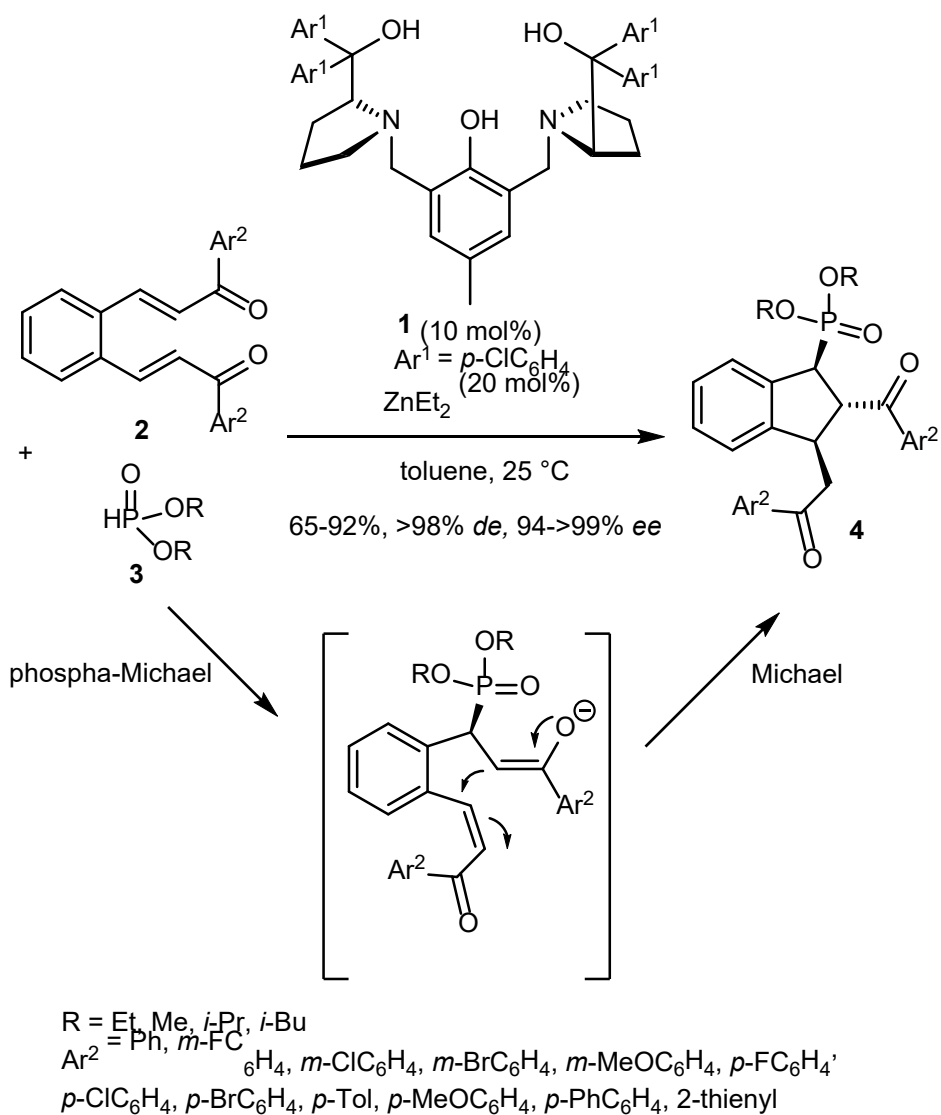
1 Introduction

The combination of asymmetric metal catalysis with the concept of domino reactions results in the direct construction of complex and densely functionalized chiral molecules.^[1] Introduced by Tietze in 1990s, domino reactions are defined as one-step two or more bond-forming transformations occurring under strictly the same reaction conditions.^[2] These powerful transformations have allowed many natural and bioactive products to be synthesized without requiring the purification of intermediates.^[3] The goal of this review is to collect the recent advances in enantioselective domino reactions catalyzed by first row metals, such as zinc, iron, copper, scandium, nickel, cobalt, titanium, chromium and magnesium as special case, published since the beginning of 2019 since this field was most recently updated this year, covering the literature until the end of 2018.^[3w] In comparison to noble metals, first row metals are generally cheaper, less toxic and offer an exceptional synthetic versatility. With the growing awareness of limited resources, considerable efforts are developed to replace existing noble-metal-catalyzed reactions with earth-abundant first row analogs for a greener and more sustainable chemistry. More importantly, there are a plethora of unique transformations mediated by first row metals, which have no classical second or third row counterpart. This review is divided into nine parts, dealing successively with enantioselective zinc-catalyzed domino reactions, iron-catalyzed domino reactions, copper-catalyzed domino reactions, scandium-catalyzed domino reactions, nickel-catalyzed domino reactions, magnesium-catalyzed domino reactions, cobalt-catalyzed domino reactions, titanium-catalyzed domino reactions and chromium-catalyzed domino reactions. It must be noted that this review does not include multicatalyzed enantioselective domino reactions.

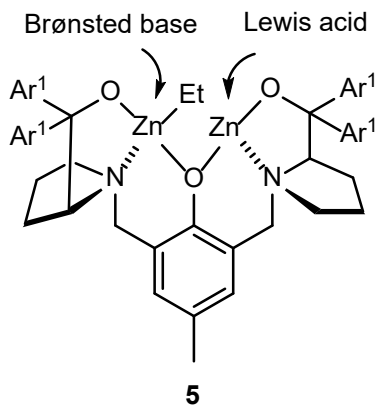
2 Enantioselective Zinc-Catalyzed Domino Reactions

2.1 Enantioselective Michael-Initiated Domino Reactions

As a cheap, abundant and less toxic metal in comparison with many transition metals, zinc has gained a significant importance in green catalysis.^[4] Especially, the last decade has seen a spectacular development of novel enantioselective domino reactions promoted by many types of chiral zinc catalysts. In a recent example reported by Wang et al. in 2019, an enantioselective domino phospho-Michael/Michael reaction between *o*-dienones **2** and dialkyl phosphates **3** was promoted at 25 °C by a chiral catalyst *in situ* generated from 20 mol% of ZnEt₂ and 10 mol% of ProPhenol-derived ligand **1** in toluene as solvent.^[5] Actually, the active catalyst depicted in Scheme 1 consisted in a dinuclear bifunctional catalyst Zn₂Et(**1**) **5**, exhibiting both a Brønsted base site and a Lewis acid site embedded within a chiral pocket formed by the semi-aza-crown ligand.^[6] The domino reaction afforded the corresponding chiral 1,2,3-trisubstituted indanes **4** exhibiting three contiguous stereocenters as single diastereomers (>98% *de*) in good yields (65-92%) and excellent enantioselectivities (94->99% *ee*). Various dialkyl phosphates were compatible with the catalytic system, all providing excellent *ee* values (96-99% *ee*). Furthermore, comparable excellent enantioselectivities were achieved in the reaction of a series of aryl substituted *o*-dienones regardless of the electronic nature of the substituents exhibited on the aryl group (Ar²).

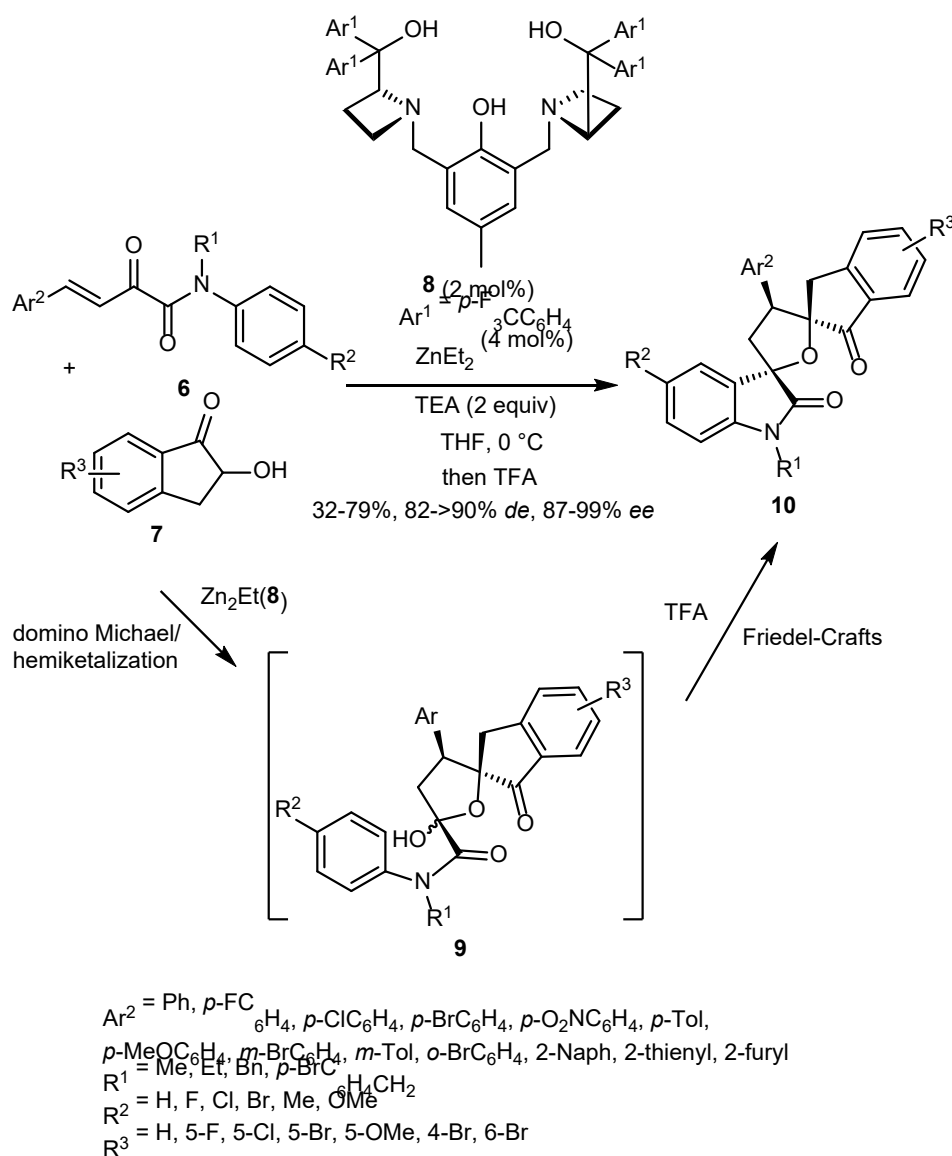


structure of the *in situ* generated active dinuclear catalyst:



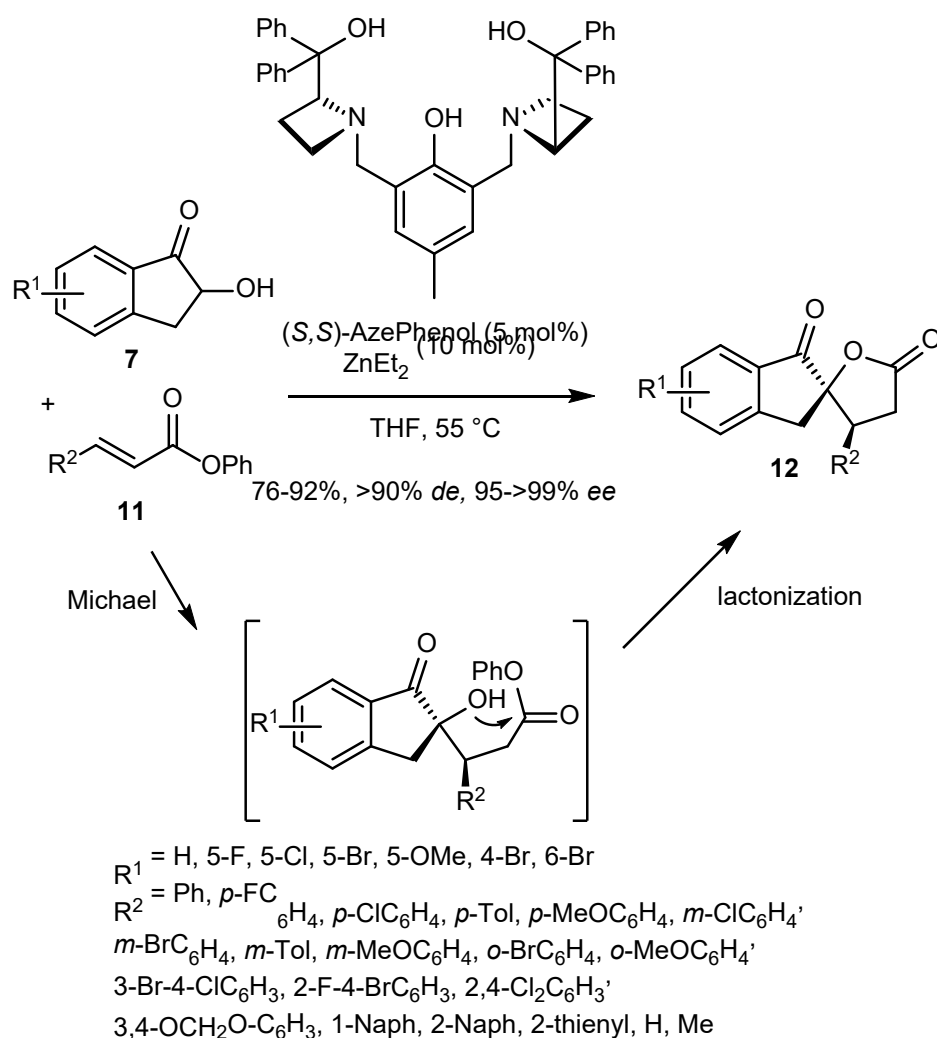
Scheme 1. Domimo phospha-Michael/Michael reaction of *o*-dienones with dialkyl phosphates.

The same group also developed in 2019 a novel route to chiral bispirotetrahydrofuran oxindoles based on an enantioselective cascade Michael/hemiketalization/Friedel–Crafts reaction of β,γ -unsaturated α -ketoamides **6** with α -hydroxy-1-indanones **7** (Scheme 2).^[7] The sequence began with an asymmetric domino Michael/hemiketalization catalyzed by a chiral dinuclear zinc complex Zn_2Et_2 (**8**) derived from 4 mol% of $ZnEt_2$ and 2 mol% of chiral AzePhenol-type ligand **8**. The reaction, performed at 0 °C in THF as solvent, afforded the unstable hemiketal domino product **9** which was not isolated but directly submitted to treatment with TFA which promoted the final Friedel–Crafts reaction, delivering chiral bispirotetrahydrofuran oxindoles **10** exhibiting three stereocenters in variable yields (32-79%) combined with both high diastereo- (82->90% *de*) and enantioselectivities (87-99% *ee*). The scope of the process was wide since a range of either electron-withdrawing or electron-donating substituents (R^2, R^3) were tolerated on the phenyl rings of both substrates. However, the reaction of a ketoamide bearing a strong electron-withdrawing group ($R^2 = NO_2$) led to the corresponding product with a low yield (32%) albeit associated with 97% *ee*. Moreover, variously *N*-substituted ketoamides all proceeded smoothly.



Scheme 2. Domino Michael/hemiketalization reaction of aryl-substituted β,γ -unsaturated α -ketoamides and α -hydroxy-1-indanones followed by Friedel–Crafts reaction.

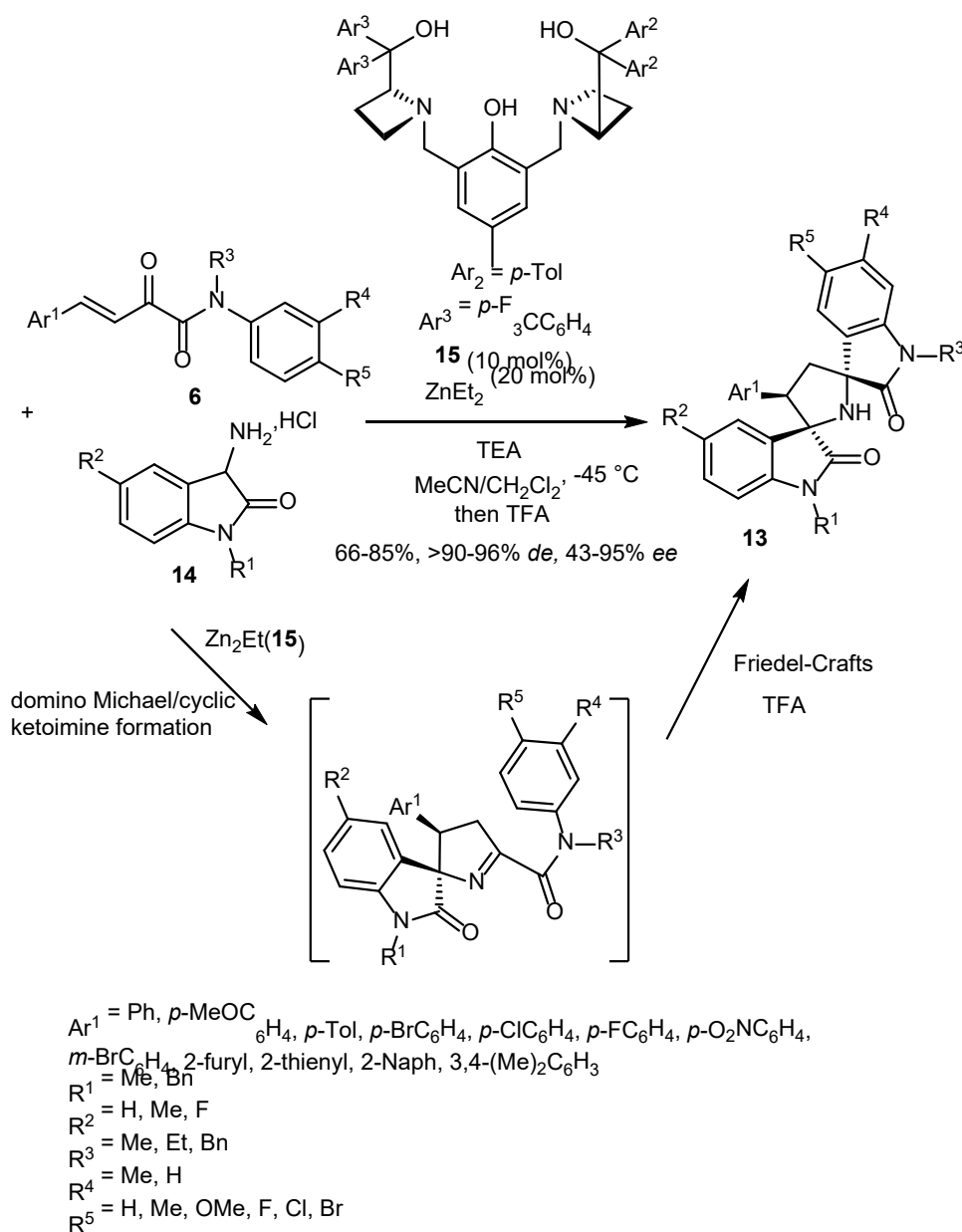
In addition, these authors employed dinuclear zinc complex $\text{Zn}_2\text{Et}((S,S)\text{-AzePhenol})$, *in situ* generated from 5 mol% of $(S,S)\text{-AzePhenol}$ and 10 mol% of ZnEt_2 , to catalyze an enantioselective domino Michael/lactonization reaction between α -hydroxy-1-indanones **7** and phenyl α,β -unsaturated esters **11**.^[8] Performed at 55 °C in THF as solvent, the process afforded a range of variously substituted chiral spiro[1-indanone-5,2'- γ -butyrolactones] **12** as almost single diastereomers (>90% *de*) in uniformly high yields (76-92%) and remarkable enantioselectivities (95->99% *ee*), as presented in Scheme 3.



Scheme 3. Domino Michael/lactonization reaction of α -hydroxy-1-indanones with phenyl α,β -unsaturated esters.

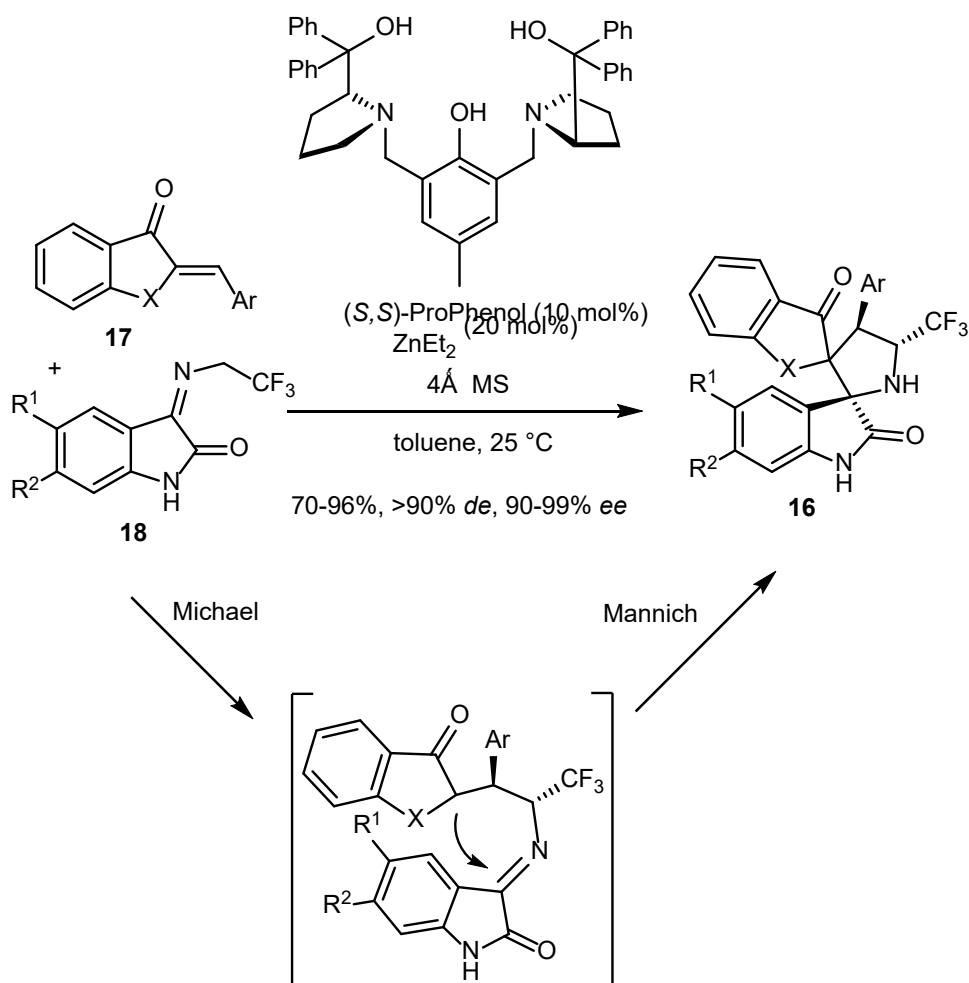
In 2019, Wang and Hua developed a novel synthesis of potentially biologically active chiral pyrrolidinyl dispirooxindoles **13**.^[9] The methodology was based on a novel enantioselective domino Michael/cyclic ketoimine formation reaction followed by a Friedel–Crafts reaction performed in a single vessel. The sequential reaction occurred at -45 °C between 3-amino oxindole hydrochlorides **14** and aryl-substituted β,γ -unsaturated α -ketoamides **6** in a mixture of acetonitrile and dichloromethane as solvent. Among chiral ligands investigated in this process, C_2 -symmetric $(S,S)\text{-ProPhenol}$ and

AzePhenol derivatives all provided low enantioselectivities ($\leq 33\%$ *ee*). In this context, the authors designed nonsymmetrical ligands, such as C_1 -symmetric ligand **15**, with electronically and sterically divergent units. The use of a combination of 10 mol% of this ligand with 20 mol% of $ZnEt_2$ allowed a range of pyrrolidinyldispirooxindoles **13** exhibiting two quaternary stereocenters as single diastereomers (>90 -96% *de*) to be synthesized in good to high yields (66-85%) and moderate to excellent enantioselectivities (43-95% *ee*), as shown in Scheme 4. The presence of various substituents at the phenyl ring of aryl-substituted β,γ -unsaturated α -ketoamides **6** was tolerated. Generally, substrates with electron-donating groups at the *para*-position of the phenyl ring (Ar^1) provided higher enantioselectivities than those with electron-withdrawing groups. In addition, heteroaromatic-substituted β,γ -unsaturated α -ketoamides and γ -naphthyl-substituted substrates were suitable substrates.



Scheme 4. Domino Michael/cyclic ketoimine formation reaction of 3-amino oxindole hydrochlorides with β,γ -unsaturated α -keto amides followed by Friedel–Crafts reaction.

The same year, these authors also developed the synthesis of very complex chiral spiro[benzofuran-pyrrolidine] derivatives **16** on the basis of an enantioselective zinc-catalyzed domino Michael/Mannich reaction between aurones **17** (X = NH) and *N*-2,2,2-trifluoroethylisatin ketimines **18**.^[10] This formal [3+2] cycloaddition was promoted at 25 °C by a combination of 20 mol% of ZnEt₂ and 10 mol% of (*S,S*)-ProPhenol in toluene as solvent, resulting in the formation of a range of chiral spiro[benzofuran-pyrrolidine] products as almost single diastereomers (>90% *de*) in good yields (70-96%) and excellent enantioselectivities (90-99% *ee*), as illustrated in Scheme 5. Aryl-substituted aurones could bear either electron-donating or electron-withdrawing at *para*-, *meta*-, and *ortho*-positions of the phenyl ring, providing the desired products in good yields (78-95%) and *ee* values (91-99% *ee*). Moreover, various trifluoromethylated imines exhibiting different substituents on the phenyl ring were tolerated. The scope of the process could also be extended to a variety of substituted thioaurones (X = S), providing the corresponding products in good to high yields (60-85%), excellent diastereoselectivity (>90% *de*) and homogeneously very high enantioselectivities (88-98% *ee*).

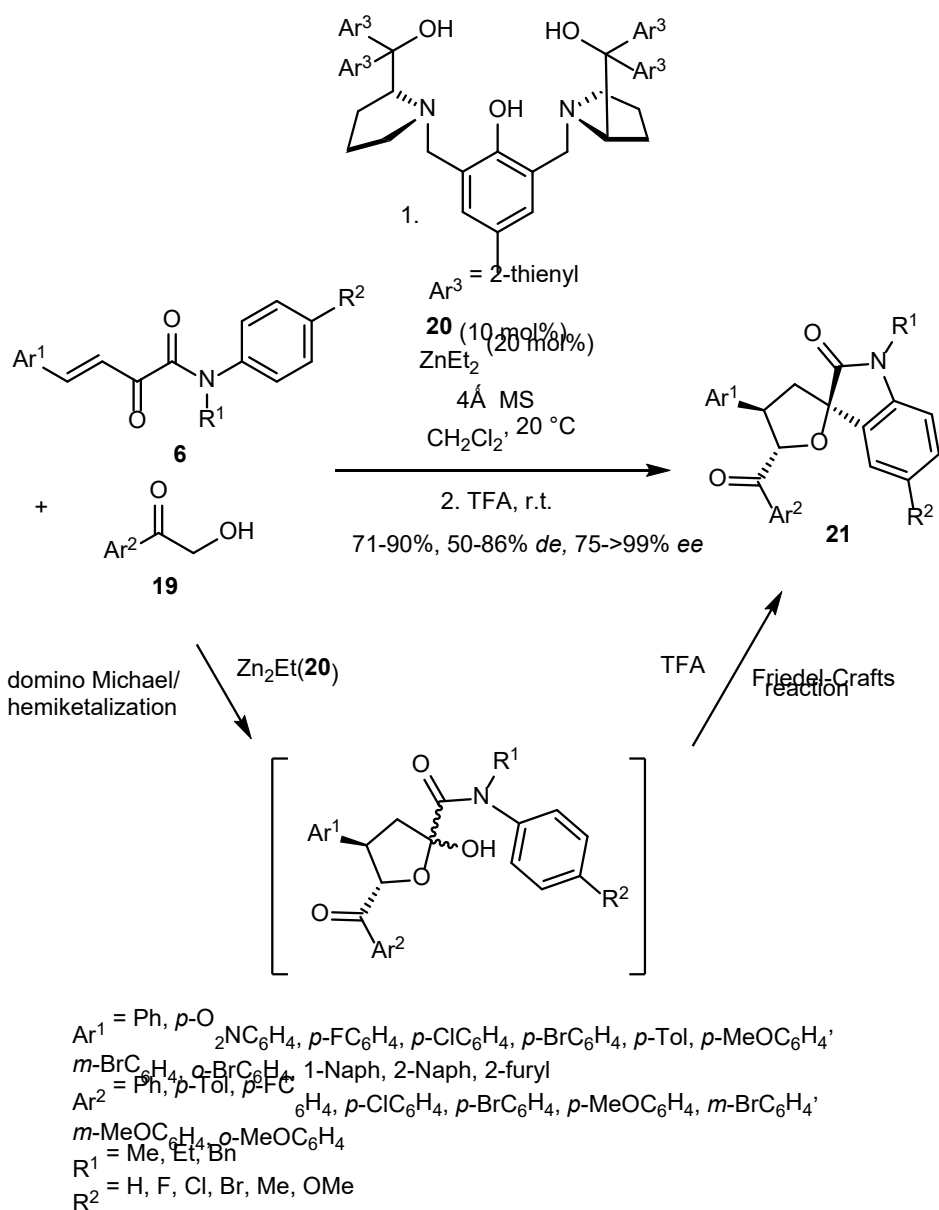


Ar = Ph, *p*-MeOC₆H₄, *m*-ClC₆H₄, *o*-BrC₆H₄, *o*-MeOC₆H₄, *m*-MeOC₆H₄,
p-ClC₆H₄, *p*-BrC₆H₄, *p*-Tol, *p*-FC₆H₄, *o*-ClC₆H₄, *o*-Tol, *m*-Tol, 2-Naph,
 2,6-Me₂C₆H₃
 R¹ = H, Me, Cl, Br, F
 R² = H, Br
 X = NH, S

Scheme 5. Domino Michael/Mannich reaction of *N*-2,2,2-trifluoroethylsatin ketimines with aurone derivatives.

The synthesis of chiral tetrahydrofuran spirooxindoles is challenging related to the various biological activities of these complex products.^[11] In 2020, Hua and Wang developed a novel route to these important molecules based on an enantioselective zinc-catalyzed domino Michael/hemiketalization reaction followed by a Friedel–Crafts reaction (Scheme 6).^[12] This sequence involved α -hydroxy aryl ketones **19** and β,γ -unsaturated α -ketoamides **6** as substrates. The domino reaction was carried out at 20 °C in dichloromethane as solvent in the presence of a chiral dinuclear zinc catalyst *in situ* generated from 20 mol% of ZnEt₂ and 10 mol% of chiral ProPhenol-derived ligand **20**. The chiral products were not isolated but directly submitted to Friedel–Crafts reaction performed at room temperature by adding trifluoroacetic acid (TFA). The one-pot sequence afforded a wide range of chiral tetrahydrofuran spirooxindoles **21** in high yields (71-90%), variable diastereoselectivities (50-86% *de*) and good to excellent enantioselectivities (75->99% *ee*). Actually, the enantioselectivities were uniformly very high (90->99% *ee*) for differently substituted substrates excepted for *ortho*-methoxy-substituted α -

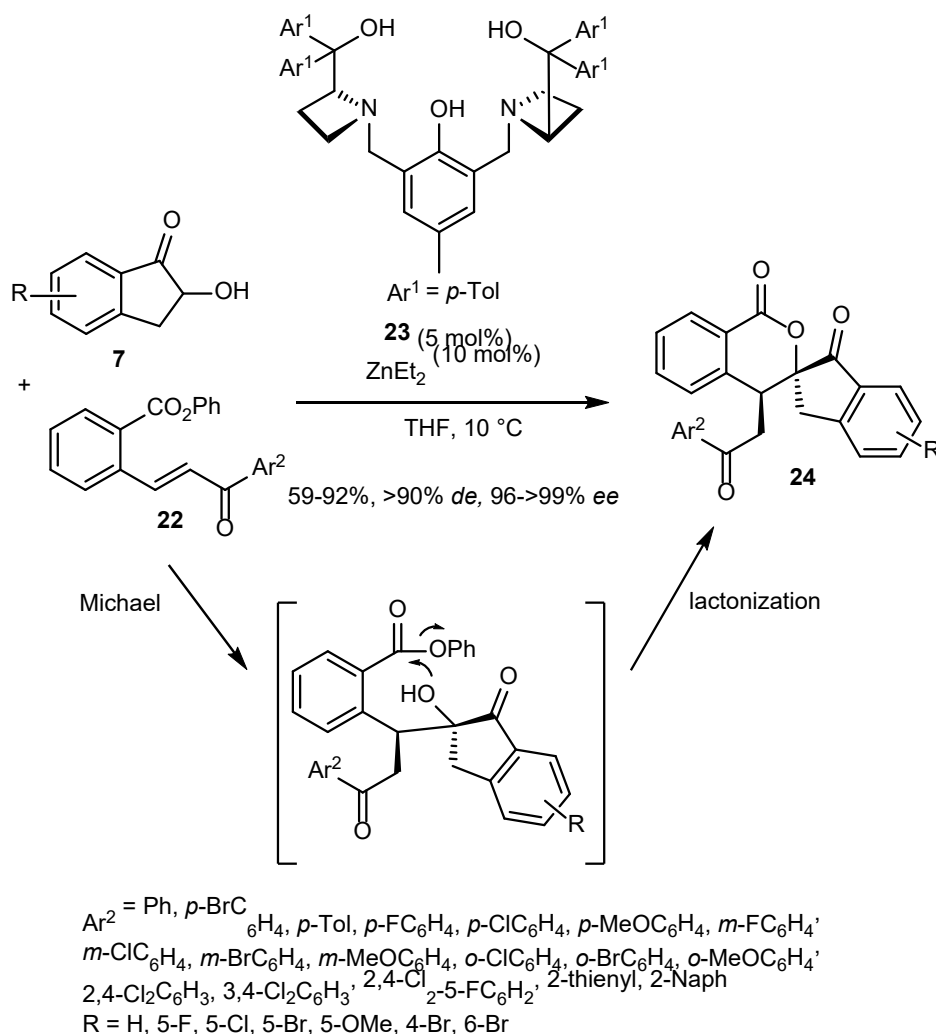
hydroxy aryl ketone ($\text{Ar}^2 = o\text{-MeOC}_6\text{H}_4$), which provided the corresponding product with the lowest *ee* value (75% *ee*).



Scheme 6. Domino Michael/hemiketalization reaction of α -hydroxy aryl ketones with β,γ -unsaturated α -ketoamides followed by Friedel–Crafts reaction.

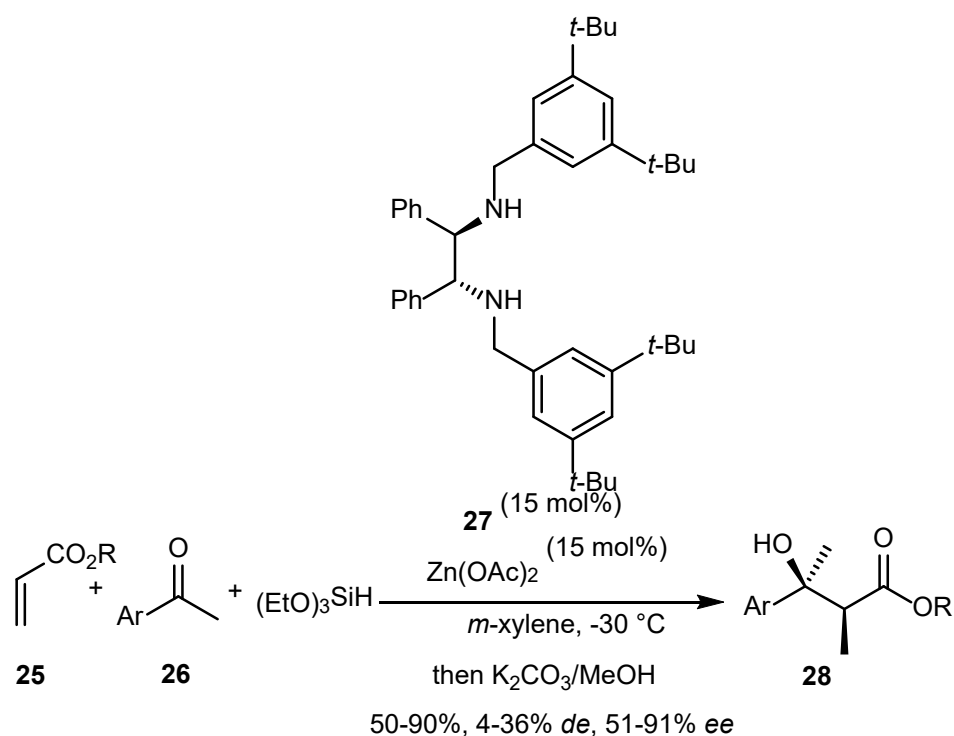
In 2020, the same group disclosed an enantioselective zinc-catalyzed domino Michael/lactonization reaction between α -hydroxy indanones **7** and *ortho*-ester chalcones **22** performed in the presence of 5 mol% of chiral AzePhenol-derived ligand **23** and 10 mol% of ZnEt_2 (Scheme 7).^[13] The corresponding *in situ* generated active chiral dinuclear zinc complex $\text{Zn}_2\text{Et}(\mathbf{23})$ allowed the domino reaction to occur at 10 °C in THF as solvent, leading to a range of enantio- and diastereomerically pure isochromanones **24** in good to high yields (59-92%) and both remarkable diastereo- and enantioselectivities (>90% *de*, and 96->99% *ee*, respectively). It was found that the electronic nature and position of substituents on

the phenyl ring of either α -hydroxy indanones or *ortho*-ester chalcones had little influence on the stereoselectivity of the reaction, as demonstrated by the homogeneously excellent results.



Scheme 7. Domino Michael/lactonization reaction of α -hydroxy-1-indanones with *ortho*-ester chalcones.

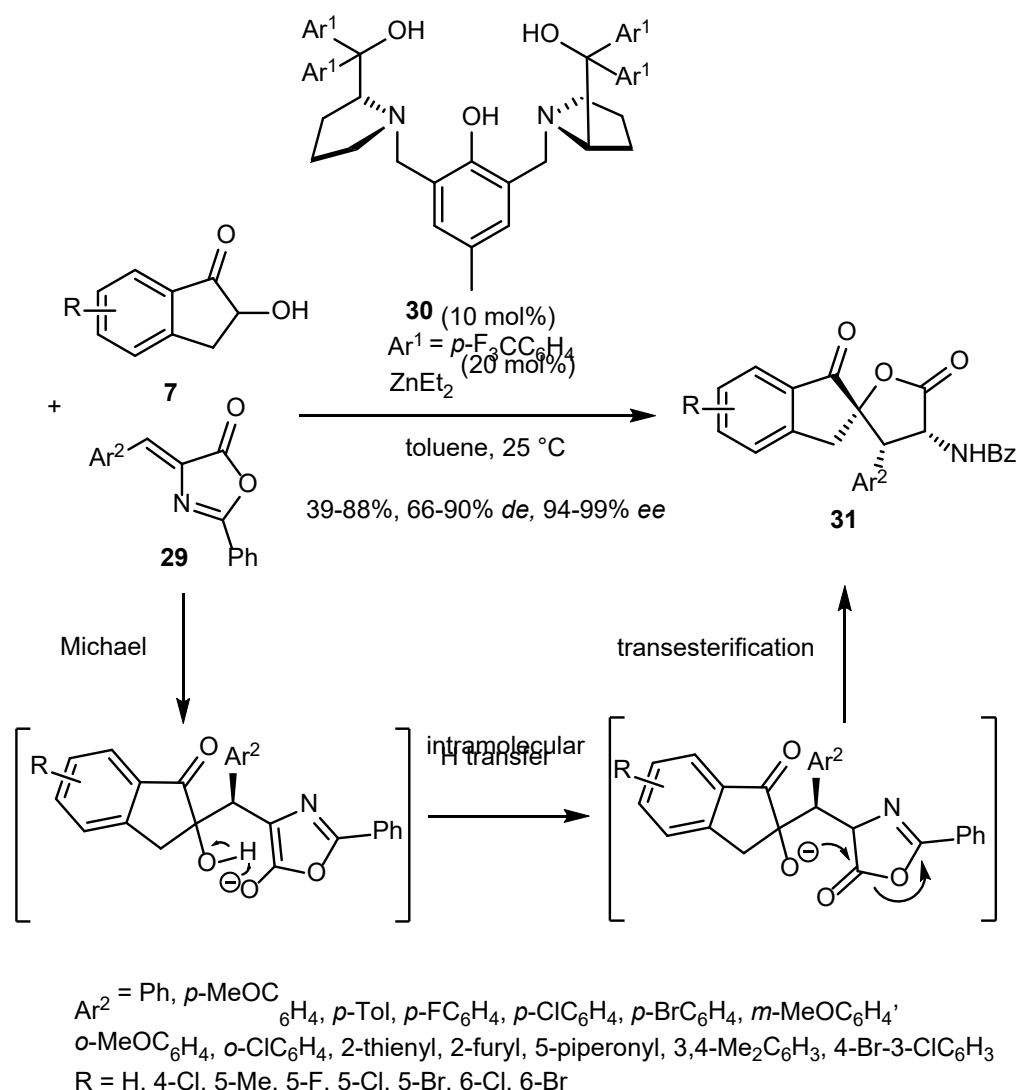
In the same year, Mlynarski et al. described a novel route to chiral β -hydroxy esters based on the first enantioselective three-component domino reductive Michael/aldol reaction of acrylates **25**, (hetero)aromatic ketones **26** and triethoxysilane using $\text{Zn}(\text{OAc})_2$ as cheap precatalyst.^[14] Among chiral ligands based on (*R,R*)-diphenylethylenediamine, diamine **27** was selected as optimal to promote this reaction at 15 mol% of catalyst loading in *m*-xylene as solvent. As illustrated in Scheme 8, a series of chiral β -hydroxy esters **28** were produced at -30 °C with both moderate to high yields (50-90%) and enantioselectivities (51-91% *ee*) combined with low diastereoselectivities (4-36% *de*).



Ar = Ph, *m*-Tol, *p*-Tol, *m*-EtC₆H₄, *m*-MeOC₆H₄, *p*-MeOC₆H₄,
m-BrC₆H₄, *m*-ClC₆H₄, *p*-ClC₆H₄, 2-furyl, 2-thienyl
 R = Me, *t*-Bu, Et

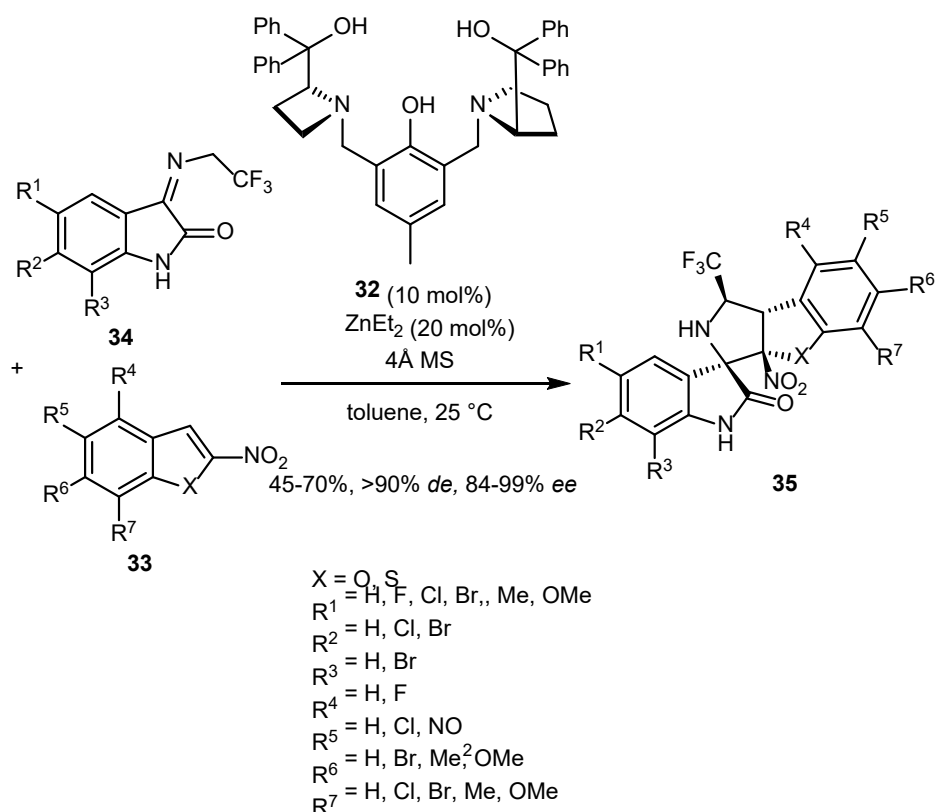
Scheme 8. Three-component domino reductive Michael/aldol reaction of acrylates, aromatic ketones and (EtO)₃SiH.

In 2021, Wang, Hua and Jia reported an enantioselective formal [3+2] cycloaddition between 2-hydroxy-1-indanones **7** and alkylidene azlactones **29**.^[15] This reaction was achieved by using a chiral dinuclear zinc catalyst *in situ* generated from 20 mol% of ZnEt₂ and 10 mol% of chiral ProPhenol-derived ligand **30** in THF at 25 °C. It evolved through domino Michael/intramolecular H-transfer/transesterification reaction (Scheme 9), allowing a convenient access to chiral α-amino-γ-butyrolactones **31** possessing three contiguous stereogenic centers. These products were obtained in moderate to high yields (39-88%), uniformly excellent enantioselectivities (94-99% *ee*) and in almost all cases as single diastereomers (90% *de*) excepted for 4-chloro-substituted 2-hydroxy-1-indanone (R = 4-Cl) which led to the corresponding product in lower diastereoselectivity (66% *de*) albeit combined with 80% yield and 94% *ee*.



Scheme 9. Domino Michael/H-transfer/transesterification reaction of 2-hydroxy-1-indanones with alkylidene azlactones.

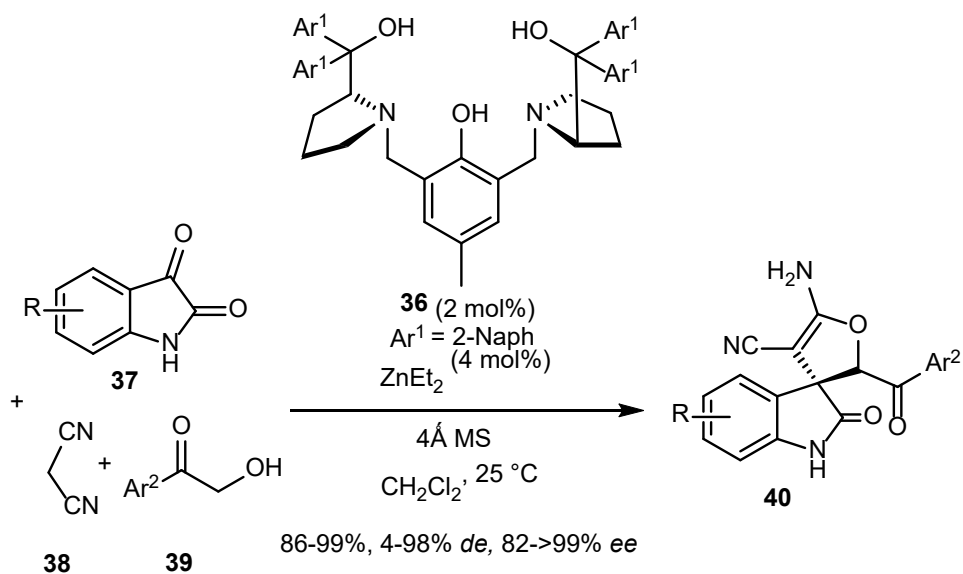
Later in 2022, the same authors employed a chiral dinuclear zinc catalyst *in situ* generated from 20 mol% of ZnEt₂ and 10 mol% of chiral C1-symmetric aza-crown ligand **32** to promote at 25 °C in toluene as solvent the enantioselective dearomative formal [3+2] cycloaddition of 2-nitrobenzofurans or 2-nitrobenzothiophenes **33** with CF₃-containing *N*-unprotected isatin-derived azomethine ylides **34**.^[16] The process evolved through asymmetric Michael addition of the latter to 2-nitrobenzofurans/2-nitrobenzothiophenes **33** which was followed by an intramolecular Mannich reaction to give the corresponding chiral pyrrolidinyl spirooxindoles **35** bearing a 2,3-fused-dihydrobenzofuran (or dihydrobenzothiophene) moiety along with four contiguous stereocenters. These functionalized complex products were synthesized as single diastereomers (>90% *de*) with good yields (45-70%) and uniformly high enantioselectivities (84-99% *ee*), as illustrated in Scheme 10. In addition to 2-nitrobenzofurans (X = O), 2-nitrobenzothiophenes (X = S) were also compatible, affording the desired products with both comparable yields (58-70%) and enantioselectivities (92-99% *ee*), despite the presence of the potentially harmful ligating sulfur atom.



Scheme 10. Domino Michael/Mannich reaction of 2-nitrobenzofurans/2-nitrobenzothiophenes with CF_3 -containing *N*-unprotected isatins.

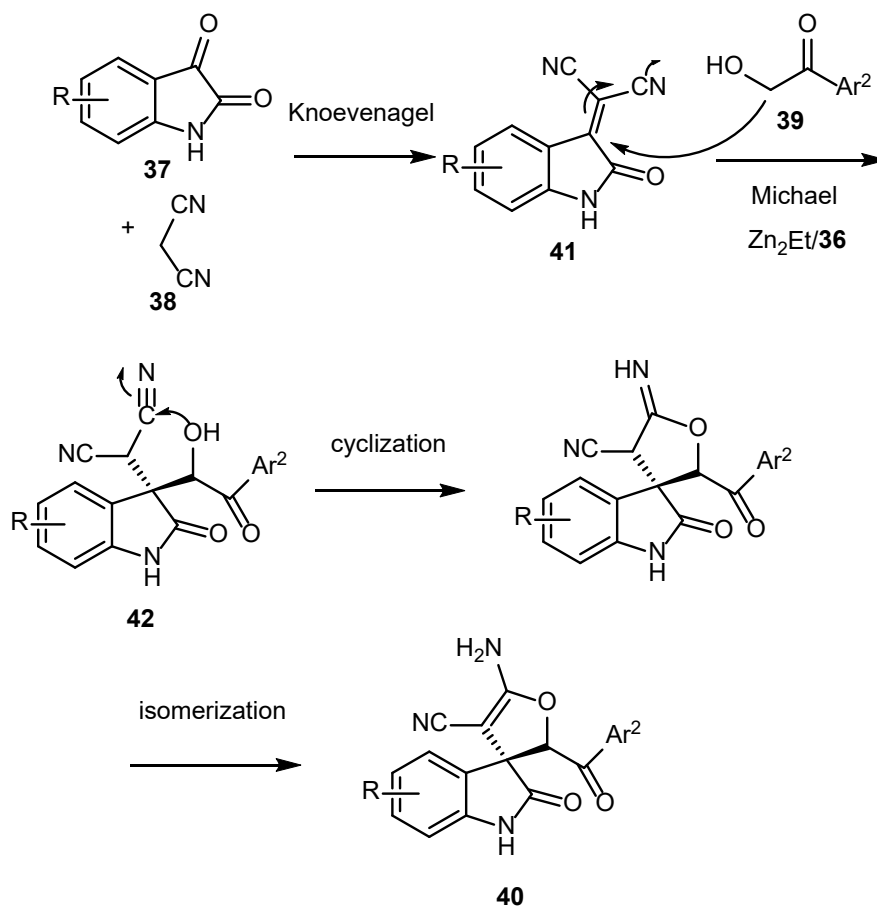
2.2 Miscellaneous Enantioselective Domino Reactions

In 2019, Wang et al. reported an enantioselective three-component domino reaction of isatins **37**, malononitrile **38** and α -hydroxy acetophenones **39** promoted by only 2 mol% of ProPhenol-type ligand **36** combined with 4 mol% of $ZnEt_2$.^[17] This domino Knoevenagel/Michael/cyclization reaction, carried out at 25 °C in dichloromethane as solvent, resulted in the formation of chiral 3,3'-dihydrofuran spirooxindoles **40** in both uniformly high yields (86-99%) and enantioselectivities (82->99% *ee*) along with low to excellent diastereoselectivities (4-98% *de*). Generally, the reaction of isatins bearing electron-rich substituents provided slightly higher enantioselectivities than those exhibiting electron-deficient groups. As depicted in Scheme 11, the sequence began with the Knoevenagel condensation of malononitrile **38** to isatin **37** to give product **41**. In the presence of the chiral dinuclear zinc catalyst *in situ* generated from $ZnEt_2$ and ligand **36**, α -hydroxy acetophenone **39** was deprotonated into a zinc enolate which underwent asymmetric Michael addition to intermediate **41**, leading to intermediate **42**. The latter was then submitted to cyclization followed by isomerization to afford the final 3,3'-dihydrofuran spirooxindole.



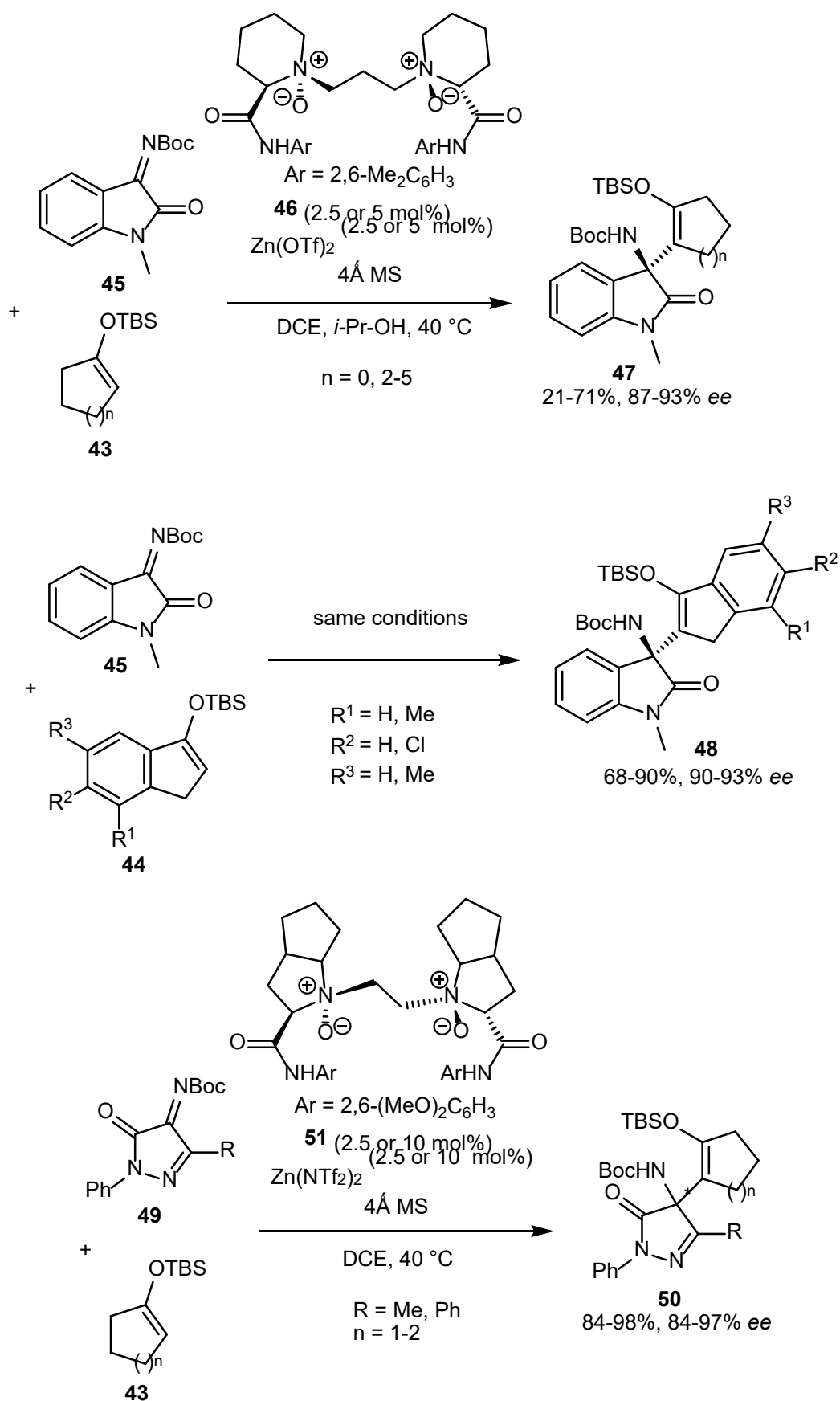
$\text{R} = \text{H}, 5\text{-Me}, 5\text{-MeO}, 5\text{-F}, 5\text{-Cl}, 5\text{-Br}, 6\text{-Br}$
 $\text{Ar}^2 = \text{Ph}, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-Tol}, m\text{-ClC}_6\text{H}_4,$
 $m\text{-BrC}_6\text{H}_4, o\text{-MeOC}_6\text{H}_4, m\text{-Tol}, 2\text{-Naph}, 2\text{-thienyl}, 2,5\text{-(MeO)}_2\text{C}_6\text{H}_3$

mechanism:



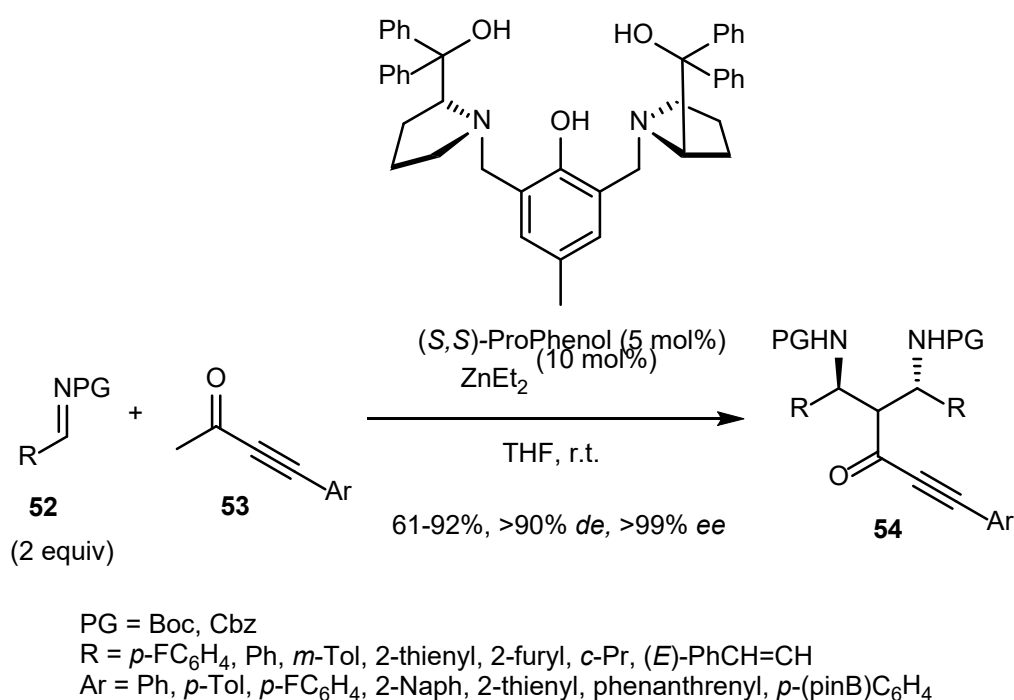
Scheme 11. Three-component domino Knoevenagel/Michael/cyclization reaction of isatins, malononitrile and α -hydroxy acetophenones.

Chiral N,N' -dioxide ligands developed by Feng et al. have been widely employed as remarkable ligands in asymmetric catalysis so far.^[18] In 2019, this type of ligands was applied to develop the first catalytic enantioselective domino α -alkenyl addition/proton shift reactions between silyl enol ethers and cyclic ketimines, such as isatin- and pyrazolinone-derived ketimines (Scheme 12).^[19] Indeed, silyl enol ethers **43** and **44** reacted at 40 °C with isatin-derived ketimine **45** in the presence of 2.5-5 mol% of a chiral zinc catalyst *in situ* generated from $Zn(OTf)_2$ and chiral N,N' -dioxide ligand **46** to give the corresponding β -amino silyl enol ethers **47** and **48**, respectively, in high enantioselectivities (87-93% *ee*) and low to high yields (21-90%). The scope of this methodology was extended to the reaction of pyrazolinone-derived ketimines **49** with silyl enol ethers **43**. In this case, the best results were achieved by using a closely related N,N' -dioxide ligand **51** in combination with $Zn(NTf_2)_2$. Under these conditions, a series of other chiral β -amino silyl enol ethers **50** were synthesized with both high yields (84-98%) and enantioselectivities (84-97% *ee*), as presented in Scheme 12.



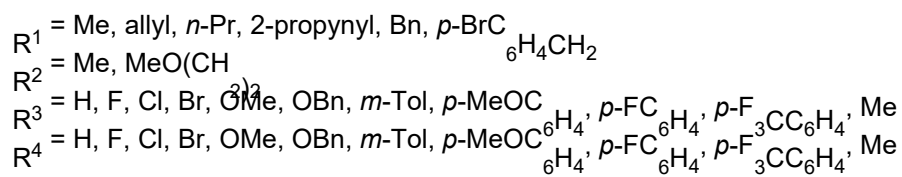
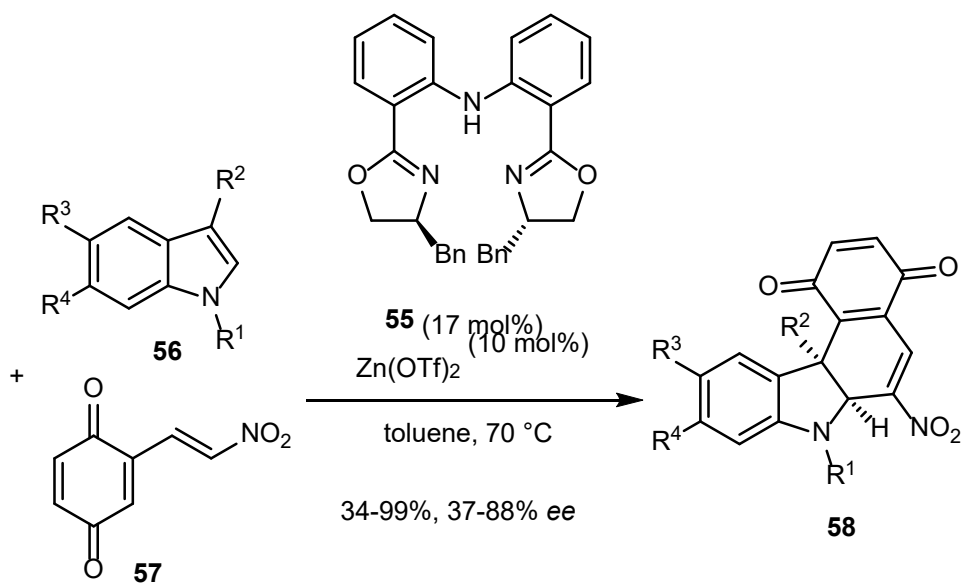
Scheme 12. Domino α -alkenyl addition/proton shift reactions of silyl enol ethers with isatin- and pyrazolinone-derived ketimines.

In 2020, Trost and Gnanamani reported an enantioselective pseudo-three-component reaction of two equivalents of *N*-protected aldimines **52** with ynones **53** catalyzed at room temperature by a combination of 5 mol% of (*S,S*)-ProPhenol with 10 mol% of ZnEt₂ in THF as solvent (Scheme 13).^[20] This domino double Mannich reaction allowed enantio- and diastereopure 1,3-diamines **54** (>99% *ee*, >90% *de*) to be synthesized in good to high yields (61-92%). In addition to a range of (hetero)aromatic aldimines which all delivered the domino products as single stereoisomers, nonaromatic aldimines, such as cyclopropyl imine (R = *c*-Pr), underwent the double Mannich reaction with 78% yield and remarkable enantio- and diastereoselectivities (>90% *de*, >99% *ee*). Various (hetero)aromatic ynones were also compatible to the catalyst system.

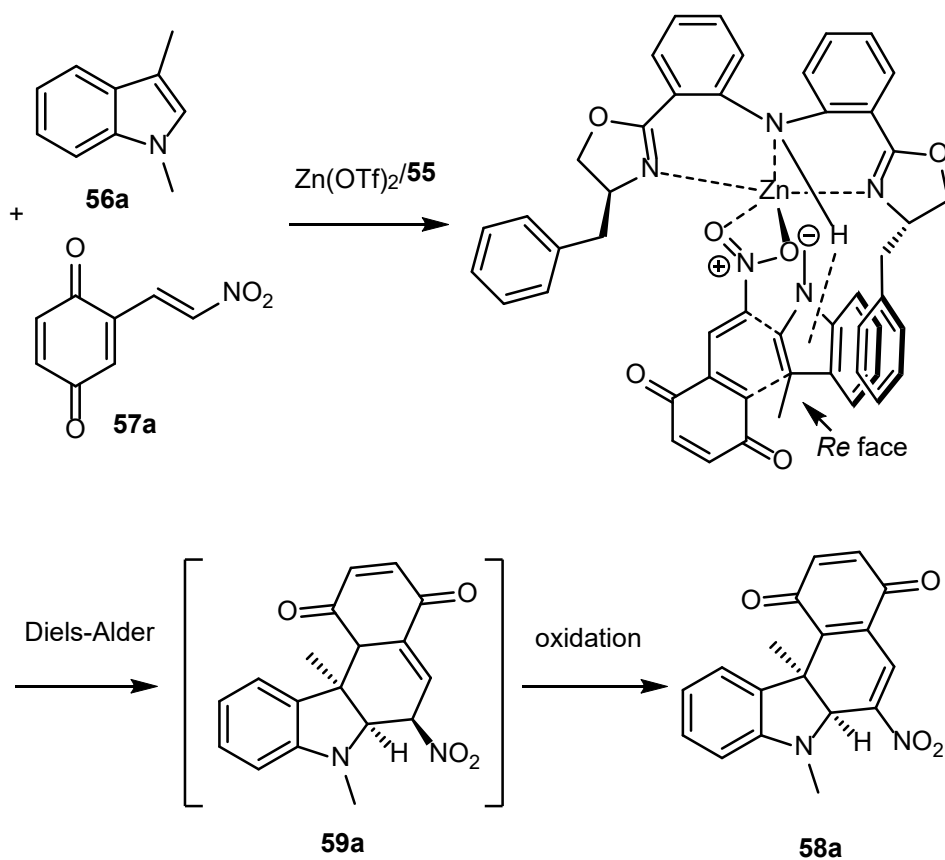


Scheme 13. Pseudo-three-component domino double Mannich reaction of ynones with aldimines.

In the same year, Zhang et al. disclosed the use of a combination of 17 mol% of chiral bisoxazoline **55** combined with 10 mol% of Zn(OTf)₂ to promote enantioselective domino inverse-electron-demand Diels–Alder/oxidation reaction between indoles **56** with 2-(2-nitrovinyl)-1,4-benzoquinone **57** (Scheme 14).^[21] Performed at 70 °C in toluene as solvent, the reaction afforded the corresponding chiral six-membered [2,3]-fused indolines **58** as single diastereomers in both moderate to quantitative yields (34-99%) and enantioselectivities (37-88% *ee*). The cycloaddition underwent through the *Re* face of the 2-(2-nitrovinyl)-1,4-benzoquinone activated by the chiral zinc catalyst which was also *N*-chelated to the indole substrate through NH– π interaction to give Diels–Alder cycloadduct **59**. The latter was unstable and subsequently underwent an oxidation to give final product **58**.

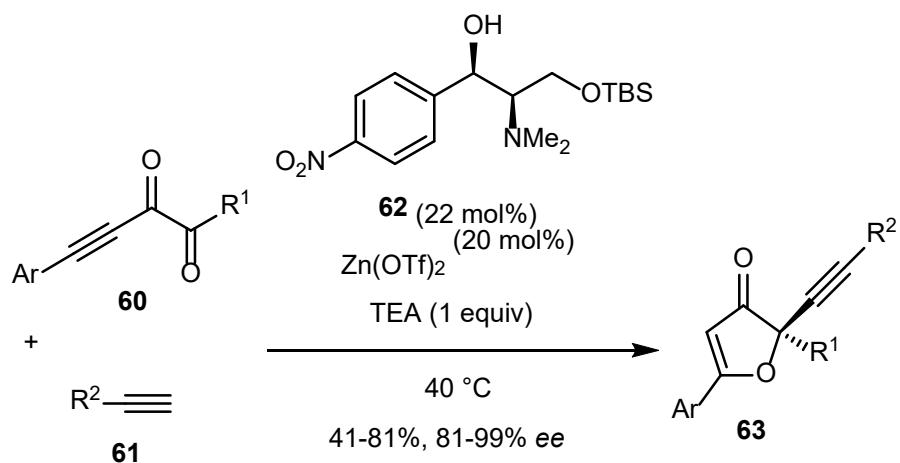


mechanism (with $\text{R}^1 = \text{R}^2 = \text{Me, R}_3 = \text{R}_4 = \text{H}$):



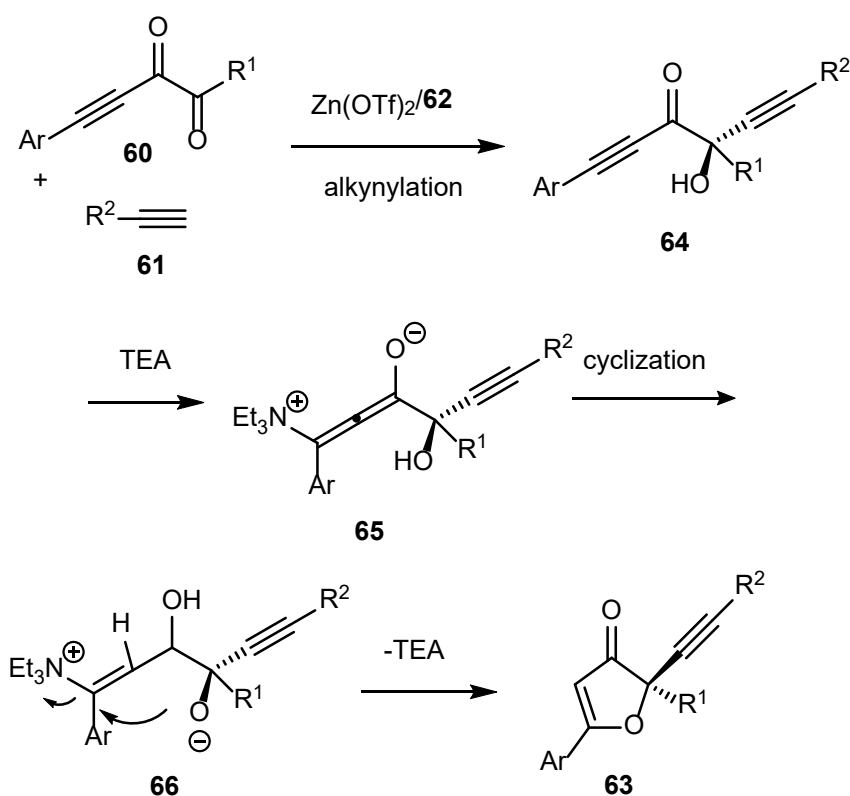
Scheme 14. Domino inverse-electron-demand Diels–Alder/oxidation reaction of indoles with 2-(2-nitrovinyl)-1,4-benzoquinone.

In 2020, an enantioselective domino alkynylation/cyclization reaction between alkynyl 1,2-diketones **60** and alkynes **61** was developed by Fang and Ding, using a chiral zinc catalyst *in situ* generated from 20 mol% of Zn(OTf)₂ and 22 mol% of chiral amino alcohol ligand **62** (Scheme 15).^[22] This process, performed at 40 °C in the presence of TEA as base, resulted in the formation of biologically important chiral 3(2*H*)-furanones **63** in high enantioselectivities (81-99% *ee*) combined with moderate to good yields (41-81%). It evolved through a nucleophilic addition of TEA to the alkyne unit of the alkynylation product **64** to give allenic intermediate **65**. Then, the latter underwent a proton transfer to provide intermediate **66** which cyclized into final domino product **63**, as illustrated in Scheme 15.



$\text{R}^1 = \text{Ph}, p\text{-ClC}_6\text{H}_4, 1\text{-Naph}, 2\text{-thienyl}, (E)\text{-PhCH=CH}, p\text{-MeOC}_6\text{H}_4, p\text{-Tol}$
 $\text{R}^2 = p\text{-Tol}, \text{Ph}, 6\text{-FC}_6\text{H}_4, 1\text{-Naph}, 2\text{-thienyl}, (E)\text{-PhCH=CH}, p\text{-EtOC}_6\text{H}_4, 3\text{-thienyl},$
 $p\text{-MeOC}_6\text{H}_4, p\text{-EtC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, o\text{-FC}_6\text{H}_4$
 $\text{Ar} = \text{Ph}, p\text{-ClC}_6\text{H}_4, p\text{-EtC}_6\text{H}_4, 3\text{-thienyl}$

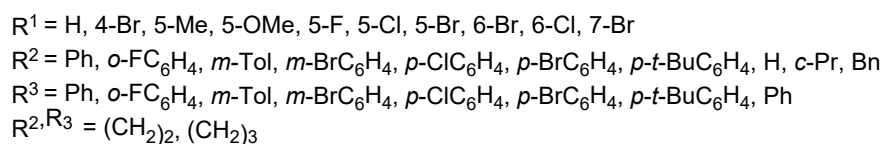
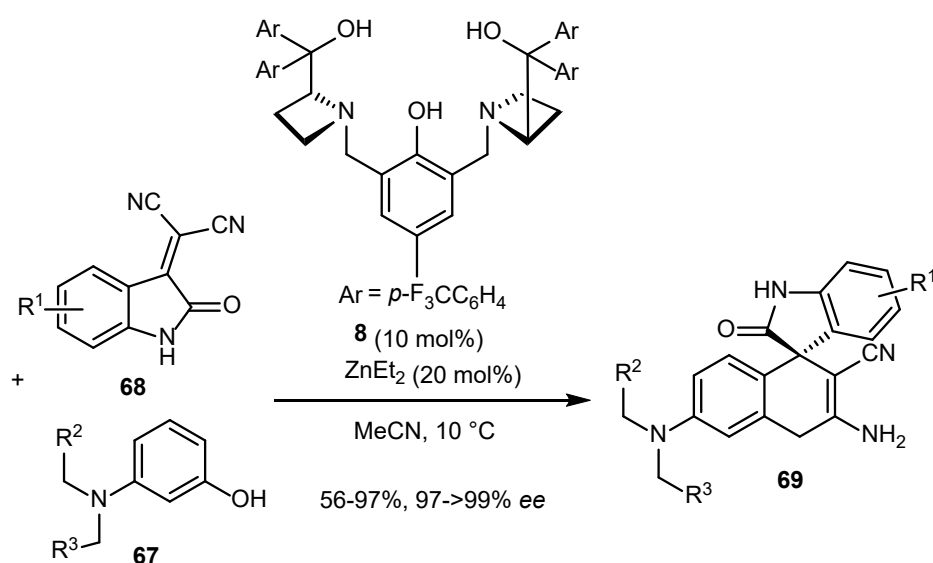
mechanism:



Scheme 15. Domino alkyne alkylation/cyclization reaction of alkynyl 1,2-diketones with alkynes.

In 2021, Wang, Hua and Jia disclosed an enantioselective domino Friedel–Crafts alkylation/cyclization reaction between 3-aminophenols **67** and isatylidene α,α -dicyanoolefins **68**

performed in the presence of a chiral zinc catalyst *in situ* generated from 20 mol% of ZnEt₂ and 10 mol% of chiral AzePhenol-derived ligand **8** in acetonitrile as solvent.^[23] The process afforded at 10 °C a range of chiral 2-amino-4H-chromenes **69** in good to quantitative yields (56-97%) and uniformly excellent enantioselectivities (97->99% *ee*), as presented in Scheme 16. The catalyst system tolerated the presence of different substituents on the phenyl ring of the α,α -dicyanoolefin. Especially, the nature of substituent at the 5-position of the aryl ring of isatylidene malononitrile was found to have little impact on the results (98->99% *ee*). Meanwhile, the reaction of malononitriles exhibiting substituents at either 6- or 7-position also provided excellent enantioselectivities (97-99% *ee*), albeit combined with lower yields (58-61%). Concerning the 3-aminophenol partner, the reaction of *N,N*-dibenzyl-substituted substrates led to the desired products with comparable very high *ee* values as well as differently unsymmetrically disubstituted 3-aminophenols (95-99% *ee*).



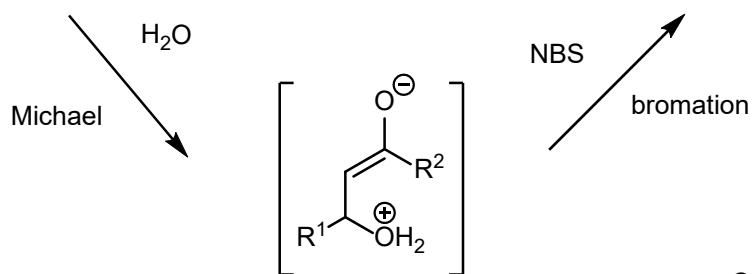
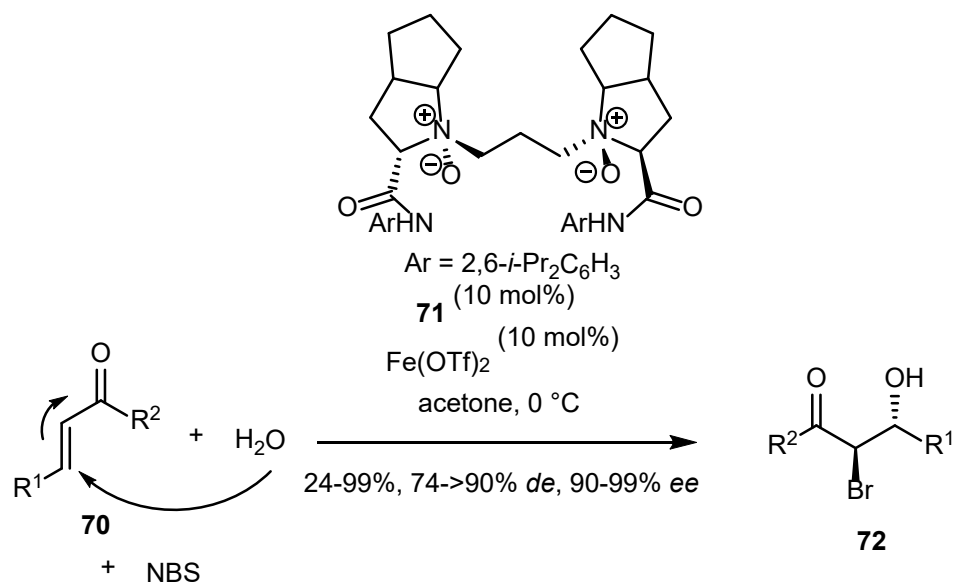
Scheme 16. Domino Friedel-Crafts/cyclization reaction of 3-aminophenols with isatylidene α,α -dicyanoolefins.

3 Enantioselective Iron-Catalyzed Domino Reactions

3.1 Three-Component Domino Reactions

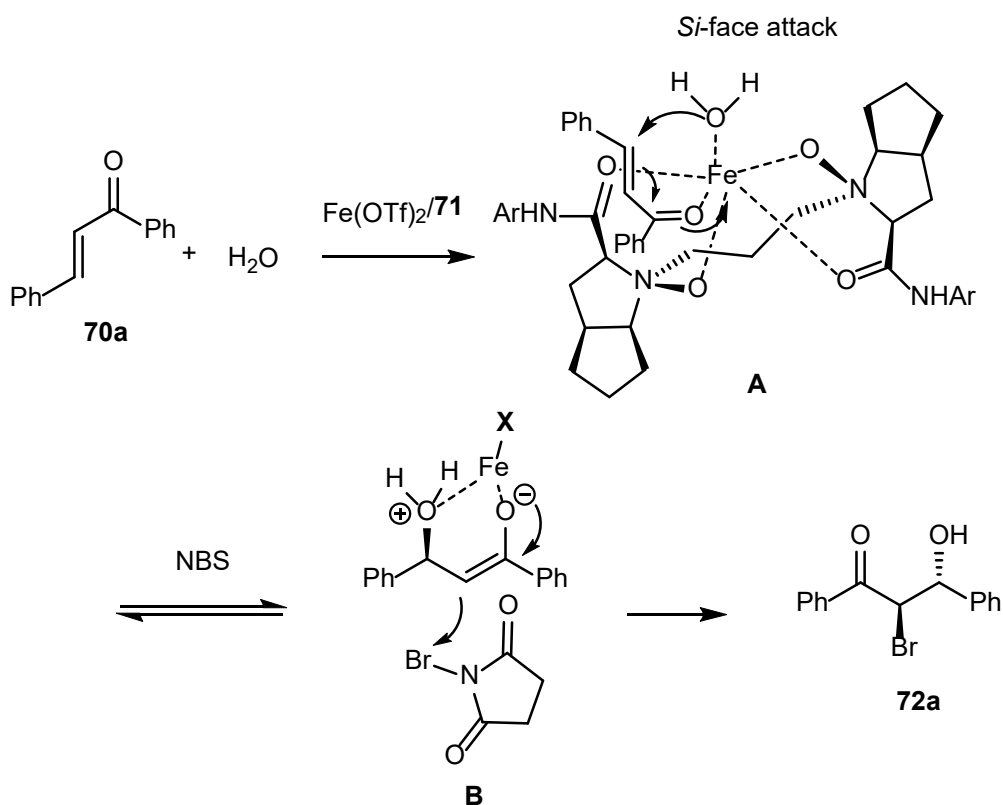
In comparison with traditional metals, such as palladium, rhodium, ruthenium, iridium among others, iron presents the advantages to be less toxic, cheaper and more abundant. Moreover, due to the various accessible oxidation states of iron, its chemistry is rich.^[24] Consequently, the use of chiral iron complexes has allowed a wide diversity of greener asymmetric transformations to be achieved, leading to many types of chiral cyclic as well as acyclic products.^[25] However, the development of enantioselective domino reactions catalyzed by chiral iron complexes is recent. In an example reported in 2020, Feng and Lin disclosed an enantioselective domino Michael/ α -bromination reaction between

α,β -unsaturated ketones **70**, water and *N*-bromosuccinimide (NBS) as the brominating agent (Scheme 17).^[26] This asymmetric three-component bromohydroxylation reaction employed water as the nucleophile and NBS as the electrophilic trapping agent. It was promoted at 0 °C in acetone as the solvent by 10 mol% of a chiral iron catalyst *in situ* generated from Fe(OTf)₂ and chiral *N,N'*-dioxide ligand **71**. Various substituted α,β -unsaturated ketones **70** reacted smoothly to give the corresponding chiral α -bromo- β -hydroxy ketones **72** with variable yields (24-99%), combined with generally high diastereoselectivities (74->90% *de*) and homogeneously excellent enantioselectivities (90-99% *ee*). In most cases, the reaction of chalcones bearing *ortho*-substituted phenyl groups (R¹ or R²) provided both lower yields (24-70% vs 81-99%) and diastereoselectivities (74->90% *de* vs >90-92% *de*) than that of chalcones with *meta*- or *para*-substituted phenyl groups, which could be related to steric hindrance. Furthermore, alkyl-substituted substrates (R¹ = *i*-Pr, adamantyl; R² = *i*-Bu) were compatible, providing the desired products with both high diastereo- and enantioselectivities (88->90% *de* and 90-99% *ee*, respectively) combined with moderate to high yields (52-93%). In the mechanism depicted in Scheme 17, chiral ligand **71** coordinated to Fe(II) with its oxygen atoms through a tetradentate manner to form two six-membered chelate rings. Then, the α,β -unsaturated ketone and water coordinated to Fe(II) through their oxygen atoms to form transition state **A**. Since the β -*Re*-face was shielded by the nearby phenyl group of the *N,N'*-dioxide ligand, the water added to the β -*Si*-face of the carbon-carbon double bond reversibly, forming an enolate intermediate **B**. Then, Br⁺ generated from NBS added to enolate intermediate **B** from the opposite face to deliver the final product.



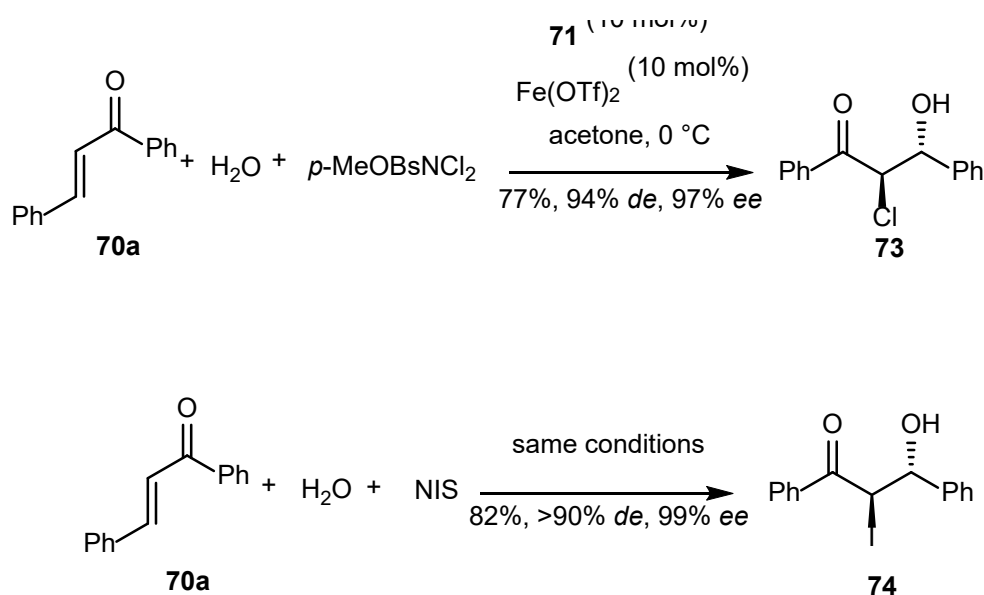
$\text{R}^1 = \text{Ph}, o\text{-Tol}, m\text{-Tol}, p\text{-Tol}, o\text{-ClC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, \text{3,4-MeO}_2\text{C}_6\text{H}_3, 1\text{-Naph}, 2\text{-Naph}, i\text{-Pr}, \text{adamantyl}, p\text{-ClC}_6\text{H}_4, p\text{-FC}_6\text{H}_4$
 $\text{R}^2 = \text{Ph}, o\text{-Tol}, m\text{-Tol}, 2\text{-Naph}, i\text{-Bu}$

proposed mechanism (with $\text{R}^1 = \text{R}^2 = \text{Ph}$):



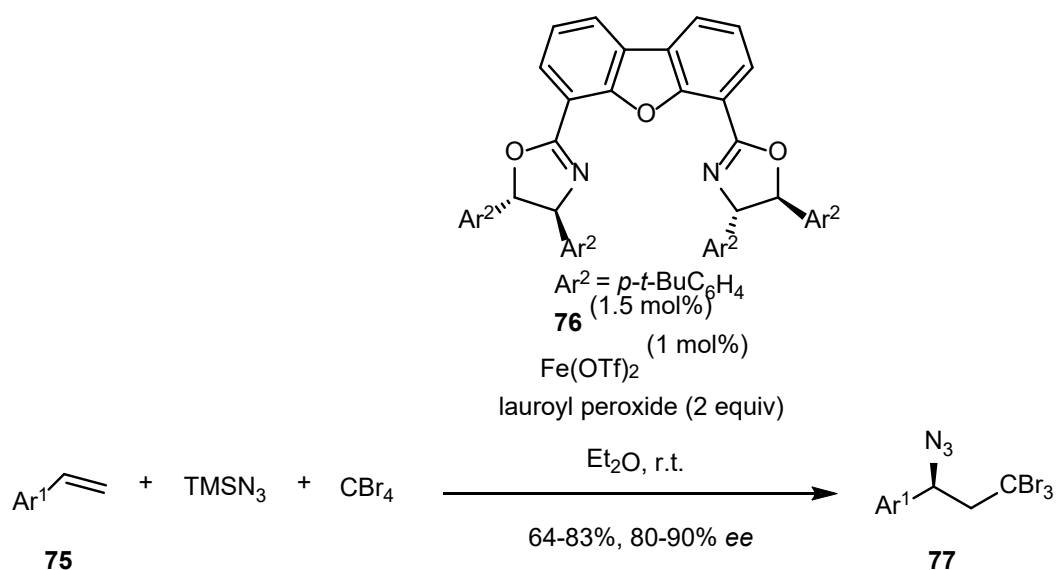
Scheme 17. Three-component domino Michael/ α -bromination reaction of α,β -unsaturated ketones with NBS and water.

The scope of the precedent methodology could be extended to other electrophilic halogenation agents.^[26] As shown in Scheme 18, the same catalytic system could be applied to develop analogous asymmetric chloro- and iodohydroxylation reactions. For example, the domino Michael/ α -chlorination reaction of chalcone **70a** with water and *p*-MeOBsNCl₂ (Bs = benzenesulfonyl) as the chloride source allowed the corresponding chiral chlorohydroxylated product **73** to be synthesized in 77% yield with both excellent diastereo- and enantioselectivities (94% *de* and 97% *ee*, respectively). In addition, chiral iodohydrin **74** could be obtained as almost single stereomer (>90% *de*, 99% *ee*) in 82% yield through the three-component domino Michael/ α -iodination of chalcone **70a**, water and *N*-iodosuccinimide (NIS) as the iodide source.



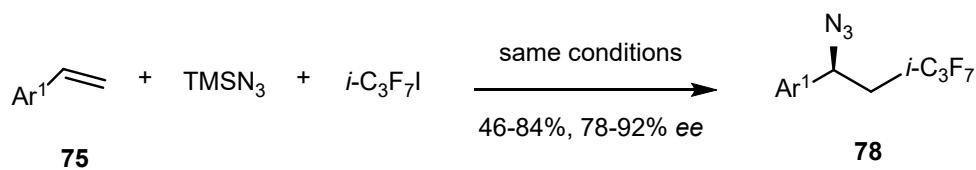
Scheme 18. Three-component domino Michael/ α -chlorination/iodination reactions of chalcone with other halogenating agents and water.

Later in 2021, Zhang and Bao described a rare example of radical asymmetric carboazidation of olefins, allowing a direct access to many chiral halogenated organoazides, which constitute precursors of many chiral nitrogen-containing molecules (Scheme 19).^[27] The reaction evolved at room temperature in diethylether as the solvent through a three-component process between styrenes **75**, TMSN₃ and alkyl halides such as CBr₄. A chiral iron catalyst *in situ* generated from only 1 mol% of Fe(OTf)₂ and 1.5 mol% of chiral bisoxazoline ligand **76** was used to promote the reaction in the presence of lauryloyl peroxide as a radical initiator. The domino radical addition/azidation reaction resulted in the formation of a wide range of chiral brominated organoazides **77** in high enantioselectivities (80-90% *ee*) and good yields (64-83%). Styrenes with either electron-donating or electron-withdrawing groups on the phenyl ring were compatible. The scope of the reaction was extended to other alkyl halides, such as *i*-C₃F₇I, which provided by reaction with styrenes and TMSN₃, the corresponding chiral fluorinated products **78** with moderate to good yields (46-84%) and high *ee* values (78-92% *ee*). Other commercially available carbon sources, such as fluoroalkyl bromides or iodides **79**, were also tolerated, affording the desired chiral products **80** with both moderate to high yields (37-87%) and enantioselectivities (52-94% *ee*). A synthetic utility of this novel methodology was demonstrated in a total synthesis of the anti-HIV drug maraviroc.

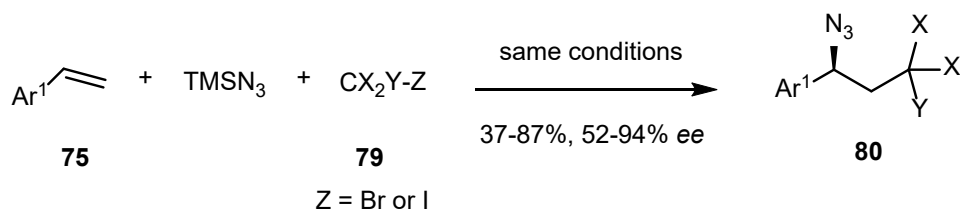


$\text{Ar}^2 = p\text{-}t\text{-BuC}_6\text{H}_4$
76 (1.5 mol%)
 Fe(OTf)₂ (1 mol%)
 lauroyl peroxide (2 equiv)

$\text{Ar}^1 = 2\text{-Naph, } m\text{-Tol, } m\text{-FC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, m\text{-F}_2\text{CH, } p\text{-Tol, } p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, 4\text{-F-3-MeC}_6\text{H}_3, 3\text{-Cl-4-FC}_6\text{H}_3, 3\text{-F}_3\text{C-4-FC}_6\text{H}_3, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, 4\text{-Me-3-O}_2\text{NC}_6\text{H}_3, 3,5\text{-Me}_2\text{C}_6\text{H}_3, 3,5\text{-Br}_2\text{C}_6\text{H}_3$



$\text{Ar}^1 = 2\text{-Naph, Ph, } m\text{-Tol, } m\text{-FC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, p\text{-Tol, } p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-(ClCH}_2\text{)}_2\text{C}_6\text{H}_4, 3,4\text{-Me}_2\text{C}_6\text{H}_3, 4\text{-F-3-MeC}_6\text{H}_3, 4\text{-F-3-ClC}_6\text{H}_3, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, 3,5\text{-F}_2\text{C}_6\text{H}_3, p\text{-O}_2\text{NC}_6\text{H}_4$

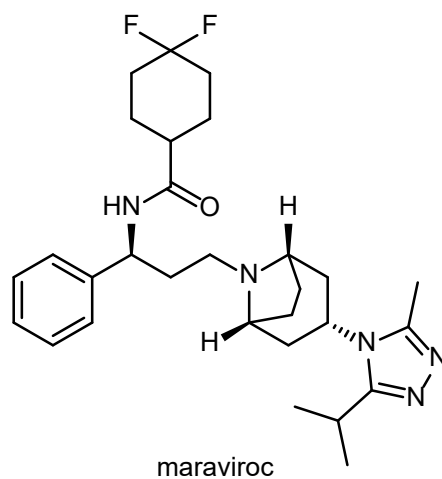
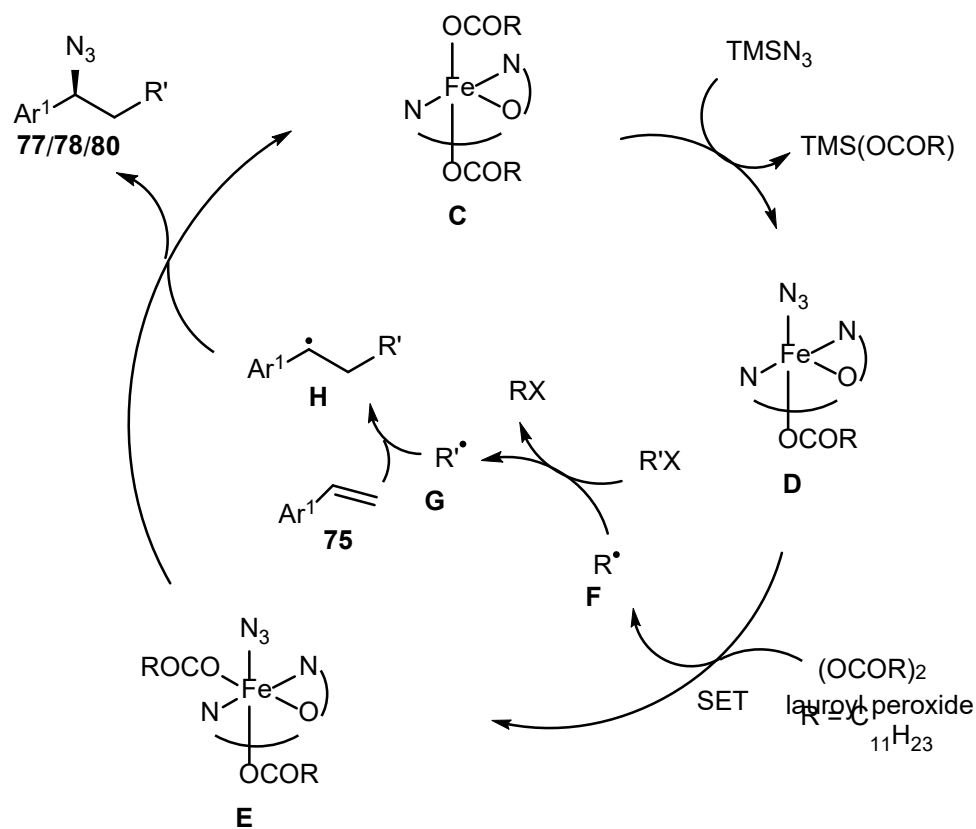


$\text{X} = \text{I, Br, Cl, F, CO}_2\text{Et, H, Br, EtO}$
 $\text{Y} = \text{H, Cl, HOCH}_2, \text{C}_2\text{CF}_2, \text{F}_3\text{CCF}_2, \text{F}_3\text{CCH}_2, \text{CF}_3, \text{PhSO}_2\text{CF}_2, \text{Cy, } \text{C}_6\text{F}_{11}, t\text{-Bu, FSO}_2(\text{CF}_2)_2\text{O}(\text{CF}_2)_2, n\text{-C}_3\text{F}_7$
 $\text{Ar}^1 = m\text{-ClC}_6\text{H}_4, 2\text{-Naph, } m\text{-FC}_6\text{H}_4$

Scheme 19. Three-component domino carboazidation reactions of styrenes, TMSN₃ and alkyl halides.

A possible mechanism based on a carbon radical addition to the double bond of styrenes followed by an iron-catalyzed azido group transfer is depicted in Scheme 20.^[27] In the catalytic cycle, initial active catalyst **C** underwent ligand exchange with TMSN₃ to give iron intermediate **D**. The latter was then oxidized by lauroyl peroxide via a single electron transfer (SET) to provide iron azide species **E**. Alkyl radical **F** could abstract iodine atom from starting fluoroalkyl iodide to form the corresponding fluoroalkyl radical **G**, which then added to the styrene to form benzylic radical **H**. Subsequently, **H** reacted with **E** to afford the final product.

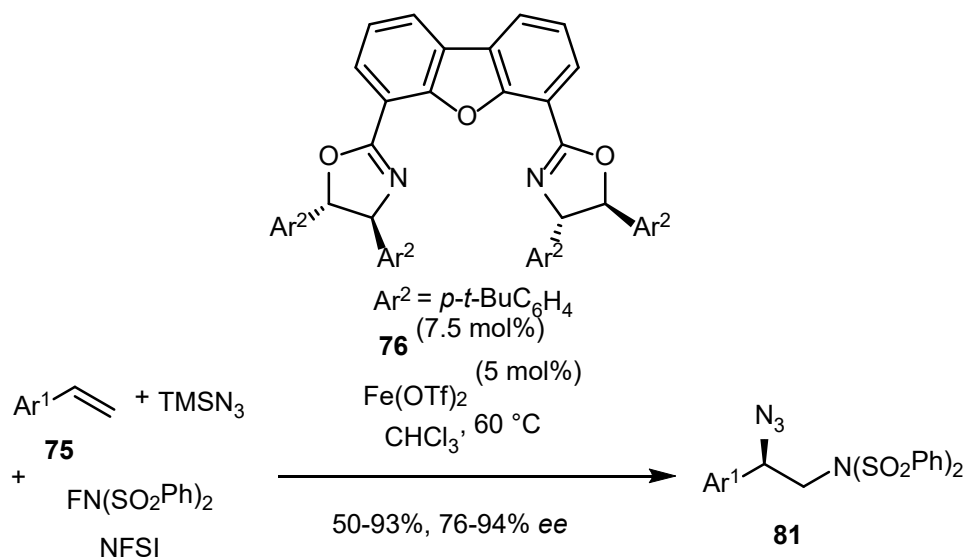
proposed mechanism (with R'X = CBr₄, *i*-C₃F₇I or CX₂Y-Z):



Scheme 20. Mechanism for three-component domino carboazidation reactions of styrenes, TMSN₃ and alkyl halides.

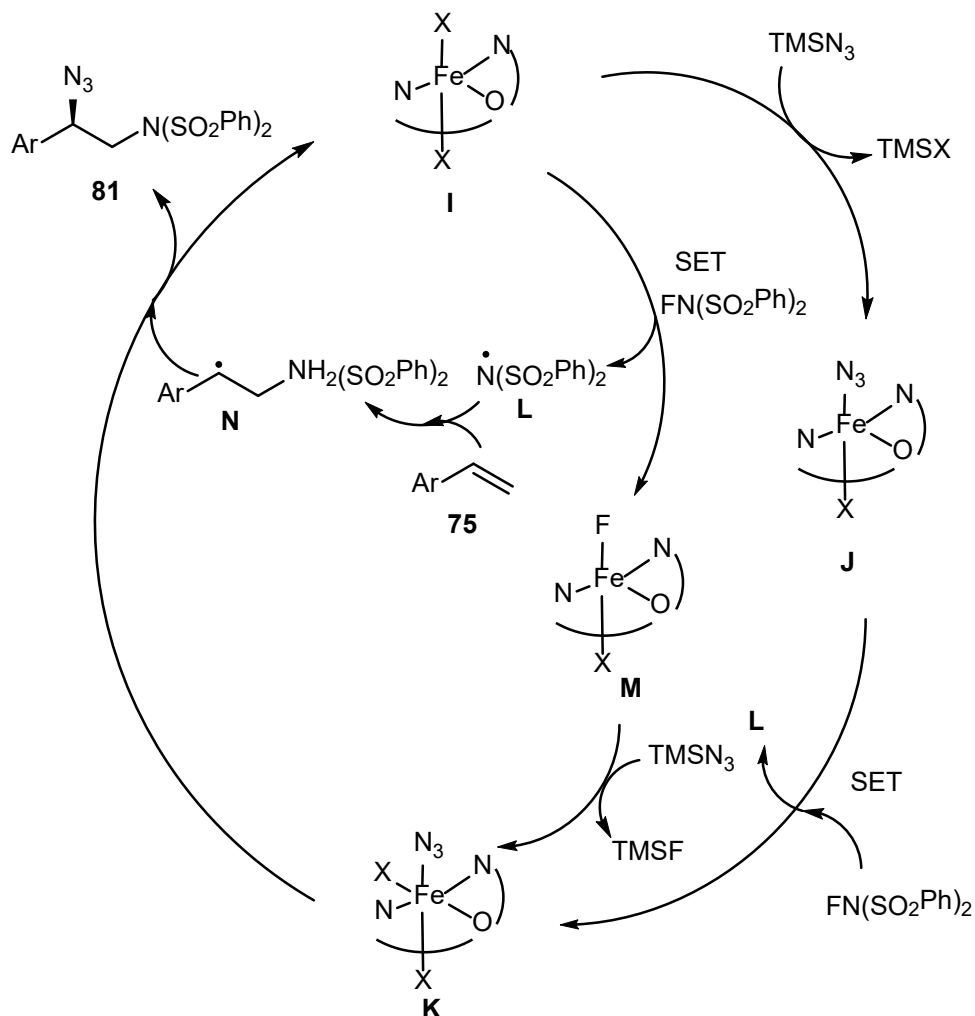
The first enantioselective radical aminoazidation of styrenes was developed by Bao et al., in 2021 (Scheme 21).^[28] In the presence of a chiral iron catalyst *in situ* generated from 5 mol% of Fe(OTf)₂ and 7.5 mol% of chiral bisoxazoline ligand **76**, styrenes **75** reacted at 60 °C with trimethylsilyl azide

(TMSN₃) as the N₃ source and *N*-fluorobenzenesulfonimide (NFSI) as the *N*-radical precursor in chloroform as solvent to give the corresponding chiral aminoazides **81** in moderate to high yields (50-93%) and good to high enantioselectivities (76-94% *ee*). These numerous products constitute potent starting materials to synthesize many useful chiral nitrogen-containing compounds. The scope of the process was found wide since a range of styrenes exhibiting one or more either electron-donating or electron-withdrawing substituents on the phenyl ring were tolerated, leading to the desired products with good yields (50-93%) and enantioselectivities (78-94% *ee*). Moreover, when vinyl and allyl/alkynyl groups (Ar¹ = allyl, acetylenyl) were present in the same molecule, the aminoazidation occurred selectively at the vinyl group to give the products with good yields (68-80%) and high *ee* values (78-80% *ee*). The lowest enantioselectivity (76% *ee*) was observed in the reaction of 2-vinylbenzo[b]thiophene. A possible mechanism depicted in Scheme 21 shows that the process began with the coordination of the iron catalyst to the ligand to give iron(II) complex **I**, which underwent ligand exchange with TMSN₃ to afford iron(II) azide complex **J**. Then, a single electron transfer (SET) process between NFSI and **J** resulted in the formation of iron(III) azide species **K** and bis-sulfonylamidyl radical **L**. Alternatively, the SET process could proceed prior to the ligand exchange with TMSN₃. Complex **I** participated in a SET with NFSI to afford oxidized iron species **L** and radical **L** and **M** reacted with TMSN₃ to generate iron(III) azide species **K**. Addition of bis-sulfonylamidyl radical **L** to the styrene afforded benzyl radical **N**, which could further participate in a group transfer mechanism with species **K** to finally deliver the product along with regenerated active catalyst species **I**.



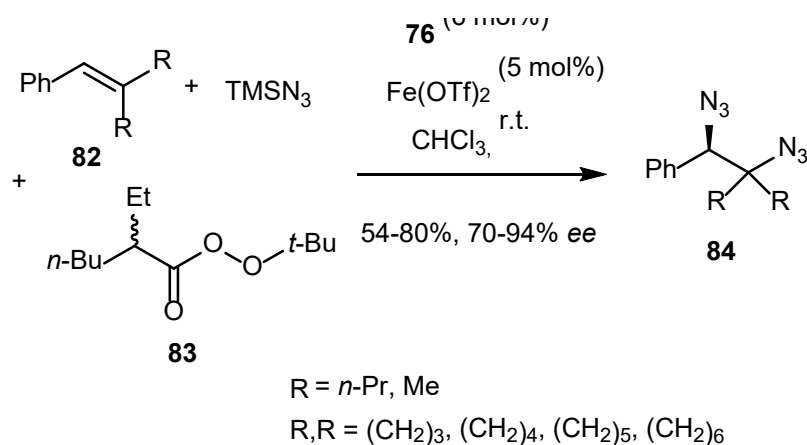
$\text{Ar}^1 = m\text{-MeOC}_6\text{H}_4$, $m\text{-Tol}$, $m\text{-}i\text{-PrC}_6\text{H}_4$, $m\text{-OctC}_6\text{H}_4$, $m\text{-FC}_6\text{H}_4$, $m\text{-BrC}_6\text{H}_4$,
 $m\text{-F}_2\text{HCC}_6\text{H}_4$, $m\text{-F}_3\text{CC}_6\text{H}_4$, $3\text{-Cl-4-MeC}_6\text{H}_3$, $3\text{-Me-4-FC}_6\text{H}_3$, $3,4\text{-F}_2\text{C}_6\text{H}_3$,
 $3\text{-Cl-4-FC}_6\text{H}_3$, $3,4\text{-Cl}_2\text{C}_6\text{H}_3$, $3\text{-Me-4-BrC}_6\text{H}_3$, $3\text{-Br-4-FC}_6\text{H}_3$, $p\text{-FC}_6\text{H}_4$,
 $p\text{-ClC}_6\text{H}_4$, $p\text{-ClCH}_2\text{C}_6\text{H}_4$, $p\text{-F}_3\text{CC}_6\text{H}_4$, 3-Me-5-OMe , $3,5\text{-Me}_2\text{C}_6\text{H}_3$,
 $3,5\text{-F}_2\text{C}_6\text{H}_3$, $3,5\text{-Br}_2\text{C}_6\text{H}_3$, $3\text{-F-5-BrC}_6\text{H}_3$, $3,5\text{-(F}_3\text{C)}_2\text{C}_6\text{H}_3$, $3\text{-F-4-(allyl)C}_6\text{H}_3$,
 $3\text{-Cl-4-(HC}\equiv\text{C)C}_6\text{H}_3$

proposed mechanism:



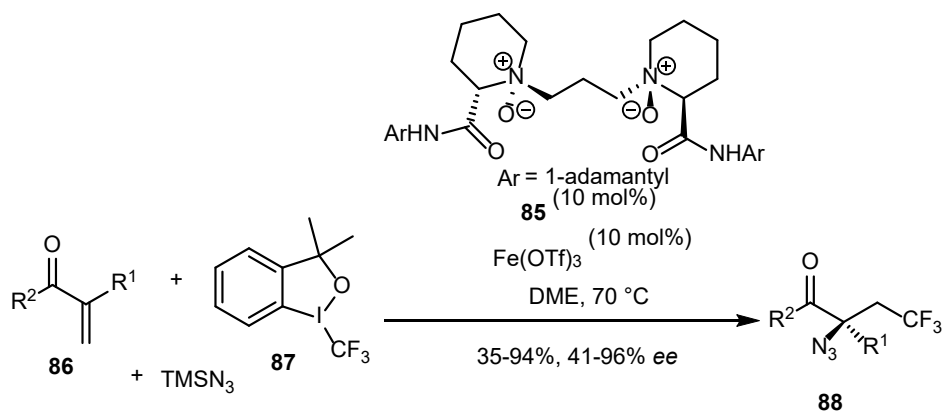
Scheme 21. Three-component aminoazidation of styrenes with TMSN₃ and NFSI.

The same group also described the first enantioselective diazidation of styrenes **82** through three-component reaction with TMSN₃ and alkyl perester **83** (Scheme 22).^[28] The process was promoted at room temperature in chloroform as the solvent by the same quantity (5 mol%) of precatalyst Fe(OTf)₂ combined with 6 mol% of chiral ligand **76**. Trisubstituted styrenes **82** led to the corresponding otherwise inaccessible chiral diazides **84** in moderate to good yields (54-80%) and moderate to high enantioselectivities (70-94% *ee*).



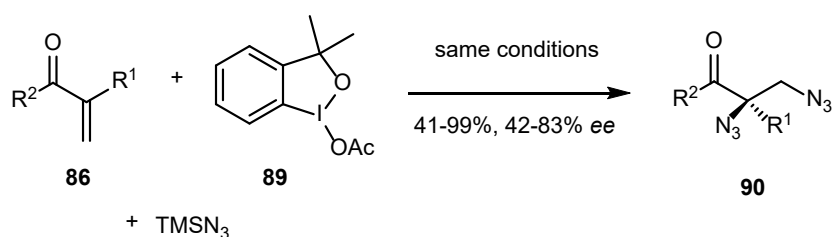
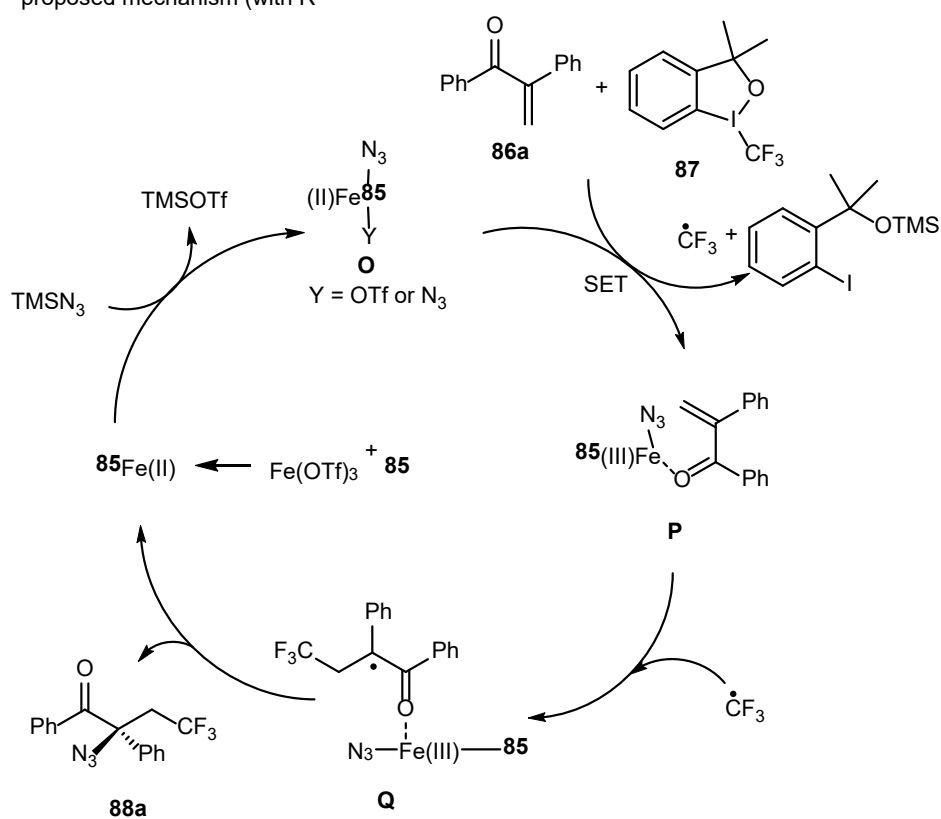
Scheme 22. Three-component diazidation of styrenes with TMSN₃ and an alkyl perester.

An enantioselective iron-catalyzed three-component radical carboazidation of α,β -unsaturated ketones was developed in 2021 by Feng, Liu and Wu (Scheme 23).^[29] Promoted at 70 °C in DME as the solvent by 10 mol% of a chiral iron catalyst *in situ* generated from Fe(OTf)₂ and chiral *N,N'*-dioxide ligand **85**, a range of substituted α,β -unsaturated ketones **86** reacted with radical precursor **87** and TMSN₃ as the azide source to deliver the corresponding chiral α -azido carbonyl derivatives **88** in both moderate to high yields (35-94%) and enantioselectivities (41-96% *ee*). A plausible mechanism is depicted in Scheme 23, beginning with the formation of iron species **O** from the chiral catalyst and TMSN₃. Then, the radical precursor **87** oxidized **O** via a single-electron transfer (SET) process to generate iron intermediate **P** and CF₃ radical. Subsequently, the latter added to catalyst-bonded enone species **P** to provide a trisubstituted radical species which coordinated to the metal center in **Q**. Finally, intermediate **Q** underwent azido group transfer to give the product along with regenerated catalyst. In a second time, the authors applied the same conditions to disclose enantioselective radical diazidation of substituted α,β -unsaturated ketones **86** through reaction with TMSN₃ as azide source and benziodoxole **89** as oxidant, affording the corresponding chiral diazides **90** with both moderate to high yields (41-99%) and enantioselectivities (42-83% *ee*), as illustrated in Scheme 23.



$\text{R}^1 = \text{Ph, } p\text{-MeOC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, o\text{-MeOC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, m\text{-F}_3\text{CC}_6\text{H}_4, m\text{-Tol, } p\text{-Tol}$
 $m\text{-MeOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-IC}_6\text{H}_4, p\text{-MeSC}_6\text{H}_4, 3\text{-F-4-MeOC}_6\text{H}_3,$
 $3,4\text{-Cl}_2\text{C}_6\text{H}_3, 2\text{-Naph, 1-Naph, } \text{C}_6\text{H}_4\text{ (1,2,3,4,5,6), } \text{C}_6\text{H}_4\text{ (1,2,3,4,5,6)}$
 $\text{R}^2 = \text{Ph, } m\text{-ClC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-Tol, } p\text{-MeOC}_6\text{H}_4, 2\text{-thienyl, PhNH}$

proposed mechanism (with $\text{R}^1 = \text{R}^2 = \text{Ph}$):

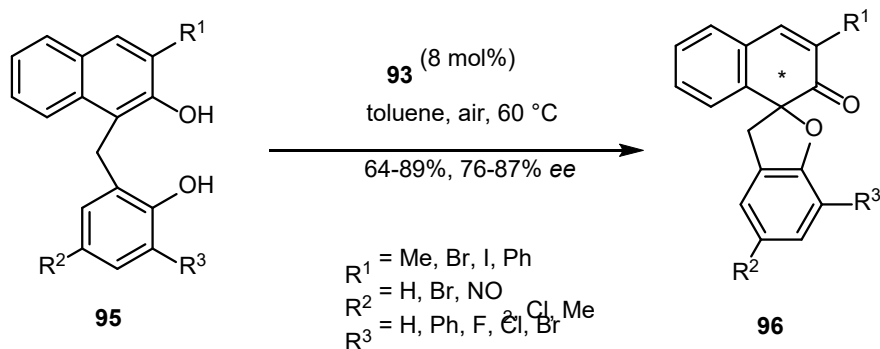
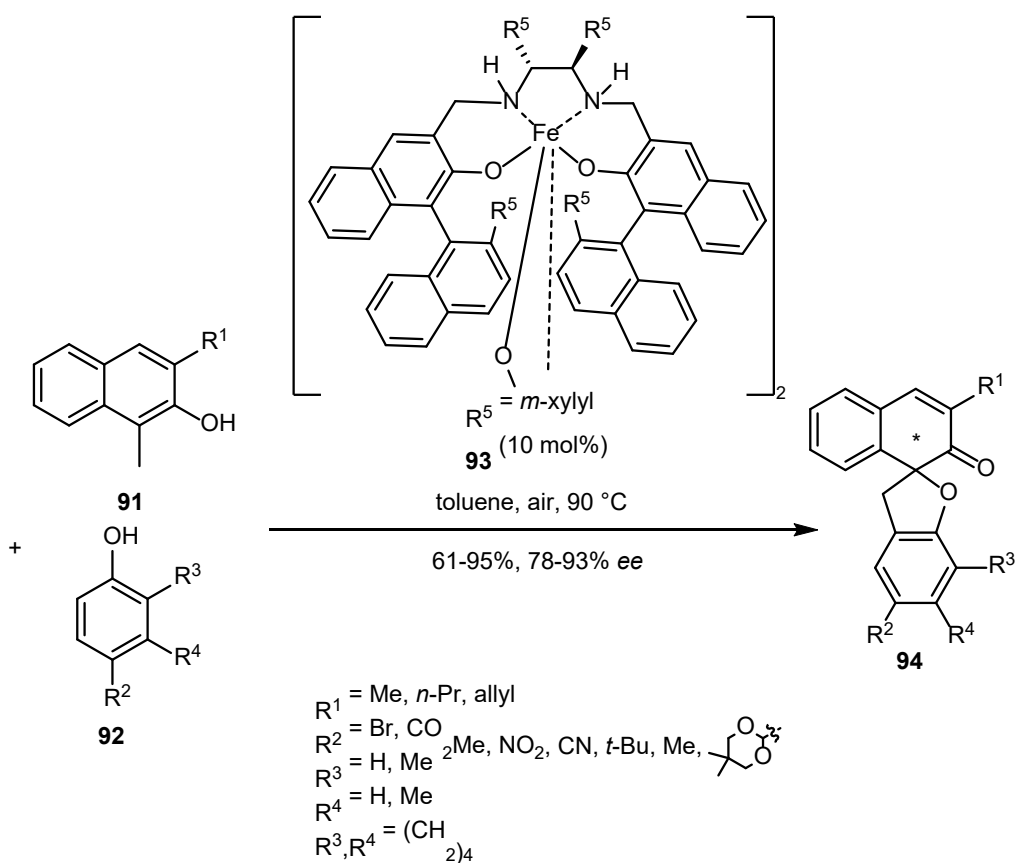


$\text{R}^1 = \text{Ph, } o\text{-FC}_6\text{H}_4, o\text{-MeOC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-Tol, } p\text{-MeSC}_6\text{H}_4,$
 $p\text{-HOC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, 3\text{-F-4-MeOC}_6\text{H}_3, 2\text{-Naph, } \text{C}_6\text{H}_4\text{ (1,2,3,4,5,6), } \text{C}_6\text{H}_4\text{ (1,2,3,4,5,6)}$
 $\text{R}^2 = \text{Ph, PhNH}$

Scheme 23. Three-component radical carboazidation/diaazidation reactions of α,β -unsaturated ketones with radical precursors and TMSN_3 .

3.2 One- and Two-Component Domino Reactions

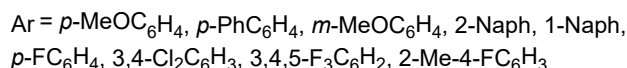
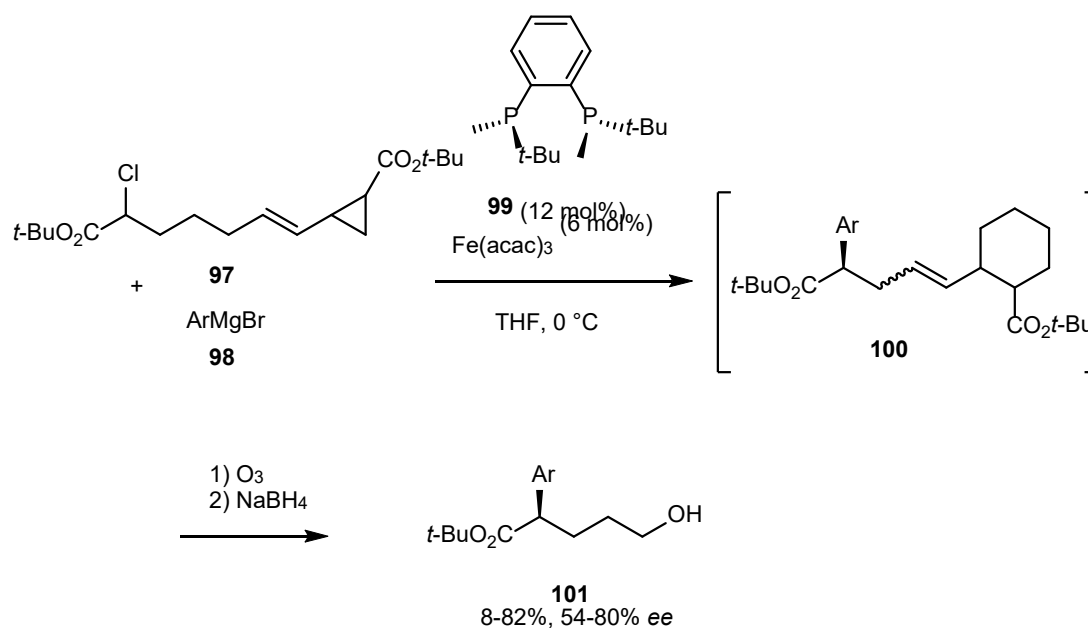
In 2020, Uchida et al. disclosed a chemo- and enantioselective oxidative dearomative spirocyclization of 1-methyl-2-naphthols **91** with phenols **92** as the nucleophiles performed at 90 °C in the presence of O_2 as the hydrogen acceptor and 10 mol% of chiral preformed iron catalyst **93** (Scheme 24).^[30] The domino process was carried out in toluene as the solvent, resulting in the formation of chiral spirocyclic ketones **94** with good to high enantioselectivities (78-93% *ee*) and moderate to high yields (61-95%). Moreover, an intramolecular version of this methodology was achieved by using only 8 mol% of the same catalyst at 60 °C. Indeed, the intramolecular domino dearomatization/spirocyclization reaction of methylenebis(arenols) **95** regioselectively provided the desired chiral spirocyclic ketones **96** with both good enantioselectivities (76-87% *ee*) and yields (64-89%).



Scheme 24. Intermolecular and intramolecular domino dearomatization/spirocyclization reactions of 2-naphthols.

In the same year, another type of enantioselective iron-catalyzed radical domino reaction was reported by Gutierrez et al., dealing with a cyclization/cross-coupling cascade reaction of vinylcyclopropanes **97** exhibiting an α -chloroester group with aryl Grignard reagents **98** (Scheme 25).^[31] The process was catalyzed at 0 °C in THF as solvent by a chiral iron complex *in situ* generated from 6 mol% of $\text{Fe}(\text{acac})_3$ and 12 mol% of chiral bisphosphine ligand **99**. The reaction produced a mixture of diastereomeric 5-exo-trig domino radical cyclization/cross-coupling products *trans*- and *cis*-**100**, which were subsequently submitted to ozonolysis followed by NaBH_4 reduction to give chiral alcohols **101** in variable yields (8-82%) and moderate to high enantioselectivities (54-80% *ee*). Various substituted aryl Grignard reagents with either electron-donating or electron-withdrawing groups were

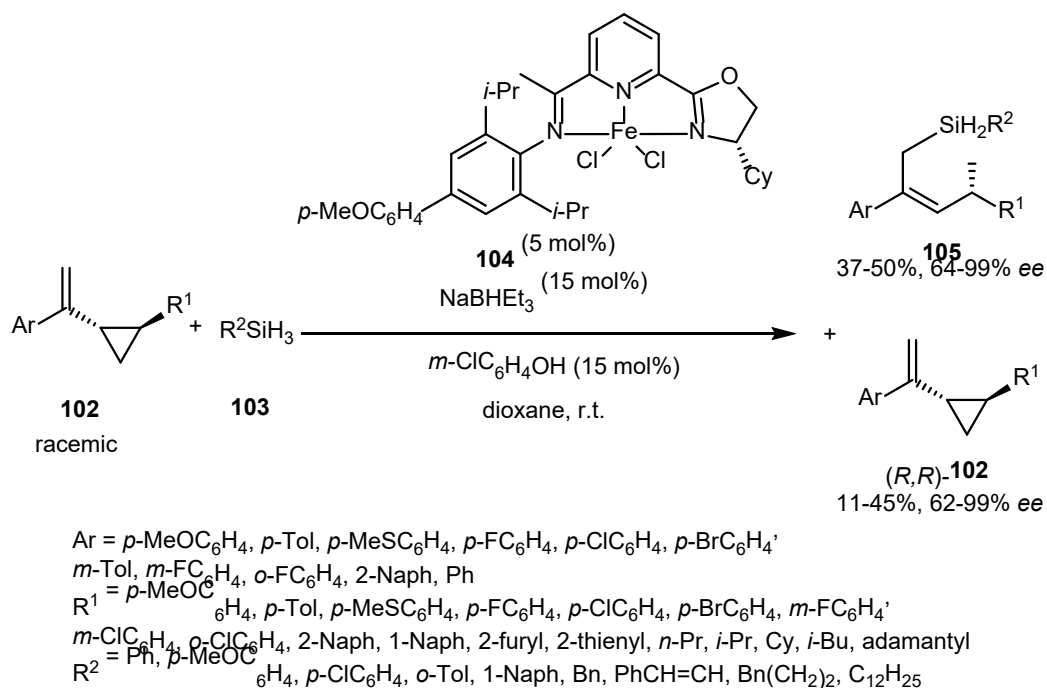
compatible. It was found that a substrate exhibiting one more methylene group between the α -chloroester and vinyl cyclopropane moieties did not undergo the corresponding 6-exo-trig radical cyclization, related to a higher energy barrier to be crossed over in comparison with the 5-exo-trig process.



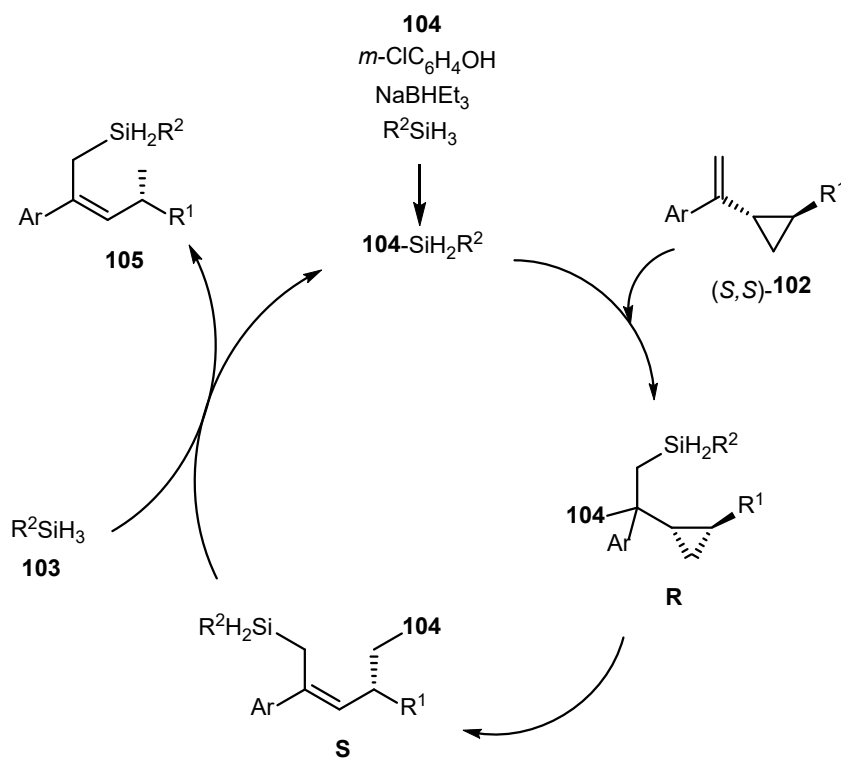
Scheme 25. Domino radical cyclization/cross-coupling reaction of vinylcyclopropanes with aryl Grignard reagents followed by ozonolysis and reduction.

Later in 2021, Lu and Hong reported an enantioselective iron-catalyzed domino silylation/ring-opening reaction of vinylcyclopropanes **102** with silanes **103** (Scheme 26).^[32] The reaction was promoted at room temperature by 5 mol% of chiral preformed iron catalyst **104** in dioxane as the solvent, affording chiral allylic silanes **105** through successive highly anti-Markovnikov selective hydrosilylation of vinylcyclopropanes **102** with silanes **103** and stereospecific carbon–carbon bond cleavage. These products were obtained in moderate yields (37-50%) and moderate to excellent enantioselectivities (64-99% *ee*) along with recovered (*R,R*)-**102** with low to moderate yields (11-45%) and moderate to excellent *ee* values (62-99% *ee*) since the process evolved through kinetic resolution. The authors found that using an additive, such as 3-chlorophenol, allowed accelerating the reaction. The catalyst system tolerated a wide range of aryl-substituted vinylcyclopropanes bearing various functional groups at the *para*-, *meta*-, or *ortho*-position of the phenyl ring (Ar), producing the corresponding chiral allylic silanes **105** with moderate yields (39-47%) and excellent enantioselectivities (92-98% *ee*). The corresponding (*R,R*)-vinylcyclopropanes were recovered with low yields (15-40%) and moderate to excellent *ee* values (63-97% *ee*). However, alkyl-substituted vinylcyclopropanes were found unsuitable substrates. Vinylcyclopropanes exhibiting either electron-withdrawing or electron-donating groups at different positions of the phenyl ring at R¹ provided the desired allylic silanes in moderate yields (40-48%) albeit with high *ee* values (78-98% *ee*) along with recovered (*R,R*)-vinylcyclopropanes with low yields (13-39%) and moderate to high *ee* values (64-97% *ee*). The lowest enantioselectivities (64-78% *ee*) were observed in the reaction of sterically hindered substrates (R¹ = *o*-ClC₆H₄, 2-Naph). A mechanism depicted in Scheme 26 proposes the generation of iron-silyl species **104**-SiH₂R² from the reaction between **104**, silane **103**, 3-chlorophenol and NaBHET₃. Then, (*S,S*)-**102** underwent a 1,2-insertion into the iron-silicon bond of **104**-SiH₂R², producing tertiary alkyl iron species **R**. Subsequently, a β -carbon elimination occurred to give primary

alkyl iron species **S**. The latter underwent δ -bond metathesis with the hydrosilane to afford the final product and regenerated iron silyl species.



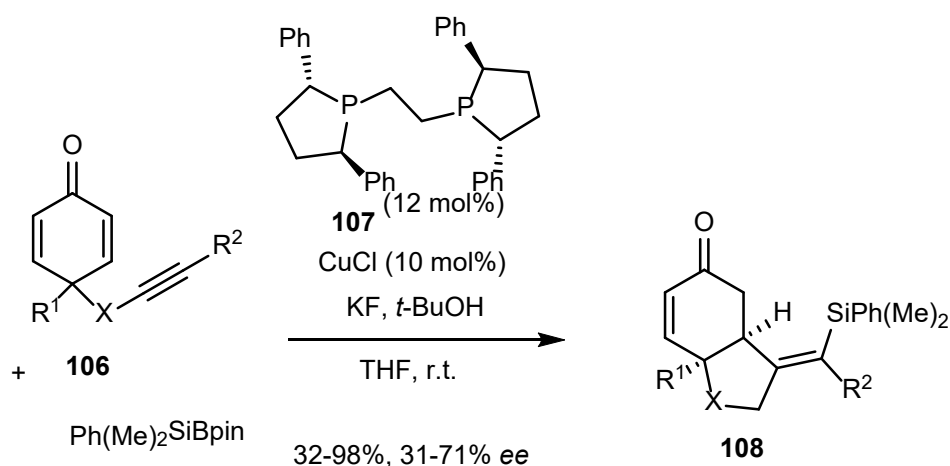
proposed mechanism:



Scheme 26. Domino silylation/ring-opening reaction of vinylcyclopropanes with silanes.

4 Enantioselective Copper-Catalyzed Domino Reactions

Taking advantages of the higher abundance and lower cost and toxicity of copper catalysts in comparison with other transition metals, many types of more ecologic and economic enantioselective domino reactions have been developed in the last decade on the basis of asymmetric copper catalysis.^[33] In an example reported in 2019, Lin and Tian described the first copper-catalyzed enantioselective silylative cyclization of cyclohexadienone-containing 1,6-enynes **106** with PhMe₂SiBpin, evolving through asymmetric domino silylation/cyclization reaction (Scheme 27).^[34] Promoted at room temperature by 10 mol% of CuCl as precatalyst and 12 mol% of chiral bisphosphine ligand **107** in THF as solvent, this process regioselectively led to a wide range of chiral *cis*-hydrobenzofuran (X = O) and *cis*-hydroindole (X = NHBoc) derivatives **108** bearing two contiguous stereocenters in moderate to excellent yields (32-98%) and moderate enantioselectivities (31-71% *ee*). The reaction evolved through a regioselective silylcupration of the alkyne-tethered cyclohexadienone in the presence of PhMe₂SiBpin and the copper catalyst, providing an alkenylsilyl copper intermediate which further reacted with the cyclohexadienone according to an enantioselective Michael addition. The catalyst system was compatible with a variety of substituents (R¹) on the cyclohexadienone, spanning from alkyl, aryl, benzyl, vinyl to allyl groups. In addition to terminal alkyne-tethered cyclohexadienones (R² = H), an internal alkyne-tethered substrate (R² = Me) also underwent the domino reaction albeit with both reduced yield (32%) and *ee* value (31% *ee*).

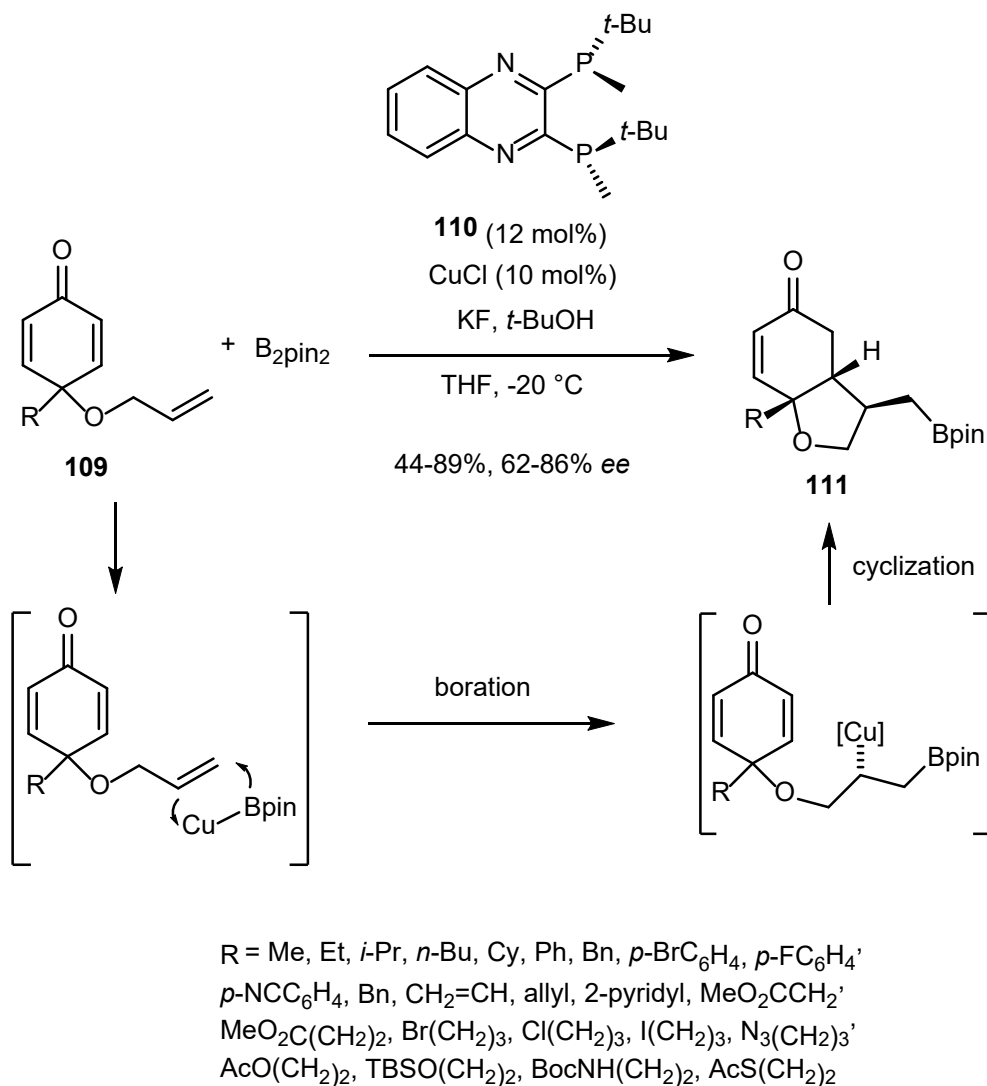


R¹ = Me, Et, *i*-Pr, *n*-Bu, Cy, Ph, Bn, *p*-BrC₆H₄, Bn,
CH₂=CH, allyl, Br(CH₂)₃, I(CH₂)₃, AcO(CH₂)₂, NCCH₂
R² = H, Me
X = O, NHBoc

Scheme 27. Domino silylation/cyclization of alkyne-tethered cyclohexadienones with PhMe₂Bpin.

In 2020, the same authors also developed an enantioselective copper-catalyzed domino boration/cyclization reaction between monosubstituted terminal alkene-tethered cyclohexadienones **109** and B₂pin₂ (Scheme 28).^[35] In this case, the chiral copper catalyst was generated from 10 mol% of CuCl and 12 mol% of chiral bisphosphine ligand **110** in THF at room temperature, allowing the formation of chiral *cis*-fused bicyclic products **111** in moderate to high yields (44-89%) and moderate to good enantioselectivities (62-86% *ee*). The latter resulted from a regioselective anti-Markovnikov

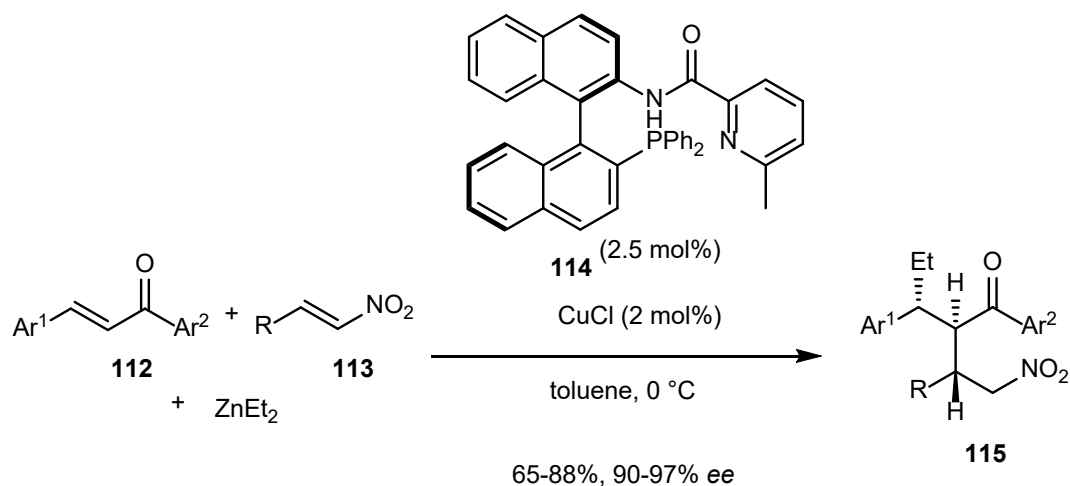
cuproboration of the tethered electron-rich terminal alkenes followed by cyclization through conjugate addition of a stereospecific alkyl copper intermediate onto the cyclohexadienone. The authors suggested that the 1,4-borylation of the electron-deficient double bonds of the cyclohexadienone was suppressed by the presence of two substituents at the C4 position which induced steric hindrance and thus, the tethered alkene was preferentially borylated.



Scheme 28. Domino boration/cyclization reaction of monosubstituted terminal alkene-tethered cyclohexadienones with B_2pin_2 .

Earlier in 2019, Hu and Hou reported an enantioselective three-component copper-catalyzed domino double Michael reaction of α,β -unsaturated ketones **112** with nitroolefins **113** and ZnEt_2 using chiral P,N-ligands.^[36] The optimal catalyst was *in situ* generated from only 2 mol% of CuCl and 2.5 mol% of chiral ligand **114**. Performed at 0 °C in toluene as solvent, the reaction afforded a wide range of functionalized chiral products **115** exhibiting three contiguous stereocenters as single diastereomers with good yields (65-88%) and uniformly excellent enantioselectivities (90-97% *ee*), as illustrated in Scheme 29. The process evolved through double Michael addition of ZnEt_2 to α,β -unsaturated ketones followed by trapping with nitroolefins. It was found that the steric and electronic properties of the aromatic substituents of both chalcones and nitroolefins had little impact on the enantioselectivity of

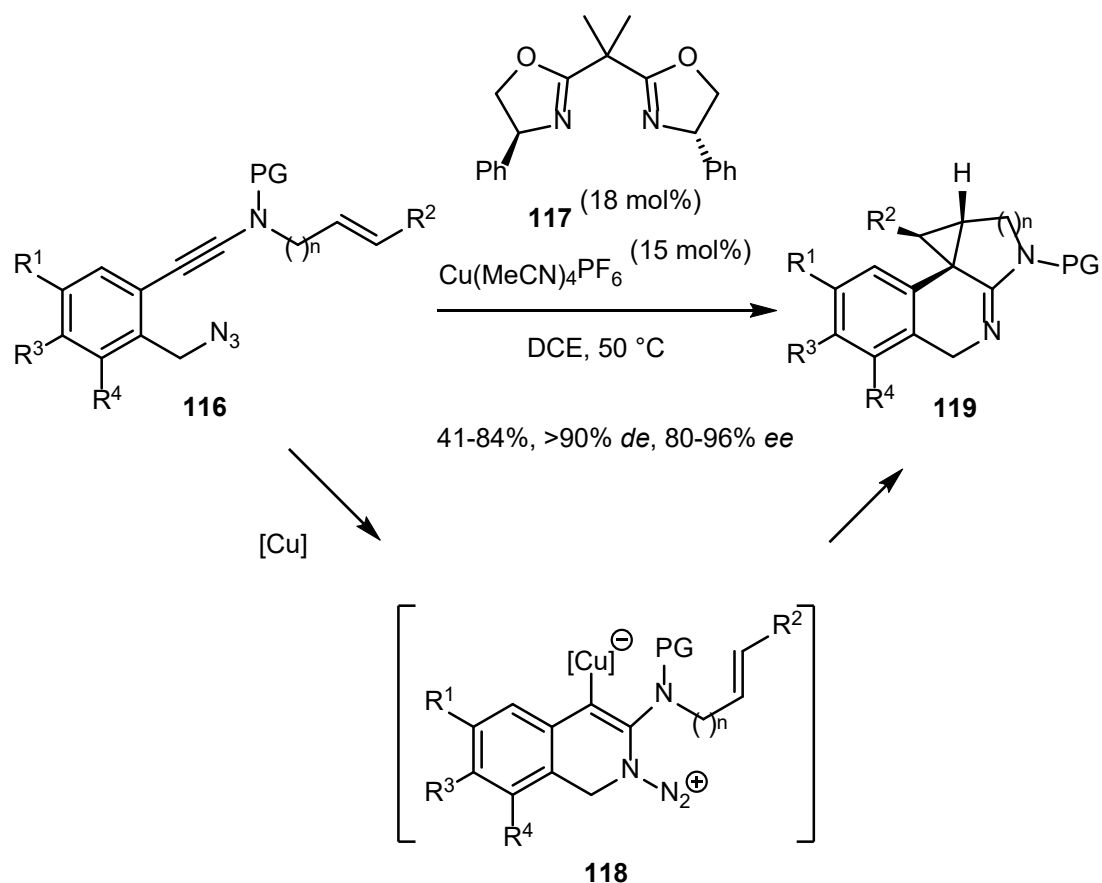
the reaction. Substrates with either electron-withdrawing or electron-donating substituents at any position of the phenyl ring of chalcones and aromatic nitroolefins were all tolerated, thereby affording the corresponding products with good yields and excellent enantioselectivities. Notably, an aliphatic nitroolefin (R = Cy) was also compatible, resulting in the formation of the corresponding product with 60% yield and 94% *ee*.



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

Scheme 29. Three-component domino double Michael reaction of α,β -unsaturated ketones, nitroolefins and ZnEt_2 .

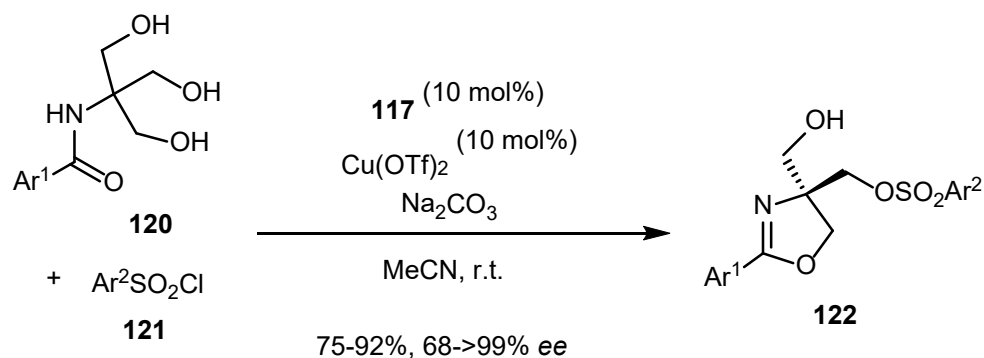
In 2020, an enantioselective copper-catalyzed cascade cyclization of azide-ynamides **116** was described by Ye and Deng.^[37] It employed a combination of 15 mol% of $\text{Cu}(\text{MeCN})_4\text{PF}_6$ and 18 mol% of chiral bisoxazoline ligand **117** as catalyst system in DCE at 50 °C (Scheme 30). The process evolved through the generation of an imino copper carbene intermediate **118** described for the first time. The latter subsequently underwent cyclopropanation to afford an array of chiral tetracyclic heterocycles **119** as almost single diastereomers (>90% *de*) in moderate to good yields (41-84%) and high *ee* values (80-96% *ee*). The conditions were compatible with different alkyl-substituted (azido)ynamides as well as phenyl-substituted substrates ($\text{R}^2 = \text{Ph}$). Furthermore, the phenyl ring of the ynamides could bear different types of substituents ($\text{R}^1, \text{R}^3, \text{R}^4$). Along with Ts-protected ynamides (PG = Ts), various other *N*-protected groups, such as Bs, MBS and SO_2Ph , were also tolerated.



$\text{R}^1 = \text{H, Cl, Br, Me}$
 $\text{R}^2 = \text{Ph, Me, Et, } n\text{-Pr, } i\text{-Pr, } n\text{-Bu, Cy}$
 $\text{R}^3 = \text{H, F, Cl, Br, CF}_3, \text{ Me, OMe}$
 $\text{R}^4 = \text{H, F}$
 $\text{PG} = \text{Ts, Bs, MBS, SO}_2\text{Ph}$
 $n = 1\text{-}2$

Scheme 30. Domino multicyclization reaction of azide-ynamides.

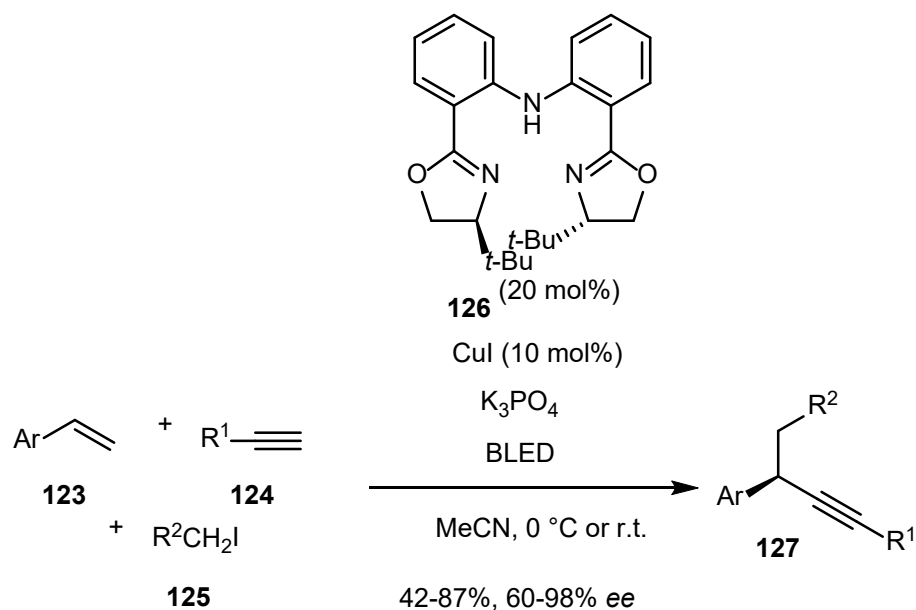
In another area, Onomura et al. applied the same chiral ligand **117** at 10 mol% of catalyst loading in combination with the same quantity of $\text{Cu}(\text{OTf})_2$ as precatalyst to promote an enantioselective copper-catalyzed domino sulfonylation/cyclization reaction of aminotriols **120** with aryl sulfonyl chlorides **121**.^[38] The process carried out at room temperature in acetonitrile as solvent resulted in the formation of the corresponding chiral multisubstituted oxazolines **122** exhibiting a quaternary carbon center and a hydroxymethyl group (Scheme 31) in good yields (75-92%) and moderate to excellent enantioselectivities (68->99% *ee*). The domino reaction involved successively a mono-sulfonylation of aminotriols, an intramolecular cyclization to afford prochiral oxazoline diols, and sulfonylative asymmetric desymmetrization of resultant oxazoline diols.



$\text{Ar}^1 = \text{Ph}, p\text{-Tol}, m\text{-Tol}, o\text{-Tol}, p\text{-MeOC}_6\text{H}_4,$
 $p\text{-ClC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, 2\text{-furyl}, 2\text{-thienyl}$
 $\text{Ar}^2 = \text{Ph}, p\text{-Tol}, p\text{-ClC}_6\text{H}_4$

Scheme 31. Domino sulfonylation/cyclization reaction of aminotriols with aryl sulfonyl chlorides.

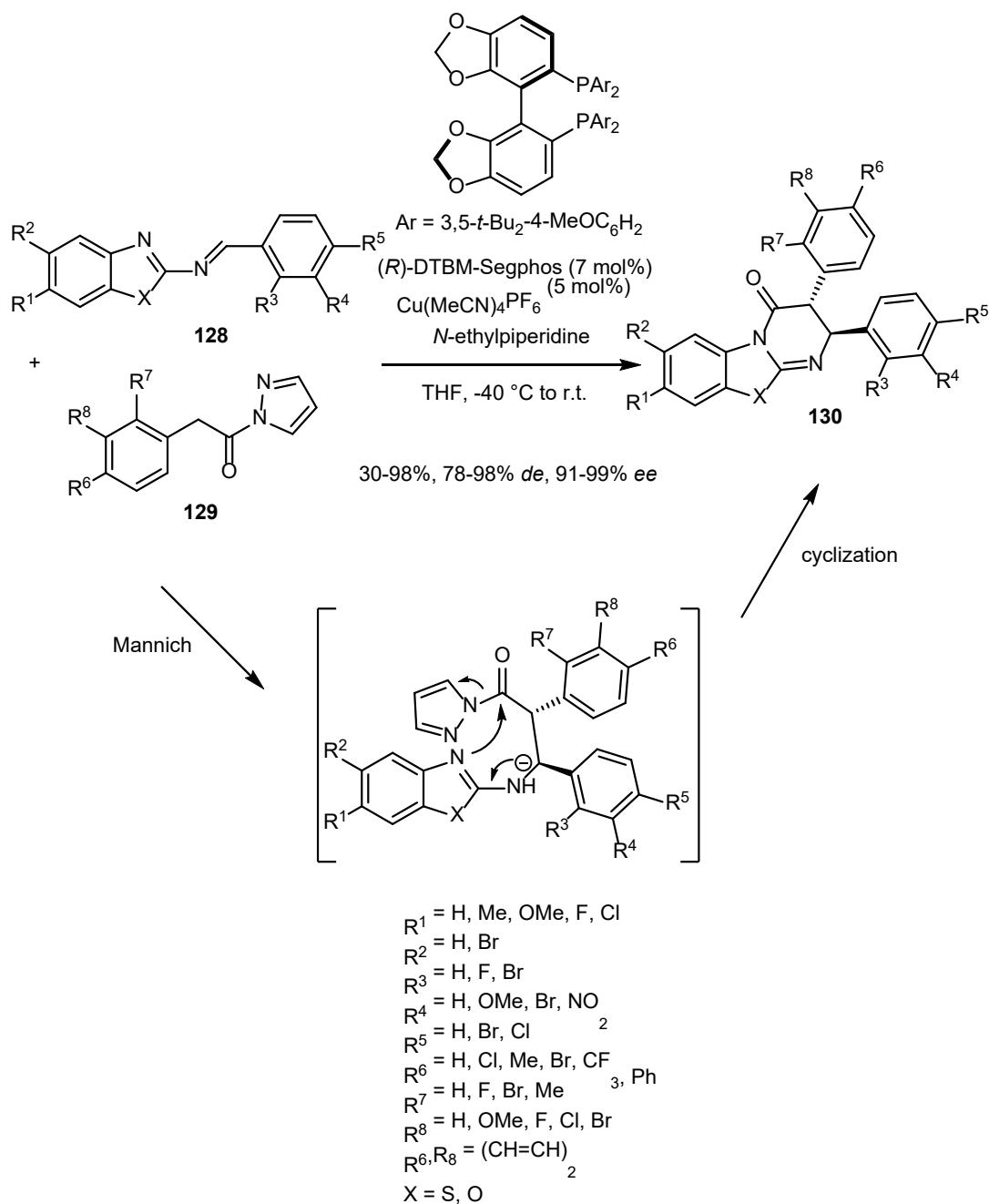
In 2020, Zhang and Zhang developed a novel simple methodology for asymmetric difunctionalization of olefins.^[39] It was based on a photo-induced enantioselective three-component domino alkylation/alkynylation of styrenes **123** with terminal alkynes **124** and alkyl iodides **125** promoted by a chiral copper catalyst derived from 20 mol% of chiral bisoxazoline ligand **126** and 10 mol% of CuI in acetonitrile as solvent. The radical process, carried out at room temperature or 0 °C under irradiation with blue light emitting diode (BLED), allowed an easy formation of a wide range of chiral propargylic products **127**, including ones featuring valuable fluorinated substituents. The latter were obtained with both moderate to high yields (42-87%) and enantioselectivities (60-98% *ee*), as shown in Scheme 32. A broad substrate scope was found for each of the three partners. Generally, the best *ee* values were obtained in the reaction of silylated and alkyl alkynes ($\text{R}^1 = \text{Si}(i\text{-Pr})_3, \text{alkyl}$) while (hetero)aryl alkynes reacted with lower enantioselectivities (60-84% *ee*). Concerning the styrene partner, it could bear different substitutions at *para*-, *ortho*- and *meta*-positions of the phenyl ring but the yields were decreased for the *ortho*-substituted components due to the steric hindrance. Moreover, a range of readily available alkyl iodides were tolerated including various fluorinated alkanes.



Ar = Ph, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-Tol, *p*-*t*-BuC₆H₄, *p*-MeOC₆H₄,
p-F₃CC₆H₄, *m*-BrC₆H₄, *o*-ClC₆H₄, *p*-PhC₆H₄, 2-thienyl, *o*-FC₆H₄, 2-Naph
 R¹ = TIPS, TMS, SiEt₃, *n*-Bu, BnCH₂, *t*-Bu, *i*-Pr, *s*-Bu, *c*-Pr, 3-pyridyl,
m-Tol, *o*-ClC₆H₄, *p*-MeOC₆H₄, 2-thienyl
 R² = F₃CCH₂, F₂CHCCH₂, F(CH₂)₂, F₂HCCF₂CH₂, F₃CCF₂CH₂, FCH₂,
n-Bu, *i*-Pr, Ph, *p*-*t*-Bu, *p*-MeOC₆H₄, *p*-BrC₆H₄, *p*-PhC₆H₄, 2-Naph,
 3-pyridyl, 2-thienyl

Scheme 32. Three-component domino alkylation/alkynylation of alkenes with terminal alkynes and alkyl iodides.

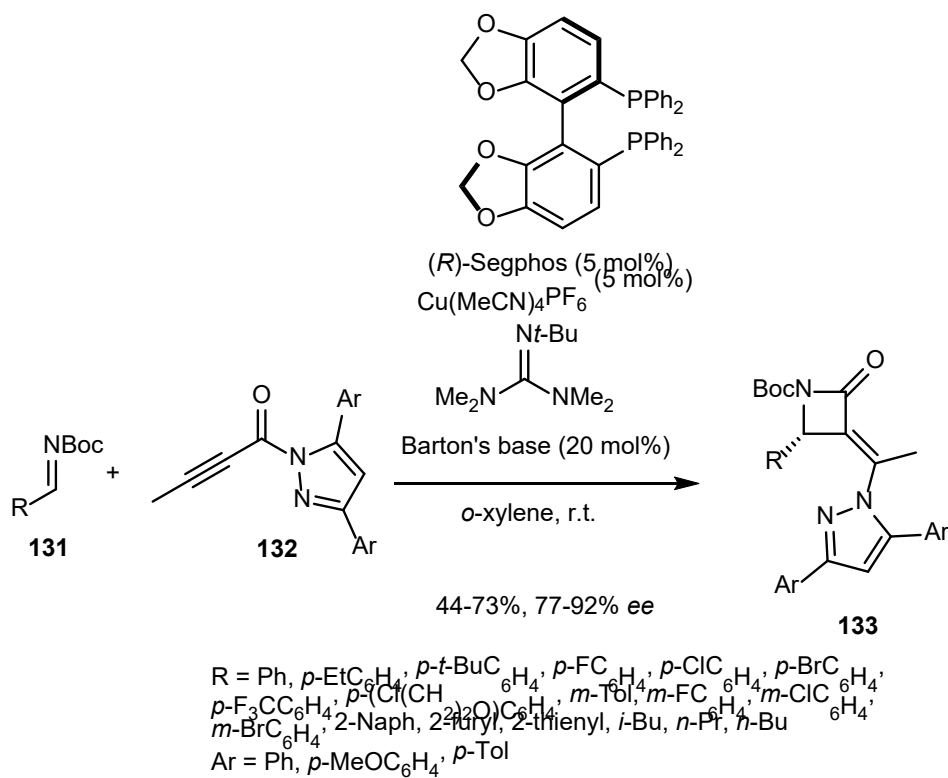
An enantioselective copper-catalyzed domino Mannich/cyclization reaction between 2-benzothiazolimines (X = S) **128** and *N*-acylpyrazoles **129** was disclosed by Chen and Dong, in 2021 (Scheme 33).^[40] It employed 5 mol% of a chiral copper catalyst *in situ* generated from Cu(MeCN)₄PF₆ and chiral bisphosphine (*R*)-DTBM-Segphos in THF as solvent in the presence of *N*-ethylpiperidine as base. The process performed at -40 °C to room temperature generated chiral benzothiazolopyrimidines **130** (X = S) with moderate to quantitative yields (30-98%), good to complete diastereoselectivities (78-98% *de*) along with uniformly excellent enantioselectivities (91-99% *ee*). A wide range of substituents at any position of the phenyl rings of both the two substrates were well tolerated. Moreover, along with benzothiazole units (X = S), a benzoxazole substrate (X = O) reacted to give the desired product with 72% yield, 98% *de* and 98% *ee*.



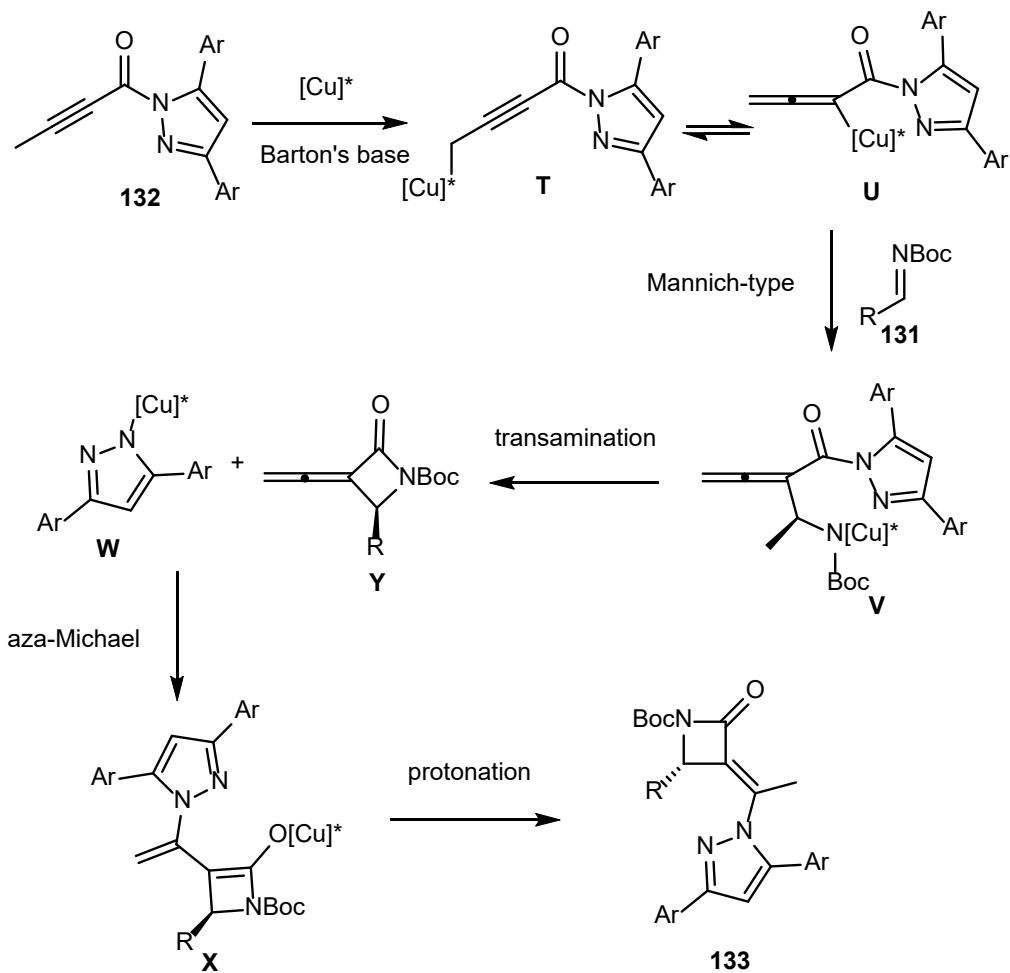
Scheme 33. Domino Mannich/cyclization reaction of 2-benzothiazolimines with *N*-acylpyrazoles.

In 2022, a closely related catalyst system was employed by Yin et al. to achieve an enantioselective cascade cyclization of aldimines **131** with pyrazoleamides **132** derived from but-2-ynoic acid.^[41] This domino reaction employed 5 mol% of $\text{Cu}(\text{MeCN})_4\text{PF}_6$ as precatalyst, the same quantity of (*R*)-Segphos as chiral ligand and 20 mol% of Barton's base in *o*-xylene as solvent. Performed at room temperature, the reaction resulted in the formation of a series of chiral β -lactams **133** containing a pyrazole moiety with moderate to good yields (44-73%) and good to high enantioselectivities (77-92% *ee*), as presented in Scheme 34. Surprisingly, in addition to (hetero)aromatic aldimines, aliphatic aldimines also underwent the reaction with comparable yields (54-73%) albeit combined with lower *ee* values (73-82% *ee*). The authors proposed the mechanism depicted in Scheme 34, beginning with the formation of intermediate **T** from the pyrazoleamide through γ -deprotonation in the presence of

copper(I)-bisphosphine complex and Barton's base. Evidently, propargyl copper(I) species **T** could be in equilibrium with allenyl copper(I) species **U**, however, the addition of **T** to the aldimine was favored. Therefore, γ -addition of allenyl copper(I) species **U** to the aldimine was significantly attenuated which led to an excellent α -regioselectivity. Indeed, an α -selective Mannich-type reaction occurred predominantly between intermediate **T** and the aldimine to give copper(I) amide species **V**. The latter was subsequently submitted to an intramolecular transamination to give intermediate **Y** along with nucleophilic (1*H*-pyrazol-1-yl)copper(I) species **W**. Then, an aza-Michael addition of **W** to **Y** led to copper(I) enolate species **X**, which underwent protonation to deliver the final β -lactam along with regenerated propargyl copper(I) species **T**.

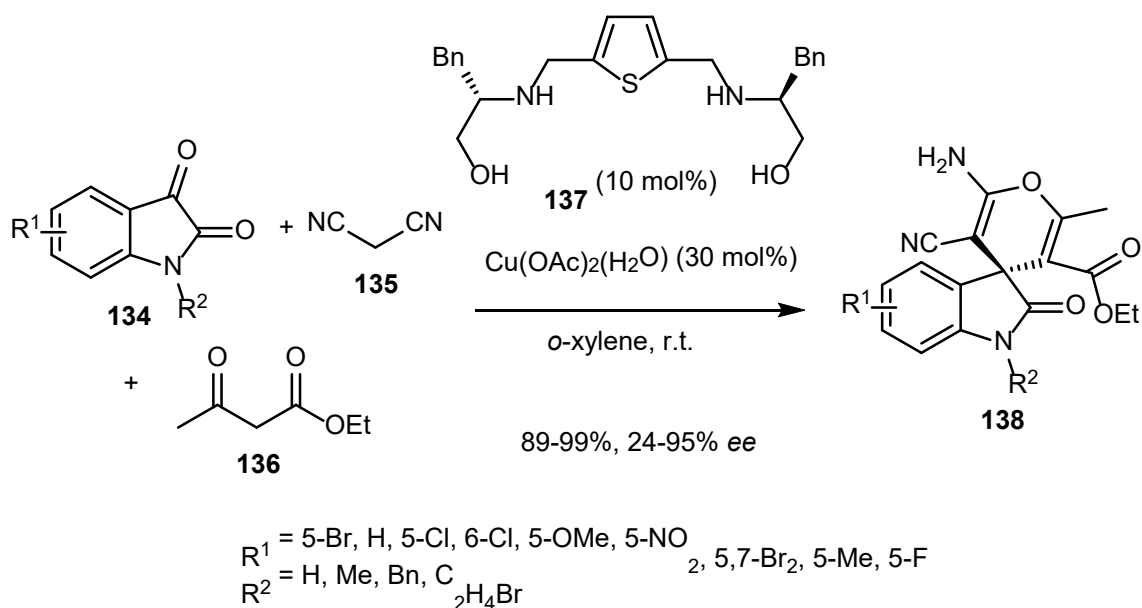


proposed mechanism:

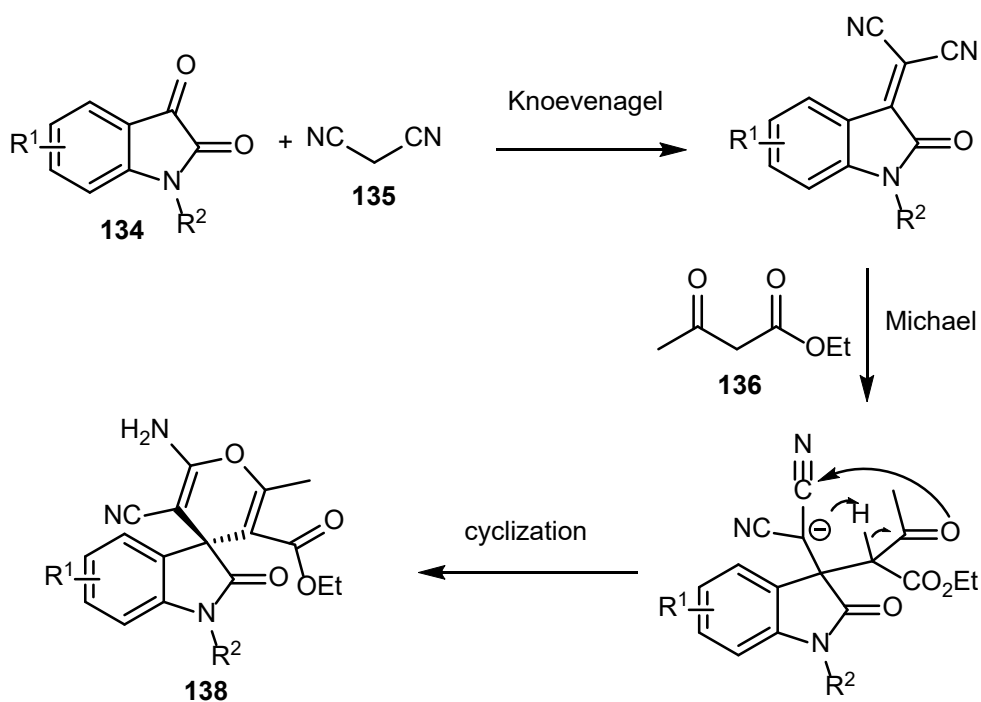


Scheme 34. Domino Mannich-type/transamination/aza-Michael/protonation reaction of aldimines with pyrazoleamides.

With the aim of discovering a novel route to biologically important chiral spirooxindoles, Al-Majid and Islam disclosed in 2022 a novel enantioselective copper-catalyzed domino reaction occurring between substituted isatins **134**, malononitrile **135** and ethyl acetoacetate **136** (Scheme 35).^[42] This three-component reaction was catalyzed at 25 °C by a combination of 30 mol% of Cu(OAc)₂·H₂O and 10 mol% of chiral thiophene-2,5-bis(amino-alcohol) ligand **137** in THF as solvent, affording the corresponding chiral spirooxindoles **138** with high yields (89-99%) and low to excellent enantioselectivities (24-95% *ee*). Their formation was explained by the mechanism shown in Scheme 35, involving a domino Knoevenagel/Michael/cyclization reaction.



proposed mechanism:

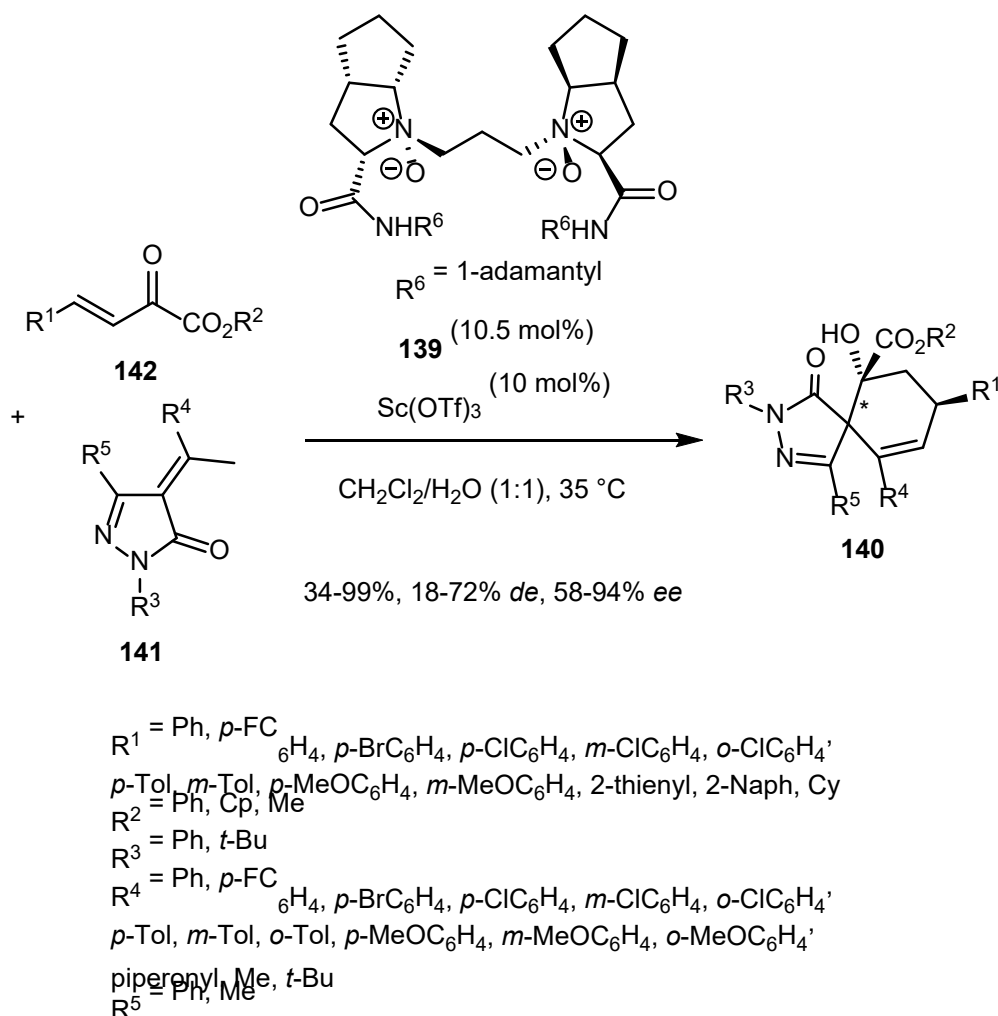


Scheme 35. Three-component domino Knoevenagel/Michael/cyclization reaction of isatins, malononitrile and ethyl acetoacetate.

5 Enantioselective Scandium-Catalyzed Domino Reactions

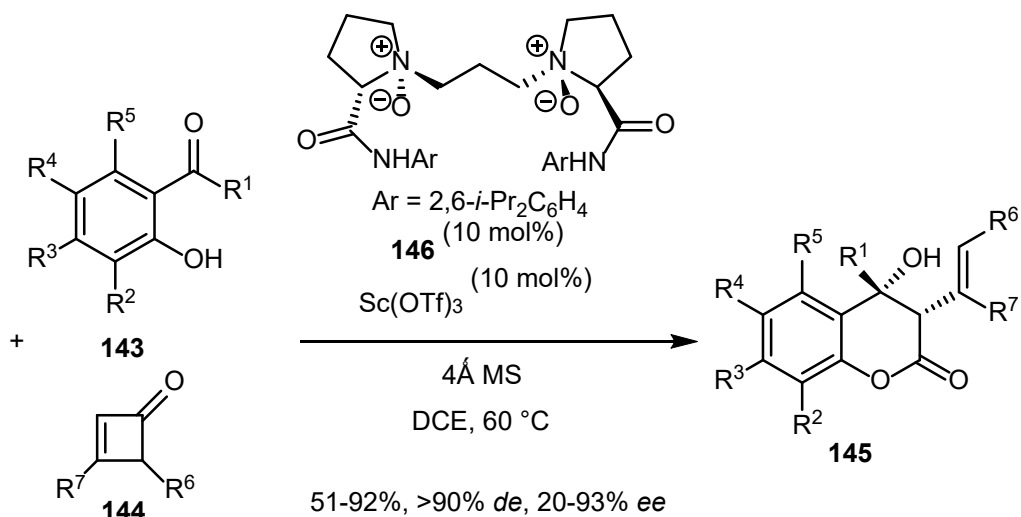
In the last few years, a variety of chiral ligands, including *N,N'*-dioxides, pyridine-2,6-bisoxazolines, bipyridines, phosphine oxides and phosphoric acids, have been chelated to scandium with the aim of catalyzing a wide diversity of novel enantioselective domino reactions. In an example reported in

2019, Feng et al. disclosed a synthesis of chiral potentially biologically interesting spirocyclohexene pyrazolones based on an enantioselective scandium-catalyzed domino Michael/aldol reaction performed in aqueous media.^[43] The sequence was promoted by a chiral scandium catalyst *in situ* generated from 10 mol% of Sc(OTf)₃ and 10.5 mol% of chiral *N,N'*-dioxide ligand **139** in a 1:1 mixture of dichloromethane/H₂O as solvent (Scheme 36). This resulted in the formation at 35 °C of a wide range of chiral functionalized spirocyclohexene pyrazolones **140** bearing three stereogenic centers starting from the corresponding α -arylidene pyrazolinones **141** and β,γ -unsaturated α -ketoesters **142**. These products were obtained in good to quantitative yields (34-99%) and moderate to high enantioselectivities (58-94% *ee*) as a mixture of diastereomers with low to good diastereoselectivities (18-72% *de*). Cyclopentyl, isopropyl and methyl ($R^2 = \text{Cp}, i\text{-Pr}, \text{Me}$) aryl-substituted ($R^1 = \text{aryl}$) β,γ -unsaturated α -ketoesters **142** generally reacted with variously substituted α -arylidene pyrazolinones **141** with high enantioselectivities (80-94% *ee*). Lower enantioselectivities (58-60% *ee*) were obtained in the reaction of *N-tert*-butyl substituted α -arylidene pyrazolinone ($R^3 = t\text{-Bu}$) in combination with a low diastereoselectivity (18% *de*). Low diastereoselectivities were also obtained in the reaction of a cyclopentyl 2-thienyl-substituted β,γ -unsaturated α -ketoester ($R^1 = 2\text{-thienyl}$, 26% *de*) and an alkyl-substituted β,γ -unsaturated α -ketoester ($R^1 = \text{Cy}$, 34% *de*).

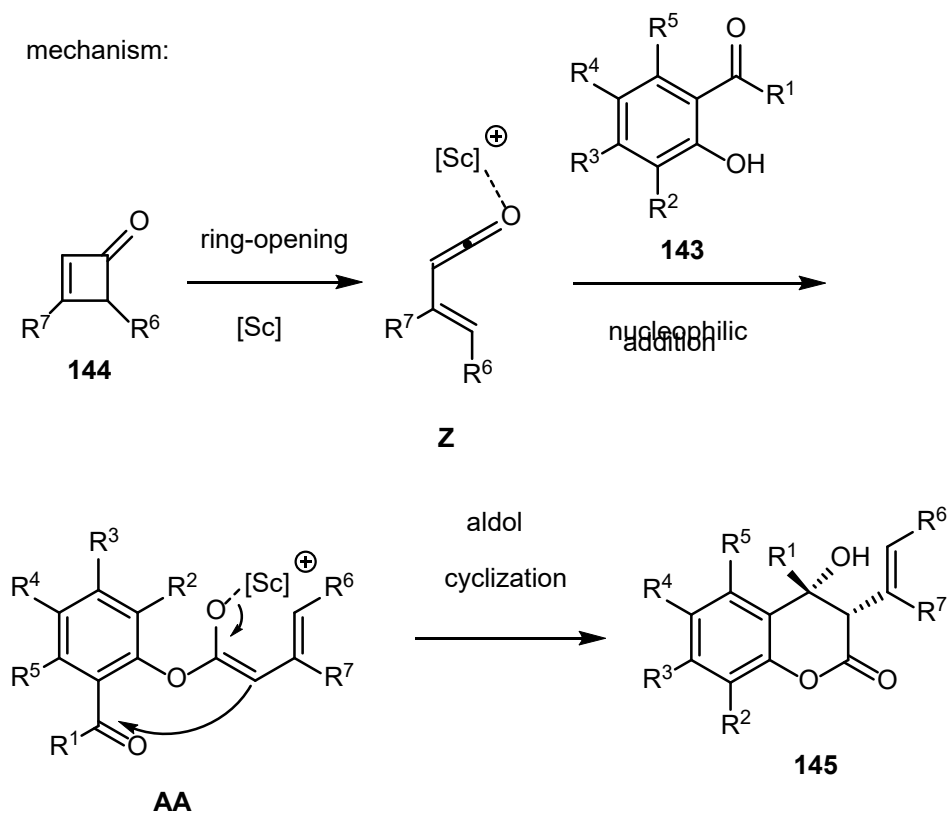


Scheme 36. Domino Michael/aldol reaction of α -arylidene pyrazolinones with β,γ -unsaturated α -ketoesters.

In the same year, this group also developed an enantioselective scandium-catalyzed domino ring-opening/nucleophilic addition/cyclization reaction of 2-hydroxyacetophenones **143** with cyclobutenones **144**, allowing the synthesis of chiral 4-hydroxy-chroman-2-ones **145** constituting important products in medicinal chemistry (Scheme 37).^[44] The reaction was promoted at 60 °C in DCE as solvent by 10 mol% of a chiral scandium catalyst *in situ* generated from Sc(OTf)₃ and chiral *N,N'*-dioxide ligand **146**. It began with the scandium-promoted ring-opening of cyclobutene **144** into the corresponding vinylketene intermediate **Z**, which subsequently underwent a nucleophilic addition of the hydroxyl group of 2-hydroxyacetophenone **143** to give dienolate intermediate **AA**. Then, the latter was submitted to an intramolecular cyclization through aldol addition to afford final 4-hydroxy-dihydrocoumarin **145** as single diastereomer (>90% *de*). A wide range of these products were synthesized with moderate to high yields (51-92%) and low to excellent enantioselectivities (20-93% *ee*). Generally, high enantioselectivities ($\geq 85\%$ *ee*) were achieved in the reaction of variously substituted 2-hydroxyacetophenones **143**, such as alkyl-, ethynyl-, as well as ester-substituted ketones ($R^1 = \text{alkyl, ethynyl, CO}_2\text{Et}$) which underwent the reaction with 85-93% *ee*. However, a dramatically lower *ee* value (20% *ee*) was obtained in the reaction of a phenyl-substituted substrate ($R^1 = \text{Ph}$). On the other hand, high enantioselectivities (87-92% *ee*) were observed in the reaction of C4-, C5, and C6-monosubstituted 2-hydroxyacetophenones, whereas a disubstituted 2-hydroxyacetophenone ($R^2 = R^4 = \text{Me}$) led to the corresponding domino product with a decreased enantioselectivity (55% *ee*). Concerning the scope of the cyclobutene partner, many monosubstituted substrates were tolerated, providing generally high enantioselectivities of up to 93% *ee* while disubstituted ones ($R^5 = p\text{-Tol, } m\text{-Tol, } R^6 = \text{Cl}$) led to the corresponding products with lower enantioselectivities (53-59% *ee*).

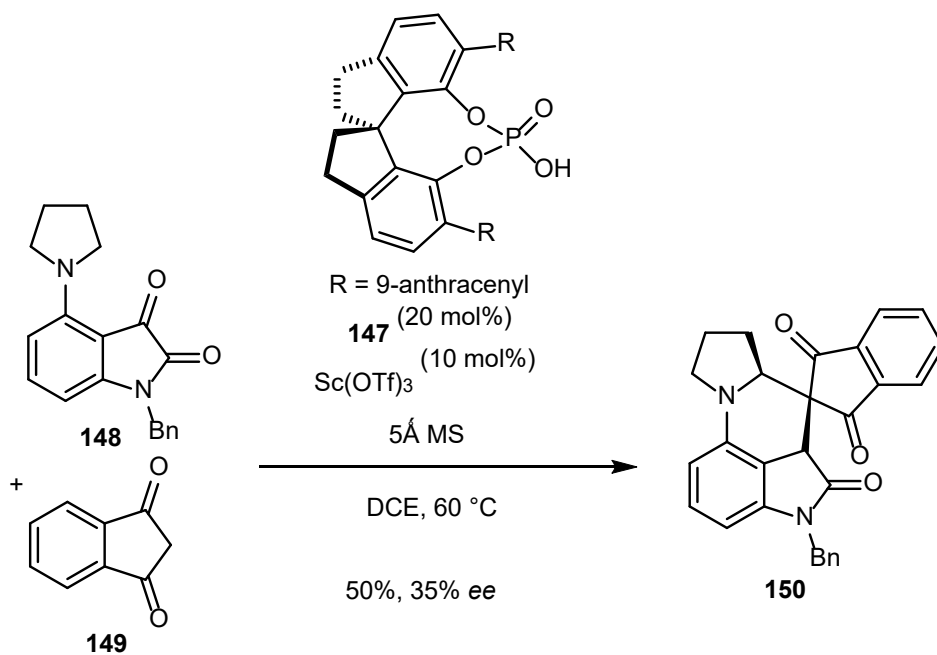


mechanism:

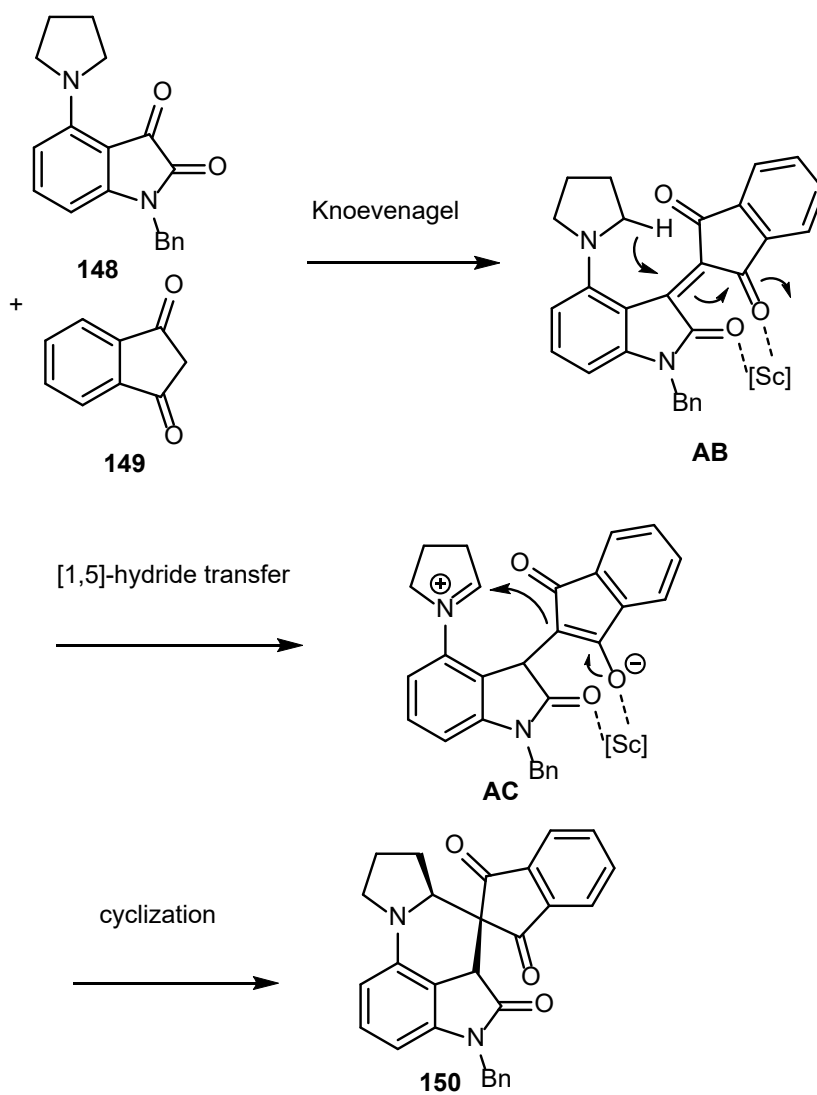


Scheme 37. Domino ring-opening/nucleophilic addition/cyclization reaction of 2-hydroxyacetophenones with cyclobutenones.

In 2019, Li and Xiao developed racemic domino Knoevenagel/[1,5]-hydride transfer/cyclization reactions between C4-amine-substituted isatins **148** and cyclic 1,3-dicarbonyl compound **149** catalyzed by Sc(OTf)₃ which produced the corresponding tricyclic [3,4]-fused oxindoles **150**.^[45] As shown in Scheme 38, the two substrates underwent a Knoevenagel condensation to give the corresponding α,β -unsaturated ketone intermediate **AB**. Then, the latter was submitted to a [1,5]-hydride transfer which afforded zwitterionic iminium intermediate **AC**, which subsequently underwent an intramolecular cyclization to provide the final domino product. An asymmetric version of this process was achieved by using 20 mol% of chiral phosphoric acid **147** in combination with 10 mol% of Sc(OTf)₃. Under this catalyst system employed at 60 °C in DCE as the solvent, C4-pyrrolidin-substituted isatin **148** reacted with 1*H*-indene-1,3(2*H*)-dione **149** to afford the corresponding chiral polycyclic product **150** in 50% yield and 35% *ee*.

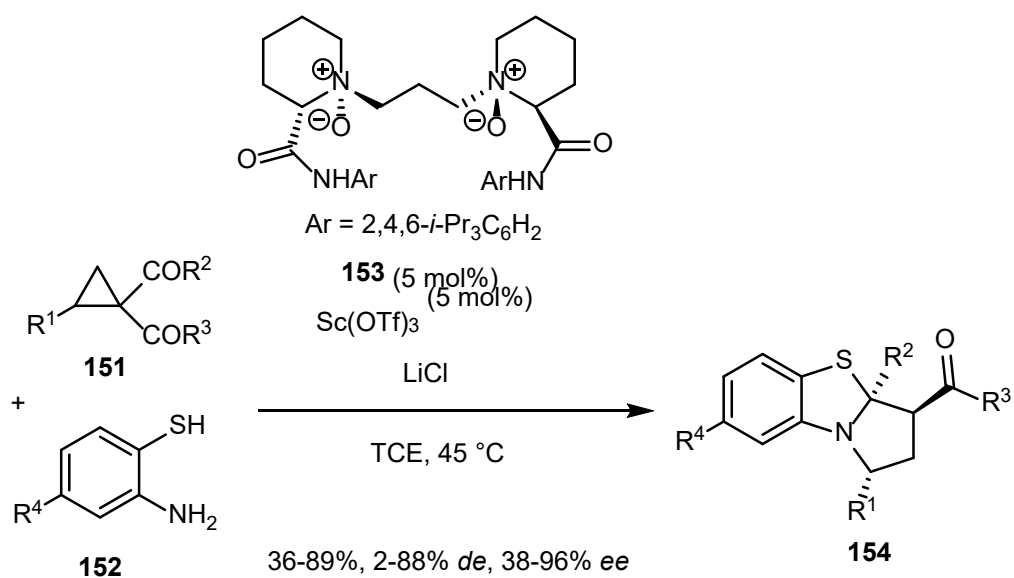


mechanism:



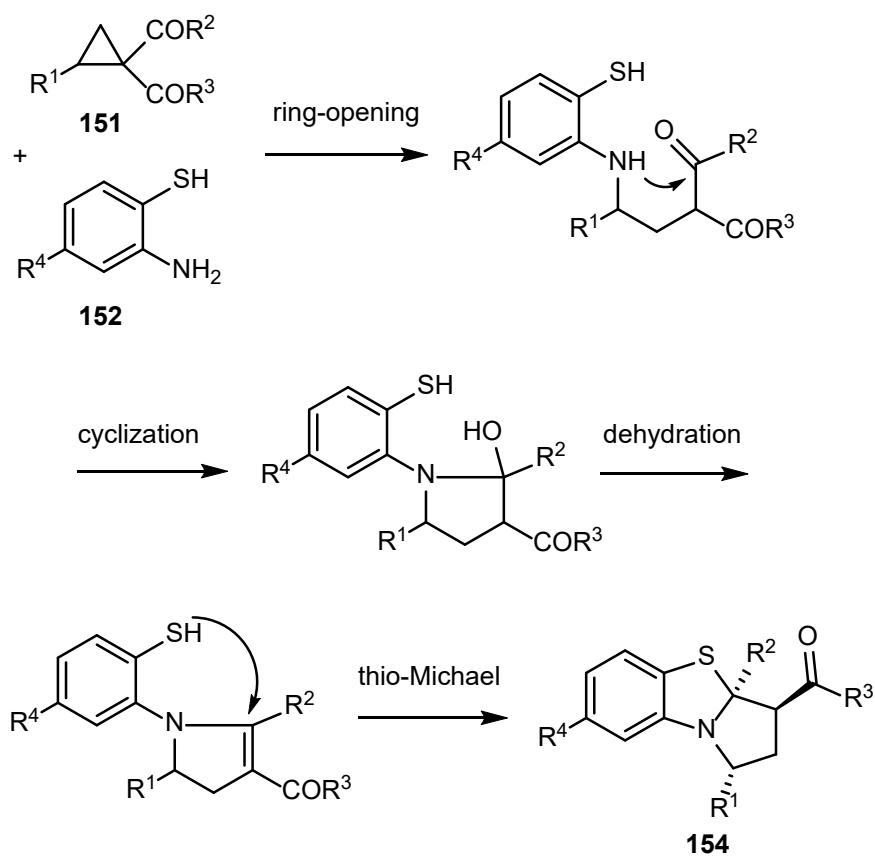
Scheme 38. Domino Knoevenagel/[1,5]-hydride transfer/cyclization reaction of a C4-pyrrolidin-substituted isatin with a cyclic 1,3-diketone.

Later in 2020, Feng and Lin described a novel enantioselective scandium-catalyzed domino ring-opening/cyclization/dehydration/thio-Michael reaction between cyclopropanes **151** and 2-aminothiophenols **152** (Scheme 39).^[46] It employed 5 mol% of a chiral catalyst derived from Sc(OTf)₃ and chiral *N,N'*-dioxide ligand **153** in trichloroethane (TCE) as solvent. Performed at 45 °C, the cascade reaction allowed the corresponding chiral hydropyrrolo[2,1-*b*]benzothiazoles **154** bearing vicinal tertiary/quaternary stereogenic centers to be synthesized in moderate to high yields (36-89%), low to high diastereoselectivities (2-88% *de*) and moderate to excellent enantioselectivities (38-96% *ee*). Concerning the cyclopropane substrates, the steric and electronic properties of substituents on the phenyl group (R¹) had no obvious effect since all the corresponding aryl-substituted products were obtained with good yields (70-89%) and with excellent enantioselectivities (87-96% *ee*) albeit combined with moderate to high *de* values (54-88% *de*). On the other hand, a methyl-substituted cyclopropane (R² = R³ = Me) reacted with a lower yield (65%), combined with both low diastereo- (6% *de*) and enantioselectivities (4% *ee*). Moreover, along with diketone cyclopropanes, substrates exhibiting a combination of ketone/ester (R³ = OMe, OEt) were compatible but led to the corresponding products with moderate yields (57-68%), and both low to moderate diastereo- (2-64% *de*) and enantioselectivities (38-57% *ee*). The mechanism of the domino ring-opening/cyclization/thio-Michael cascade reaction is shown in Scheme 39, beginning with the nucleophilic ring-opening of the cyclopropane by attack of the nitrogen atom of the 2-aminothiophenol promoted by the chiral scandium catalyst. Then, the nitrogen atom added intramolecularly to one carbonyl group of the electron acceptor part, forming a tetrahydropyrrole intermediate. Then, a dehydration generated a dihydropyrrole intermediate, which subsequently underwent a thio-Michael reaction to afford the final hydropyrrolo[2,1-*b*]benzothiazole.



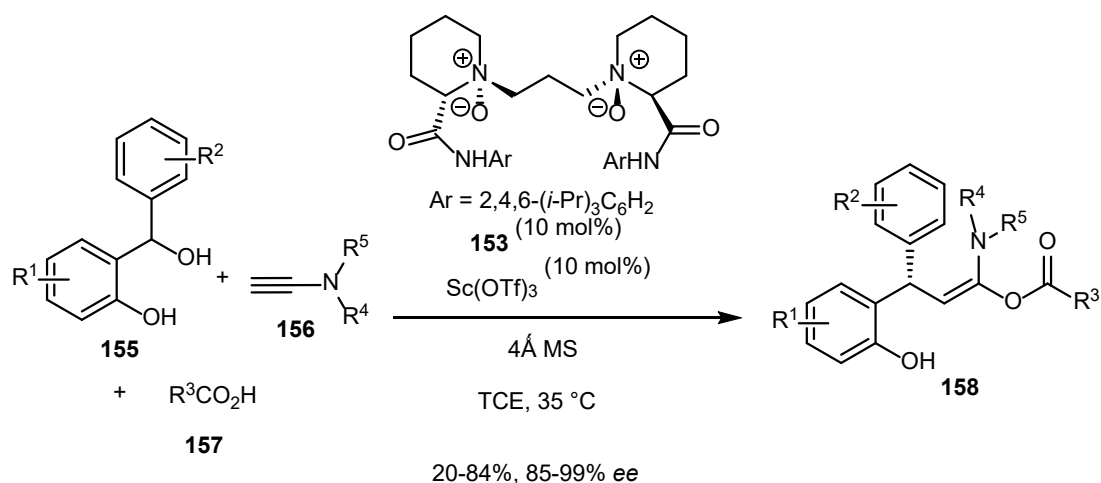
$R^1 = p\text{-Tol}, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, m\text{-Tol}, m\text{-ClC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4,$
 $\textit{o}\text{-BrC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, 1\text{-Naph}, 2\text{-Naph}, \text{vinyl}, \text{Ph}$
 $R^2 = \text{Ph}, p\text{-FC}_6\text{H}_4, \text{Me}$
 $R^3 = \text{Ph}, p\text{-FC}_6\text{H}_4, \text{Me}, \text{OEt}, \text{OMe}$
 $R^4 = \text{H}, \text{Cl}$

mechanism:



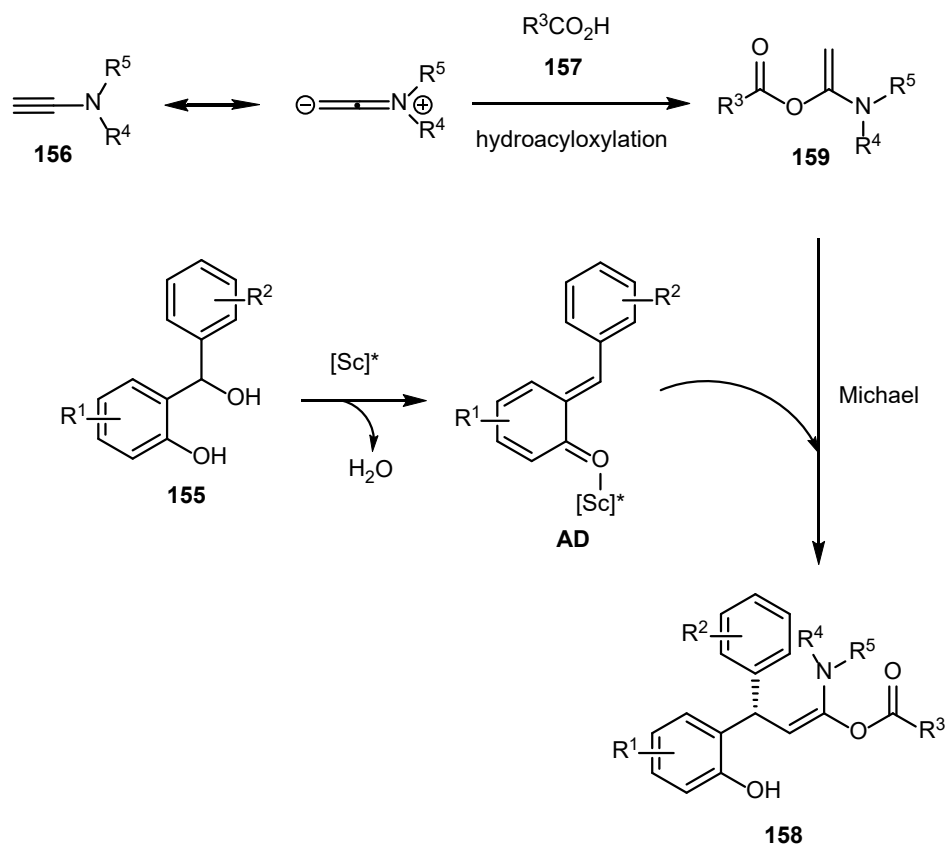
Scheme 39. Domino ring-opening/cyclization/dehydration/thio-Michael reaction of cyclopropanes with 2-aminothiophenols.

In the same year, Cao and Feng reported the use of 10 mol% of a chiral catalyst *in situ* generated from Sc(OTf)₃ and chiral *N,N'*-dioxide ligand **153** to promote at 35 °C in trichloroethylene (TCE) as the solvent an enantioselective three-component domino hydroacyloxylation/Michael reaction between *ortho*-hydroxybenzyl alcohols **155**, ynamides **156** and carboxylic acids **157**.^[47] In the mechanism proposed in Scheme 40, acyloxyenamide **159** was generated through hydroacyloxylation of ynamide **156** with carboxylic acid **157**, which then underwent a Michael addition to *ortho*-quinone methide **AD** arisen from the dehydration of *ortho*-hydroxybenzyl alcohol **155** facilitated by coordination with the chiral zinc complex. The reaction delivered chiral α -acyloxyenamides **158** in variable yields (20-84%) and uniformly high enantioselectivities (85-99% *ee*). The catalyst system was compatible with a variety of carboxylic acids bearing different substituents on the phenyl ring and also with 2-naphthalene formic acid (R³ = 2-naphthyl) and 2-thiophenoic acid (R³ = 2-thiophenyl). Moreover, an aliphatic acid (R³ = allyl) was compatible, providing the desired product with 98% *ee* albeit combined with 35% yield. Excellent enantioselectivities were also obtained in the reaction of *ortho*-hydroxybenzyl alcohols bearing different halogen groups at the 4- or 5-position of the phenol ring. Furthermore, variously substituted ynamides were suitable substrates.



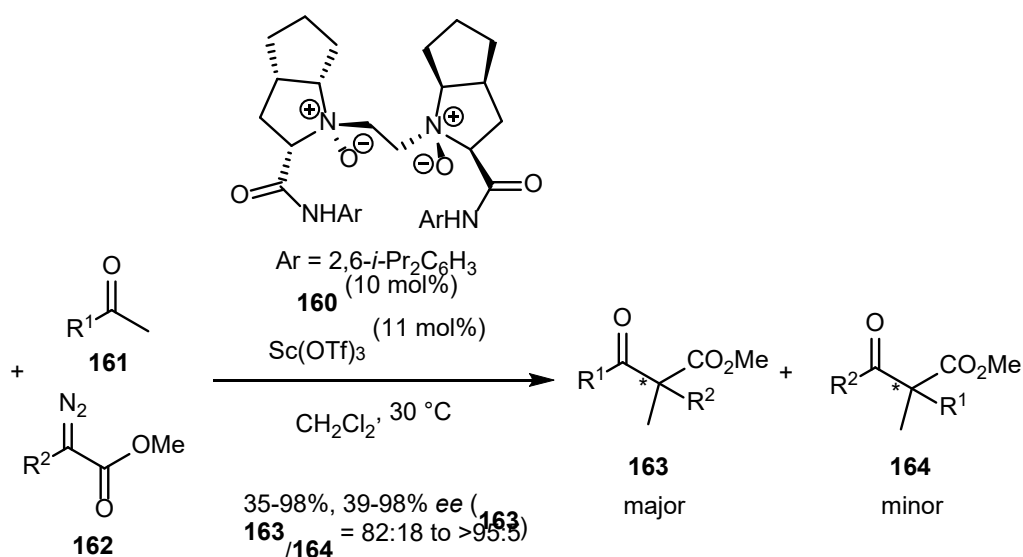
$R^1 = \text{H, 5-F, 5-Cl, 5-Br, 4-Cl, 5-Me}$
 $R^2 = \text{H, 4-Me, 4-F, 4-Cl, 3-F}$
 $R^3 = \text{Ph, } p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-O}_2\text{NC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-Tol, } m\text{-O}_2\text{NC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, o\text{-BrC}_6\text{H}_4, 2\text{-Naph, 2-thiophenyl, allyl}$
 $R^4 = \text{Me, Bn, allyl, HC} \equiv \text{CCH}_2, \text{allylCH}_2$
 $R^5 = \text{Ts, Mes}$

mechanism:

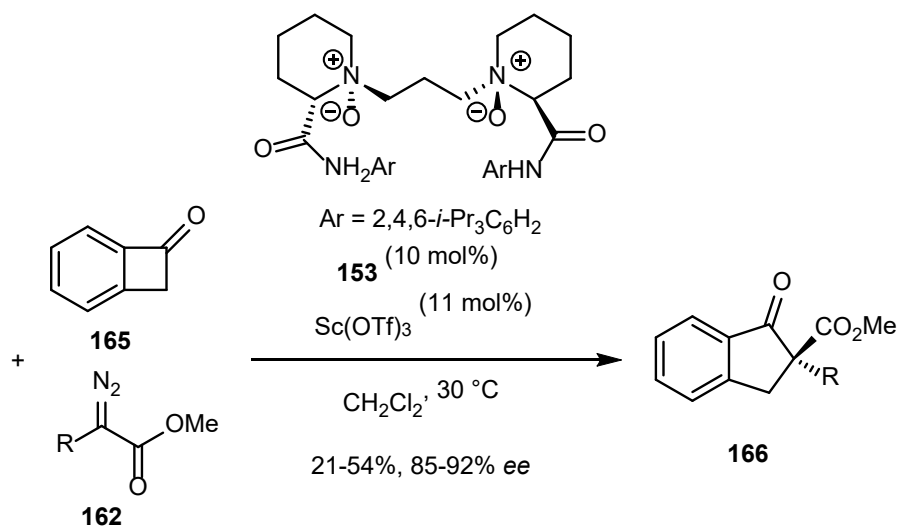


Scheme 40. Three-component domino hydroacyloxylation/Michael reaction of *ortho*-hydroxybenzyl alcohols, ynamides and carboxylic acids.

In 2021, Feng and Wu reported the use of related chiral *N,N'*-dioxide ligand **160** at 10 mol% of catalyst loading in combination with 11 mol% of Sc(OTf)₃ to catalyze an enantioselective domino addition/rearrangement reaction between acyclic ketones **161** and α -alkyl α -diazo esters **162** (Scheme 41).^[48] This regio- and enantioselective homologation of acyclic ketones gave rise to the corresponding chiral β -keto esters **163** as major products along with minor regioisomers **164** with moderate to quantitative yields (35-98%). Major regioisomers **163** were obtained with moderate to excellent enantioselectivities (39-98% *ee*) combined with high regioselectivities (**163/164** = 82:18 to >95:5) arisen from a highly selective alkyl-group migration of the ketones (Scheme 41). Actually, all the enantioselectivities were found higher than 89% *ee* with the exception of 39% *ee* obtained in the reaction of acetone (R¹ = Me). The catalyst system tolerated a range of (hetero)aryl- as well as alkyl-substituted ketones but also a variety of α -diazo esters, such as α -benzyl α -diazo esters, 2-naphthalenyl-, allyl-, alkynyl-, phenylethyl-, and ethyl-substituted α -diazo esters. Moreover, it was found that cyclic ketones, such as benzocyclobutenone **165**, underwent ring expansion under modified conditions. Indeed, in the presence of 10 mol% of related chiral *N,N'*-dioxide ligand **153** combined with 11 mol% of Sc(OTf)₃ in dichloromethane at 30 °C, cyclic ketone **165** reacted with α -diazo esters **162** to give the corresponding chiral cyclic β -keto esters **166** with high *ee* values (85-92% *ee*) albeit combined with low to moderate yields (21-54%), as illustrated in Scheme 41. Various substituted α -benzyl α -diazo esters, 2-naphthyl-substituted α -diazo ester, α -diazo esters bearing unsaturated moieties, such as allyl or alkynyl moieties but also ethylphenyl-, dodecyl-, and methyl-substituted α -diazo esters were all compatible.



$\text{R}^1 = \text{Ph}, o\text{-FC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, o\text{-NCC}_6\text{H}_4, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4,$
 $p\text{-MeSC}_6\text{H}_4, 2\text{-Naph}, 2\text{-furyl}, 2\text{-thienyl}, (E)\text{-PhCH=CH}, \text{Me}, \text{PhC}\equiv\text{C}$
 $\text{R}^2 = \text{Bn}, o\text{-FC}_6\text{H}_4\text{CH}_2, m\text{-FC}_6\text{H}_4\text{CH}_2, m\text{-MeOC}_6\text{H}_4\text{CH}_2, p\text{-FC}_6\text{H}_4\text{CH}_2, p\text{-ClC}_6\text{H}_4\text{CH}_2,$
 $p\text{-BrC}_6\text{H}_4\text{CH}_2, p\text{-F}_3\text{CC}_6\text{H}_4\text{CH}_2, p\text{-TolCH}_2, 2\text{-NaphCH}_2, \text{allyl}, \text{BnCH}_2, \text{Et}, \text{MeO}_2\text{CCH}_2,$
 $\text{F}_3\text{CCH}_2, \text{TBSO}(\text{CH}_2)_3, \text{HC}\equiv\text{CCH}_2$

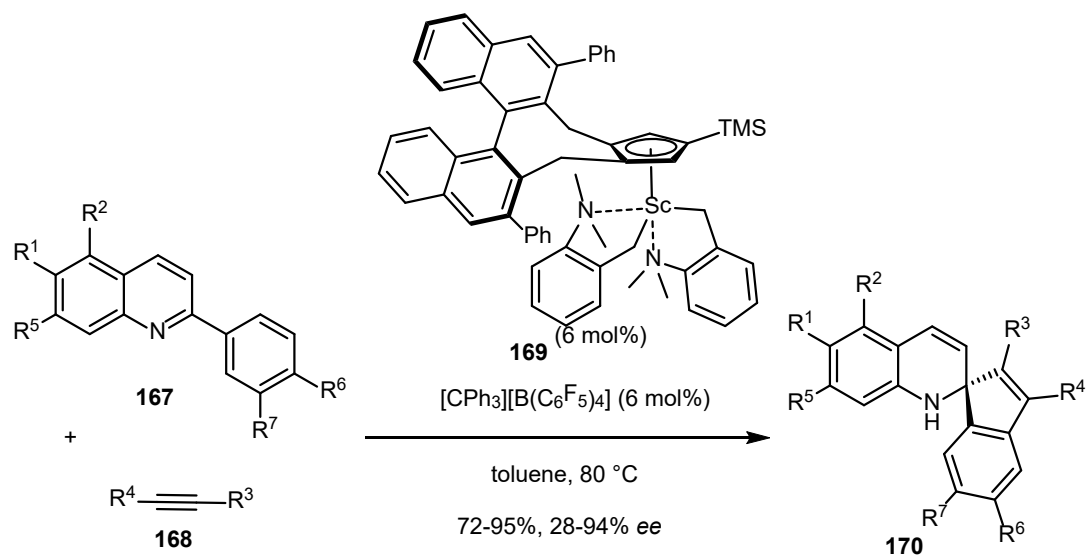


$\text{R} = \text{Bn}, o\text{-FC}_6\text{H}_4\text{CH}_2, m\text{-FC}_6\text{H}_4\text{CH}_2, m\text{-TolCH}_2, m\text{-MeOC}_6\text{H}_4\text{CH}_2, p\text{-FC}_6\text{H}_4\text{CH}_2,$
 $p\text{-ClC}_6\text{H}_4\text{CH}_2, p\text{-BrC}_6\text{H}_4\text{CH}_2, p\text{-IC}_6\text{H}_4\text{CH}_2, p\text{-F}_3\text{CC}_6\text{H}_4\text{CH}_2, p\text{-F}_3\text{COC}_6\text{H}_4\text{CH}_2,$
 $p\text{-TolCH}_2, 2\text{-NaphCH}_2, \text{allyl}, \text{BnCH}_2, n\text{-C}_{12}\text{H}_{25}, \text{HC}\equiv\text{CCH}_2$

Scheme 41. Domino addition/rearrangement reactions of ketones with α -diazoacetates.

In another area, Luo and Hou reported in 2021 an enantioselective dearomative spiroannulation of quinolines **167** with alkynes **168** catalyzed by 6 mol% of chiral half-sandwich scandium complex **169** bearing binaphthyl-substituted cyclopentadienyl ligands (Scheme 42).^[49] This domino process performed at 80 °C in toluene as solvent allowed the synthesis of chiral spiro-dihydroquinolines **170**

exhibiting a quaternary carbon center and an unprotected N–H group in good to high yields (72-95%) and variable enantioselectivities (28-94% *ee*). The presence of various substituents on the phenyl rings of quinolines was tolerated as well as different types of alkynes. The reaction proceeded through the C–H activation of the 2-aryl substituent in the quinoline substrate by the scandium catalyst followed by alkyne insertion into the Sc–aryl bond to give intermediate **AE** (Scheme 42). Then, the latter underwent dearomative nucleophilic 1,2-addition of the resulting scandium alkenyl species to the C=N unit in the quinoline moiety to provide intermediate **AF**, which was finally protonated into final product **170**. This domino C–H activation/alkyne insertion/dearomative nucleophilic 1,2-addition reaction allowed a novel family of N–H free chiral spiro-dihydroquinolines to be achieved, which are important molecules for medicinal chemistry.



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

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

$\text{R}^3 = \text{Ph, } p\text{-}t\text{-BuC}_6\text{H}_4, p\text{-PhC}_6\text{H}_4, p\text{-TMS C}_6\text{H}_4, p\text{-BrC}_6\text{H}_4,$

$p\text{-PhOC}_6\text{H}_4, 2\text{-Naph, } p\text{-ClC}_6\text{H}_4, \text{Me}_2\text{SiPh, Me}$

$\text{R}^4 = \text{Me, } c\text{-Pr, Ph}$

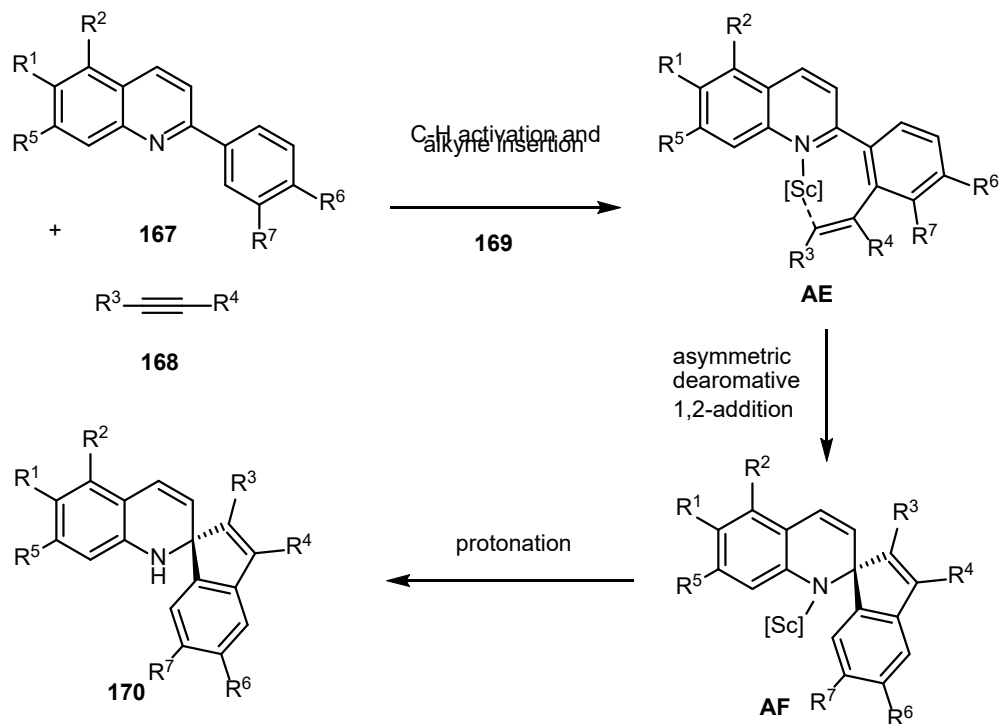
$\text{R}^5 = \text{H, Br, Me}$

$\text{R}^1, \text{R}^5 = (\text{CH}=\text{CH})_2$

$\text{R}^6 = \text{H, Me, } i\text{-Pr, } i\text{-Bu, Ph, Br, I, OPh, SMe}$

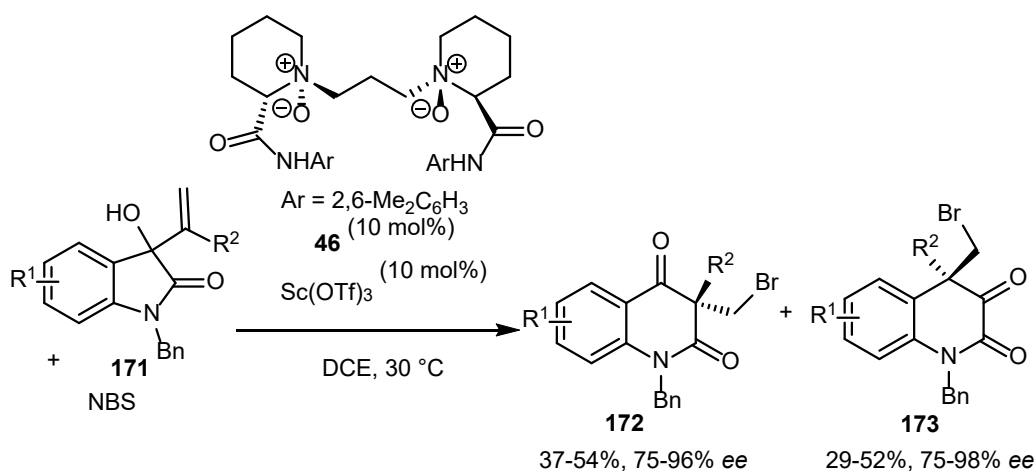
$\text{R}^7 = \text{H, Me}$

mechanism:



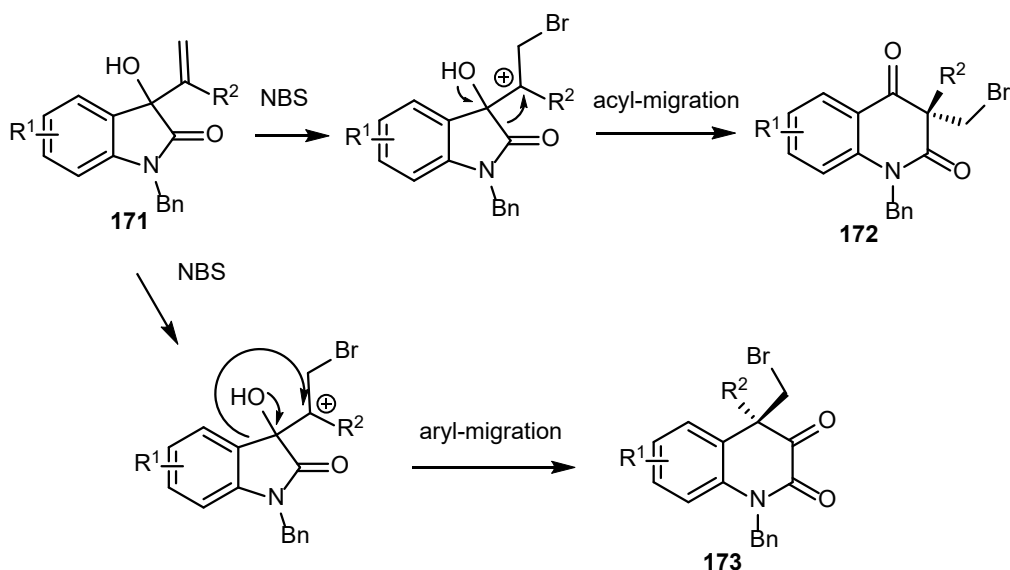
Scheme 42. Domino spiroannulation of 2-arylquinolines with alkynes.

In 2021, Feng and Cao described an enantioselective domino bromination/semipinacol rearrangement of isatin-derived allylic alcohols **171** with NBS promoted at 30 °C in DCE by 10 mol% of a chiral scandium catalyst *in situ* generated from *N,N'*-dioxide ligand **46** and Sc(OTf)₃.^[50] The process resulted in the formation of two types of chiral products, such as brominated dihydroquinoline-2,4-diones **172** arisen from an acyl-migration, and bromo-substituted dihydroquinoline-2,3-diones **173** generated from an aryl-migration (Scheme 43). A kinetic resolution yielded these two products exhibiting a quaternary stereocenter with moderate yields (37-54% and 29-52%, respectively for **172** and **173**) combined with moderate to excellent *ee* values (75-96% *ee* and 75-98% *ee*, respectively for **172** and **173**). This novel strategy will be useful for the synthesis of bioactive chiral bromo-substituted quinolone derivatives and quinoline alkaloids.



R¹ = H, 7-F, 7-Cl, 7-Br, 7-Me, 7-CF₃, 6-F, 6-Cl, 6-Br, 5-F, 5-Cl, 5-Br, 5-Me, 4-Cl, 4,6-F₂, 4,7-Cl₂, 4,7-Me₂
 R² = Ph, *m*-Tol, *m*-ClC₆H₄, *m*-FC₆H₄, *m*-MeOC₆H₄, *p*-FC₆H₄,
p-ClC₆H₄, *p*-PhC₆H₄, *p*-*t*-BuC₆H₄, 2-Naph, Cy

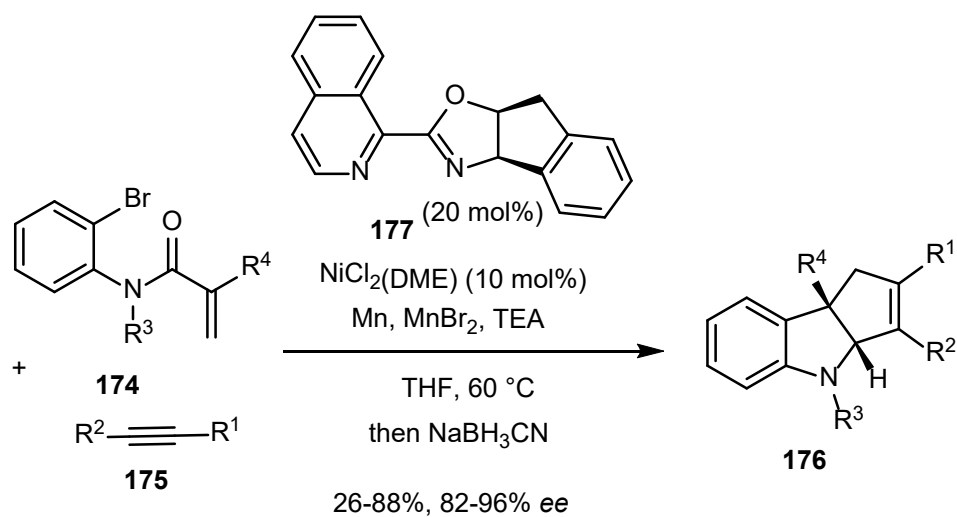
mechanism:



Scheme 43. Domino bromation/semipinacol rearrangement of isatin-derived allylic alcohols with NBS.

6 Enantioselective Nickel-Catalyzed Domino Reactions

Compared with many transition metals, nickel catalysts present the advantage to be cheaper and abundant.^[51] This usefulness has been applied in the development of enantioselective nickel-catalyzed transformations of many types,^[52] including domino reactions.^[53] In an example reported in 2019, Kong et al. described an enantioselective nickel-catalyzed domino reductive cyclization reaction of alkene-tethered aryl bromides **174** with internal alkynes **175**, resulting in the formation of the corresponding chiral substituted 2,3-fused cyclopentannulated indolines **176** after subsequent reduction with NaBH₃CN.^[54] The domino process was promoted at 60 °C in THF as solvent by a chiral nickel catalyst *in situ* generated from 10 mol% of NiCl₂(DME) as precatalyst and 20 mol% of chiral oxazoline ligand **177**. A wide variety of tricyclic products were produced with variable yields (26-88%) and uniformly high enantioselectivities (82-96% *ee*), as illustrated in Scheme 44. A possible mechanism is depicted in this Scheme, beginning with the oxidative addition of aryl bromide **174** to Ni(0) species followed by an intramolecular carbonickelation to produce σ -alkyl-Ni(II) species **AG**. The latter further underwent a regioselective migratory insertion of internal alkyne **175** to give seven-membered alkenylnickel species **AH**. Intramolecular nucleophilic addition of the nickel-carbon bond in **AH** to the amide led to nickel alkoxide intermediate **AI**, which subsequently underwent protonolysis to deliver the product and regenerated Ni(0) catalyst upon reduction.



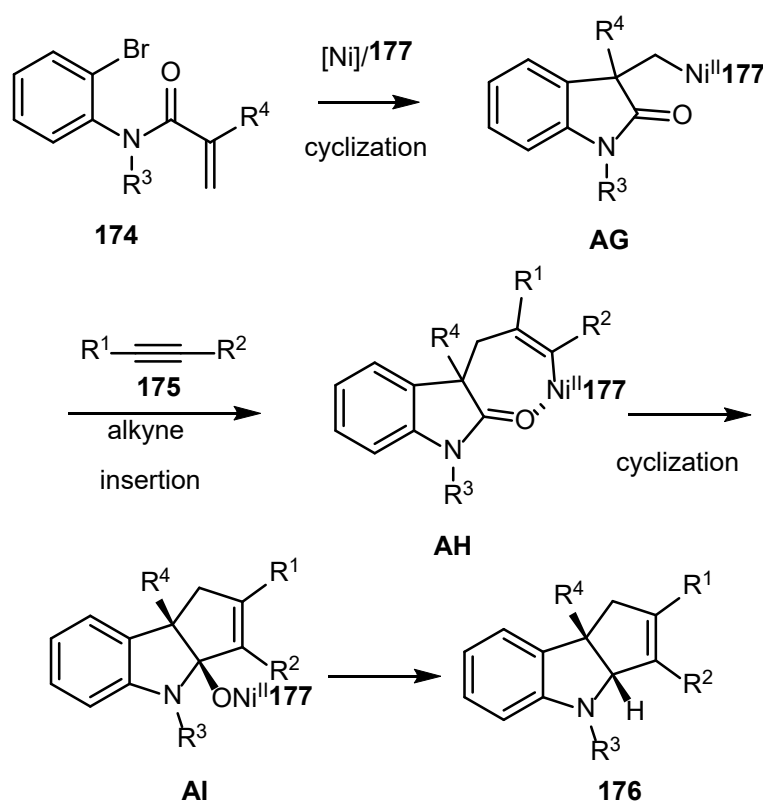
$R^1 = \text{Me, } n\text{-Pent, Ph, } n\text{-Pr}$

$R^2 = \text{Ph, } p\text{-MeOC}_6\text{H}_4, p\text{-Tol, } p\text{-ClC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, \text{2-Naph, } n\text{-Pr, PhC}\equiv\text{C,}$

$R^3 = \text{Me, Bn}$

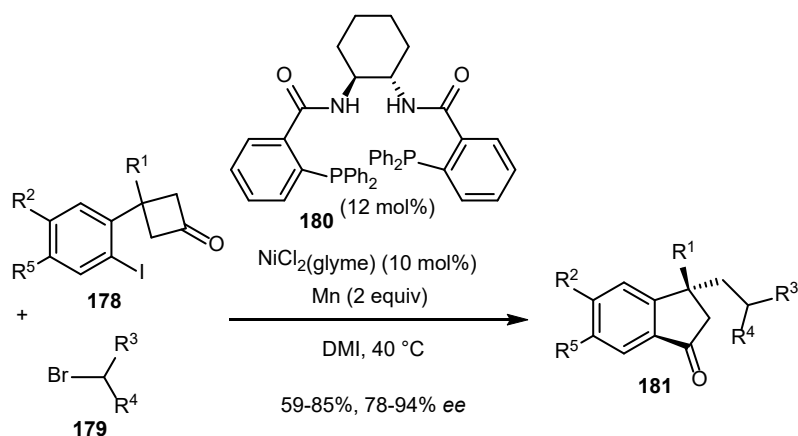
$R^4 = \text{Me, Bn, } n\text{-Hex}$

mechanism:



Scheme 44. Domino reductive cyclization reaction of alkene-tethered aryl bromides with internal alkynes.

In 2020, Wang et al. developed a novel enantioselective nickel-catalyzed domino ring-opening/cross-coupling reaction of aryl iodide-tethered cyclobutanones **178** with secondary alkyl bromides **179** as electrophilic coupling partners.^[55] As illustrated in Scheme 45, the reaction was promoted by a chiral nickel catalyst *in situ* generated from 10 mol% of NiCl₂(glyme) and 12 mol% of chiral bisphosphine ligand **180** in 1,3-dimethyl-2-imidazolidinone (DMI) as solvent. It occurred at 40 °C in the presence of Mn as reducing agent, thus forming a variety of chiral indanones **181** bearing a quaternary stereogenic center in moderate to good yields (59-85%) and good to high enantioselectivities (78-94% *ee*). An impressive variety of functional groups could be exhibited by the secondary alkyl bromides. The authors proposed the mechanism depicted in Scheme 45, starting with the generation of a Ni(0) species under reductive condition, which underwent oxidative addition with the tethered aryl iodide to form Ni(II) complex **AJ**. The latter was then reduced in the presence of Mn into the corresponding Ni(I) intermediate **AK**, which was subsequently submitted to enantioselective insertion into one of the two C(sp²)-C(sp³) σ-bonds of the cyclobutanone to give bicyclic Ni(III) complex **AL**. A further C(sp²)-C(sp²) reductive elimination provided alkyl Ni(I) intermediate **AM** exhibiting the indanone scaffold. Then, oxidative addition of the alkyl bromide to complex **AM** led to intermediate **AN** consisting of a combination of an alkyl radical and a Ni(II) species. Upon reductive elimination from intermediate **AO**, the indanone product was finally delivered. The Ni(0) species was regenerated for the next catalytic cycle via Mn-mediated reduction of Ni(I)Br.



R¹ = Me, Et, *n*-Pr

R² = H, Me, OMe, F, Cl

R³ = *n*-Hept, Cy, F(CH₂)₄, Cl(CH₂)₅, HO(CH₂)₂, MeOCH₂, NC(CH₂)₃, (CH₂)₅,

Cy(CH₂)₂O₂C(CH₂)₅, MeO₂C(CH₂)₄, PhO₂C(CH₂)₄, *p*-ClC₆H₄O₂C(CH₂)₄,

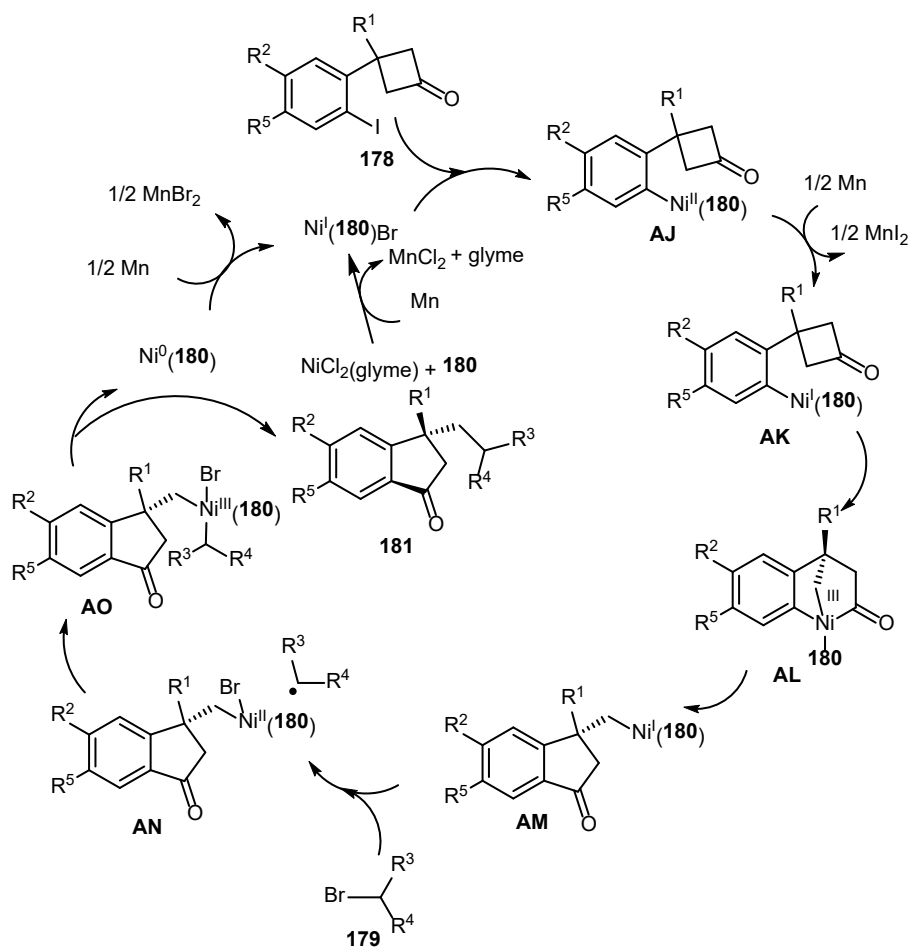
F₃CH₂O₂C(CH₂)₄, (2-adamantyl)O₂C(CH₂)₄, *n*-Bu, AcO(CH₂)₅, (CH₂)₅

R⁴ = H, *n*-Bu

R³, R⁴ = (CH₂)₅, (CH₂)₆, (CH₂)₂O(CH₂)₂

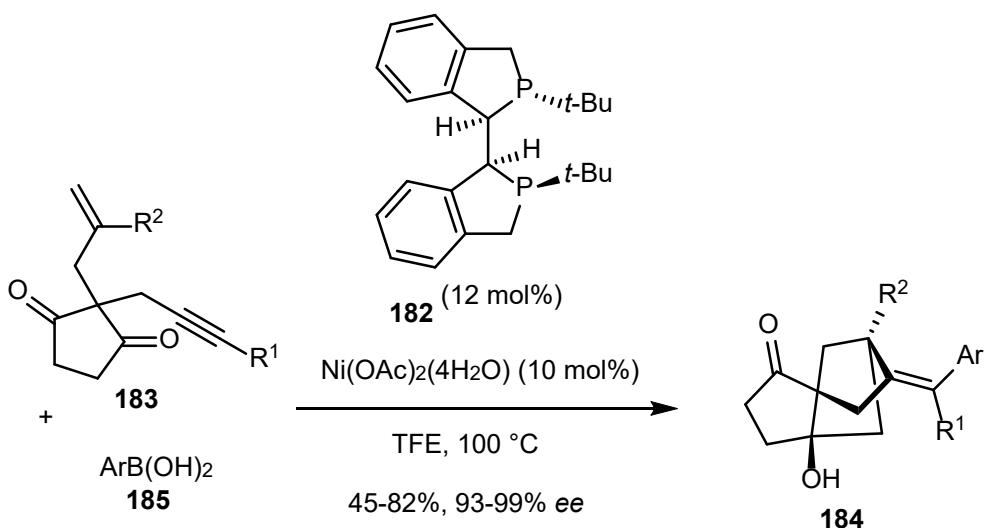
R⁵ = H, Me, OMe

mechanism:



Scheme 45. Domino ring-opening/cross-coupling reaction of aryl iodide-tethered cyclobutanones with secondary alkyl bromides.

In 2020, an enantioselective nickel-catalyzed domino addition/cyclization reaction was developed by Kong et al.^[56] It involved the coupling of an alkyne, a ketone and an alkene promoted by a combination of 10 mol% of Ni(OAc)₂·4H₂O as precatalyst and 12 mol% of chiral bisphosphine **182** as ligand. As illustrated in Scheme 46, the domino reaction of 1,3-diketone-tethered 1,6-enynes **183** with aryl boronic acids **185** occurred regio- and enantioselectively at 100 °C in trifluoroethane (TFE) as solvent to afford the corresponding chiral bridged tricyclo[5.2.1.0^{1,5}]decanes **184** bearing three quaternary stereocenters in moderate to high yields (45-82%) and uniformly excellent enantioselectivities (93-99% *ee*). The latter were generated through regioselective 1,2-addition of the aryl boronic acids to the alkynes followed by enantioselective cyclization with the unactivated alkenes. A wide variety of *para*-substituted arylboronic acids were compatible including those with different types of functional groups. *Meta*- and *ortho*-substituted substrates as well as heteroaryl boronic acids also reacted with high *ee* values. Furthermore, high enantioselectivities were obtained in the reaction of differently substituted 1,3-diketone-tethered 1,6-enynes. To explain the results, the authors proposed the mechanism depicted in Scheme 46, beginning with the transmetallation of the aryl boronic acid with the chiral nickel complex **AP** to give nickel intermediate **AQ**. Subsequently, 1,2-addition of the latter to the triple bond of the 1,3-diketone generated alkenylnickel intermediate **AR**, which further underwent intramolecular insertion into the double bond to afford σ -alkylnickel intermediate **AS**. A subsequent nucleophilic cyclization of **AS** led to nickel alkoxide species **AT**. A final protonolysis delivered the product along with regenerated active nickel catalyst.

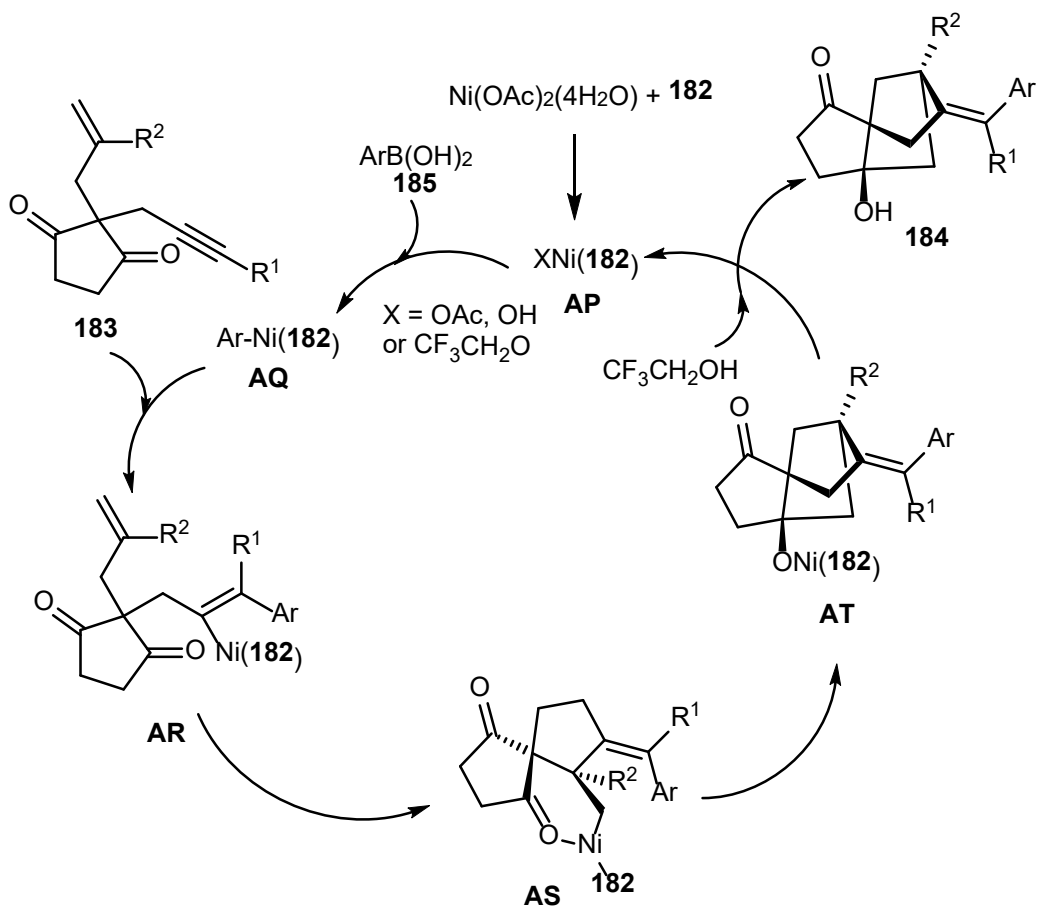


$\text{R}^1 = \text{Me, Ph, } p\text{-NCC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, n\text{-Pent, Bn, allyl, TBSOCH}_2, \text{BzOCH}_2, \text{HOCH}_2,$

$\text{R}^2 = \text{Me, Ph, MeOCH}_2, \text{CO}_2\text{Me,}$

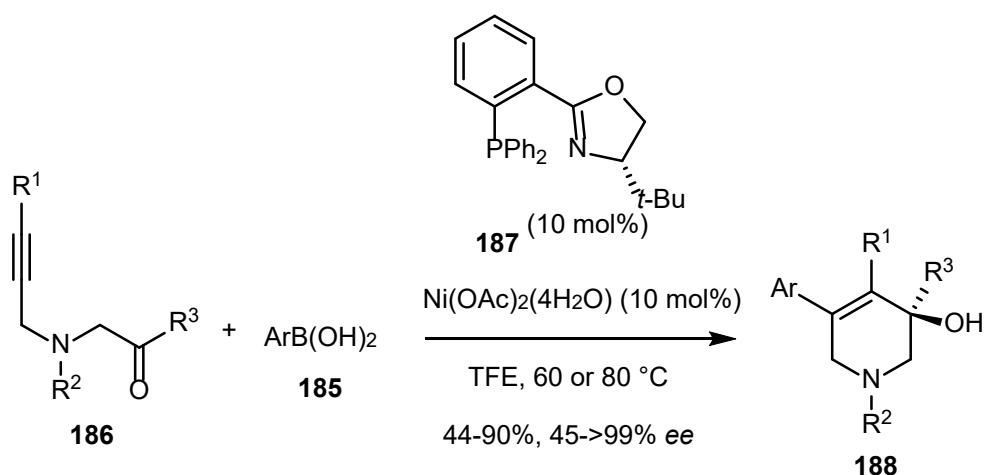
$\text{Ar} = \text{Ph, } p\text{-PhC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, p\text{-MeO}_2\text{SC}_6\text{H}_4, p\text{-F}_3\text{COC}_6\text{H}_4, p\text{-O}_2\text{NC}_6\text{H}_4, p\text{-OHCC}_6\text{H}_4, p\text{-AcC}_6\text{H}_4, p\text{-Me}_2\text{NOCC}_6\text{H}_4, p\text{-EtO}_2\text{CC}_6\text{H}_4, m\text{-IC}_6\text{H}_4, 3\text{-F-4-MeC}_6\text{H}_3, 2,4\text{-F}_2\text{C}_6\text{H}_3, 2\text{-Naph,}$

mechanism:



Scheme 46. Domino addition/cyclization reaction of 1,3-diketone-tethered 1,6-enynes with aryl boronic acids.

Later in 2021, Lam et al. disclosed an enantioselective nickel-catalyzed domino addition/cyclization reaction of alkyne-tethered ketones **186** with aryl boronic acids **185**.^[57] A combination of 10 mol% of chiral phosphine-oxazoline ligand **187** with the same quantity of Ni(OAc)₂·4H₂O as precatalyst was employed as catalyst system at 60 or 80 °C in TFE as solvent, which resulted in the formation of chiral 1,2,3,6-tetrahydropyridines **188** bearing a tertiary alcohol in moderate to high yields (44-90%) and moderate to excellent enantioselectivities (45->99% *ee*), as illustrated in Scheme 47. In addition to a variety of aryl alkyl ketones, dialkyl ketones were well tolerated in these reactions. Regarding the alkynyl substituent of the alkynyl ketone, the catalyst system tolerated differently substituted phenyl groups. In all cases of substrates studied, the *ee* values were $\geq 94\%$ *ee* excepted in the reaction of a substrate exhibiting a vinyl group (R¹ = CH=CH₂) which delivered the desired product with only 45% *ee*. Related to the fact that many important natural products include in their structure a 4,5-diaryl-1,2,3,6-tetrahydropyridine ring system, this novel domino reaction was welcome.



R¹ = Ph, MeO₂CC₆H₄, *m*-MeOC₆H₄, CH₂=CH

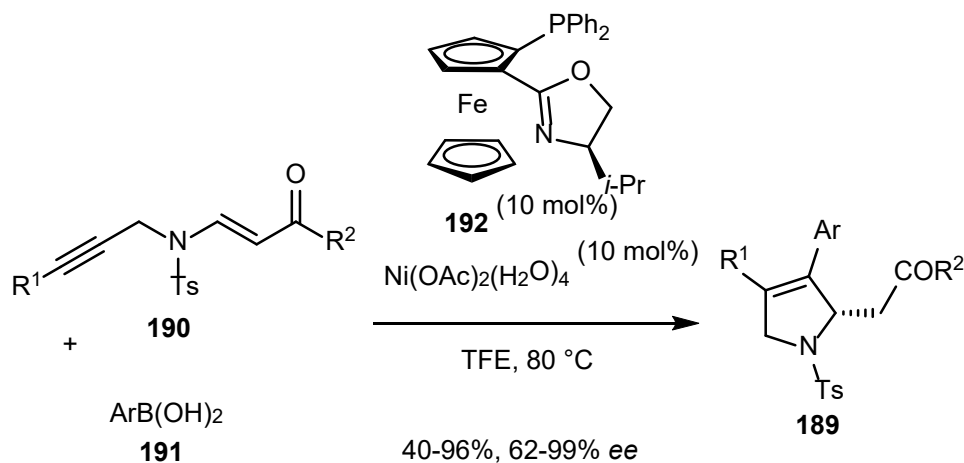
R² = Ts, Ns

R³ = Ph, *p*-ClC₆H₄, *m*-F₃CC₆H₄, *o*-Tol, Me, *i*-Pr, MeO₂C(CH₂)₂, Et

Ar = Ph, *p*-TMSC₆H₄, *m*-HOC₆H₄, *o*-ClC₆H₄, 2-Naph, 2-thienyl

Scheme 47. Domino addition/cyclization reaction of alkyne-tethered ketones with aryl boronic acids.

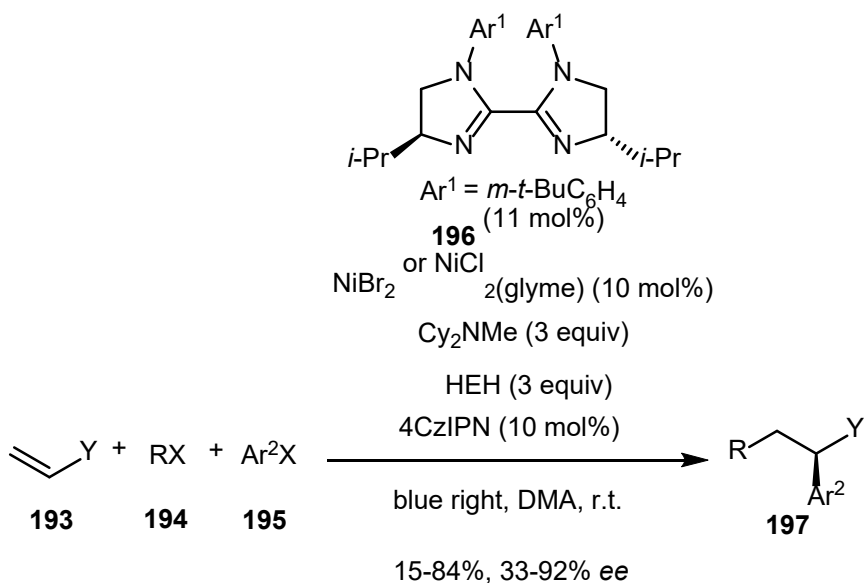
In 2022, Iqbal and Cho described an original novel methodology to synthesize 2,3,4-trisubstituted chiral 3-pyrrolines **189** on the basis of an enantioselective nickel-catalyzed domino addition/cyclization reaction of various alkyne-tethered *N*-sulfonamide acrylates **190** with (hetero)arylboronic acids **191**.^[58] The reaction employed 10 mol% of Ni(OAc)₂·4H₂O as precatalyst and the same quantity of chiral phosphinoferrocenyloxazoline ligand **192**. Performed at 80 °C in TFE as solvent, it led to a wide range of highly functionalized chiral 3-pyrrolines **189** with both moderate to excellent yields (40-96%) and enantioselectivities (62-99% *ee*), as shown in Scheme 48.



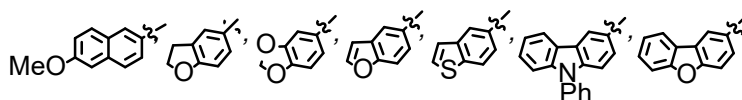
Ar = *p*-Tol, 3,4-Me₂C₆H₃, *p*-*i*-PrC₆H₄, *p*-MeOC₆H₄, *o*-H₂NC₆H₄, *p*-AcC₆H₄,
p-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *m*-F₃CC₆H₄, 2-thienyl, 2-pyridinyl, Ph
 R¹ = Ph, *m*-Tol, *p*-F₃CC₆H₄, *p*-*t*-BuC₆H₄, *p*-MeOC₆H₄, *p*-PhC₆H₄, *p*-FC₆H₄,
p-ClC₆H₄, *m*-NCC₆H₄, *p*-HOC₆H₄, *m*-(CH₂=CH)C₆H₄, (*E*)-PhCH=CH
 R² = OMe, OEt, Me, Ph, 2-thienyl

Scheme 48. Domino addition/cyclization reaction of alkyne-tethered *N*-sulfonamide acrylates with arylboronic acids.

Earlier in 2021, Mao and Walsh described an enantioselective three-component domino alkylation/arylation reaction of acrylates **193** with alkyl halides **194** and aryl halides **195** promoted under asymmetric nickel and photoredox catalysis (Scheme 49).^[59] The catalyst system consisted in a combination of 10 mol% of NiBr₂ or NiCl₂(glyme) and 11 mol% of chiral bis-(3-imidazoline) ligand **196** employed at room temperature in DMA as solvent. The reaction was performed under blue light in the presence of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) as photocatalyst and Hantzsch ester (HEH) as reductant. The radical cascade allowed a wide range of chiral nonsteroidal anti-inflammatory drug derivatives **197** with potential use in medicinal chemistry to be achieved in low to good yields (15-84%) and moderate to high enantioselectivities (33-92% *ee*). This reductive cross-coupling process presented the advantage to avoid the use of stoichiometric metal reductants which were replaced by an organic reductant, such as Hantzsch ester. An impressive broad range of functional groups were well tolerated.

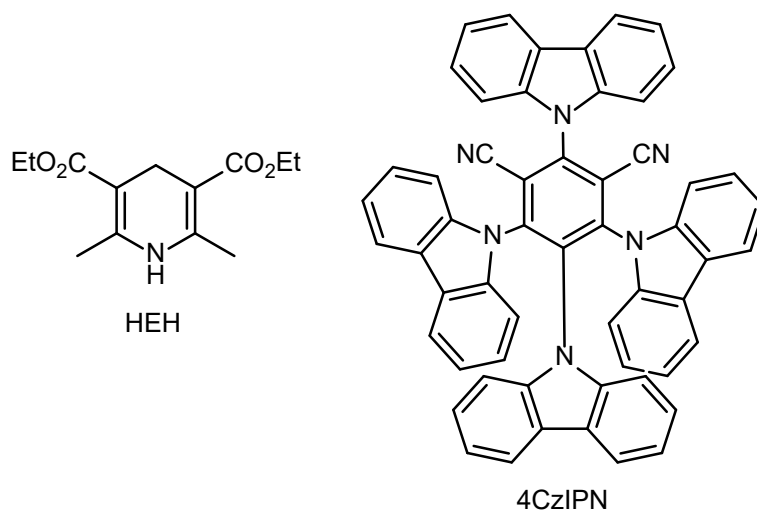


$Ar^2 = p\text{-AcC}_6\text{H}_4, p\text{-MeO}_2\text{CC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, p\text{-OHCC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4,$
 $p\text{-F}_3\text{COC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, \text{Ph}, p\text{-PhC}_6\text{H}_4, p\text{-}t\text{-BuC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4,$
 $p\text{-MeSC}_6\text{H}_4, p\text{-Me}_2\text{NC}_6\text{H}_4, p\text{-pinBC}_6\text{H}_4, m\text{-AcC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4,$
 $3\text{-F-4-MeC}_6\text{H}_3, 3\text{-F-4-PhC}_6\text{H}_3, 2\text{-Naph},$



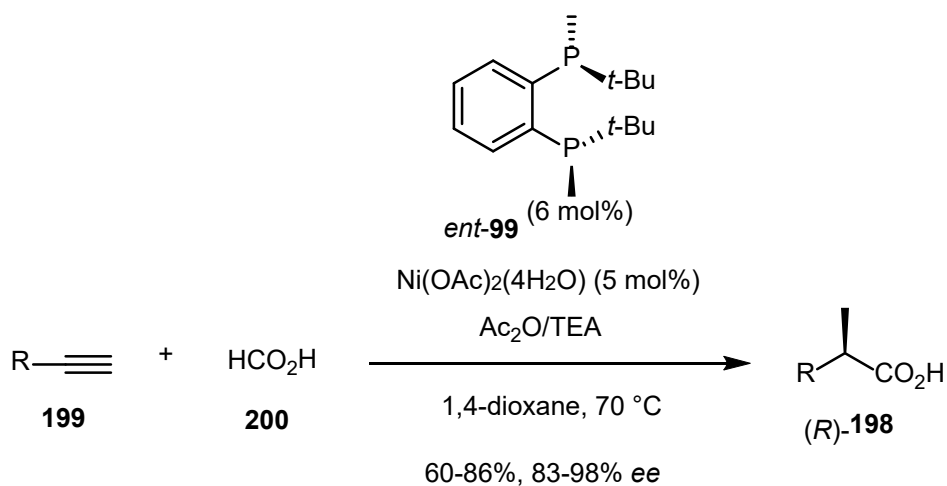
$R = Me_2EtC, Bn(CH_2)_2C(Me)_2, BnCH_2C(Me)_2, BzO(CH_2)_2C(Me)_2,$
 $p\text{-NCC}_6\text{H}_4CO_2(CH_2)_2C(Me)_2, (4\text{-pyridyl})CO_2(CH_2)_2C(Me)_2,$
 $(2\text{-thienyl})CO_2(CH_2)_2C(Me)_2, (2\text{-furyl})CO_2(CH_2)_2C(Me)_2,$
 $Ph_2CHCH_2CO_2(CH_2)_2C(Me)_2, Bz(CH_2)_2CO_2C(Me)_2, Et_2CMe, n\text{-Bu},$
 $i\text{-Pr}, c\text{-Pent}, Cy, c\text{-Hept}, c\text{-Oct}, t\text{-Bu},$
 $X = Br, I$

 $Y = CO_2t\text{-Bu}, CONHPh, OBz$

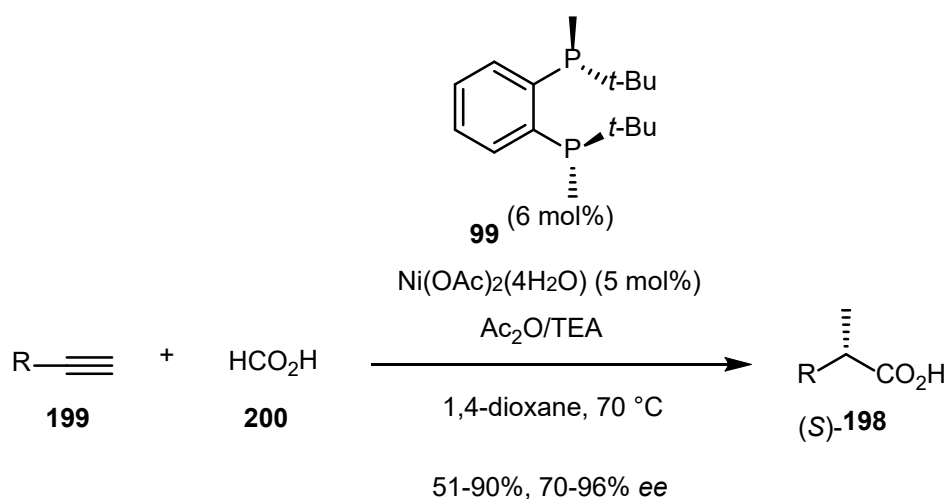


Scheme 49. Three-component domino alkylation/arylation reaction of acrylates, alkyl halides and aryl halides.

In 2022, Ma, Zhou and Tang reported a novel asymmetric synthesis of α -chiral carboxylic acids **198** based on an enantioselective nickel-catalyzed domino reaction involving an alkyne hydrocarboxylation of the corresponding terminal alkynes **199** with formic acid **200** followed by a transfer hydrogenation.^[60] The catalyst was *in situ* generated from 6 mol% of bisphosphine ligand *ent*-**99** and 5 mol% of Ni(OAc)₂·4H₂O as precatalyst in 1,4-dioxane as solvent. The reaction afforded a series of aryl- and benzyl-substituted α -chiral carboxylic acids (*R*)-**198** in good yields (60-86%) and homogeneously high enantioselectivities (83-98% *ee*), as illustrated in Scheme 50. Using enantiomeric bisphosphine ligand **99**, enantiomeric α -chiral carboxylic acids (*S*)-**198** were synthesized under the same conditions with moderate to high yields (51-90%) and good enantioselectivities (70-96% *ee*), as shown in Scheme 50. In this case, aliphatic terminal alkynes all reacted with $\geq 90\%$ *ee* while an heteroaromatic substrate (R = 2-thienyl) afforded the corresponding (*S*)-product with only 70% *ee*.



R = Ph, *o*-Tol, *o*-MeOC₆H₄, *o*-FC₆H₄, *o*-ClC₆H₄, *m*-MeOC₆H₄,
p-FC₆H₄, Bn, *p*-Tol, *p*-MeOC₆H₄, *p*-FC₆H₄, *p*-ClC₆H₄CH₂

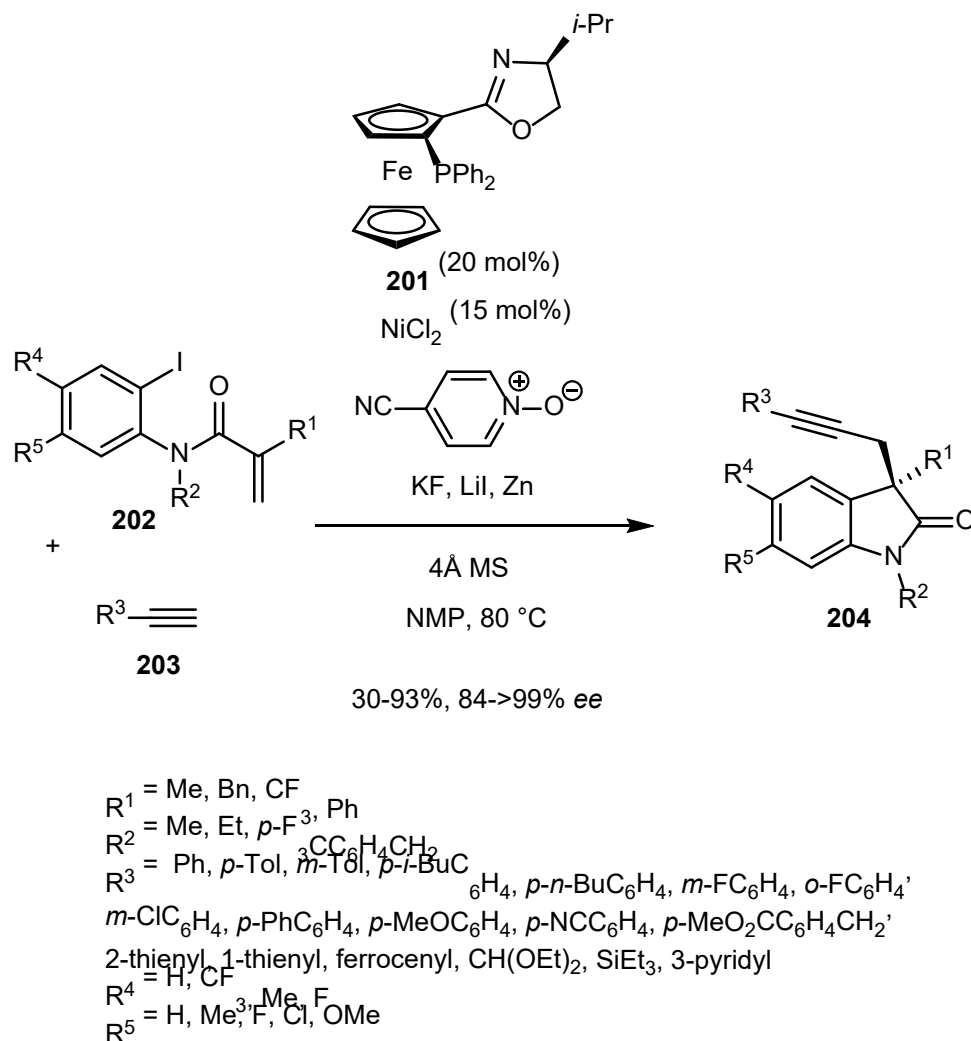


R = 2-thienyl, *m*-TolCH₂, 3,5-MeO₂C₆H₄CH₂, BzNHCH₂,
 BnCH₂, BzO(CH₂)₂, *o*-BrC₆H₄CO₂(CH₂)₂, BzO(CH₂)₄,
o-BrC₆H₄CO₂(CH₂)₄, MeO₂CCH₂

Scheme 50. Domino hydrocarboxylation/hydrogenation reactions of terminal alkynes with formic acid.

In order to propose a complementary methodology to achieve palladium-catalyzed enantioselective domino Heck/Sonogashira reactions, Liao and Tian investigated in 2022 a cheaper and more environmentally friendly chiral nickel catalyst to promote these reactions.^[61] As shown in Scheme 51, the optimal catalyst was *in situ* generated from 15 mol% of NiCl₂ as precatalyst and 20 mol% of chiral phosphinoferrocenylloxazoline ligand **201**. Performed at 80 °C in 1-methyl-2-pyrrolidinone (NMP) as solvent in the presence of 4-cyanopyridine *N*-oxide as base and KF and LiI as additives, the asymmetric domino Heck/Sonogashira reaction of a wide variety of *N*-(2-iodophenyl)-*N*-alkylmethacrylamides **202** with terminal alkynes **203** afforded the corresponding chiral 3,3-disubstituted-2-oxindoles **204** with moderate to high yields (30-93%) and uniformly high

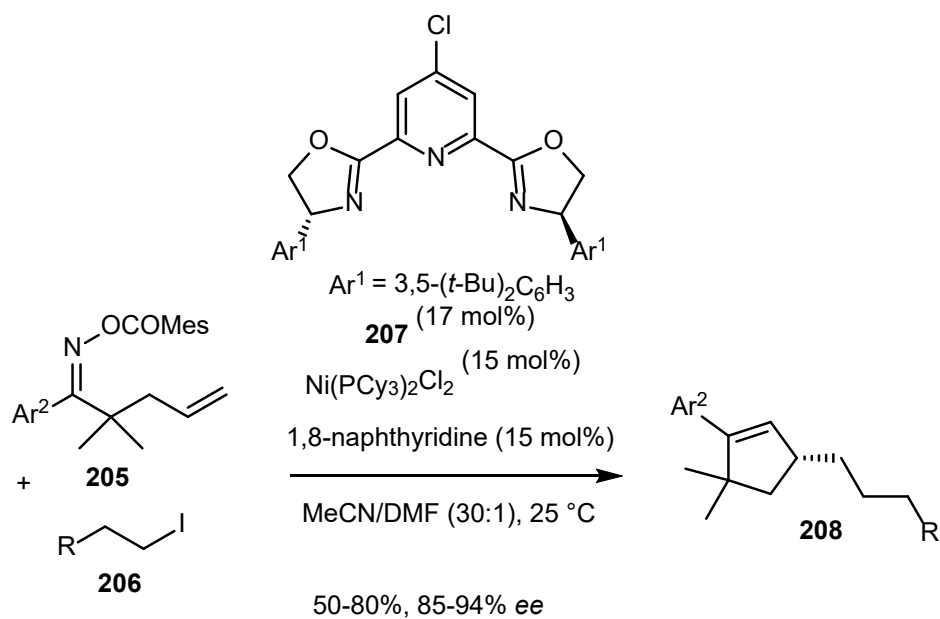
enantioselectivities (84->99% *ee*). In particular, a range of potentially bioactive chiral trifluoromethyl-disubstituted 2-oxindoles ($R^1 = \text{CF}_3$) were produced with good yields (40-91%) and excellent *ee* values (87-98% *ee*) from the reaction of the corresponding trifluoromethyl-substituted *o*-iodoacrylanilides with terminal alkynes.



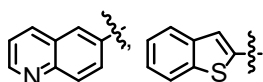
Scheme 51. Domino Heck/Sonogashira reaction of *N*-(2-iodophenyl)-*N*-alkylmethacrylamides with terminal alkynes.

In 2022, Shu et al. reported a highly enantioselective reductive *N*-cyclization/alkylation of alkene-tethered oxime esters **205** with alkyl iodides **206** through asymmetric nickel catalysis (Scheme 52).^[62] This work represents the first highly enantioselective domino aza-Heck-type/cross-coupling reaction. It required the use of 15 mol% of $\text{Ni}(\text{PCy}_3)_2\text{Cl}_2$ as precatalyst combined with 17 mol% of chiral pyridinebis-(oxazoline) ligand **207** in the presence of 1,8-naphthyridine as an additive and four equivalents of zinc as reductor agent. Performed at 25 °C in a 30:1 mixture of acetonitrile and DMF as solvent, this challenging difunctionalization of alkenes afforded a wide range of variously substituted chiral pyrrolines **208** with moderate to high yields (50-80%) and high enantioselectivities (85-94% *ee*). A possible mechanism is proposed in Scheme 52, beginning with the reaction of the oxime ester with the chiral $\text{Ni}(0)$ catalyst to give intermediate **AU**. Then, the latter underwent an enantioselective migratory insertion into alkene to afford cyclized intermediate **AV**. The combination of this $\text{Ni}(\text{II})$

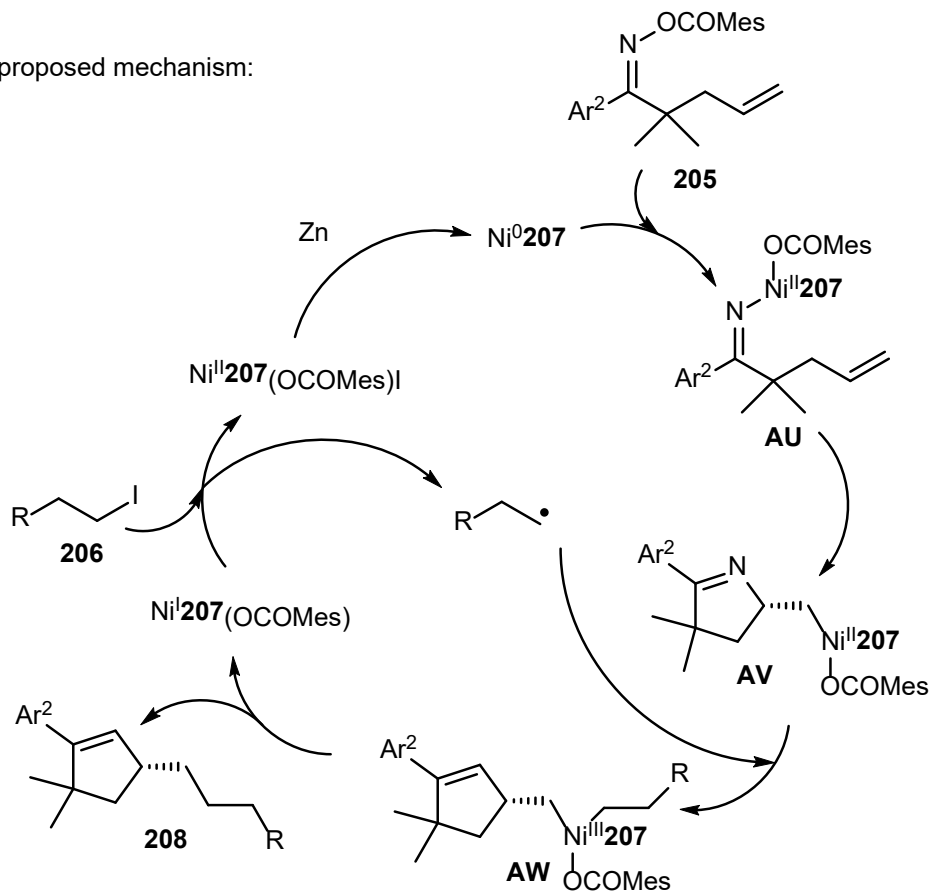
species with an alkyl radical, followed by reductive elimination, provided the final product along with Ni(I) complex. The alkyl radical could be generated by the reaction of the alkyl iodide with Ni(I) species.



$\text{R} = \text{Et}, \text{C}_6\text{H}_{13}, p\text{-BrC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, \text{FCH}_2, \text{ClCH}_2, \text{CF}_3, \text{AcO}(\text{CH}_2)_2, \text{MeOCH}_2,$
 $\text{AcO}(\text{CH}_2)_2, \text{TBSOCH}_2, \text{MeO}(\text{CH}_2)_2, \text{CO}_2\text{Et}, \text{Ac}, \text{BocNH}(\text{CH}_2)_4, (\text{Me})_2\text{C}=\text{CH}$
 $\text{Ar}^2 = p\text{-t-BuC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, 3,4\text{-F}_2\text{C}_6\text{H}_3, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4,$
 $p\text{-MeO}_2\text{CC}_6\text{H}_4, p\text{-Tol}, 3,5\text{-Me}_2\text{C}_6\text{H}_3, o\text{-Tol}, 2\text{-Naph}, 2\text{-thienyl}, \text{Ph}, (E)\text{-PhCH}=\text{CH},$

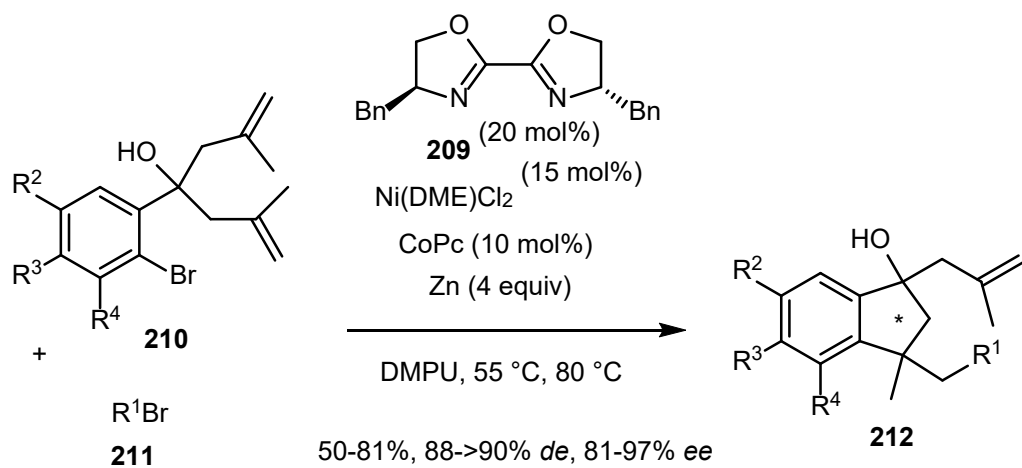


proposed mechanism:



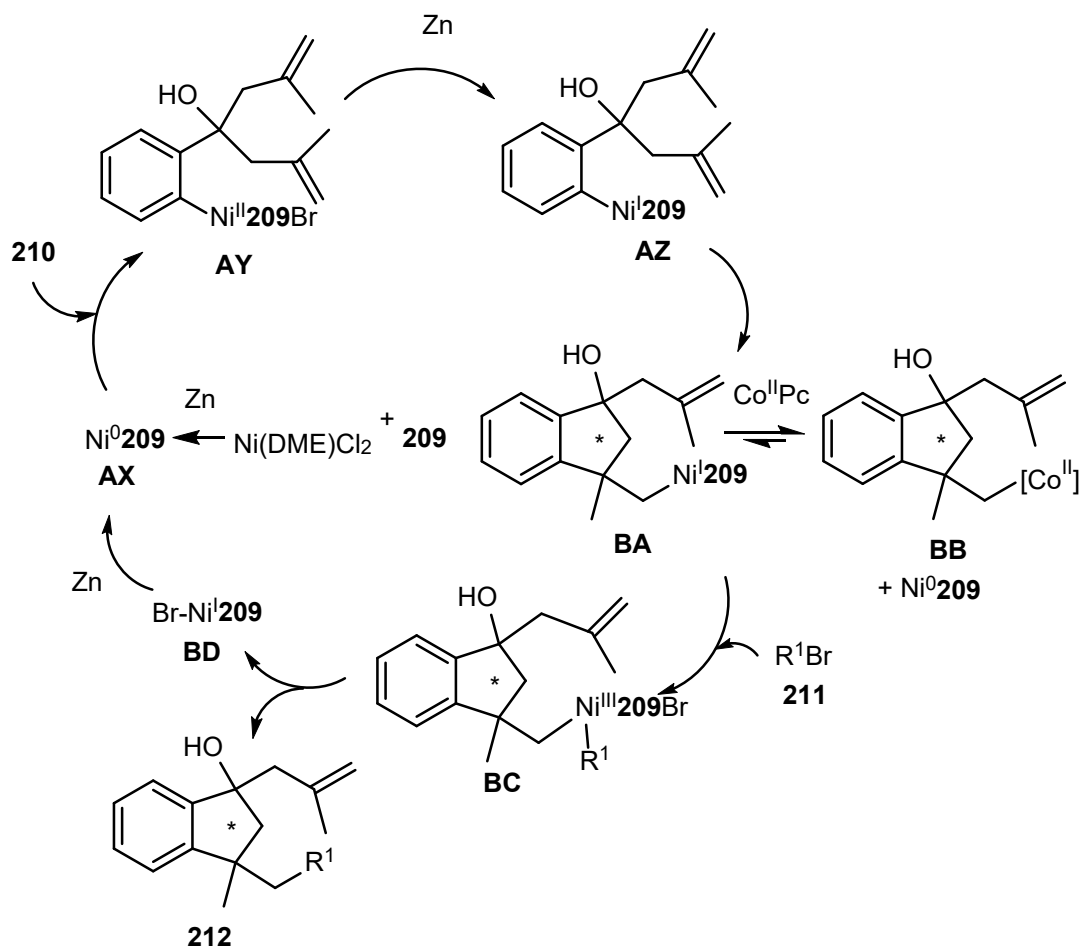
Scheme 52. Domino aza-Heck-type/cross-coupling reaction of oxime ester-tethered alkenes with alkyl iodides.

An enantioselective reductive domino cyclization/coupling reaction of 1,6-dienes with alkyl bromides was disclosed by Zhou et al., in 2022.^[63] The desymmetrization process was performed at 55 °C in DMPU as solvent in the presence of 15 mol% of [Ni(DME)Cl₂] as precatalyst, 20 mol% of chiral bisoxazoline ligand **209**, zinc as reductor, and cobalt phthalocyanine (CoPc) as additive. A range of 1,6-dienes **210** and alkyl bromides **211** reacted smoothly to afford the corresponding chiral cyclic tertiary alcohols **212** containing a chiral quaternary stereocenter with moderate to good yields (50-81%) and uniformly high diastereo- (88->90% *de*) and enantioselectivities (81-97% *ee*), as presented in Scheme 53. To explain their results, the authors proposed the mechanism depicted in this Scheme. In a first time, precatalyst [Ni(DME)Cl₂] was reduced by zinc to active Ni⁰ catalyst **AX**, which reacted with the aryl bromide included in diene **209** to form ArNi^{II} intermediate **AY**. The latter was subsequently reduced by zinc to give ArNi^I intermediate **AZ**, which underwent a migratory insertion into one C=C bond of the diene, thus generating alkyl Ni^I intermediate **BA**. Then, oxidative addition of intermediate **BA** with the alkyl bromide led to intermediate **BC**, which released the product along with Ni^I species **BD** through reductive elimination. Finally, **BD** was reduced by zinc to give regenerated Ni⁰ complex **AX**. The very active alkyl Ni^I intermediate **BA** could be stabilized by cobalt phthalocyanine (CoPc) through a redox equilibration, forming alkyl Co^{III} intermediate **BB**.



$R^1 = n-Oct, n-Hex, t-Bu(CH_2)_2, CH_2=CH(CH_2)_7, Cy(CH_2)_2, BnCH_2, Bn(CH_2)_3,$
 $TBSO(CH_2)_4, MeO(CH_2)_4, MeO_2C(CH_2)_6, F(CH_2)_5, Cl(CH_2)_6, \text{cyclohexane ring}-(CH_2)_4$
 $R^2 = H, OMe, Me, F, Cl, OBn, OH, NMe_2$
 $R^3 = H, OMe, Me$
 $R^2, R^3 = OCH_2O$
 $R^4 = H, Me$
 $R^3, R^4 = (CH=CH)_2$

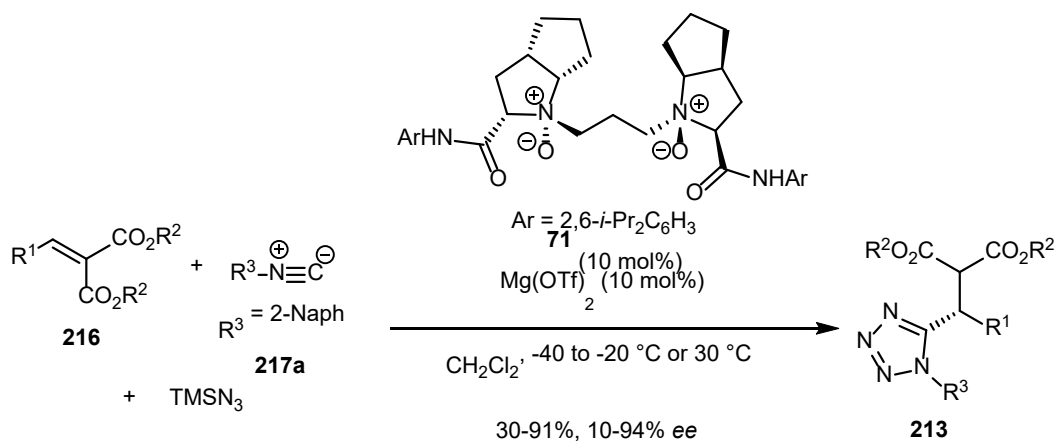
proposed mechanism (with $R^2 = R_3 = R_4 = H$):



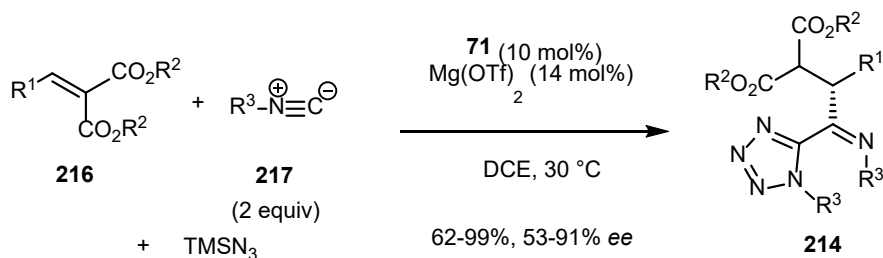
Scheme 53. Domino cyclization/coupling reaction of 1,6-dienes with alkyl bromides.

7 Enantioselective Magnesium-Catalyzed Domino Reactions

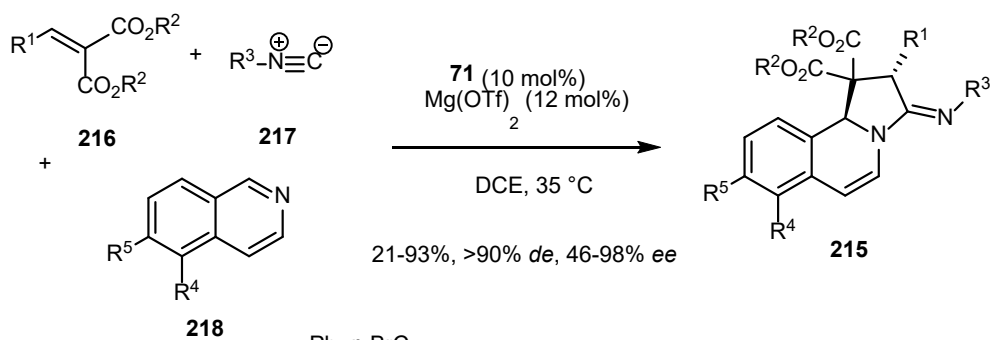
In 1992, Corey and Ishihara described the first ecological and economical enantioselective magnesium-catalyzed transformations.^[64] Ever since, many types of chiral magnesium catalysts have been designed and developed as mild Lewis acids to promote a diversity of enantioselective processes generally performed under mild reaction conditions, including domino reactions.^[1m,65] Chiral *N,N'*-dioxide ligands have been widely employed in the asymmetric catalysis of enantioselective magnesium-promoted isocyanide-based multicomponent reactions. In an example described in 2019, Feng et al. developed asymmetric syntheses of different types of chiral heterocyclic products, including 1,5-disubstituted tetrazoles **213** and **214**, and tricyclic 1,2-dihydroisoquinoline-based amidine derivatives **215** (Scheme 54).^[66] All the multicomponent reactions, occurring between alkylidene malonates **216**, isocyanides **217** and TMSN₃ or isoquinolines **218**, were performed in dichloromethane or DCE as solvent by using a chiral magnesium catalyst *in situ* generated from 10-14 mol% of Mg(OTf)₂ and 10 mol% of chiral *N,N'*-dioxide ligand **71**. When the three-component reaction of alkylidene malonates **216**, isocyanides **217** and TMSN₃ was performed at -40 to -20 °C for alkyl-substituted alkylidene malonates or 30 °C for aryl-substituted alkylidene malonates in the presence of 10 mol% of Mg(OTf)₂, it afforded the corresponding chiral tetrazoles **213** with both variable yields (30-91%) and enantioselectivities (10-94% *ee*), as shown in Scheme 54 (first equation). The authors found that performing the reaction at 30 °C in DCE as solvent and by using 14 mol% of Mg(OTf)₂, resulted in the formation of another types of products, such as chiral tetrazoles **215**, arisen from a pseudo-four-component reaction involving two equivalents of isocyanides **217**. These products were obtained in good to quantitative yields (62-99%) and moderate to excellent enantioselectivities (53-91% *ee*), as presented in Scheme 54 (second equation). In addition, enantioselective three-component reaction between alkylidene malonates **216**, isocyanides **217** and isoquinolines **218** were achieved at 35 °C in DCE as solvent by using 12 mol% of Mg(OTf)₂, thus providing chiral tricyclic products **215** as almost single diastereomers (>90% *de*) with low to high yields (21-93%) and moderate to excellent *ee* values (46-98% *ee*), as illustrated in Scheme 54 (third equation). It was found that the enantioselectivity decreased dramatically when aromatic isocyanides or less bulky aliphatic isocyanides were used.



$\text{R}^1 = \text{Cy, } c\text{-Hept, } c\text{-Pent, } c\text{-Bu, } c\text{-Pr, } i\text{-Pr, Me, } i\text{-Bu, } n\text{-Bu, Ph, } p\text{-Tol, } m\text{-Tol, } p\text{-BrC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, 2\text{-Naph}$
 $\text{R}^2 = \text{Me, Et, } i\text{-Pr, Bn}$



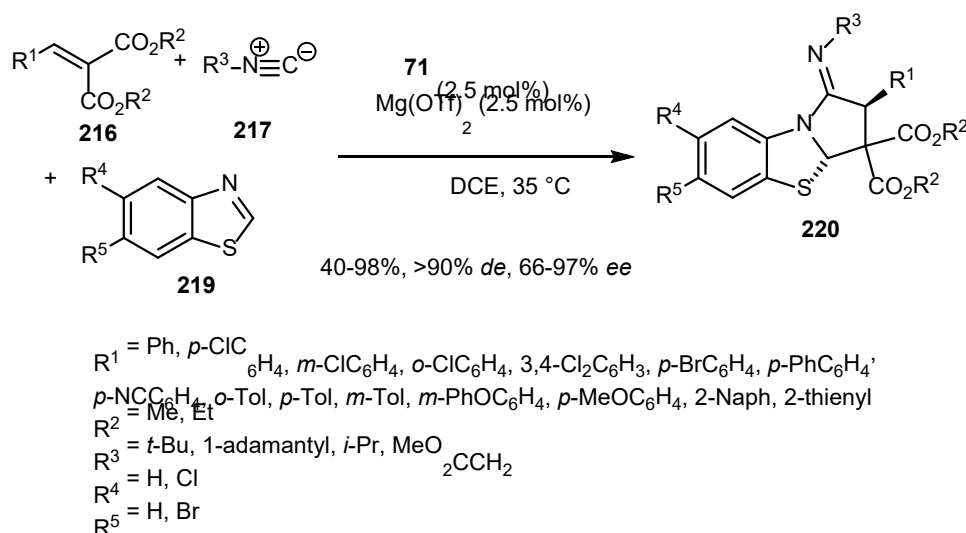
$\text{R}^1 = \text{Cy, } c\text{-Hept, } c\text{-Pent, } c\text{-Bu, } t\text{-Bu, } i\text{-Bu, } i\text{-Pr, Ph, } p\text{-MeOC}_6\text{H}_4, p\text{-CNC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, o\text{-ClC}_6\text{H}_4, m\text{-Tol, } 2\text{-Naph}$
 $\text{R}^2 = \text{Me, Et, Bn, } i\text{-Pr}$
 $\text{R}^3 = 2\text{-Naph, } p\text{-MeOC}_6\text{H}_4, \text{ (fused ring system)}$



$\text{R}^1 = \text{Ph, } p\text{-BrC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, p\text{-Tol, } m\text{-Tol, } 2\text{-Naph, } p\text{-MeOC}_6\text{H}_4, p\text{-CNC}_6\text{H}_4, c\text{-Hept}$
 $\text{R}^2 = \text{Me, Et}$
 $\text{R}^3 = t\text{-Bu, } 1\text{-adamantyl, } i\text{-Pr, MeO}_2\text{CCH}_2, 2\text{-Naph}$
 $\text{R}^4 = \text{H, NO}$
 $\text{R}^5 = \text{H, CN}^2, \text{OMe}$

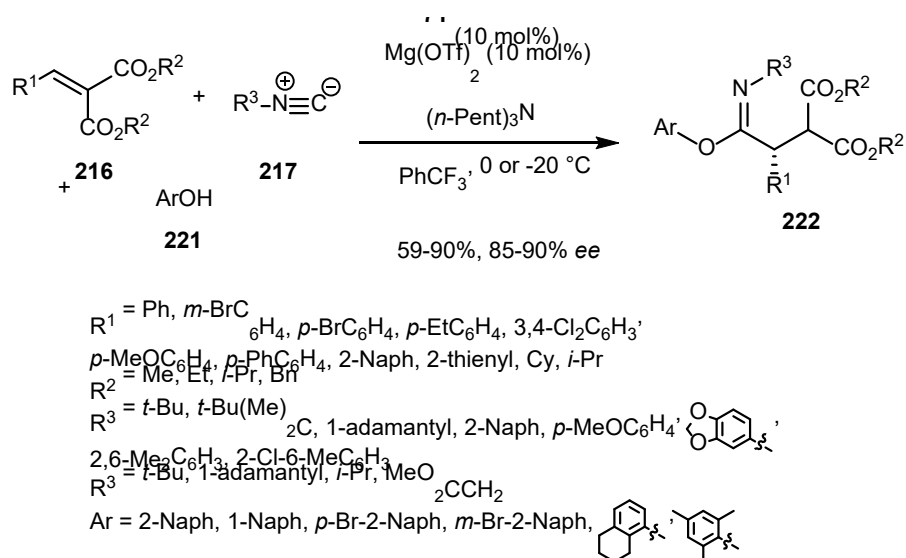
Scheme 54. Three- and pseudo-four-component domino reactions of alkylidene malonates, isocyanides and TMSN_3 /isoquinolines.

As an extension of the precedent methodology, the same authors also developed the first enantioselective three-component reactions between benzothiazoles **219**, alkylidene malonates **216** and isocyanides **217**, which was promoted by only 2.5 mol% of the same catalyst system (Scheme 55).^[67] Indeed, in the presence of 2.5 mol% of Mg(OTf)₂ and the same quantity of chiral *N,N'*-dioxide ligand **71** in DCE as solvent, these substrates underwent at 35 °C a formal [2+1+2] cycloaddition which resulted in the formation of chiral hydrothiazoles **220** as almost single diastereomers (>90% *de*) in both moderate to excellent yields (40-98%) and enantioselectivities (66-97% *ee*).



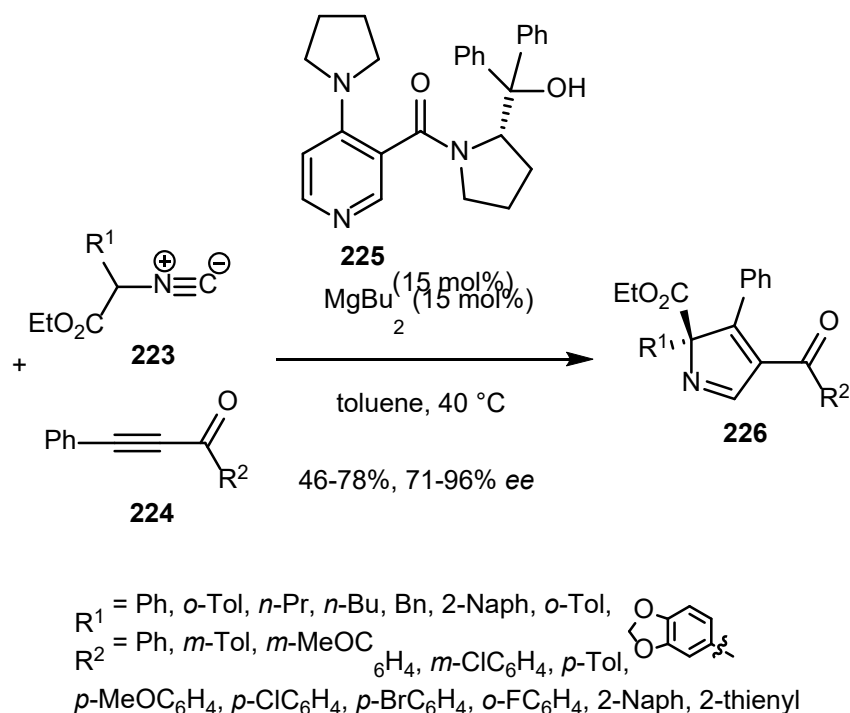
Scheme 55. Three-component domino reaction of alkylidene malonates, isocyanides and benzothiazoles.

Later in 2021, Feng and Cao also applied this catalyst system at 10 mol% of catalyst loading to promote enantioselective three-component reaction between alkylidene malonates **216**, isocyanides **217** and phenols **221**.^[68] In this case, the reaction was performed at 0 or -20 °C in PhCF₃ as solvent in the presence of tri(*n*-pentyl)amine as base, delivering the corresponding chiral phenoxyimidates **222** with good to high yields (59-90%) and enantioselectivities (85-90% *ee*), as presented in Scheme 56. Both alkyl- and aryl-substituted isocyanides were tolerated as well as differently substituted alkylidene malonates and phenols spanning from 1- and 2-naphthols to more simple phenols.



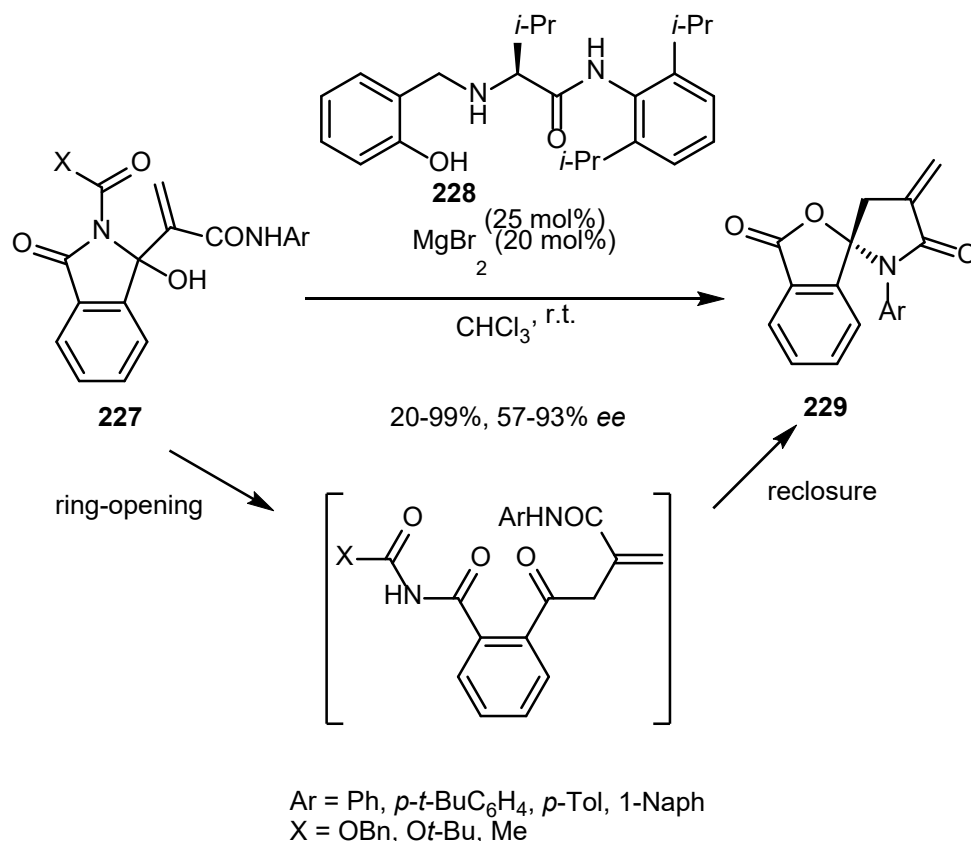
Scheme 56. Three-component reaction of alkylidene malonates, isocyanides and phenols.

In another area, the first enantioselective magnesium-catalyzed domino Michael/cyclization reaction of readily available α -isocyanoacetates **223** with alkynyl ketones **224** was disclosed in 2019 by Wang et al.^[69] As illustrated in Scheme 57, the reaction employed 15 mol% of a chiral magnesium catalyst *in situ* generated from MgBu_2 and chiral prolinol ligand **225** in toluene as solvent. Performed at 40 °C, the domino process afforded chiral functionalized 2H-pyrroles **226** in moderate to high yields (46-78%) and good to excellent enantioselectivities (71-96% *ee*).



Scheme 57. Domino Michael/cyclization reaction of α -isocyanoacetates with alkynyl ketones.

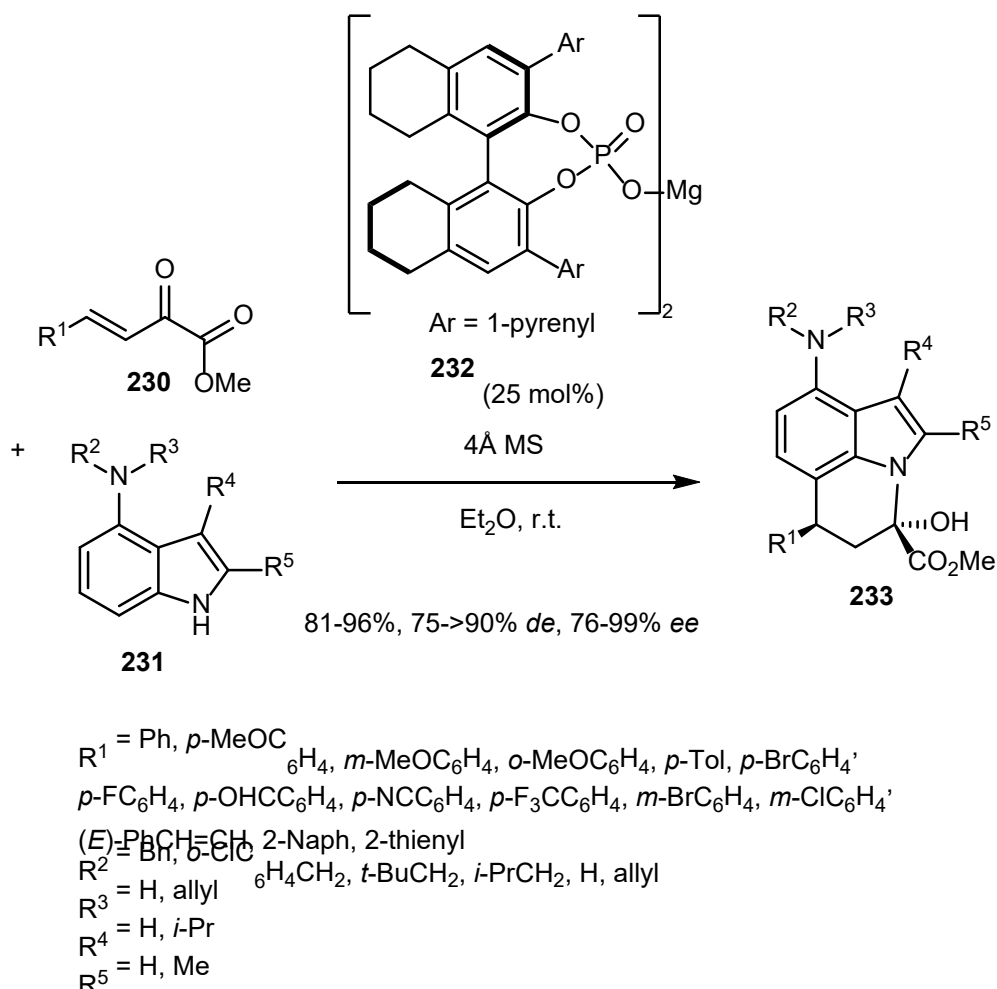
Later in 2020, Yoda et al. developed a novel asymmetric synthesis of biologically interesting methylenelactam-based *N,O*-spirocyclic products based on an enantioselective magnesium-catalyzed intramolecular domino ring-opening/reclosure reaction of hydroxylactam precursors **227**.^[70] As shown in Scheme 58, when these substrates were treated at room temperature in chloroform as solvent by a combination of 20 mol% of MgBr₂ and 25 mol% of chiral aminophenol ligand **228**, they led to the corresponding chiral methylenelactam-based *N,O*-spirocyclic products **229** with low to quantitative yields (20-99%) and moderate to high enantioselectivities (57-93% *ee*). The lowest *ee* value (57% *ee*) was obtained in the reaction of a *N*-Boc substrate (X = *O*-*t*-Bu) while enantioselectivities of $\geq 84\%$ *ee* were obtained for all other substrates. The lowest yield (20%) was observed in the reaction of a substrate bearing a small acetyl group (X = Me) albeit combined with a high *ee* value (84% *ee*).



Scheme 58. Domino ring-opening/reclosure reaction of hydroxylactams.

In 2021, an enantioselective magnesium-catalyzed domino Friedel–Crafts alkylation/*N*-hemiacetalization reaction of 4-aminoindoles **231** with β,γ -unsaturated α -ketoesters **230** was disclosed by Antilla et al. (Scheme 59).^[71] In the presence of 10 mol% of dinuclear preformed H₈-BINOL-derived bis(phosphate) magnesium catalyst **232**, the reaction occurred at room temperature in diethylether as solvent to afford the corresponding chiral polycyclic 4H-pyrrolo[3,2,1-*ij*]quinoline derivatives **233** in both high diastereo- (75->90% *de*) and enantioselectivities (76-99% *ee*) combined with high yields (81-96%). These functionalized 1,7-annulated indole products arose from an asymmetric C-7 Friedel–Crafts alkylation followed by a *N*-hemiacetalization reaction. Homogeneous good results were achieved for a range of aryl-substituted β,γ -unsaturated α -ketoesters bearing either electron-donating or electron-withdrawing groups at any position of the phenyl ring. Moreover, 2-naphthyl- ($\text{R}^1 = 2\text{-Naph}$) and diene- ($\text{R}^1 = (E)\text{-PhCH=CH}$) substituted substrates were compatible. Concerning the 4-aminoindole partner, various substituents were tolerated on the secondary amine

group (R^2) as well as at C-2- (R^5) or C-3 (R^4)-positions of the 4-aminoindoles. A tertiary amine ($R^2 = R^3 = \text{allyl}$) also reacted with high yield (95%) and stereoselectivities (86% *de*, 97% *ee*).

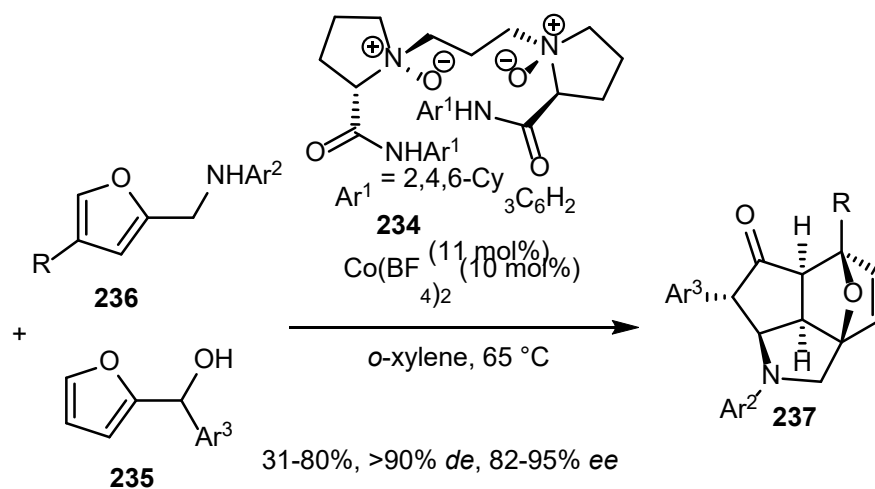


Scheme 59. Domino Friedel–Crafts alkylation/*N*-hemiacetalization reaction of 4-aminoindoles with β,γ -unsaturated α -ketoesters.

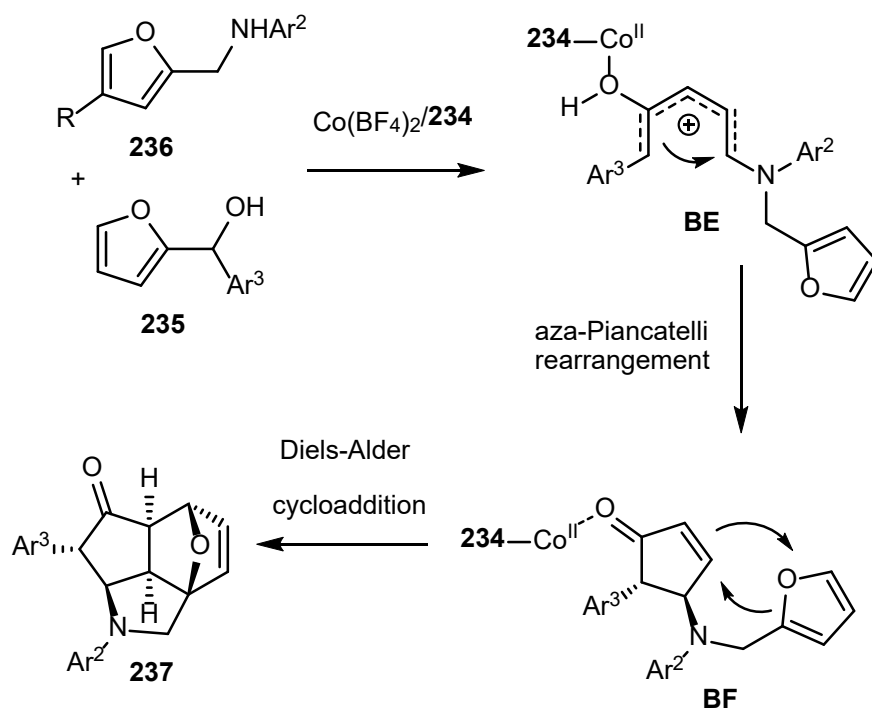
8 Enantioselective Cobalt-Catalyzed Domino Reactions

In comparison with other transition metals, cobalt catalysts present the advantage to be less toxic and cheaper. In this context, an impressive development of enantioselective cobalt-catalyzed transformations has been developed, including domino reactions.^[1j,n,72] In an example reported in 2020 by Liu and Feng, a chiral cobalt catalyst *in situ* generated from 10 mol% of $\text{Co}(\text{BF}_4)_2$ and 11 mol% of chiral *N,N'*-dioxide ligand **234** was found capable of promoting a novel enantioselective domino aza-Piancatelli rearrangement/intramolecular Diels–Alder reaction of 2-furylcarbinols **235** with *N*-(furan-2-ylmethyl)anilines **236**.^[73] Performed at 65 °C in *o*-xylene as solvent, the process afforded a wide range of chiral complex hexahydro-2a,5-epoxycyclopenta[cd]isoindoles **237** exhibiting six contiguous stereocenters in moderate to good yields (31-80%) with both remarkable diastereo- (>90% *de*) and enantioselectivities (82-95% *ee*), as presented in Scheme 60. The authors proposed the mechanism depicted in this Scheme in which there was formation of hydrocyclopentadienyl cation cobalt intermediate **BE**. Then, the latter was submitted to an aza-Piancatelli rearrangement to give 3-amino

substituted cyclopentenone **BF**, which subsequently underwent a cobalt-promoted diastereoselective intramolecular Diels–Alder cycloaddition which delivered the final product.

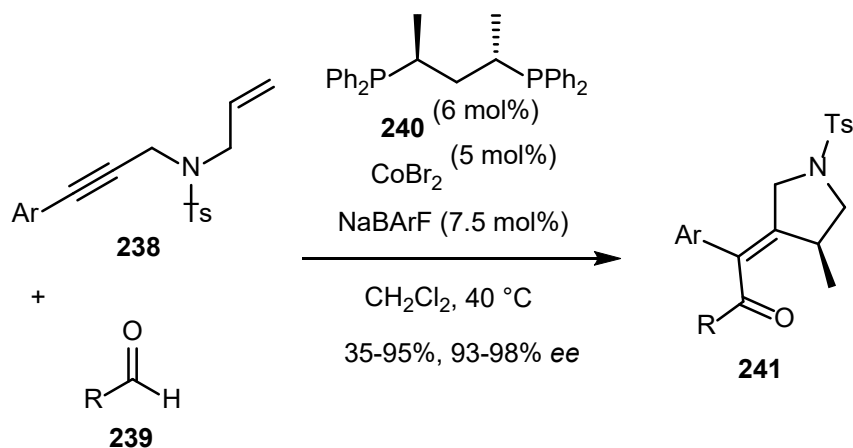


mechanism (with R = H):



Scheme 60. Domino aza-Piancatelli rearrangement/Diels–Alder reaction of 2-furylcarbinols with *N*-(furan-2-ylmethyl)anilines.

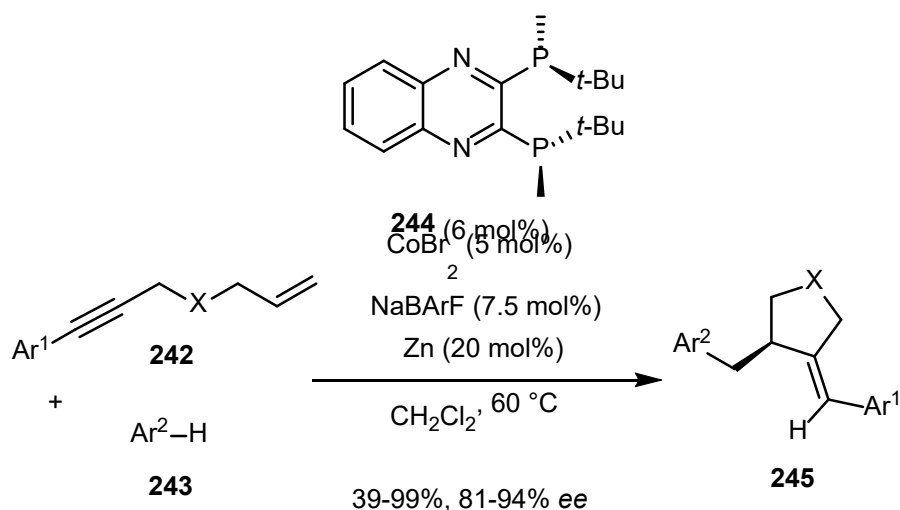
An enantioselective domino cyclization/hydroacylation reaction of 1,6-enynes **238** with aldehydes **239** was described by Lautens et al., in 2020 (Scheme 61).^[74] Promoted by a chiral cobalt catalyst *in situ* generated from 5 mol% of CoBr₂ and 6 mol% of chiral bisphosphine ligand **240**, the reaction afforded regioselectively the corresponding chiral functionalized ketones **241** in good yields (35-95%) and uniformly high enantioselectivities (93-98% *ee*).



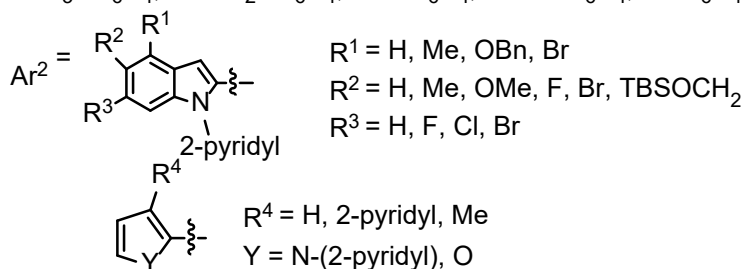
Ar = Ph, *m*-Tol, 2-thienyl, *p*-BrC₆H₄, *p*-MeOC₆H₄, *p*-F₃CC₆H₄,
p-(TIPSOCH₂)C₆H₄, *m*-BrC₆H₄, *m*-EtO₂CC₆H₄, 3,5-MeO₂C₆H₃,
o-MeOC₆H₄
R = Ph, *p*-BrC₆H₄, *p*-F₃CC₆H₄, 3-Br-4-FC₆H₃, *m*-BnOC₆H₄,
2,5-MeO₂C₆H₃, 2-thienyl, 2-furyl, PhCH=C(Br), CH₂=C(Me)

Scheme 61. Domino cyclization/hydroacylation reaction of 1,6-enynes with aldehydes.

The same authors also developed a novel enantio- and regioselective cobalt-catalyzed domino cyclization/C–H functionalization reaction between 1,6-enynes **242** and indoles **243**.^[75] This asymmetric hydroarylate cyclization of 1,6-enynes involving a C–H bond cleavage was promoted at 60 °C by a chiral catalyst *in situ* generated from 5 mol% of CoBr₂ and 6 mol% of chiral bisphosphine ligand **244** in dichloromethane as solvent in the presence of zinc and NaBARF as additives (Scheme 62). A wide range of chiral five-membered products **245** were thus formed with moderate to quantitative yields (39-99%) and uniformly high enantioselectivities (89-94% *ee*) in the case of 2-pyridyl-protected indoles as substrates. In addition, the scope of the process was extended to 2-pyridyl-protected pyrroles which afforded the corresponding products with both high yields (83-86%) and *ee* values (94% *ee*). Furthermore, a furan-based substrate (Y = O) was found compatible, leading to the desired product with 79% yield and 81% *ee*.

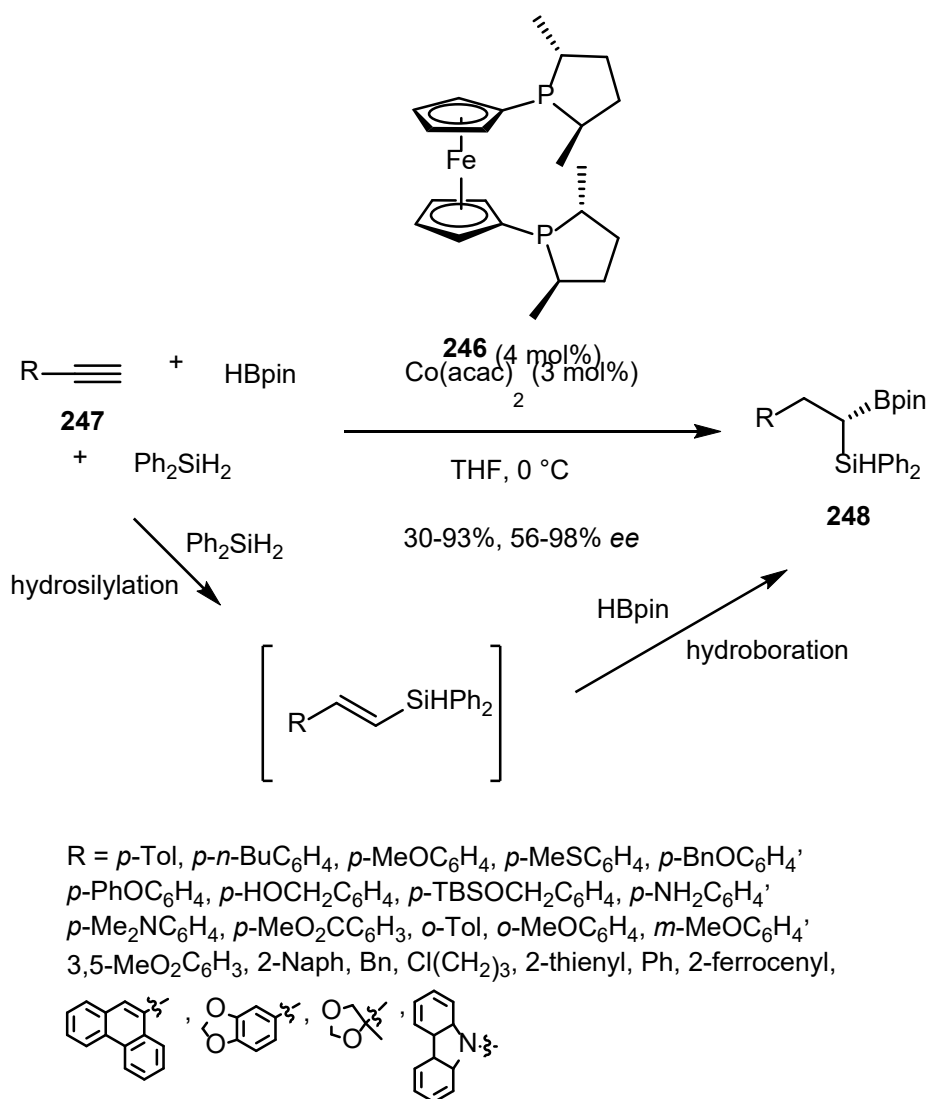


X = NTs, O, (EtO₂C)₂C, (2-thienyl)-SO₂N
 Ar¹ = Ph, *p*-BrC₆H₄, *p*-Tol, *p*-*i*-PrC₆H₄, *p*-PhC₆H₄, *p*-(3-thienyl)C₆H₄,
p-MeOC₆H₄, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-F₃CC₆H₄, *p*-(EtO₂CCH₂O)C₆H₄,
p-(TIPSOCH₂O)C₆H₄, 3,5-MeO₂C₆H₃, *m*-Tol, *m*-MeOC₆H₄, *m*-FC₆H₄,
m-F₃CC₆H₄, *m*-EtO₂CC₆H₄, *m*-BrC₆H₄, *o*-MeOC₆H₄, *o*-FC₆H₄, 2-thienyl



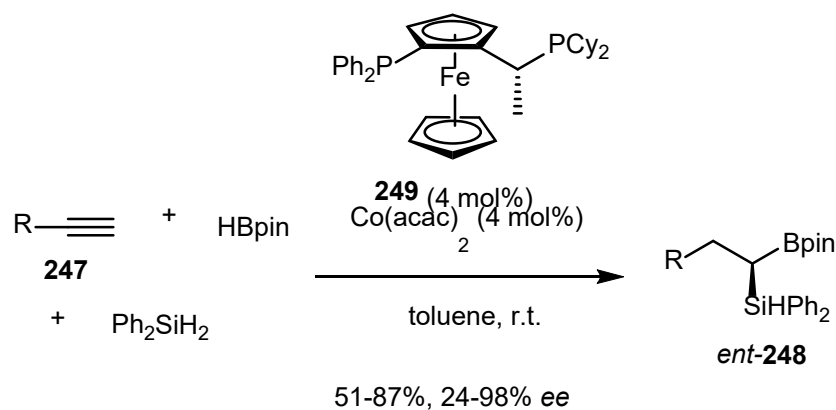
Scheme 62. Domino cyclization/C–H functionalization reaction of 1,6-enynes with indoles/pyrroles/furans.

A simple regio- and enantioselective cobalt-catalyzed three-component domino hydrosilylation/hydroboration reaction of terminal alkynes with Ph₂SiH₂ and HBpin was described by Ge and You, in 2021.^[76] As shown in Scheme 63, the reaction was performed at 0 °C in THF as solvent in the presence of 3 mol% of Co(acac)₂ as precatalyst and 4 mol% of chiral bisphosphine ligand **246**. Successive anti-Markovnikov hydrosilylation and asymmetric hydroboration reaction of alkynes **247** resulted in the formation of the corresponding chiral *gem*-(borylsilyl)alkanes **248** with both moderate to high yields (30-93%) and enantioselectivities (56-98% *ee*). A wide range of aryl-substituted alkynes reacted smoothly to give the desired chiral 1,1-silylboryl alkanes with high enantioselectivities (80-98% *ee*) while lower *ee* values (70-79% *ee*) were obtained for alkyl-substituted alkynes (R = Bn, Cl(CH₂)₃). The lowest enantioselectivity (56% *ee*) was observed in the reaction of an alkyne containing an unprotected hydroxyl group (R = CH₂OH). On the other hand, an impressive variety of functional groups were tolerated by the catalyst system.



Scheme 63. Three-component domino hydrosilylation/hydroboration reaction of terminal alkynes, Ph₂SiH₂ and HBpin in the presence of Me-Ferrocene ligand.

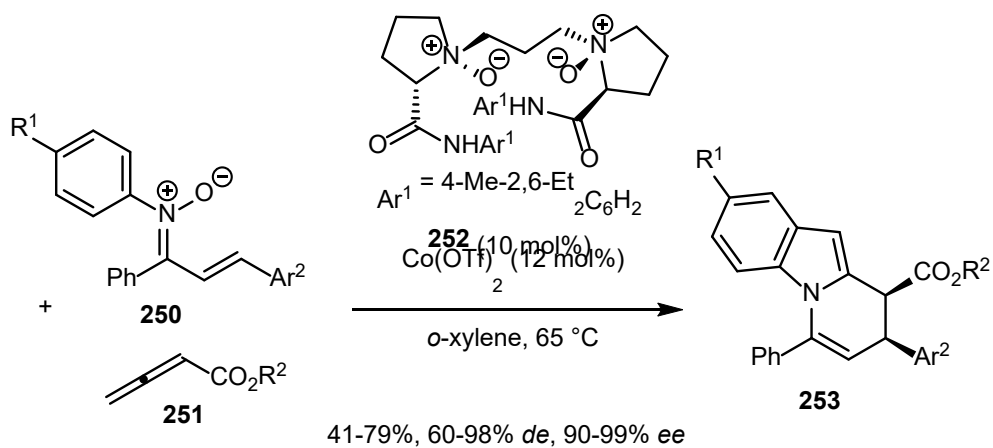
Concomitantly, Song et al. developed the same reactions in the presence of 4 mol% of the same precatalyst Co(acac)₂ and 4 mol% of chiral Josiphos ligand **249** in toluene at room temperature.^[77] As illustrated in Scheme 64, a range of both aliphatic and aromatic terminal alkynes **247** reacted with Ph₂SiH₂ and HBpin to give the corresponding chiral 1,1-silylboryl alkanes *ent*-**248** in moderate to high yields (51-87%) and low to excellent enantioselectivities (24-98% *ee*). While aliphatic terminal alkynes reacted with uniformly high *ee* values (78-94% *ee*), the reaction of aromatic substrates provided the corresponding products with more variable enantioselectivities (24-98% *ee*).




R = BnCH₂, Bn, *c*-Pr, *c*-Pent, CyCH₂, *n*-Pr, *n*-Pent, *n*-Hex, *n*-Hept, *i*-Pent, TBSO(CH₂)₂, *i*-HeptCO, PhCH=C(Me)CO, Ph, *p*-*i*-PrC₆H₄, *p*-*t*-BuC₆H₄, *p*-MeOC₆H₄, *m*-MeOC₆H₄, *p*-Me₂NC₆H₄, 2-thienyl, 1-thienyl, 2-ferrocenyl, 2-Naph, O₂S, N, CO₂(CH₂)₃

Scheme 64. Three-component domino hydrosilylation/hydroboration reaction of terminal alkynes, Ph₂SiH₂ and HBpin in the presence of a Josiphos ligand.

In 2022, Feng and Li described an enantioselective cobalt-catalyzed domino [3+2] cycloaddition/[3,3] rearrangement/retro-Mannich/[4+2] cycloaddition/dehydration reaction of α,β -unsaturated-*N*-aryl nitrones **250** with allenes **251**.^[78] The process was promoted at 30 °C by a combination of 12 mol% of Co(OTf)₂ and 10 mol% of chiral *N,N'*-dioxide ligand **252** in ethyl acetate as solvent, thus leading to a diversity of chiral *syn*-dihydropyridoindoles **253** with both moderate to good yields (41-79%) and diastereoselectivities (60-98% *de*) combined with uniformly high enantioselectivities (90-99% *ee*), as illustrated in Scheme 65. The mechanism of the reaction depicted in this Scheme begins with a [3+2] cycloaddition between the α,β -unsaturated-*N*-aryl nitron and the allene, providing intermediate **BG**. The latter further undergoes a [3,3]-rearrangement to afford benzazepine intermediate **BH**, which then reacted through a retro-Mannich opening to form dihydropyridoindole **BI**. Then, this intermediate undergoes a [4+2] cycloaddition followed by dehydration to deliver the final product.

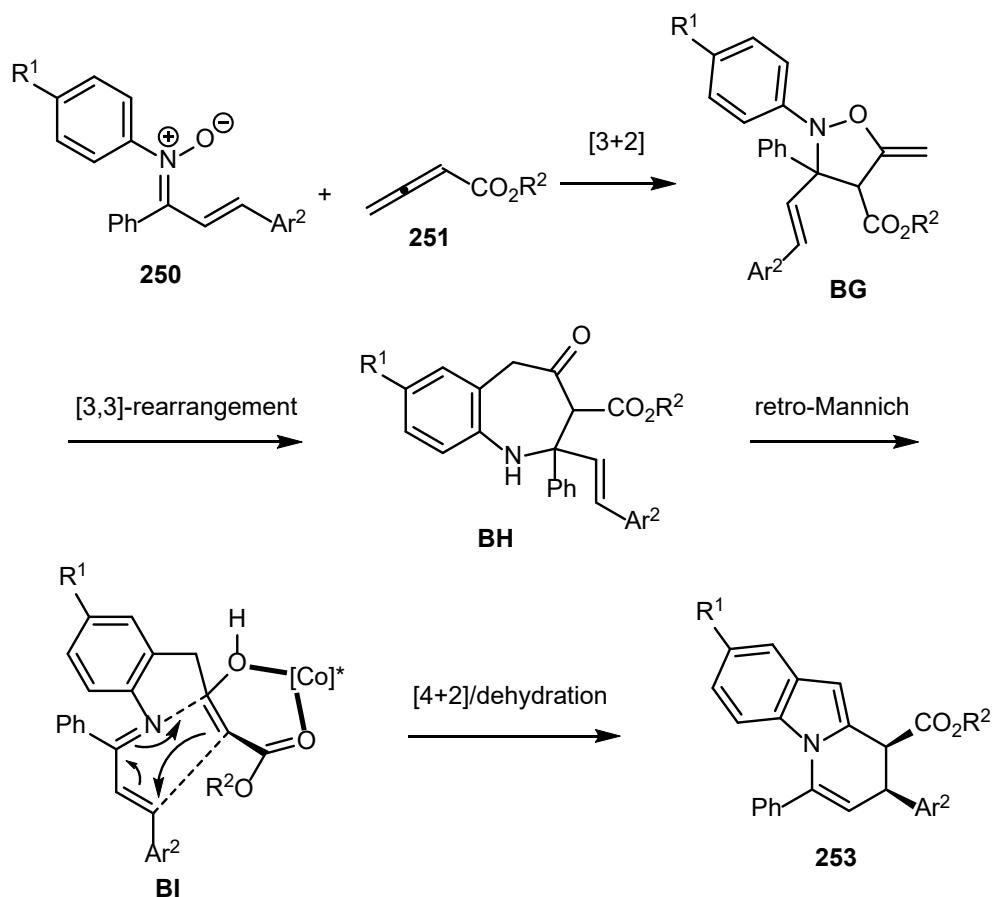


R^1 = OMe, Me, *t*-Bu, Cl, Br

Ar^2 = Ph, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-O₂NC₆H₄, *p*-Tol, , *p*-MeOC₆H₄, *m*-BrC₆H₄, *m*-Tol, *o*-BrC₆H₄, *o*-Tol, 2-furyl, 2-thienyl

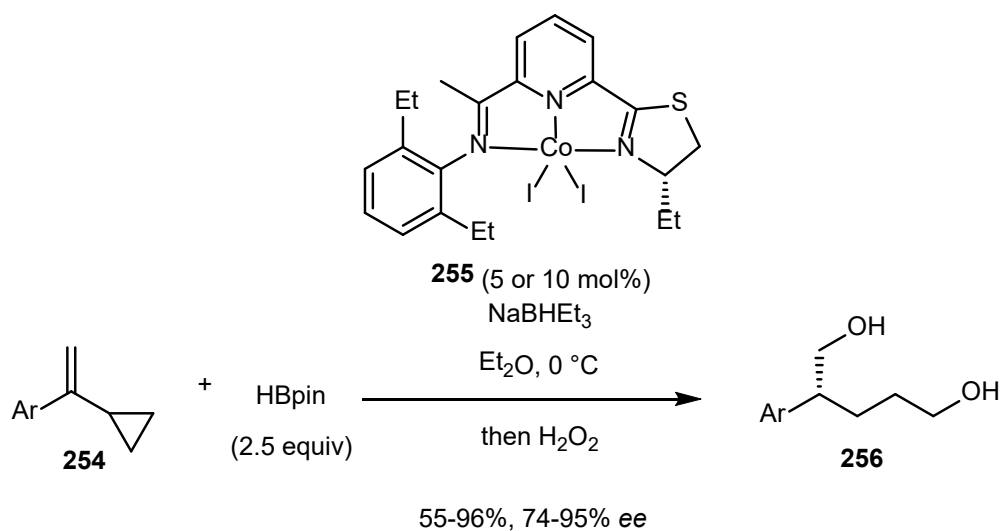
R^2 = Et, Me, *n*-Bu, propargyl, Ph, Bn, *i*-Pr

proposed mechanism:

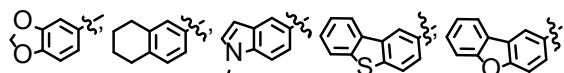


Scheme 65. Domino [3+2] cycloaddition/[3,3] rearrangement/retro-Mannich/[4+2] cycloaddition/dehydration reaction of α,β -unsaturated-*N*-aryl nitrones.

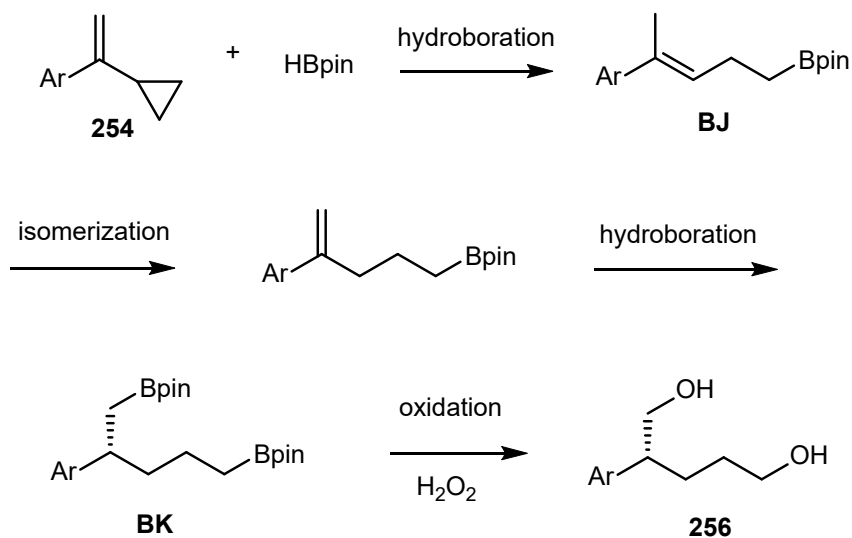
The first asymmetric cobalt-catalyzed domino hydroboration/isomerization/hydroboration of 2-aryl vinylcyclopropanes **254** with HBpin was reported by Lu and Hong, in 2022.^[79] This double hydroboration reaction was performed at 0 °C in diethyl ether as solvent in the presence of 5 or 10 mol% of chiral preformed cobalt catalyst **255** derived from a thiazoline iminopyridine ligand. Under these conditions, the reaction afforded the corresponding chiral 1,5-bis(boronates) which were directly oxidized with peroxide to give 1,5-diols **256** in both moderate to high yields (55-96%) and enantioselectivities (74-95% *ee*), as presented in Scheme 66. The mechanism of the domino reaction is shown in this Scheme, beginning with a first hydroboration to give trisubstituted alkene intermediate **BJ**. The latter underwent isomerization followed by a second hydroboration to yield chiral 1,5-bis(boronates) **BK**. The utility of this novel methodology was demonstrated in its application to a total synthesis of dopamine antagonist (-)-preclamol.



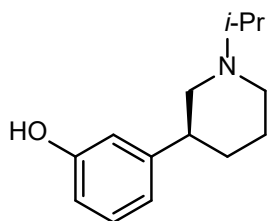
Ar = *p*-MeOC₆H₄, *p*-MeSC₆H₄, *p*-Tol, *p*-HOCH₂C₆H₄, *p*-FC₆H₄,
p-ClC₆H₄, *p*-BrC₆H₄, *m*-FC₆H₄, *p*-F₃CC₆H₄, *m*-Tol, *m*-MeOC₆H₄,
o-FC₆H₄, *o*-Tol, 3,4-Me₂C₆H₃, 3,5-Me₂C₆H₃, 2-Naph,



proposed mechanism:



domino products

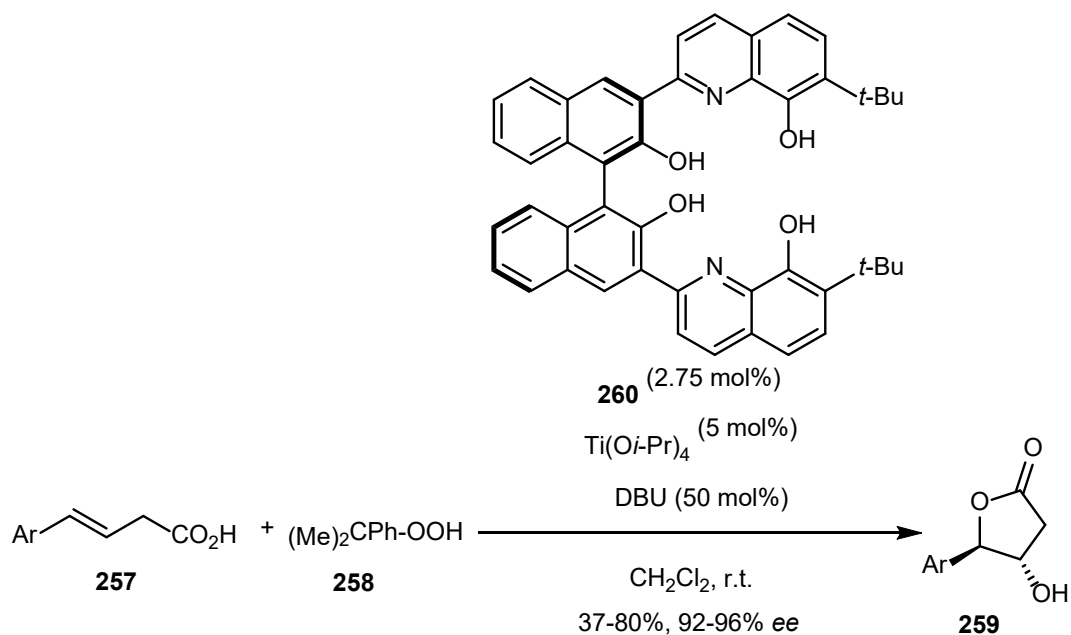


(-)-preclamol

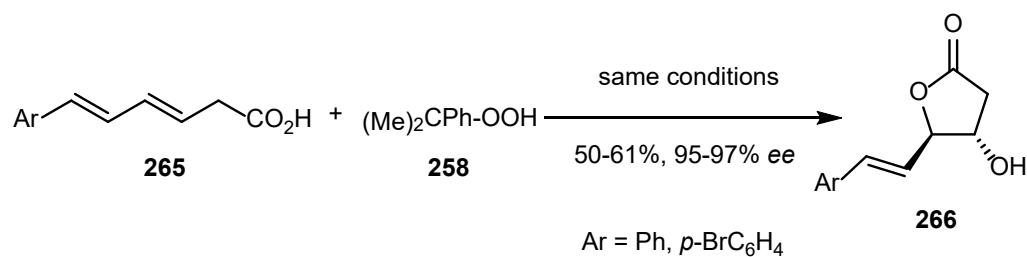
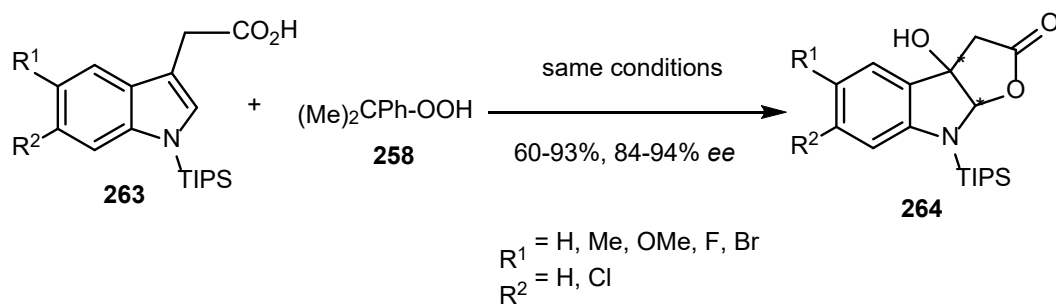
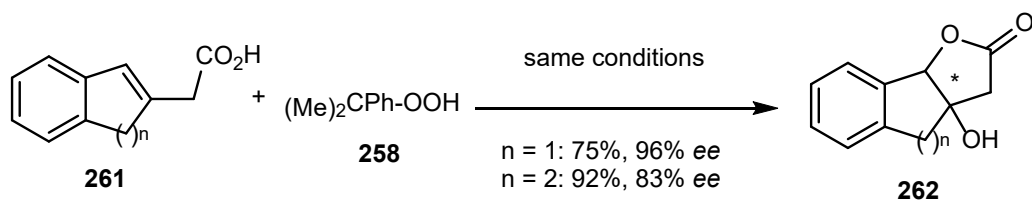
Scheme 66. Domino hydroboration/isomerization/hydroboration of 2-aryl vinylcyclopropanes with HBpin.

9 Enantioselective Titanium-Catalyzed Domino Reactions

In 2019, Sawano and Yamamoto developed an enantioselective titanium-catalyzed domino epoxidation/cyclization reaction between β,γ -unsaturated carboxylic acids **257** and cumene hydroperoxide **258** as oxidant, providing chiral γ -lactones **259** as single diastereomers (Scheme 67).^[80] The reaction occurred at room temperature in dichloromethane as solvent in the presence of a chiral catalyst *in situ* generated from 5 mol% of $\text{Ti}(\text{O}i\text{-Pr})_4$ and 2.75 mol% of (*R*)-BINOL-derived tetraol ligand **260**. After epoxidation of the double bond of the β,γ -unsaturated carboxylic acid with cumene hydroperoxide, the formed intermediate epoxide was submitted to ring-opening through intramolecular attack of the carboxylic acid in the presence of DBU as base to give the final cyclic product. A series of β,γ -unsaturated carboxylic acids **257** bearing an (hetero)aromatic group (*R*) afforded the corresponding almost enantiopure γ -lactones **259** (92-96% *ee*) with variable yields (37-80%). In addition to disubstituted olefins **257**, trisubstituted alkenes **261** were also tolerated, leading to products **262** in both high yields (75-92%) and enantioselectivities (83-96% *ee*). Moreover, more complex *N*-triisopropylsilylated indole 3-acetic acid derivatives **263** reacted to give chiral tricyclic products **264** in high *ee* values (84-94% *ee*) and good yields (60-93%). In addition, the reaction of $\beta,\gamma,\delta,\epsilon$ -unsaturated carboxylic acids **265** bearing a conjugated double bond occurred regioselectivity since only almost enantiopure (95-97% *ee*) products **266** were produced in good yields (50-61%) with no epoxidation of the other double bond (Scheme 67).

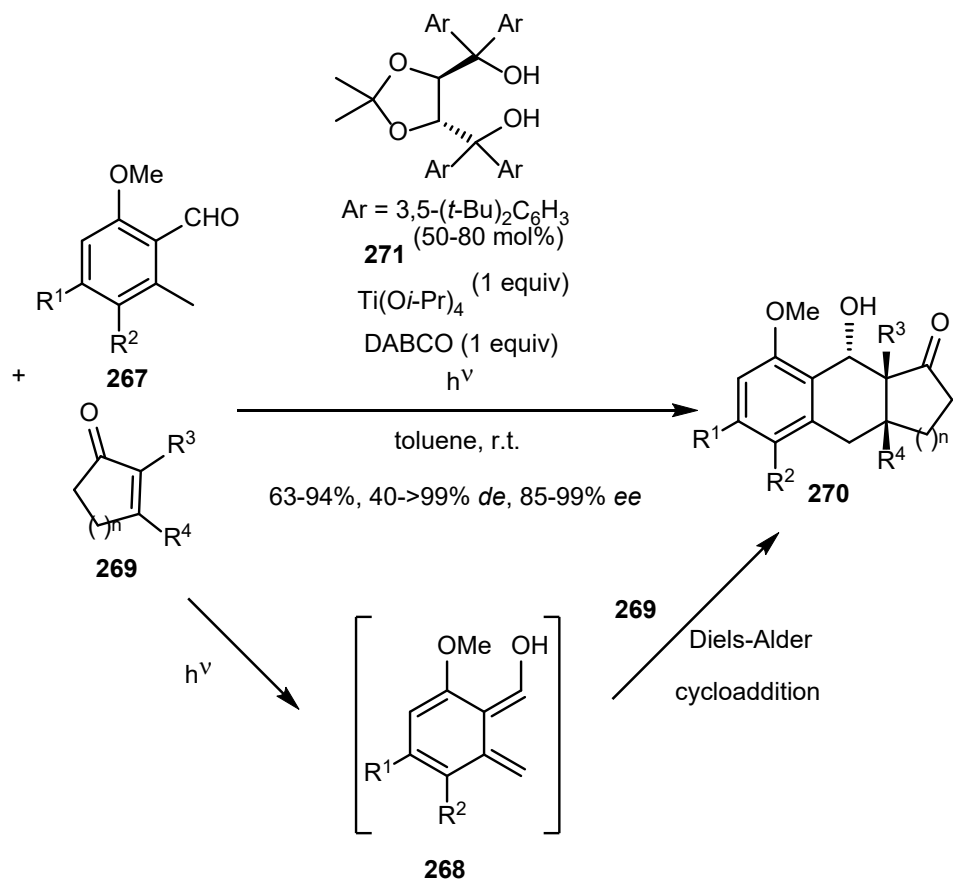


Ar = Ph, *p*-Tol, *p*-MeOC₆H₄, *p*-FC₆H₄, *p*-ClC₆H₄,
p-BrC₆H₄, *m*-Tol, *o*-Tol, 2-Naph, 2-furyl, 2-thienyl

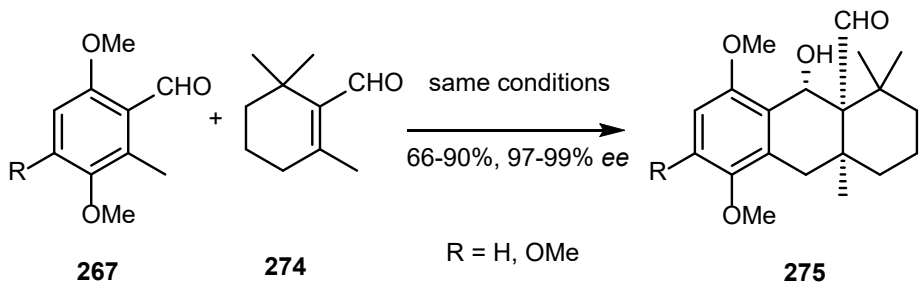
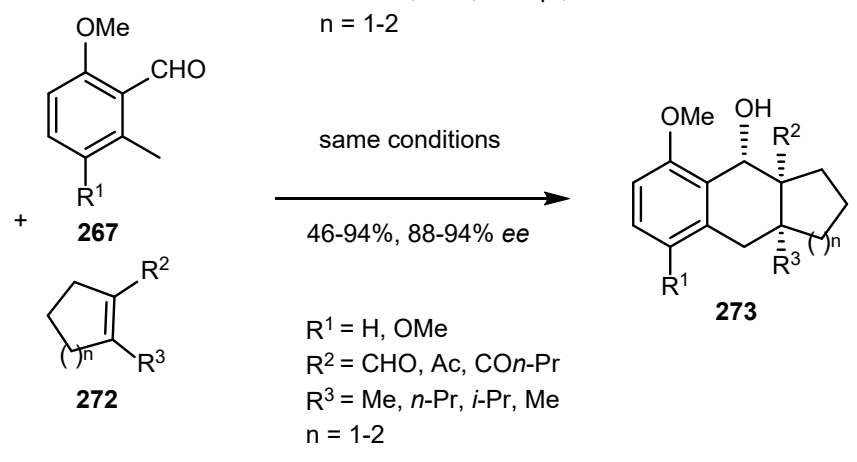


Scheme 67. Domino epoxidation/cyclization reactions of β,γ -unsaturated carboxylic acids with cumene hydroperoxide.

In 2021, Gao et al. described enantioselective domino photoenolization/Diels–Alder reactions of benzaldehydes with sterically hindered dienophiles (Scheme 68).^[81] The reaction involved the UV light-induced enolization of electron-rich 2-methylbenzaldehydes **267**, generating a highly active diene hydroxy-*o*-quinodimethane **268** via an excited-state species. The latter was then trapped by a dienophile, such as cyclic enones **269**, through Diels–Alder cycloaddition to form the corresponding chiral cycloadducts **270**. The process was performed at room temperature in toluene as solvent in the presence of one equivalent of $\text{Ti}(\text{O}i\text{-Pr})_4$ as precatalyst combined with 50-80 mol% of chiral TADDOL-derived ligand **271**. Under these conditions, a series of tetrasubstituted cyclopentenones and cyclohexenones reacted with differently substituted 2-methylbenzaldehydes to afford the corresponding tricyclic chiral products **270** with good yields (63-94%), variable diastereoselectivities (40->99% *de*) and high enantioselectivities (85-99% *ee*). The scope of the domino reaction was extended to other sterically hindered cyclic dienophiles, such as tetrasubstituted cyclopentenones and cyclohexenones **272**, which led by reaction with 2-methylbenzaldehydes **267**, to the desired cycloadducts **273** with variable yields (46-94%) and high *ee* values (88-94% *ee*). Furthermore, even betacyclocitral **274** bearing geminal dimethyl groups adjacent to the tetrasubstituted unsaturated aldehyde was compatible with the catalyst system since it provided by reaction with different 2-methylbenzaldehydes **267** the corresponding products **275** bearing three vicinal all-carbon quaternary centers as single diastereomers in good yields (66-90%) and excellent enantioselectivities (97-99% *ee*).

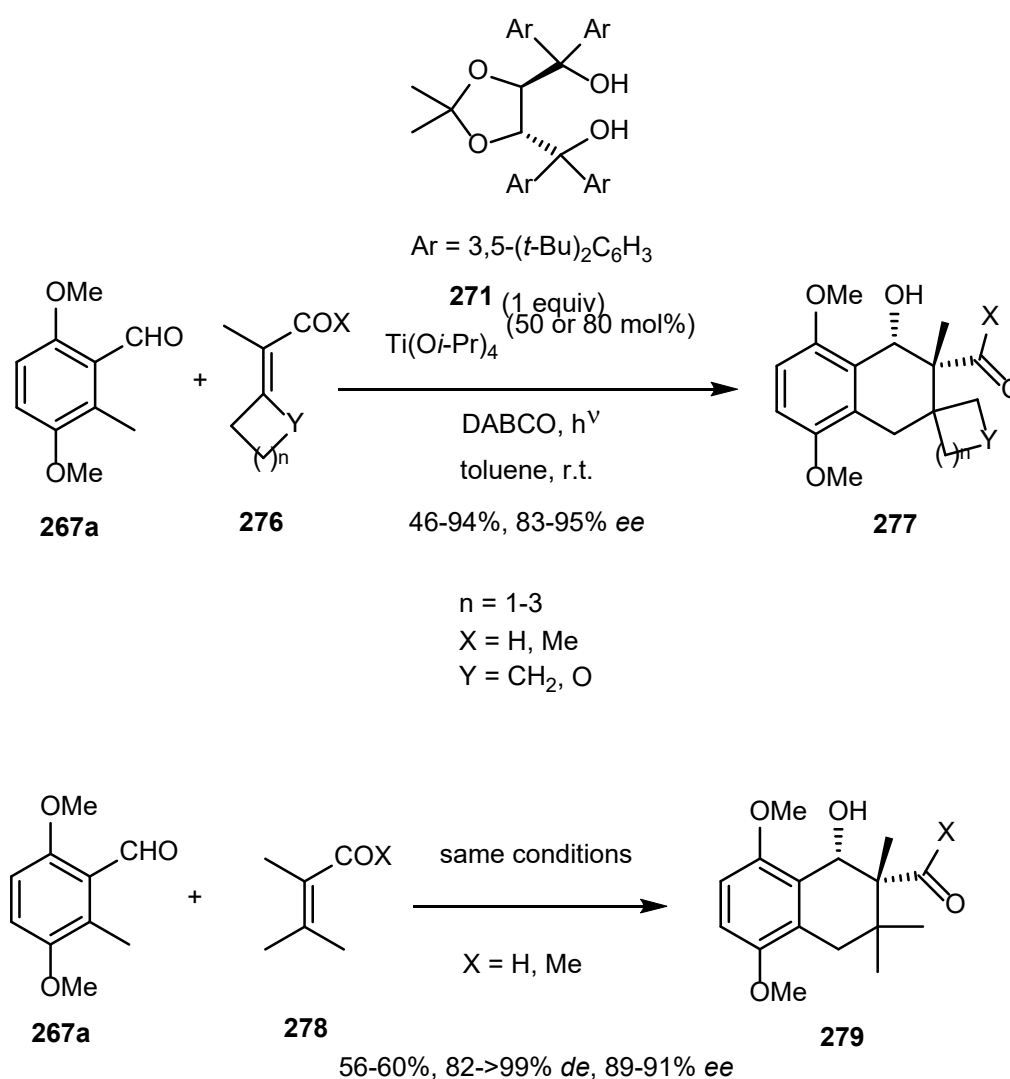


R¹ = H, OMe
 R² = H, OMe
 R³ = Me, *n*-Pr, Bn, *n*-Hept
 R⁴ = Me, *n*-Pr, *n*-Hept, Bn
 n = 1-2



Scheme 68. Domino photoenolization/Diels–Alder reactions of 2-methylbenzaldehydes with cyclic tetrasubstituted olefins.

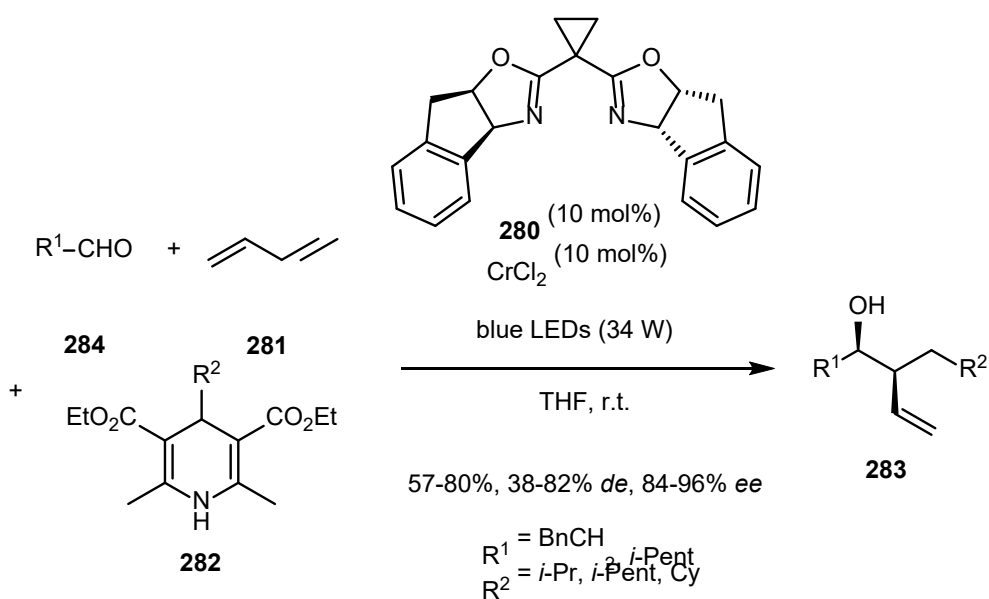
As illustrated in Scheme 69, the same catalyst system was also compatible with acyclic tetrasubstituted olefins **276** bearing an *exo*-unsaturated aldehyde (X = H) or acetyl group (X = Me) as dienophiles. Indeed, acyclic tetrasubstituted olefins **276** smoothly reacted with 2-methyl-3,6-dimethoxybenzaldehyde **267a** to afford the corresponding chiral products **277** containing a spiro all-carbon quaternary stereocenter with moderate to high yields (46-94%) and high enantioselectivities (83-95% *ee*), as shown in Scheme 69.^[81] These spirocyclic molecules ranged from cyclobutane to cyclohexane (n = 1-3) and also included pyran rings (Y = O). Moreover, acyclic tetrasubstituted alkenes **278** were compatible, leading by reaction with the same benzaldehyde **267a**, to the corresponding bicyclic adducts **279** with both high diastereo- (82->99% *de*) and enantioselectivities (89-91% *ee*) albeit combined with moderate yields (56-60%). It must be noted that this novel simple one-pot methodology constituted the first example of using a direct UV-light-mediated cycloaddition to build chiral adjacent quaternary centers at bridgeheads, which demonstrates its potential in the synthesis of many useful complex chiral polycyclic rings for medicinal chemistry.



Scheme 69. Domino photoenolization/Diels–Alder reactions of 2-methylbenzaldehydes with acyclic olefins.

10 Enantioselective Chromium-Catalyzed Domino Reactions

A chiral chromium catalyst was applied by Glorius et al. to promote an asymmetric radical three-component reaction, in 2020.^[82] This catalyst was *in situ* generated from 10 mol% of CrCl₂ and the same quantity of chiral bisoxazoline ligand **280** in THF at room temperature (Scheme 70). It involved a regio- and enantioselective domino 1,3-dialkylation reaction of butadiene **281** with aldehydes **284** and 4-alkyl Hantzsch esters **282** as alkyl radical precursors performed under blue LED irradiation. Primary or secondary aliphatic aldehydes **284** reacted with butadiene **281** and different 4-alkyl Hantzsch esters **282** to give the corresponding chiral homoallylic alcohols **283** in good yields (57-80%) with moderate to high diastereoselectivities (38-82% *de*) and high enantioselectivities (84-96% *ee*).



Scheme 70. Three-component domino radical dialkylation reaction of butadiene, aliphatic aldehydes and 4-alkyl Hantzsch esters.

11 Conclusions

This review updates the recent advances in the field of enantioselective domino reactions promoted by chiral catalysts derived from first row metals (including magnesium as special case), covering the literature since the beginning of 2019. It demonstrates that an impressive diversity of novel enantioselective domino processes promoted by first row metal catalysts has been developed in a short period of four years, allowing a direct access to very complex and functionalized chiral molecules. The diversity of these transformations reflect that of metals employed to induce them, spanning from zinc, iron, copper, scandium, nickel, magnesium, cobalt, titanium to chromium. These metals have been chelated to many types of chiral ligands, such as bisphosphines, P,N-ligands, oxazolines, bisoxazolines, bisimidazolines, phosphines, diamines, amino alcohols, *N,N'*-dioxides, phosphoric acids, cyclopentadienyl derivatives, prolinols, as well as BINOL, TADDOL, ProPhenol and AzePhenol derivatives. Remarkable enantioselectivities have been described for a wide variety of domino processes including multicomponent reactions. For example, Michael-initiated domino reactions have been performed highly enantioselectively in the presence of chiral zinc catalysts *in situ* generated from ProPhenol and AzePhenol derivatives or diamines. In addition, an impressive number

of other types of asymmetric one-, two-, three- and four-component domino reactions have been promoted by zinc complexes of diamines, *N,N'*-dioxides, bisoxazolines and amino alcohols; iron catalysts derived from *N,N'*-dioxides, bisoxazolines, amino alcohols, bisphosphines and oxazolines; copper complexes of bisphosphines, P,N-ligands and bisoxazolines; scandium catalysts of *N,N'*-dioxides, phosphoric acids and cyclopentadienyl derivatives; nickel complexes derived from bisphosphines, bisimidazolines and P,N-ligands; magnesium catalysts generated from *N,N'*-dioxides, amino alcohols, phosphoric acids and prolinol derivatives; cobalt complexes of *N,N'*-dioxides and bisphosphines; titanium catalysts from BINOL and TADDOL derivatives; and bisoxazoline-derived chromium catalysts. In the future, this field will undoubtedly continue to be expanded with the discovery of novel enantioselective domino reactions thanks to the development of novel chiral metal catalysts with a preference for more environmentally benign metals to remain competitive with growing greener organocatalyzed domino reactions.

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