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# Green Copper Catalysis in Enantioselective Domino Reactions

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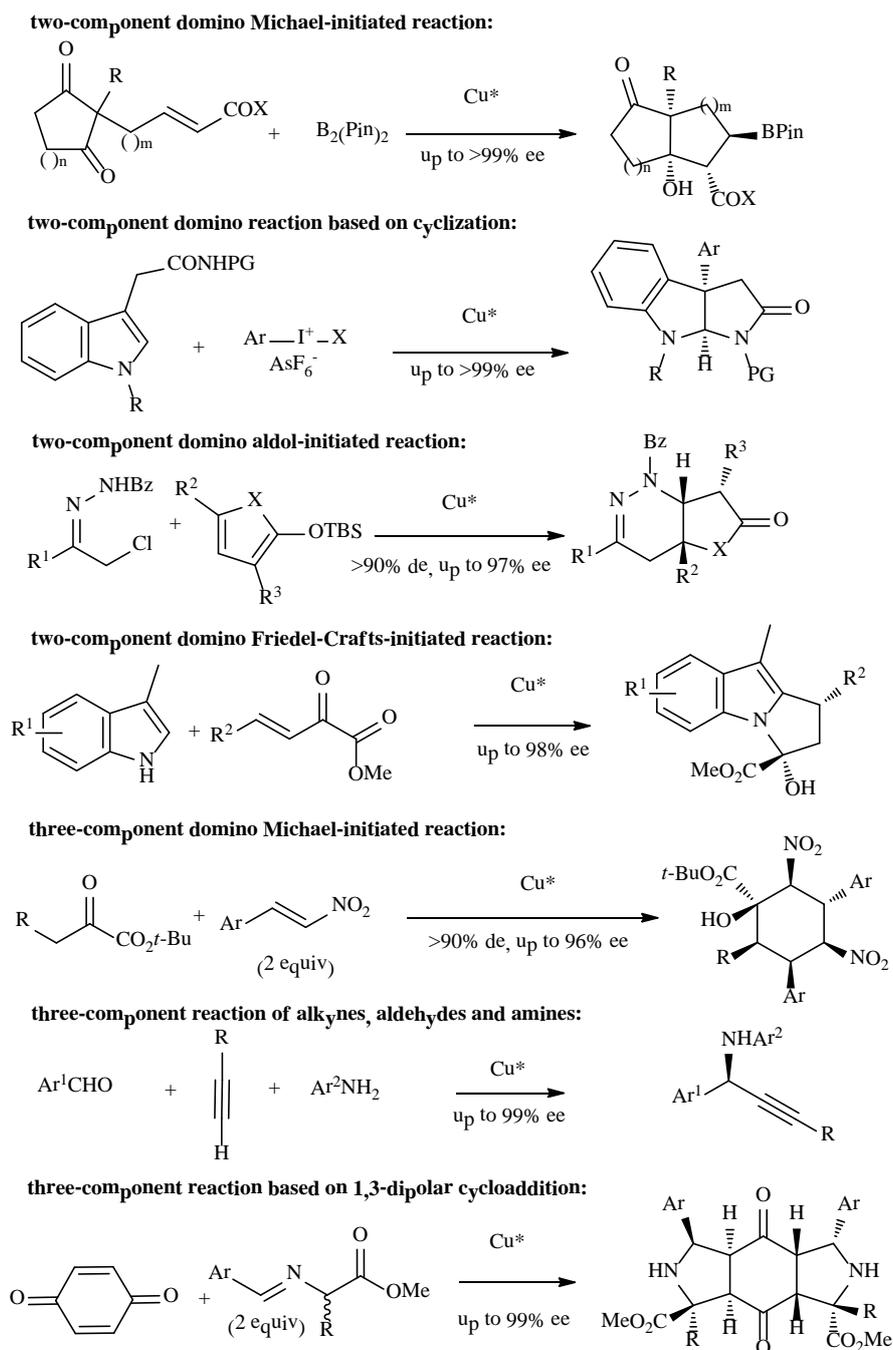
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**Abstract:** This review collects for the first time enantioselective domino reactions promoted by chiral green copper catalysts, covering the literature since the beginning of 2006. It is divided into two parts dealing successively with asymmetric two-component domino reactions and three-component processes. The first part is dedicated to two-component asymmetric domino reactions, including Michael-initiated processes, domino reactions based on cyclizations, domino reactions initiated by aldol-type condensations and Friedel–Crafts-initiated domino processes. The second part collects asymmetric three-component processes, such as Michael-initiated domino reactions, domino reactions between alkynes, aldehydes and amines, domino reactions based on 1,3-dipolar cycloadditions among other three-component reactions.

**Keywords:** enantioselective domino reactions; copper catalysis; metal catalysis; green chemistry; asymmetric catalysis; chirality.

## 1. INTRODUCTION

The combination of asymmetric metal catalysis [1] with the concept of domino reactions [2] has so far allowed many chiral complex products to be synthesized with excellent enantioselectivities on the basis of simple and economic one-pot procedures, not requiring the purification of intermediates [3]. Taking advantages of the higher abundance and lower costs and toxicity of copper catalysts in comparison with other transition metals, more ecologic and economic enantioselective domino reactions have been developed in the last decade on the basis of asymmetric copper catalysis. The goal of this review is to collect the major developments in enantioselective copper-catalyzed domino reactions. It is divided into two parts, dealing successively with enantioselective copper-catalyzed two-component domino reactions and three-component domino processes. The review is divided into two parts dealing successively with two-component domino reactions and three-component processes. The first part includes asymmetric Michael-initiated processes, domino reactions based on cyclizations, domino reactions initiated by aldol-type condensations and Friedel–Crafts-initiated domino processes. The second part collects asymmetric three-component processes, such as Michael-initiated domino reactions, domino reactions between alkynes, aldehydes and amines, domino reactions based on 1,3-dipolar cycloadditions among other three-component reactions. Relevant examples of each type of these reactions are collected in Scheme 1.

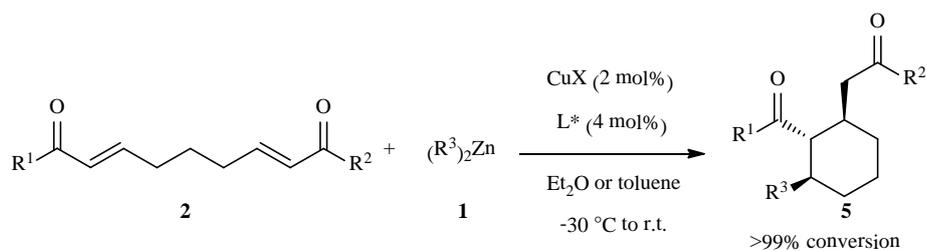


**Scheme 1.** Relevant examples of asymmetric copper-catalyzed two- and three-component domino reactions.

## 2. TWO-COMPONENT DOMINO REACTIONS

### 2.1. Michael-Initiated Domino Reactions

A number of domino reactions have been initiated by enantioselective copper-catalyzed Michael additions [4]. As an example in 2007, Alexakis and Li reported asymmetric copper-catalyzed domino double Michael reactions between dialkylzinc reagents **1** and bis- $\alpha,\beta$ -unsaturated carbonyl compounds **2** performed in the presence of chiral phosphoramidite ligands **3** and **4** [5]. This process led to the corresponding chiral six-membered products **5** exhibiting three contiguous stereogenic centers as mixtures of two diastereomers with moderate to excellent diastereoselectivities (60->98% de), good to high enantioselectivities (79-94% ee) and complete conversions, as shown in Scheme 2.



with  $\text{CuX} = \text{Cu}(\text{OTf})_2$  and  $\text{L}^* = \mathbf{3}$ :

$\text{R}^1 = \text{R}^2 = \text{Me}$ ,  $\text{R}^3 = \text{Et}$ : 60% de, 79% ee (major), 88% ee (minor)

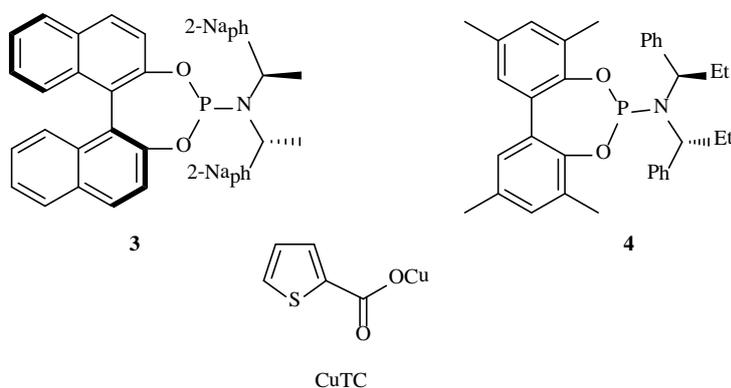
$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$ : 40% de, 88% ee (major), 94% ee (minor)

with  $\text{CuX} = \text{CuTC}$  and  $\text{L}^* = \mathbf{4}$ :

$\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{OMe}$ ,  $\text{R}^3 = \text{Et}$ : 43%, 86% de, 92% ee (major), 86% ee (minor)

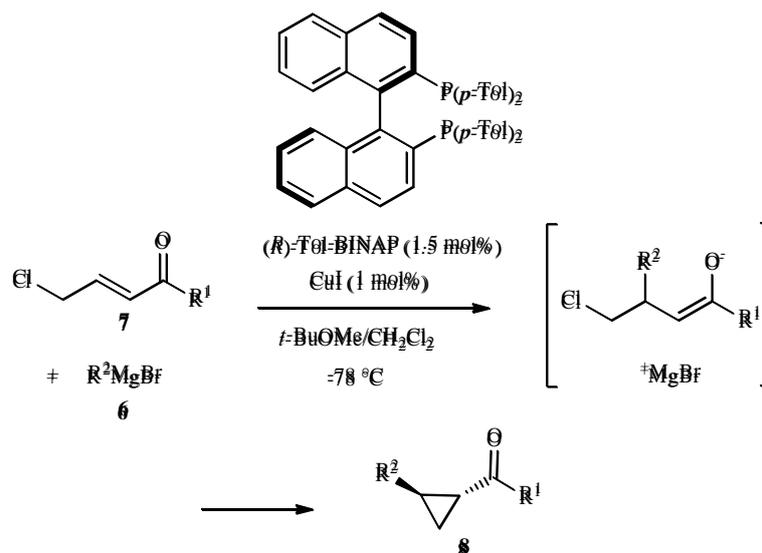
with  $\text{CuX} = \text{Cu}(\text{OTf})_2$  and  $\text{L}^* = \mathbf{4}$ :

$\text{R}^1 = \text{R}^2 = \text{Ph}$ ,  $\text{R}^3 = \text{Et}$ : 97%, >98% de, 88% ee (major)



**Scheme 2.** Domino double Michael reaction of bis- $\alpha,\beta$ -unsaturated carbonyl compounds with dialkylzinc reagents.

Later in 2010, Feringa et al. developed enantioselective copper-catalyzed domino Michael/intramolecular alkylation reactions of Grignard reagents **6** with 4-chloro- $\alpha,\beta$ -unsaturated esters, thioesters and ketones **7** to afford the corresponding *trans*-1-alkyl-2-substituted cyclopropane esters, thioesters and ketones **8**, respectively, in moderate to high yields (56->95%) and high enantioselectivities (84-98% ee), as shown in Scheme 3 [6]. The process was catalyzed by a combination of CuI and (*R*)-Tol-BINAP as chiral ligand. The utility of this novel methodology was applied to the synthesis of key intermediates in the total syntheses of cascarillic acid and grenadamide.

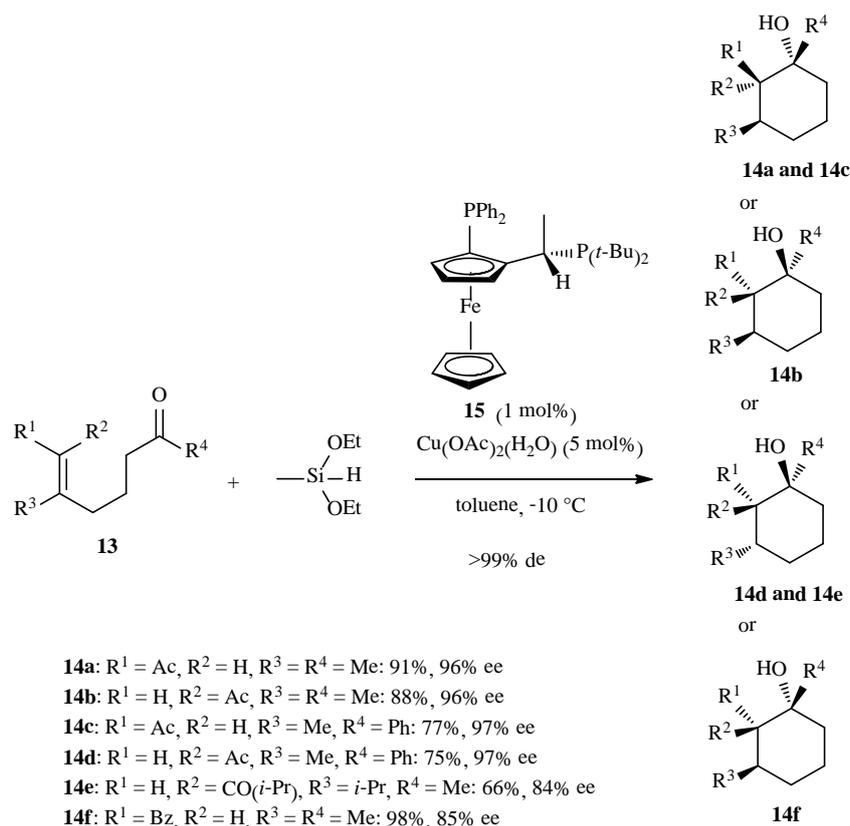


$\text{R}^1 \equiv \text{SEt}, \text{R}^2 \equiv n\text{-Hex}: 87\%, 94\% \text{ ee}$   
 $\text{R}^1 \equiv \text{SEt}, \text{R}^2 \equiv \text{Me}: 56\%, 87\% \text{ ee}$   
 $\text{R}^1 \equiv \text{SEt}, \text{R}^2 \equiv \text{Et}: 67\%, 95\% \text{ ee}$   
 $\text{R}^1 \equiv \text{SEt}, \text{R}^2 \equiv (\text{CH}_2)_3\text{Ot-Bu}: >95\%, 96\% \text{ ee}$   
 $\text{R}^1 \equiv \text{SEt}, \text{R}^2 \equiv \text{BnCH}_2: 92\%, 84\% \text{ ee}$   
 $\text{R}^1 \equiv n\text{-C}_{11}\text{H}_{23}, \text{R}^2 \equiv \text{BnCH}_2: 75\%, 96\% \text{ ee}$   
 $\text{R}^1 \equiv n\text{-C}_{11}\text{H}_{23}, \text{R}^2 \equiv \text{Me}: 87\%, 98\% \text{ ee}$   
 $\text{R}^1 \equiv \text{OMe}, \text{R}^2 \equiv \text{BnCH}_2: 68\%, >95\% \text{ ee}$

**Scheme 3.** Domino Michael/intramolecular alkylation reaction of 4-chloro- $\alpha,\beta$ -unsaturated esters, thioesters and ketones with Grignard reagents.

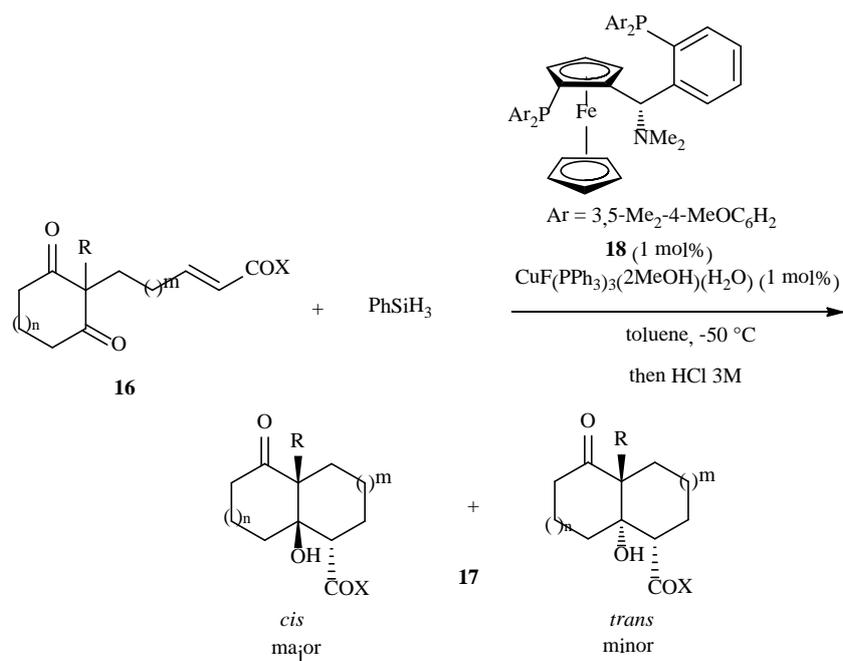
In 2012, Lam et al. reported enantioselective copper-catalyzed asymmetric Michael-initiated domino reactions occurring between enone diones **9** and  $\text{B}_2(\text{Pin})_2$  [7]. After the enantioselective conjugate boration of enone diones **9** with  $\text{B}_2(\text{Pin})_2$  performed in the presence of a combination of  $\text{CuCl}$  with Josiphos ligand **10**, the thus-formed intermediate **11** underwent an aldol cyclization reaction to give the corresponding domino conjugate boration/aldol products **12**. As shown in Scheme 4, a range of densely functionalized decalin-, hydrindane- and diquinane-based chiral products, exhibiting four contiguous stereocenters with two of which quaternary, were synthesized generally in moderate to excellent yields (52->95%), very high diastereoselectivity of >90% de in most cases, and uniformly excellent enantioselectivities (92->99% ee).



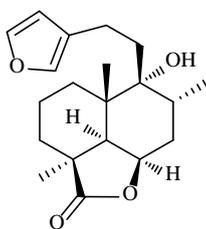


**Scheme 5.** Domino reductive Michael/aldol reaction of  $\beta,\beta$ -disubstituted keto enones with diethoxymethylsilane.

Only few methodologies of domino reductive Michael/aldol reactions allowed the synthesis of bi- and tricyclic compounds. In 2009, a rare example was reported by Riant and Deschamp [10]. As shown in Scheme 6, the diastereo- and enantioselective domino reductive Michael/aldol reaction of functionalized  $\alpha,\beta$ -unsaturated *tert*-butyl esters ( $\text{X} = t\text{-Bu}$ ) **16** with phenylsilane afforded the corresponding bicyclic domino products **17** as major *cis*-diastereomers in moderate to high yields (70-85%) and enantioselectivities (66-97% ee). The reaction catalyzed by a copper(I) complex of chiral biphosphine **18**, provided the *cis*-product as major diastereomer with moderate to complete diastereoselectivities (78->99% de). The stereoselectivity of the process was found to increase with the steric hindrance of the ester moiety, since the best results were obtained with *t*-butyl esters. Moreover, increasing the steric hindrance around the phosphorus atoms of the ligand gave further improvement of both *cis*-diastereoselectivity and enantioselectivity. Later in 2012, comparable results were obtained by the same authors by extending the scope of this methodology to other  $\alpha,\beta$ -unsaturated alkyl esters having various ring sizes and substitutions [11]. Moreover, the reaction conditions could be applied to a diketoenone ( $\text{X} = \text{R} = \text{Me}$ ,  $n = m = 1$ ) which provided the corresponding domino product as a single *syn*-diastereomer in 75% yield albeit with a moderate enantioselectivity (65% ee). The utility of this novel methodology was shown by its application to the synthesis of the natural diterpene marrubiin.



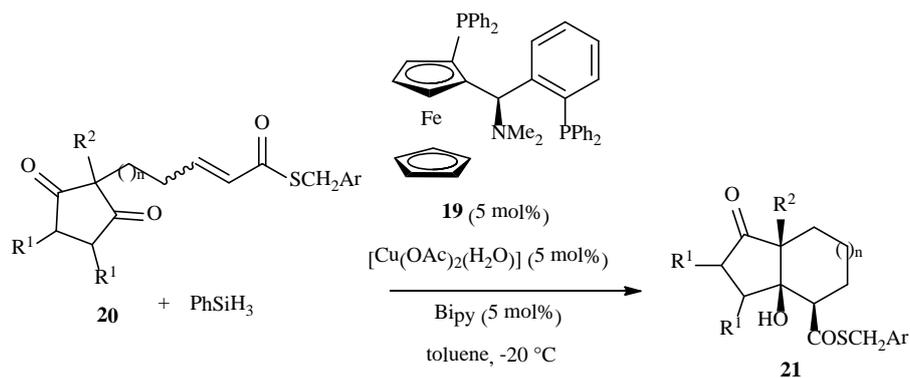
R = Me, X = *Or*-Bu, n = 1, m = 0: 85%, *cis/trans* = 94:6, 80% ee (*cis*), 85% ee (*trans*)  
 R = Me, X = *Or*-Bu, n = 0, m = 2: 80%, *cis/trans* = 89:11, 97% ee (*cis*), 72% ee (*trans*)  
 R = Me, X = *Or*-Bu, n = m = 0: 85%, *cis/trans* >99:1, 66% ee (*cis*)  
 R = Me, X = *Or*-Bu, n = 2, m = 1: 85%, *cis/trans* >99:1, 94% ee (*cis*)  
 R = allyl, X = *Or*-Bu, n = m = 1: 70%, *cis/trans* >99:1, 94% ee (*cis*)  
 R = Me, X = *Or*-Bu, n = 1, m = 2: 80%, *cis/trans* >99:1, 95% ee (*cis*)  
 R = Me, X = *Or*-Bu, n = 0, m = 1: 80%, *cis/trans* >99:1, 95% ee (*cis*)  
 R = Me, X = *Or*-Bu, n = m = 1: 85%, *cis/trans* >99:1, 95% ee (*cis*)  
 R = allyl, X = *Or*-Bu, n = m = 1: 70%, *cis/trans* >99:1, 94% ee (*cis*)  
 R = Me, X = OMe, n = m = 1: 75%, 44% de, 84% ee (*cis*)  
 R = Me, X = OEt, n = m = 1: 80%, *cis/trans* = 82:18, 92% ee (*cis*)  
 R = Me, X = OEt, n = 0, m = 1: 78%, *cis/trans* = 88:12, 92% ee (*cis*)  
 R = Me, X = Me, n = m = 1: 75%, *cis/trans* >99:1, 65% ee (*cis*)



marrubijn

**Scheme 6.** Domino reductive Michael/aldol reaction of  $\alpha,\beta$ -unsaturated esters and a ketone with phenylsilane.

The same year, Chiu et al. employed related chiral ligand **19** in combination with  $\text{Cu}(\text{OAc})_2(\text{H}_2\text{O})$  to promote enantioselective domino reductive Michael/aldol reactions between enethioate derivatives of 1,3-diones **20** and phenylsilane [12]. The reactions were performed in the presence of bipyridine (Bipy) as an additive. Under these conditions, a range of unsaturated thioesters **20** afforded the corresponding chiral bicyclic  $\beta$ -hydroxythioesters **21** exhibiting three contiguous stereocenters with moderate to high yields (65-94%) and diastereoselectivities (56->96% de) combined with low to excellent enantioselectivities (27-98% ee), as shown in Scheme 7. The lowest enantioselectivity (27% ee) was obtained in the formation of a five-membered ring (n = 0) whereas uniformly excellent enantioselectivities of 88-98% ee were achieved in the formation of six- and seven-membered rings.

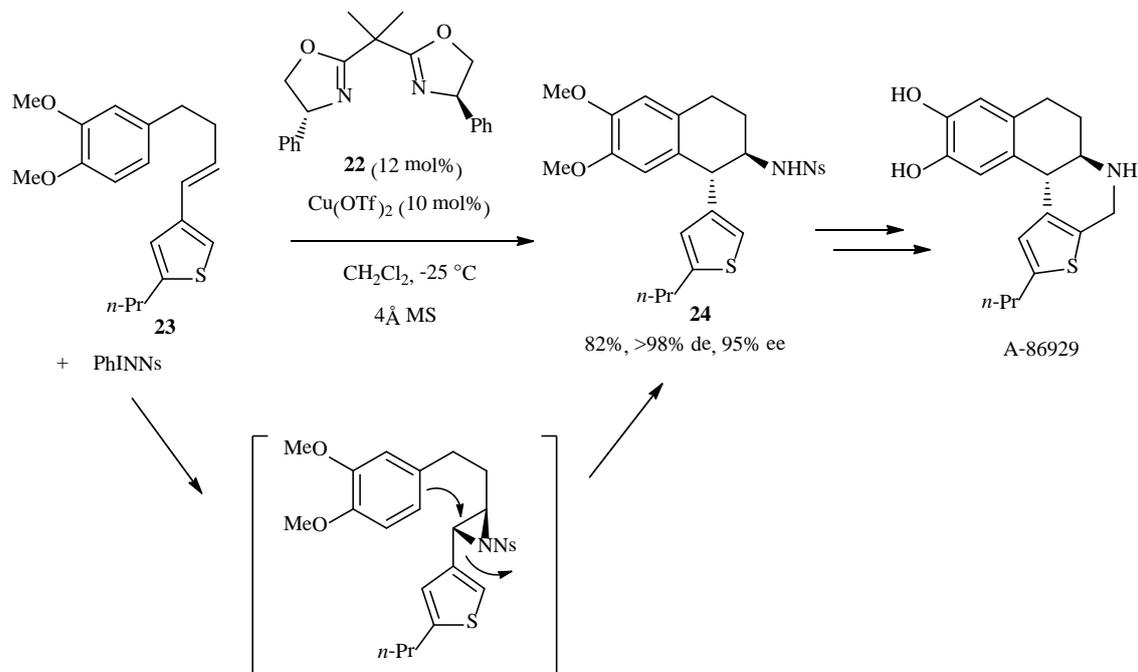


$\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}, n = 1, \text{Ar} = \text{Ph}: 84\%, >96\% \text{ de}, 90\% \text{ ee}$   
 $\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}, n = 1, \text{Ar} = p\text{-}t\text{-BuC}_6\text{H}_4: 94\%, >96\% \text{ de}, 90\% \text{ ee}$   
 $\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}, n = 1, \text{Ar} = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2: 93\%, >96\% \text{ de}, 93\% \text{ ee}$   
 $\text{R}^1, \text{R}^1 = (\text{CH}=\text{CH})_2, \text{R}^2 = \text{Me}, n = 1, \text{Ar} = \text{Ph}: 71\%, >96\% \text{ de}, 96\% \text{ ee}$   
 $\text{R}^1, \text{R}^1 = (\text{CH}=\text{CH})_2, \text{R}^2 = \text{allyl}, n = 1, \text{Ar} = \text{Ph}: 71\%, 74\% \text{ de}, 95\% \text{ ee}$   
 $\text{R}^1, \text{R}^1 = (\text{CH}=\text{CH})_2, \text{R}^2 = \text{CH}_2(p\text{-BrC}_6\text{H}_4), n = 1, \text{Ar} = \text{Ph}: 65\%, 56\% \text{ de}, 98\% \text{ ee}$   
 $\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}, n = 2, \text{Ar} = \text{Ph}: 72\%, >96\% \text{ de}, 93\% \text{ ee}$   
 $\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}, n = 2, \text{Ar} = p\text{-}t\text{-BuC}_6\text{H}_4: 86\%, 80\% \text{ de}, 88\% \text{ ee}$   
 $\text{R}^1 = \text{H}, \text{R}^2 = \text{Bn}, n = 2, \text{Ar} = \text{Ph}: 65\%, >96\% \text{ de}, 93\% \text{ ee}$   
 $\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}, n = 0, \text{Ar} = \text{Ph}: 56\%, >96\% \text{ de}, 27\% \text{ ee}$

**Scheme 7.** Domino reductive Michael/aldol reaction of  $\alpha,\beta$ -unsaturated thioesters with phenylsilane.

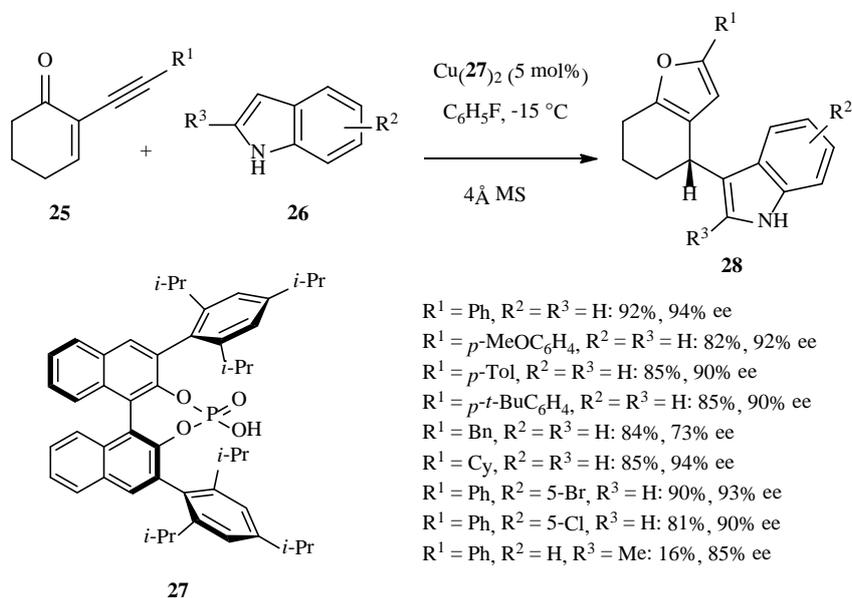
## 2.2. Domino Reactions Based on Cyclizations

Various enantioselective copper-catalyzed domino reactions have been based on cyclizations. For example in 2011, an asymmetric copper-catalyzed domino aziridination/Friedel–Crafts reaction was reported by Hajra and Bar [13]. It was promoted by a chiral copper catalyst in situ generated from  $\text{Cu}(\text{OTf})_2$  and chiral bisoxazoline **22**. The process evolved through the aziridination of a functionalized alkene **23** by treatment with PhINNs followed by ring-opening through a Friedel–Crafts reaction to provide the corresponding chiral domino product **24** as single *trans*-diastereomer (>98% de) in good yield (82%) and excellent enantioselectivity (95% ee), as illustrated in Scheme 8. This product was further converted into A-86929.



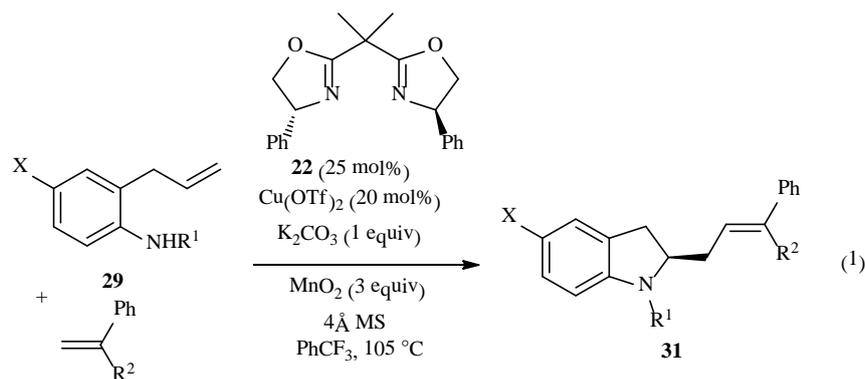
**Scheme 8.** Domino aziridination/Friedel–Crafts reaction of a functionalized alkene with PhINNs and synthesis of A-86929.

In the same year, Toste et al. reported a novel enantioselective copper-catalyzed domino cycloisomerization/nucleophilic addition reaction between 2-(1-alkynyl)-2-alkene-1-ones **25** and indoles **26** (Scheme 9) [14]. It was promoted by a chiral preformed copper catalyst derived from phosphoric acid **27**. The domino process evolved through the intramolecular heterocyclization of the alkyne substrates followed by the nucleophilic attack of the indoles, leading to the corresponding chiral domino products **28** in high yields (81-92%) and moderate to high enantioselectivities (73-94% ee). However, a much lower yield (16%) was obtained in the reaction of 2-methyl indole ( $R^3 = \text{Me}$ ).



**Scheme 9.** Domino cycloisomerization/nucleophilic addition reaction of 2-(1-alkynyl)-2-alkene-1-ones with indoles.

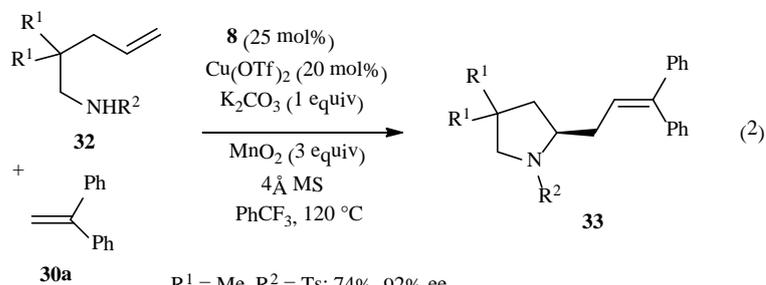
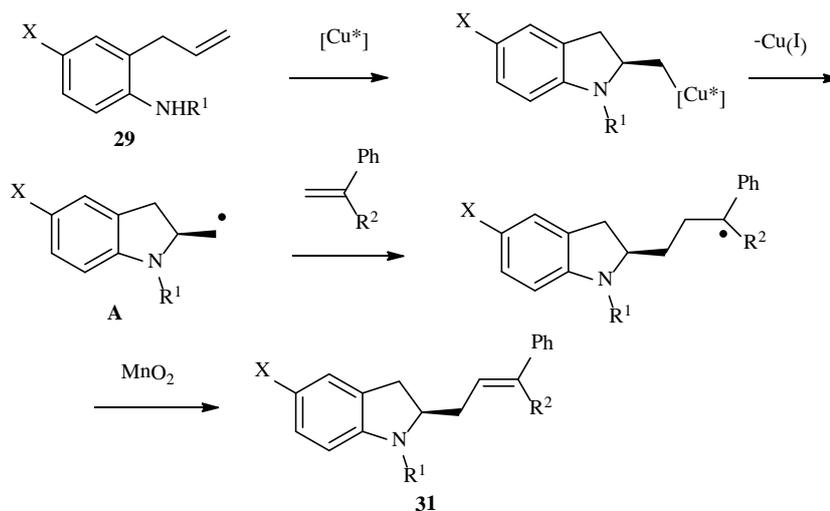
In another context, Chemler and Liwosz have described asymmetric domino amination/Heck-type reactions of  $\gamma$ -alkenylsulfonamides **29** with vinylarenes **30a-b** promoted by a chiral copper catalyst in situ generated from  $\text{Cu}(\text{OTf})_2$  and chiral bisoxazoline **22** [15]. Performed in the presence of  $\text{MnO}_2$  as oxidant, the reactions led to the corresponding chiral 2-substituted indolines **31** in moderate to good yields (65-85%) and enantioselectivities (71-91% ee). As shown in Scheme 10 (first equation), *N*-arylsulfonylanilines afforded the corresponding products with relatively higher enantioselectivities than *N*-mesyl- and *N*-trimethylsilylethylsulfonyl analogues. On the other hand, the yields and enantioselectivities were relatively insensitive to the nature of the substituent at the 4-position (X) on the aniline ring. Concerning the vinylarenes, diphenylethylene **30a** ( $R^2 = \text{Ph}$ ) was shown to be the most reactive substrate. A radical mechanism was assumed by the authors in which the vinylarene intercepted a chiral  $\beta$ -aminoalkyl radical **A** generated from enantioselective aminocupration of the  $\gamma$ -alkenylsulfonamide **29** followed by C-Cu(II) homolysis (Scheme 10). In the presence of  $\text{MnO}_2$  as oxidant, the resulting carbon radical intermediate could be oxidized into the final alkene. Furthermore, the scope of this methodology could be extended to relatively less reactive 4-pentenylsulfonamides **32** which required higher temperature (120 °C) to provide by reaction with diphenylethylene **30a** the corresponding chiral pyrrolidines **33** in moderate to high yields (62-88%) and enantioselectivities (55-95% ee), as shown in Scheme 10 (second equation).



**30a-b**

X = H, R<sup>1</sup> = Ts, R<sup>2</sup> = Ph: 75%, 91% ee  
 X = H, R<sup>1</sup> = Bs, R<sup>2</sup> = Ph: 85%, 88% ee  
 X = H, R<sup>1</sup> = Ns, R<sup>2</sup> = Ph: 65%, 87% ee  
 X = H, R<sup>1</sup> = Ms, R<sup>2</sup> = Ph: 84%, 83% ee  
 X = H, R<sup>1</sup> = SES, R<sup>2</sup> = Ph: 80%, 71% ee  
 X = F, R<sup>1</sup> = Ts, R<sup>2</sup> = Ph: 84%, 88% ee  
 X = OMe, R<sup>1</sup> = Ts, R<sup>2</sup> = Ph: 77%, 86% ee  
 X = Cl, R<sup>1</sup> = Ts, R<sup>2</sup> = Ph: 83%, 91% ee  
 X = R<sup>2</sup> = H, R<sup>1</sup> = Ts: 71%, 88% ee

proposed mechanism:

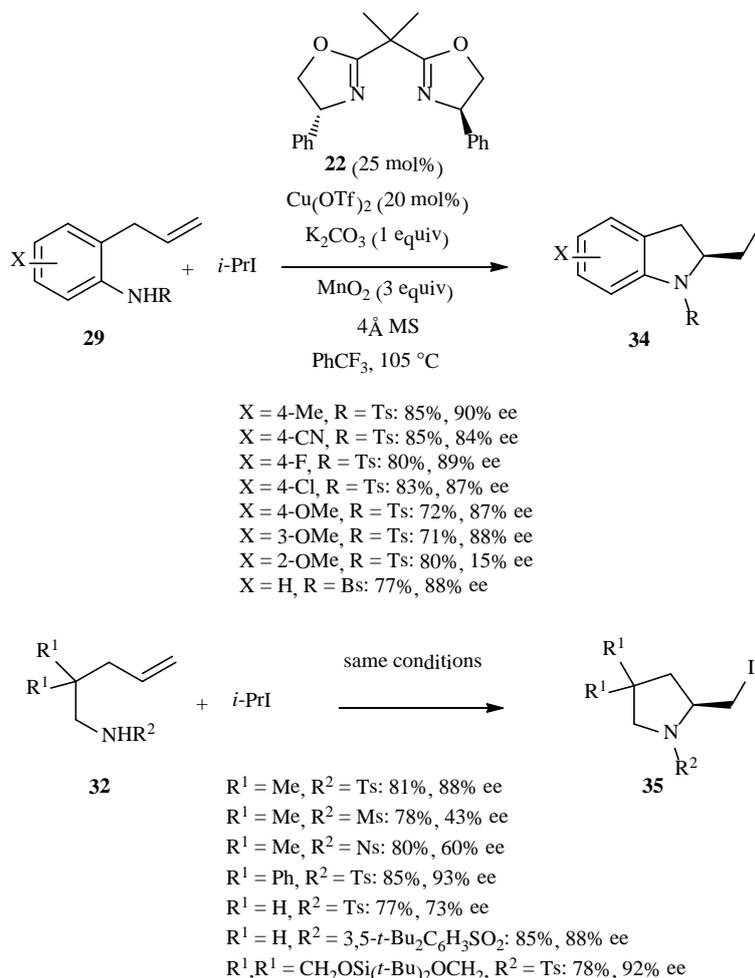


**30a**

R<sup>1</sup> = Me, R<sup>2</sup> = Ts: 74%, 92% ee  
 R<sup>1</sup> = Me, R<sup>2</sup> = Ms: 88%, 55% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = Ts: 68%, 95% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = Ms: 68%, 90% ee  
 R<sup>1</sup> = H, R<sup>2</sup> = Ts: 62%, 80% ee

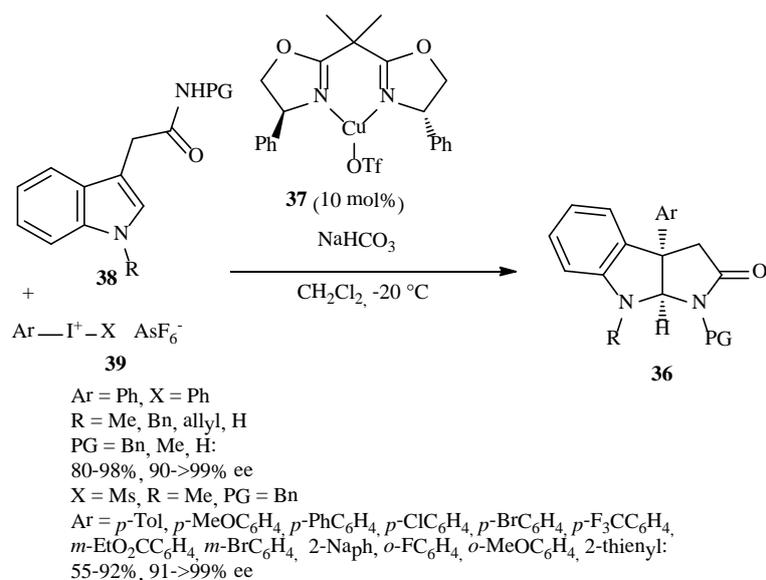
**Scheme 10.** Domino amination/Heck-type reactions of  $\gamma$ -alkenylsulfonamides and 4-pentenylsulfonamides with vinylarenes.

The same reaction conditions were also applied by these authors to develop enantioselective domino aminohalogenation/cyclization reactions between the same sulfonamide substrates and 2-iodopropane [16]. In this case, the chiral  $\beta$ -aminoalkyl radical intermediate **A** (Scheme 10) was intercepted by 2-iodopropane as halogen source to give chiral 2-iodomethylindolines **34** and 2-iodomethylpyrrolidines **35** starting respectively from the corresponding  $\gamma$ -alkenylsulfonamides **29** and 4-pentenylsulfonamides **32**. These functionalized heterocycles were produced in 71-85% and 77-85% yields in combination with 15-90% ee and 43-93% ee, respectively (Scheme 11).



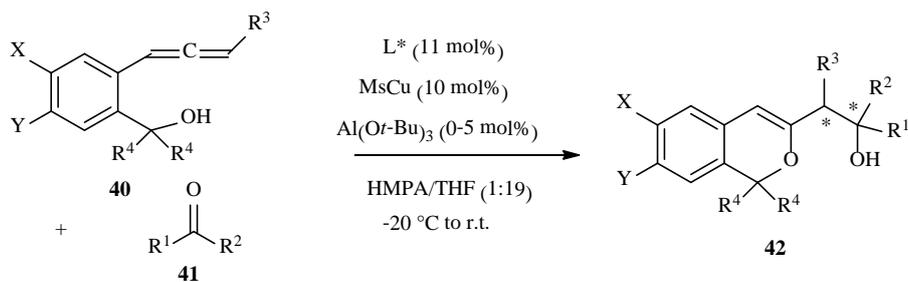
**Scheme 11.** Domino aminohalogenation/cyclization reactions of  $\gamma$ -alkenylsulfonamides and 4-pentenylsulfonamides with 2-iodopropane.

In another area, biologically important chiral C3-aryl pyrroloindoline derivatives **36** were synthesized by MacMillan and Zhu on the basis of enantioselective copper-catalyzed domino arylation/cyclization reactions [17]. Indeed, in the presence of preformed bisoxazoline copper catalyst **37**, the reaction between various indole acetamides **38** and diphenyliodonium salt **39** (Ar = X = Ph) evolved through an arylation followed by cyclization of the formed intermediates to afford the corresponding chiral pyrroloindolines **36** in high yields (80-98%) combined with uniformly excellent enantioselectivities (90->99% ee), as shown in Scheme 11. In particular, *N*-methyl-, *N*-allyl-, and *N*-benzyl-substituted indole acetamides all provided uniformly excellent enantioselectivities (97-99% ee), while slightly lower enantioselectivities (90-95% ee) were obtained for unsubstituted indole substrates. Moreover, the scope of the methodology was extended to non-symmetric arylidonium salts (X = Ms). Indeed, various *ortho*-, *meta*-, and *para*-substituted aryl rings (Ar) with diverse steric and electronic properties reacted with methyl-protected indole benzylacetamide (R = Me, PG = Bn) to provide the corresponding chiral pyrroloindolines **36** in moderate to high yields (55-92%) and uniformly high enantioselectivities (91->99% ee), as shown in Scheme 12 (X = Ms).



**Scheme 12.** Domino arylation/cyclization reaction of indole acetamides with arylidonium salts.

Later in 2013, enantioselective domino cyclization/addition reactions of allenic alcohols **40** with carbonyl compounds **41** were reported by Shimizu and Kanai, allowing a novel entry to chiral *1H*-isochromene derivatives **42** [18]. The process evolved through the intramolecular oxycupration of the allene followed by asymmetric addition of the in situ generated allylcopper intermediate to the carbonyl compound. As shown in Scheme 13, a range of allenic alcohols **40** reacted with aldehydes **41** ( $R^2 = H$ ) in the presence of a copper catalyst in situ generated from 10 mol% of MsCu and 11 mol% of a chiral biphosphine ligand, such as (*R*)-DTBM-Segphos or (*S,S*)-Ph-bpe, that afforded the corresponding chiral *1H*-isochromene derivatives **42**. When using (*R*)-DTBM-Segphos as ligand, moderate to high yields (60-91%) combined with good to high enantioselectivities (81-93% ee) were obtained while low to quantitative yields (30-99%) and high enantioselectivities (81-97% ee) were achieved by employing (*S,S*)-Ph-bpe as ligand. The use of an additive, such as Al(*O**t*-Bu)<sub>3</sub>, was found to be essential to improve the reactivity. A range of aliphatic and aromatic aldehydes were tolerated, but a less reactive carbonyl compound, such as acetophenone ( $R^1 = Ph$ ,  $R^2 = Me$ ) was also found to be compatible, leading to the corresponding product in 77% yield and 76% ee.



with  $L^* = (R)$ -DTBM- $Se_{gphos}$ :

$X = Y = R^2 = R^3 = R^4 = H$ ,  $R^1 = Ph$ : 70%, 81% ee

$X = Y = R^2 = R^3 = R^4 = H$ ,  $R^1 = t-Bu$ : 77%, 91% ee

$X = Y = R^2 = R^3 = R^4 = H$ ,  $R^1 = Cy$ : 66%, 91% ee

$X = Y = R^2 = R^3 = R^4 = H$ ,  $R^1 = c-Pent$ : 60%, 89% ee

$X = Y = R^2 = R^3 = R^4 = H$ ,  $R^1 = i-Pent$ : 91%, 93% ee

$X = Y = R^2 = R^3 = R^4 = H$ ,  $R^1 = c-Pr$ : 78%, 84% ee

$X = R^2 = R^3 = R^4 = H$ ,  $Y = Cl$ ,  $R^1 = Cy$ : 72%, 86% ee

$X = R^2 = R^3 = R^4 = H$ ,  $Y = Cl$ ,  $R^1 = i-Pent$ : 76%, 91% ee

$X = F$ ,  $R^2 = R^3 = R^4 = H$ ,  $Y = Cl$ ,  $R^1 = i-Pent$ : 86%, 93% ee

$X = Y = R^3 = R^4 = H$ ,  $R^1 = Ph$ ,  $R^2 = Me$ : 77%, 76% ee

with  $L^* = (S,S)$ -Ph-bpe:

$X = Y = R^2 = R^3 = H$ ,  $R^1 = Ph$ ,  $R^4 = Me$ : 92%, 92% ee

$X = Y = R^2 = R^3 = H$ ,  $R^1 = p\text{-MeOC}_6\text{H}_4$ ,  $R^4 = Me$ : 91%, 90% ee

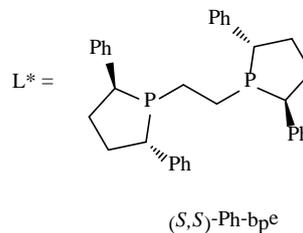
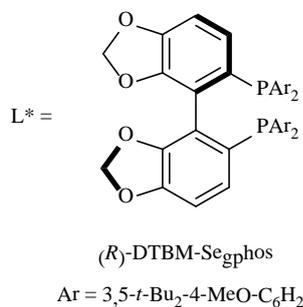
$X = Y = R^2 = R^3 = H$ ,  $R^1 = p\text{-(}t\text{-Bu)C}_6\text{H}_4$ ,  $R^4 = Me$ : 90%, 91% ee

$X = Y = R^2 = R^3 = H$ ,  $R^1 = p\text{-FC}_6\text{H}_4$ ,  $R^4 = Me$ : 85%, 90% ee

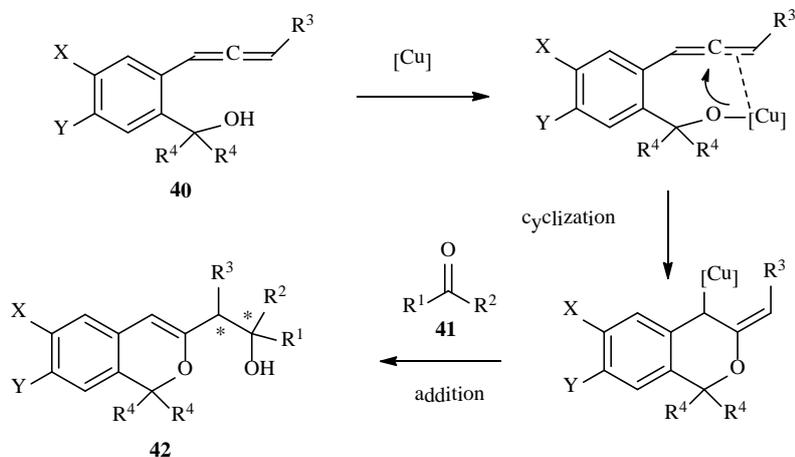
$X = R^2 = R^3 = H$ ,  $Y = OMe$ ,  $R^1 = Ph$ ,  $R^4 = Me$ : 69%, 92% ee

$X = Y = R^2 = H$ ,  $R^1 = Ph$ ,  $R^3 = R^4 = Me$ : 98%, 58% de, 97% ee and 82% ee

$X = Y = R^2 = H$ ,  $R^1 = R^4 = Ph$ ,  $R^3 = Me$ : 99%, 30% de, 81% ee and 95% ee

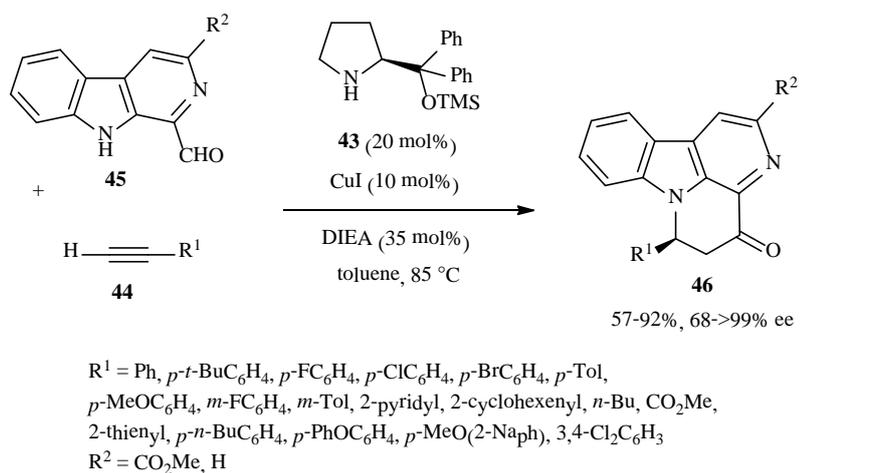


proposed mechanism:

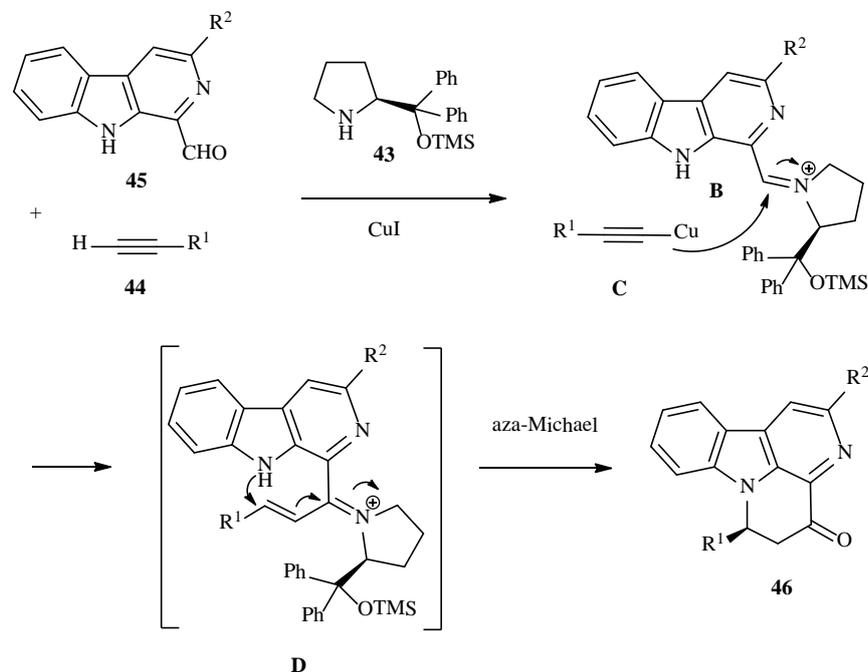


**Scheme 13.** Domino cyclization/addition reaction of allenic alcohols with carbonyl compounds.

In 2016, Batra et al. employed a combination of CuI with chiral proline-derived organocatalyst **43** to cooperatively catalyze enantioselective domino reactions between terminal alkynes **44** and 1-formyl-9*H*- $\beta$ -carboline **45** [19]. This efficient multicatalysis opened a novel route for achieving biologically interesting chiral 5,6-dihydroanthin-4-ones **46** in moderate to high yields (57-92%) and enantioselectivities (68->99% ee), as shown in Scheme 14. A number of variously substituted alkynes were compatible with the highest enantioselectivities (84->99% ee) obtained with (hetero)aryl alkynes ( $R^1 =$  (hetero)aryl). A possible mechanism is depicted in Scheme 14 which began with the reaction of the aldehyde substrate **45** with the chiral pyrrolidine catalyst **43** to give the corresponding iminium ion **B** which then reacted with the in situ generated Cu-coordinated alkyne **C** to give intermediate **D**. The latter subsequently underwent an intramolecular aza-Michael addition to provide the final domino product **46** after hydrolysis.



proposed mechanism:

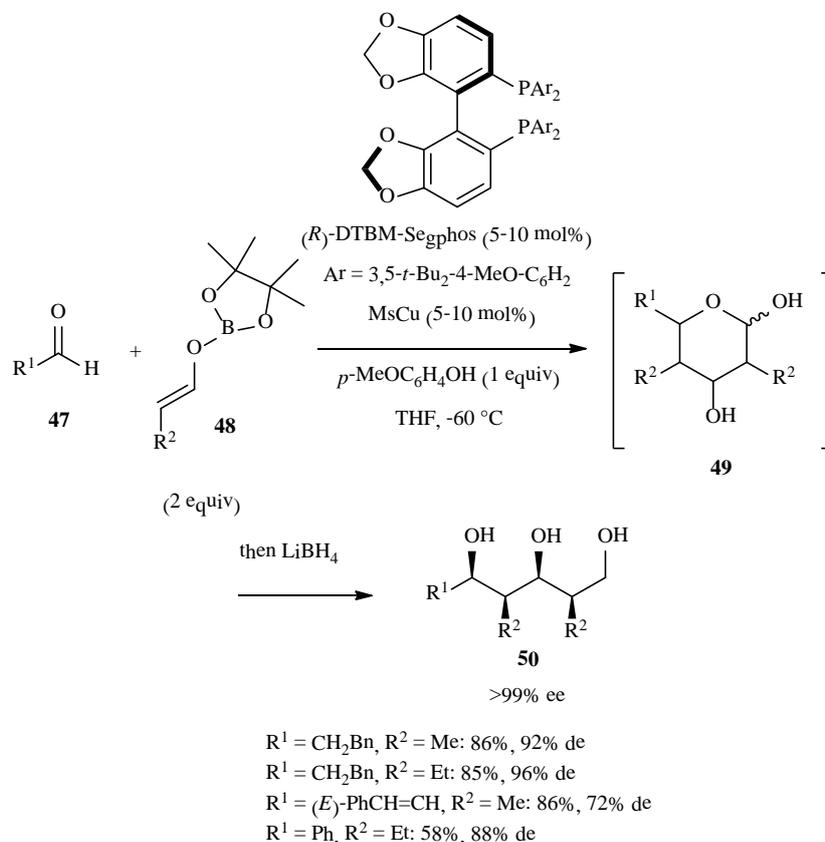


**Scheme 14.** Domino condensation/aza-Michael reaction of alkynes with 1-formyl-9*H*- $\beta$ -carboline in the presence of a chiral proline-derived organocatalyst.

### 2.3. Domino Reactions Initiated by Aldol-type Reactions

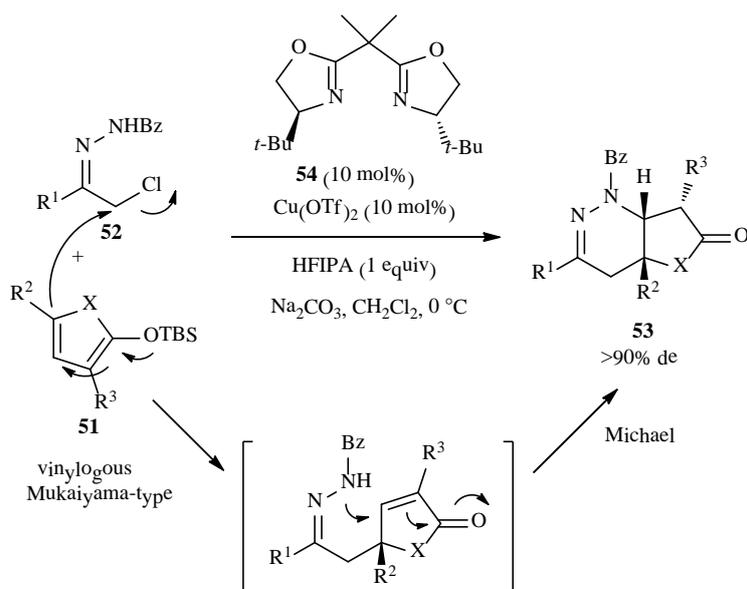
In 2015, Matsunaga and Kanai employed a chiral copper catalyst in situ generated from MsCu and (*R*)-DTBM-Segphos as ligand to promote the enantioselective domino double aldol/hemiacetalization reaction of

aldehydes **47** with boron enolates **48** [20]. Actually, the process led to the corresponding cyclized hemiacetals **49** as domino products which were not isolated but directly reduced by subsequently treatment with  $\text{LiBH}_4$  to give the corresponding enantiopure triols **50** (>99% ee) in good yields (85-86%) and good to high diastereoselectivities (72-96% de), as shown in Scheme 15. This methodology was extended to more than double aldol reactions, including triple and quadruple asymmetric domino aldol condensations, affording chiral 1,3-polyols with excellent enantioselectivities of up to >99% ee.



**Scheme 15.** Domino double aldol/hemiacetalization reaction of aldehydes with boron enolates followed by reduction.

In the area of enantioselective copper-catalyzed domino reactions initiated by aldol-type condensations, Wang et al. have developed an asymmetric domino vinylogous Mukayama-type/Michael reaction of 2-silyloxyfurans **51** with hydrazones **52**, providing a novel entry to chiral fused biologically interesting butyrolactones **53** [21]. The process was promoted at 0 °C by a chiral copper catalyst in situ generated from  $\text{Cu}(\text{OTf})_2$  and chiral bisoxazoline ligand **54** in the presence of hexafluoroisopropanol (HFIPA) as stoichiometric additive in dichloromethane as solvent, providing the corresponding fused chiral butyrolactones **53** (X = O) as almost single diastereomers (>90% de) in good yields (75-88%) and enantioselectivities (71-97% ee), as shown in Scheme 16. The scope of the reaction was extended to a pyrrole-based dioxysilane **51** (X = NBoc), which reacted with hydrazones **52** to give the corresponding chiral butyrolactams **53** in both high yields (80-92%) and enantioselectivities (90-98% ee), as shown in Scheme 16.

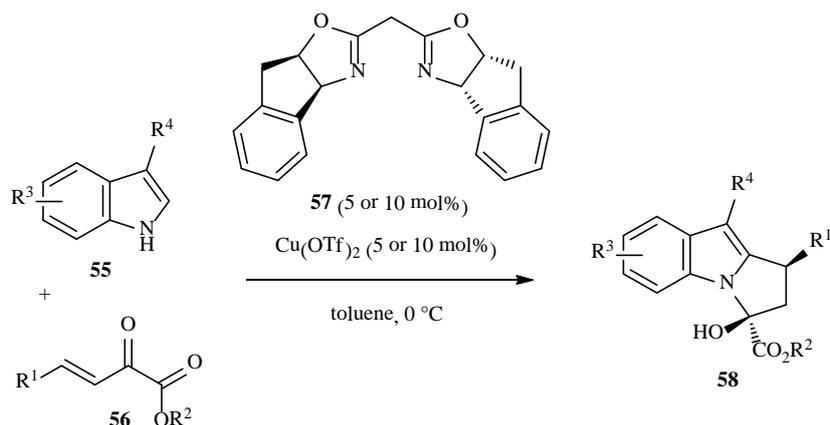


- $R^1 = \text{Ph}, R^2 = R^3 = \text{H}, X = \text{O}: 85\%, 97\% \text{ ee}$   
 $R^1 = p\text{-BrC}_6\text{H}_4, R^2 = R^3 = \text{H}, X = \text{O}: 86\%, 94\% \text{ ee}$   
 $R^1 = p\text{-ClC}_6\text{H}_4, R^2 = R^3 = \text{H}, X = \text{O}: 88\%, 94\% \text{ ee}$   
 $R^1 = m\text{-ClC}_6\text{H}_4, R^2 = R^3 = \text{H}, X = \text{O}: 81\%, 91\% \text{ ee}$   
 $R^1 = o\text{-FC}_6\text{H}_4, R^2 = R^3 = \text{H}, X = \text{O}: 86\%, 93\% \text{ ee}$   
 $R^1 = p\text{-Tol}, R^2 = R^3 = \text{H}, X = \text{O}: 80\%, 96\% \text{ ee}$   
 $R^1 = p\text{-MeOC}_6\text{H}_4, R^2 = R^3 = \text{H}, X = \text{O}: 87\%, 94\% \text{ ee}$   
 $R^1 = m\text{-Tol}, R^2 = R^3 = \text{H}, X = \text{O}: 78\%, 92\% \text{ ee}$   
 $R^1 = 2\text{-Naph}, R^2 = R^3 = \text{H}, X = \text{O}: 88\%, 94\% \text{ ee}$   
 $R^1 = (E)\text{-PhCH=CH}, R^2 = R^3 = \text{H}, X = \text{O}: 83\%, 71\% \text{ ee}$   
 $R^1 = \text{Ph}, R^2 = \text{H}, R^3 = \text{Me}, X = \text{O}: 82\%, 97\% \text{ ee}$   
 $R^1 = p\text{-ClC}_6\text{H}_4, R^2 = \text{H}, R^3 = \text{Me}, X = \text{O}: 75\%, 96\% \text{ ee}$   
 $R^1 = p\text{-F}_3\text{CC}_6\text{H}_4, R^2 = \text{H}, R^3 = \text{Me}, X = \text{O}: 83\%, 97\% \text{ ee}$   
 $R^1 = p\text{-Tol}, R^2 = \text{H}, R^3 = \text{Me}, X = \text{O}: 78\%, 93\% \text{ ee}$   
 $R^1 = m\text{-Tol}, R^2 = \text{H}, R^3 = \text{Me}, X = \text{O}: 75\%, 93\% \text{ ee}$   
 $R^1 = \text{Ph}, R^2 = \text{Me}, R^3 = \text{H}, X = \text{O}: 81\%, 97\% \text{ ee}$   
 $R^1 = p\text{-BrC}_6\text{H}_4, R^2 = \text{Me}, R^3 = \text{H}, X = \text{O}: 86\%, 95\% \text{ ee}$   
 $R^1 = p\text{-ClC}_6\text{H}_4, R^2 = \text{Me}, R^3 = \text{H}, X = \text{O}: 84\%, 96\% \text{ ee}$   
 $R^1 = p\text{-Tol}, R^2 = \text{Me}, R^3 = \text{H}, X = \text{O}: 80\%, 94\% \text{ ee}$   
 $R^1 = m\text{-Tol}, R^2 = \text{Me}, R^3 = \text{H}, X = \text{O}: 76\%, 96\% \text{ ee}$   
 $R^1 = \text{Ph}, R^2 = R^3 = \text{H}, X = \text{NBoc}: 92\%, 90\% \text{ ee}$   
 $R^1 = p\text{-BrC}_6\text{H}_4, R^2 = R^3 = \text{H}, X = \text{NBoc}: 87\%, 95\% \text{ ee}$   
 $R^1 = o\text{-FC}_6\text{H}_4, R^2 = R^3 = \text{H}, X = \text{NBoc}: 82\%, 97\% \text{ ee}$   
 $R^1 = p\text{-Tol}, R^2 = R^3 = \text{H}, X = \text{NBoc}: 80\%, 98\% \text{ ee}$   
 $R^1 = p\text{-BrC}_6\text{H}_4, R^2 = R^3 = \text{H}, X = \text{NBoc}: 87\%, 95\% \text{ ee}$

**Scheme 16.** Domino vinylogous Mukaiyama-type/Michael reaction of 2-silyloxyfurans and 2-siloxypyrroles with hydrazones.

#### 2.4. Domino Reactions Initiated by Friedel–Crafts Reactions

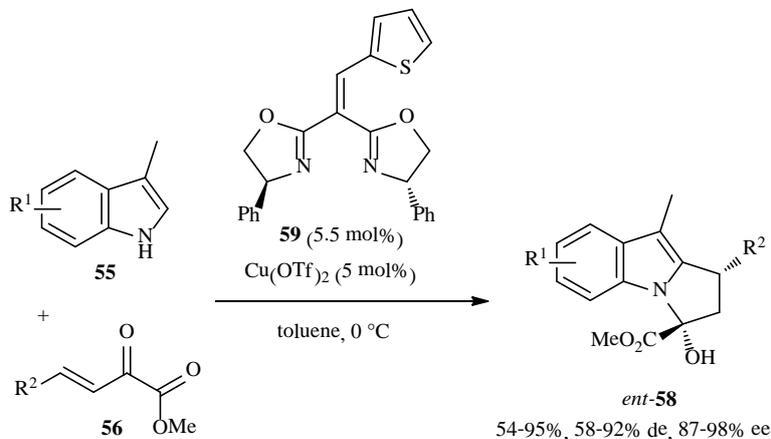
While the Friedel–Crafts reaction constitutes a fundamental reaction in organic chemistry [22], catalyzed asymmetric versions are still rare. Among them, some examples have been included in domino reactions, such as enantioselective copper-catalyzed domino Friedel–Crafts/*N*-hemiacetalization reactions of 3-substituted indoles **55** with  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters **56** developed by Xiao et al., in 2013 [23]. These reactions were promoted by a chiral catalyst in situ generated from  $\text{Cu}(\text{OTf})_2$  and chiral bisoxazoline ligand **57**, leading to the corresponding functionalized chiral 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles **58** in good to high yields (67–97%) and low to excellent diastereo- (12–94% de) and enantioselectivities (27–>99% ee), as shown in Scheme 17.



$\text{R}^1 = \text{Ph}, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, 2\text{-thiophenyl}, (E)\text{-PhCH=CH}, \text{CO}_2\text{Et}, \text{Cy}, (\text{MeO})_2\text{CH}, n\text{-Pr}$   
 $\text{R}^2 = \text{Me}, \text{Et}, \text{Bn}, i\text{-Pr}$   
 $\text{R}^3 = \text{H}, 4\text{-Me}, 5\text{-Me}, 6\text{-Me}, 5\text{-MeO}, 5\text{-BnO}, 5\text{-F}, 5\text{-Cl}, 5\text{-Br}, 6\text{-Cl}, 6\text{-F}$   
 $\text{R}^4 = \text{Me}, \text{Et}, i\text{-Pr}, \text{Cy}, \text{Bn}, \text{Ph}, \text{CH}_2\text{CO}_2\text{Me}, (\text{CH}_2)_2\text{OTBS}, (\text{CH}_2)_2\text{NPhth}$   
 67-97%, 12-94% de, 27->99% ee

**Scheme 17.** Domino Friedel–Crafts/*N*-hemiacetalization reaction of 3-substituted indoles with  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters in the presence of a bisoxazoline ligand.

Later in 2015, these reactions were reinvestigated by Fu et al. in the presence of another chiral bisoxazoline ligand, such as heteroarylidene-tethered bisoxazoline ligand **59** [24]. As shown in Scheme 18, the reactions of 3-methyl indoles **55** with  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters **56** afforded the corresponding enantiomeric functionalized pyrroloindoles *ent*-**58** in moderate to high yields (54-95%) and diastereoselectivities (58-92% de) combined with uniformly high enantioselectivities (87-98% ee).



$\text{R}^1 = \text{H}, 5\text{-Me}, 5\text{-MeO}, 5\text{-F}, 5\text{-Cl}, 5\text{-Br}, 6\text{-F}, 4\text{-MeO}, 7\text{-F}$   
 $\text{R}^2 = \text{Ph}, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, m\text{-Tol}, m\text{-FC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, 2\text{-furyl}, 2\text{-thienyl}$   
 $(E)\text{-PhCH=CH}, \text{CO}_2\text{Et}, \text{Cy}, (\text{MeO})_2\text{CH}, n\text{-Pr}$

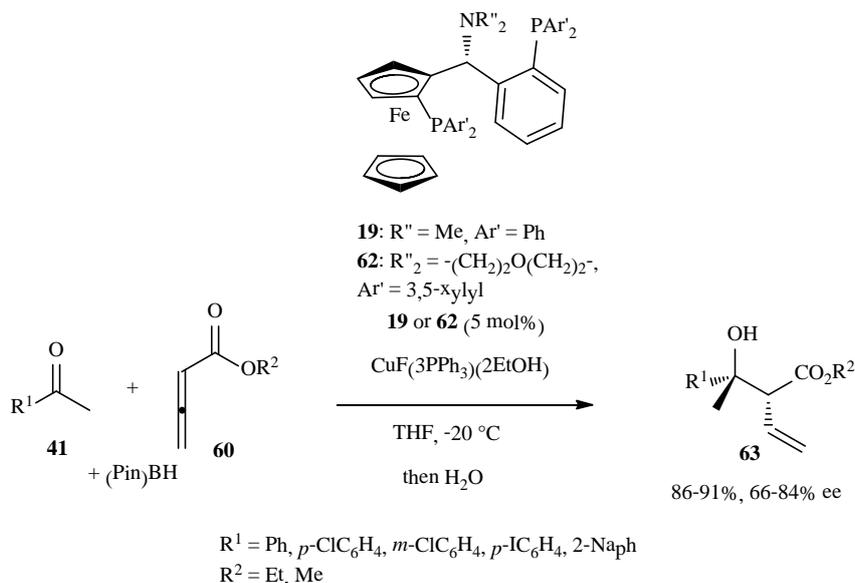
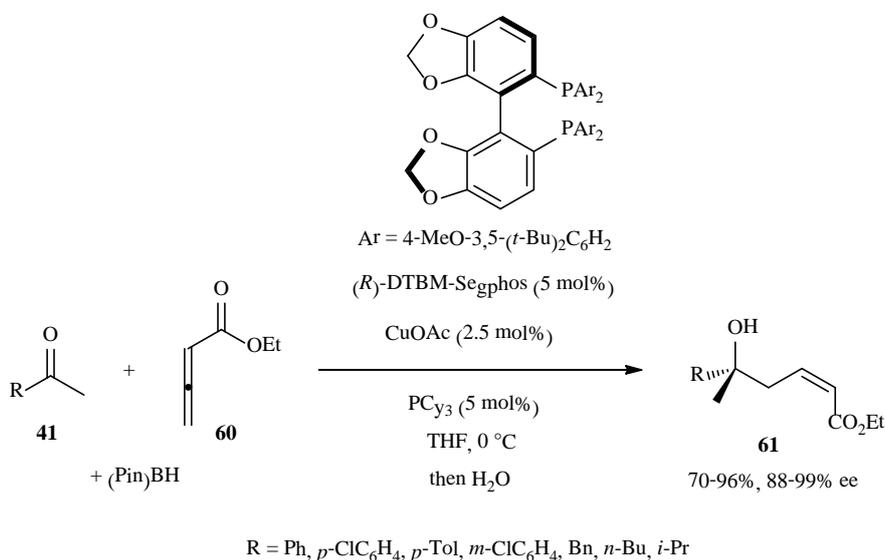
**Scheme 18.** Domino Friedel–Crafts/*N*-hemiacetalization reaction of 3-methyl indoles with  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters in the presence of a heteroarylidene-tethered bisoxazoline ligand.

### 3. THREE-COMPONENT DOMINO REACTIONS

#### 3.1. Michael-Initiated Domino Reactions

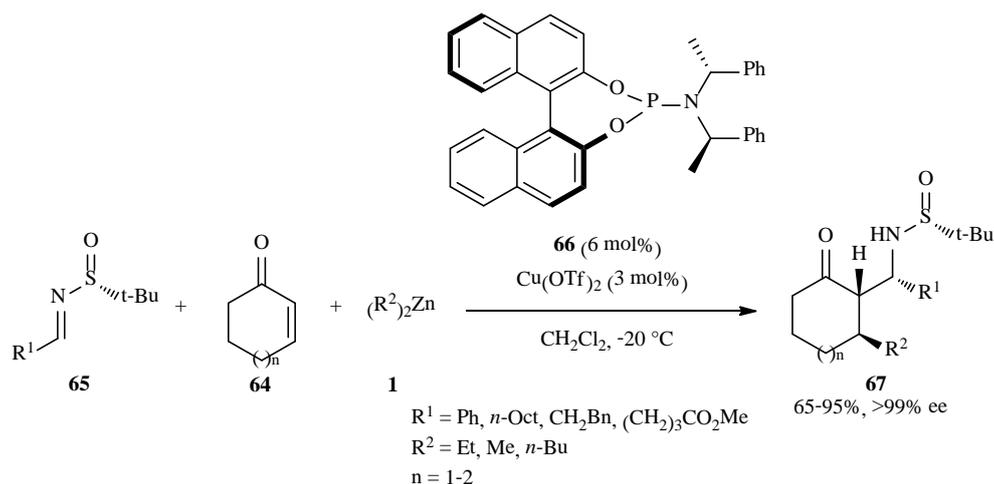
A number of multicomponent reactions [25] have been catalyzed by chiral metal catalysts, including enantioselective copper-catalyzed three-component reactions of different types. For example, Shibasaki et al. reported in 2006 the first catalytic enantioselective three-component domino reductive aldol reaction of ketones

**41** with allenic esters **60** and pinacolborane as reductant [26]. The process was promoted by a chiral copper catalyst in situ generated from CuOAc and (*R*)-DTBM-Segphos as ligand, leading regio- and stereoselectively to the corresponding chiral  $\gamma$ -*cis*-alcohols **61** as single products in good to excellent yields (80-96%) and uniformly high enantioselectivities (88-99% ee), as shown in Scheme 18 (first equation). Interestingly, it was found that using another type of ligands, such as Taniaphos ligands **19** and **62**, allowed to synthesize the corresponding  $\alpha$ -regioisomers **63** in high yields (86-91%) and moderate to good enantioselectivities (66-84% ee), as shown in Scheme 19 (second equation).



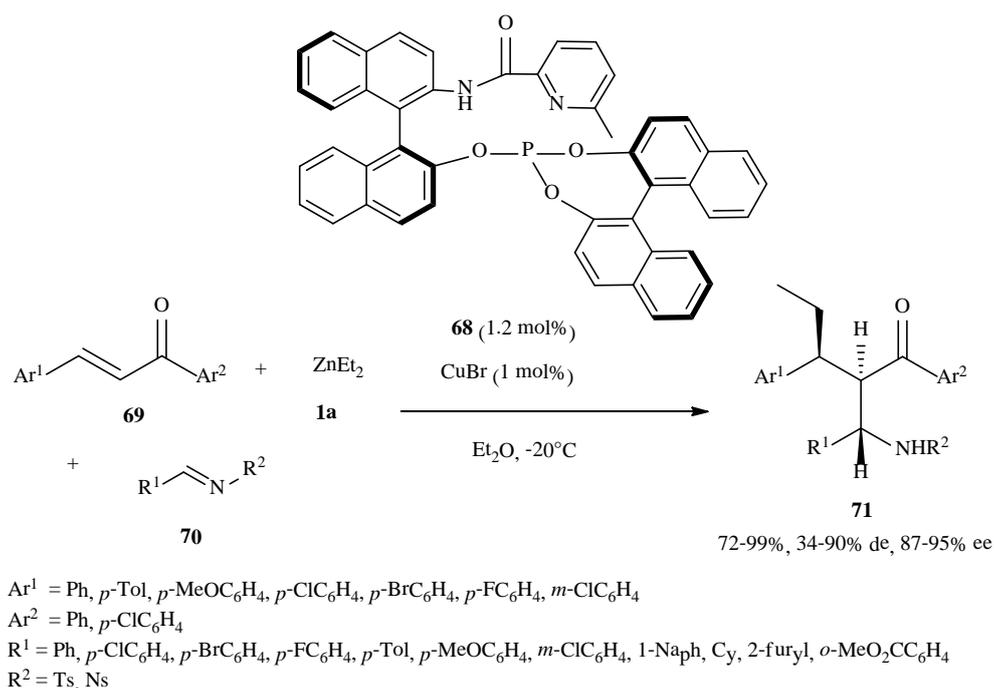
**Scheme 19.** Domino reductive aldol reactions of ketones with allenic esters.

In 2008, Yus et al. reported an enantioselective three-component domino Michael/Mannich reaction of cyclic enones **64**, chiral *N-tert*-butanesulfinimines **65** and dialkyl zinc reagents **1** catalyzed by a chiral copper complex in situ generated from Cu(OTf)<sub>2</sub> and chiral phosphoramidite ligand **66** [27]. Remarkably, the reaction led through double induction to the corresponding enantiopure  $\beta$ -amino ketones **67** exhibiting three contiguous stereogenic carbon centers in moderate to high yields (65-95%), as shown in Scheme 20.



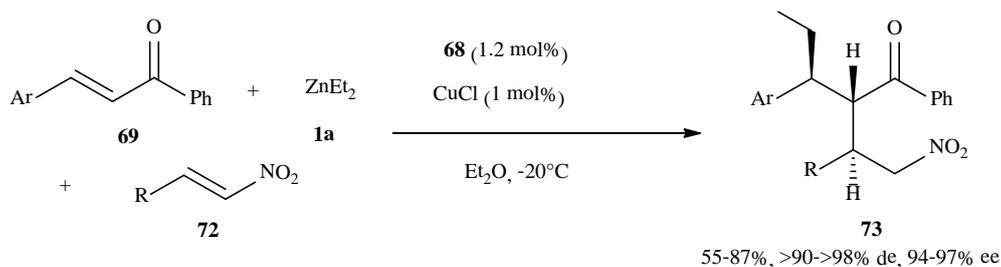
**Scheme 20.** Domino Michael/Mannich reaction of cyclic enones, chiral *N-tert*-butanesulfinimines and dialkyl zinc reagents.

In 2010, Huang et al. reported the use of a chiral copper complex in situ generated from CuBr and chiral phosphite **68** to promote the asymmetric three-component domino Michael/Mannich reaction between acyclic chalcones **69**, achiral *N*-sulfonyl aldimines **70** and diethylzinc **1a** [28]. The process afforded the corresponding chiral  $\beta$ -aminocarbonyl derivatives **71** bearing three contiguous stereocenters with both good to excellent yields (72-99%) and enantioselectivities (87-95% ee) combined with low to high diastereoselectivities (34-90% de), as illustrated in Scheme 21.



**Scheme 21.** Domino Michael/Mannich reaction of chalcones, *N*-sulfonyl aldimines and diethylzinc.

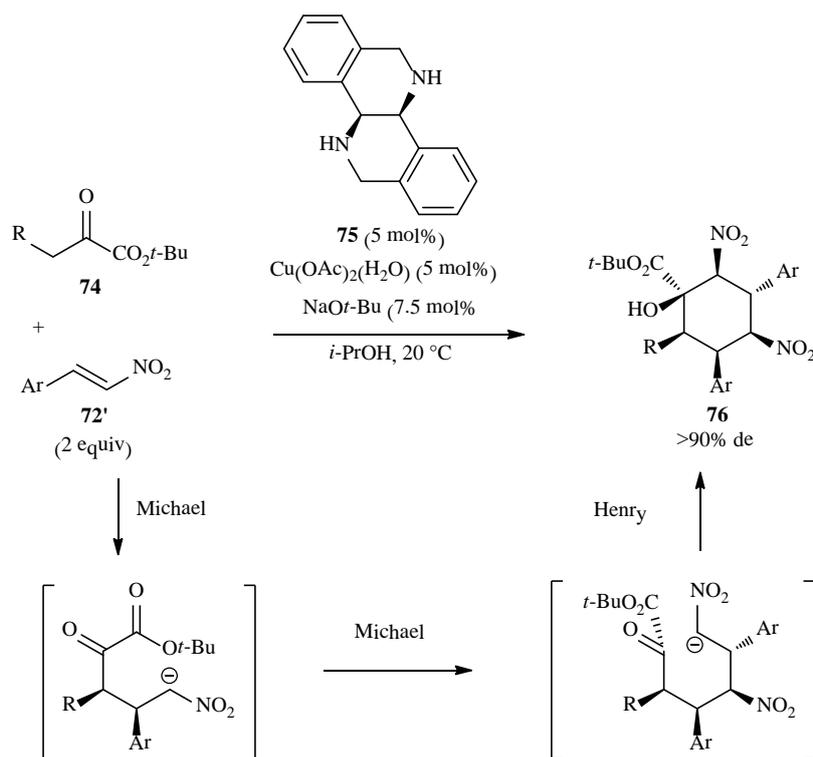
In another context, the same authors reported in 2011 enantioselective three-component double Michael reactions of diethylzinc **1a**,  $\alpha,\beta$ -unsaturated ketones **69** and nitroalkenes **72** [29]. Performed in the presence of a chiral catalyst in situ generated from CuCl and the same chiral phosphite ligand **68**, the domino double Michael reaction afforded the corresponding chiral products **73** bearing three contiguous stereocenters in moderate to good yields (55-87%), and both remarkable diastereo- and enantioselectivities (>90->98% de and 94-97% ee, respectively), as depicted in Scheme 22.



Ar = Ph, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>,  
 R = *p*-BrC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, *p*-Tol, *p*-MeOC<sub>6</sub>H<sub>4</sub>, 1-Naph, 2-furyl, Cy, AcNH, (*E*)-PhCH=CH, Ph

**Scheme 22.** Domino double Michael reaction of  $\alpha,\beta$ -unsaturated ketones, nitroalkenes and diethylzinc.

In 2012, enantioselective copper-catalyzed pseudo-three-component domino Michael/Henry reactions were also described by these authors [30]. They involved  $\alpha$ -ketoesters **74** and two equivalents of nitroalkenes **72'** as substrates, which led, in the presence of a chiral copper catalyst in situ generated from Cu(OAc)<sub>2</sub>(H<sub>2</sub>O) and chiral 1,2-diamine ligand **75**, to the corresponding highly functionalized cyclohexanes **76** bearing six stereogenic centers in moderate to excellent yields (42-95%), almost complete diastereoselectivity (>90% de) and moderate to excellent enantioselectivities (60-98% ee), as shown in Scheme 23.

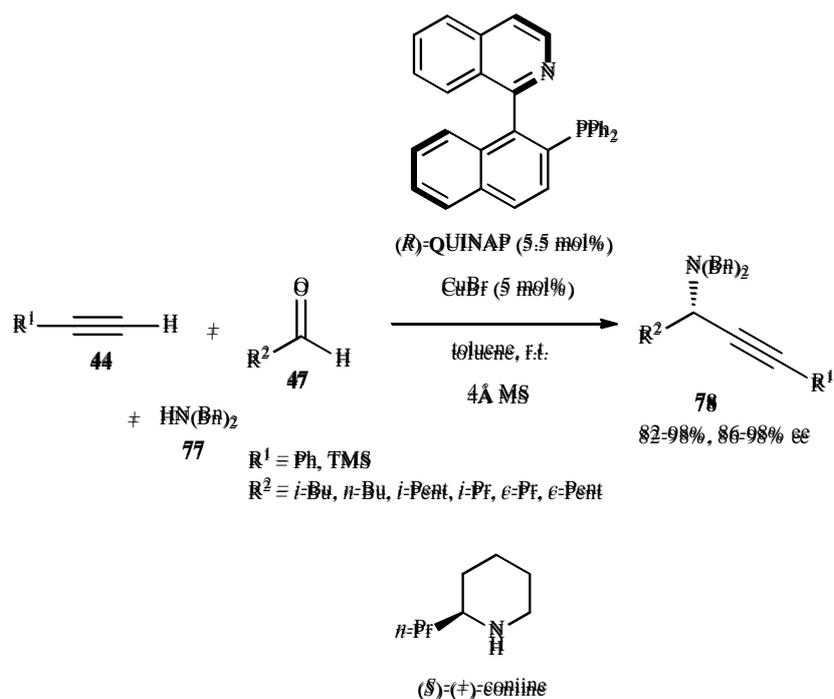


R = Bn, Ar = Ph: 95%, 95% ee  
 R = *p*-TolCH<sub>2</sub>, Ar = Ph: 83%, 94% ee  
 R = 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>, Ar = Ph: 74%, 94% ee  
 R = BnCH<sub>2</sub>, Ar = Ph: 80%, 95% ee  
 R = *n*-Pr, Ar = Ph: 82%, 94% ee  
 R = *n*-Pent, Ar = Ph: 81%, 94% ee  
 R = *n*-Hept, Ar = Ph: 88%, 94% ee  
 R = PhO(CH<sub>2</sub>)<sub>3</sub>, Ar = Ph: 85%, 95% ee  
 R = CH<sub>2</sub>=CH(CH<sub>2</sub>)<sub>2</sub>, Ar = Ph: 80%, 94% ee  
 R = TMSOC≡C(CH<sub>2</sub>)<sub>2</sub>, Ar = Ph: 85%, 93% ee  
 R = Bn, Ar = *p*-ClC<sub>6</sub>H<sub>4</sub>: 92%, 96% ee  
 R = Bn, Ar = *p*-BrC<sub>6</sub>H<sub>4</sub>: 70%, 95% ee  
 R = Bn, Ar = *p*-FC<sub>6</sub>H<sub>4</sub>: 81%, 94% ee  
 R = Bn, Ar = *p*-Tol: 88%, 96% ee  
 R = Bn, Ar = *p*-MeOC<sub>6</sub>H<sub>4</sub>: 80%, 94% ee  
 R = Bn, Ar = *m*-ClC<sub>6</sub>H<sub>4</sub>: 83%, 94% ee  
 R = Bn, Ar = 1-Naph: 85%, 94% ee  
 R = Bn, Ar = *o*-MeOC<sub>6</sub>H<sub>4</sub>: 76%, 60% ee  
 R = Bn, Ar = 2-furyl: 90%, 98% ee  
 R = Bn, Ar = (*E*)-PhCH=CH: 42%, 94% ee  
 R = CH<sub>2</sub>=CH, Ar = 2-furyl: 80%, 96% ee

**Scheme 23.** Domino double Michael/Henry reaction of two equivalents of nitroalkenes with  $\alpha$ -ketoesters.

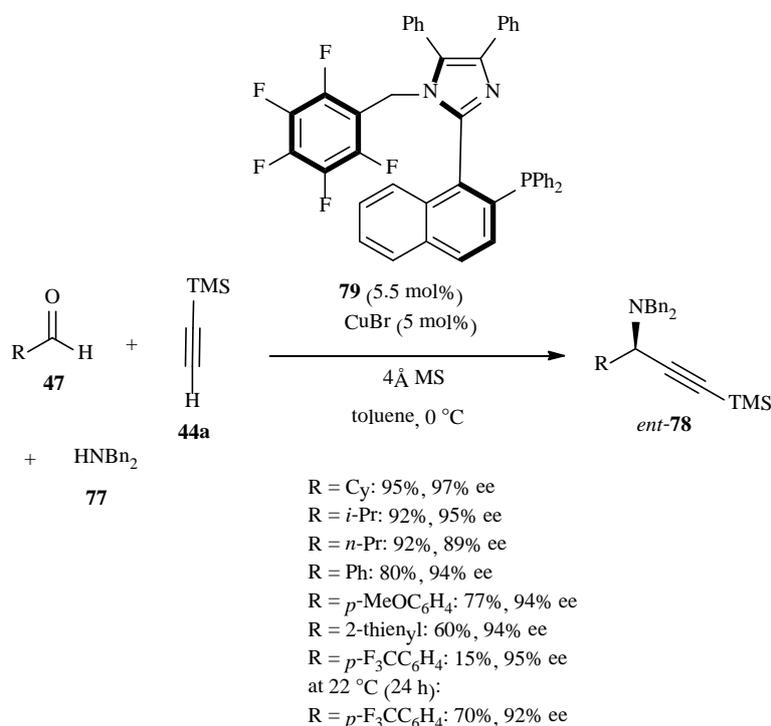
### 3.2. Three-Component Domino Reactions of Alkynes, Aldehydes and Amines

The copper-catalyzed three-component domino imination/alkynylation reaction between terminal alkynes, aldehydes and amines, allowing chiral propargylamines to be easily synthesized, has been widely investigated in the last decade. For example in 2006, Knochel and Gommermann employed a chiral copper catalyst in situ generated from CuBr and (*R*)-QUINAP to promote the reaction of secondary amines, such as dibenzylamine **77**, with terminal alkynes **44** and aldehydes **47**, affording the corresponding propargylamines **78** in both high yields (82-98%) and enantioselectivities (86-98% ee), as depicted in Scheme 24 [31]. The utility of this methodology was demonstrated by its application in the total synthesis of alkaloid (*S*)-(+)-coniine.



**Scheme 24.** Three-component reaction of aldehydes, alkynes and dibenzylamine.

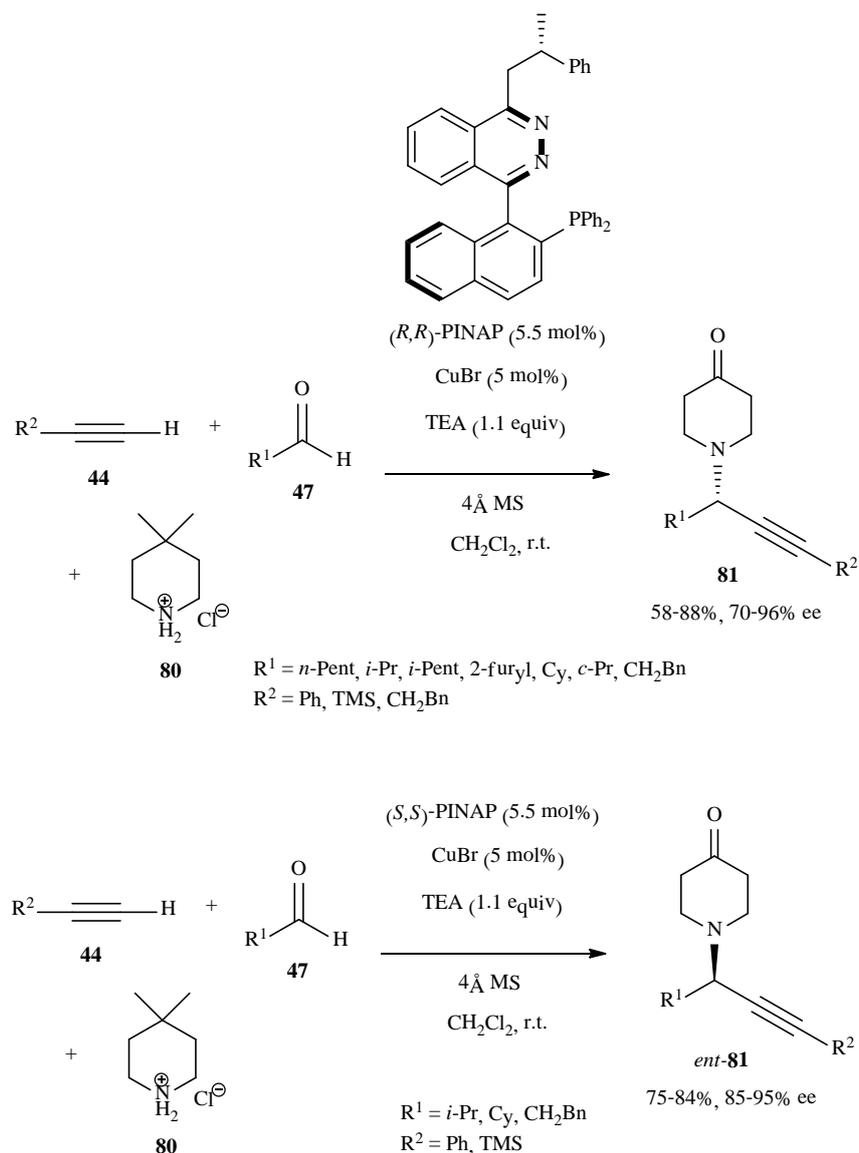
Later in 2013, another chiral P,N-ligand **79** was used by Aponick et al. to promote comparable reactions between aldehydes **47**, trimethylsilylacetylene **44a** and dibenzylamine **77** [32]. They afforded the corresponding chiral propargylamines *ent*-**78** with low to high yields (15-95%) and uniformly high enantioselectivities (89-97% ee), as illustrated in Scheme 25.



**Scheme 25.** Three-component reaction of aldehydes, trimethylsilylacetylene and dibenzylamine.

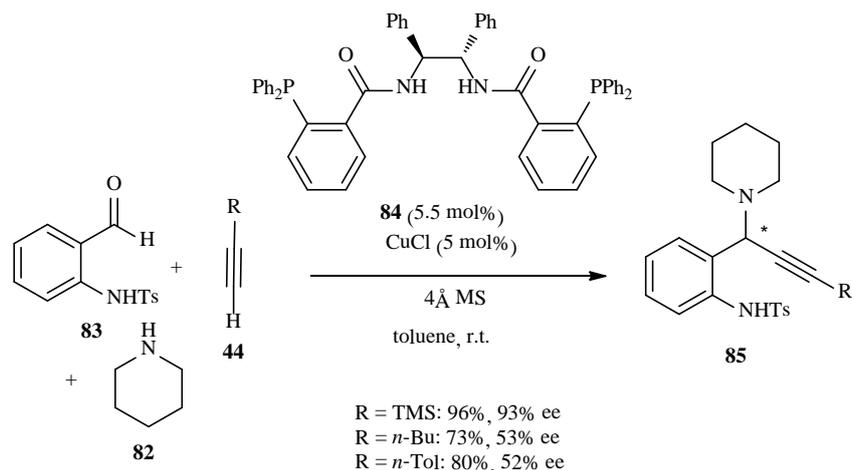
Earlier in 2006, 4-piperidone hydrochloride hydrate **80** was involved by Carreira et al. as equivalent of secondary amine partner in related reactions with alkynes **44** and aldehydes **47**, leading in the presence of (*R,R*)-PINAP as copper ligand to the corresponding tertiary propargylamines **81** in moderate to good yields (58-88%) and enantioselectivities (70-96% ee), as depicted in Scheme 26 (first equation) [33]. Furthermore, the corresponding enantiomeric products *ent*-**81** could be synthesized in uniformly good yields (75-84%) and

enantioselectivities (85-95% ee) by using enantiomeric ligand (*S,S*)-PINAP under the same reaction conditions, as shown in Scheme 26 (second equation).



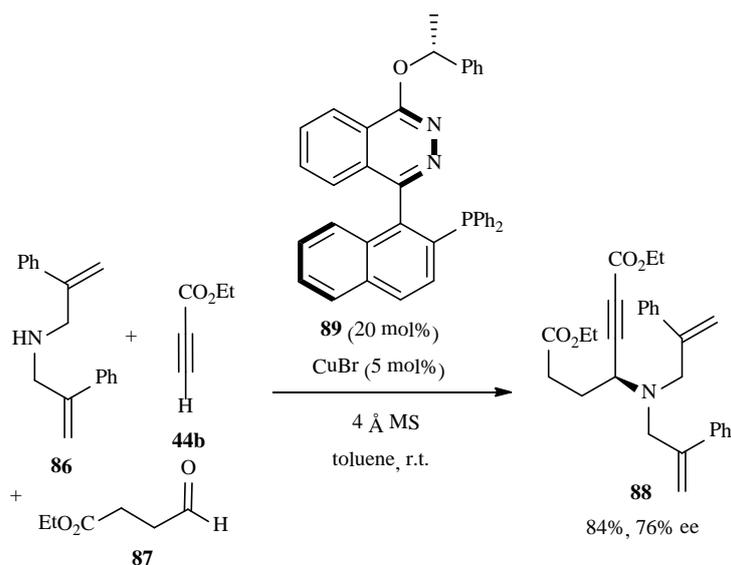
**Scheme 26.** Three-component reactions of aldehydes, alkynes and 4-piperidone hydrochloride hydrate.

In 2010, Gevorgyan et al. investigated the enantioselective copper-catalyzed three-component reaction of another secondary amine, such as piperidine **82**, with alkyl- and arylacetylenes **44** and *N*-(2-formylphenyl)-4-methylbenzenesulfonamide **83** (Scheme 27) [34]. The process was catalyzed by a combination of CuCl with chiral biphosphine ligand **84**, providing the corresponding chiral propargylamines **85** in good to high yields (73-96%) and moderate to high enantioselectivities (52-93% ee).



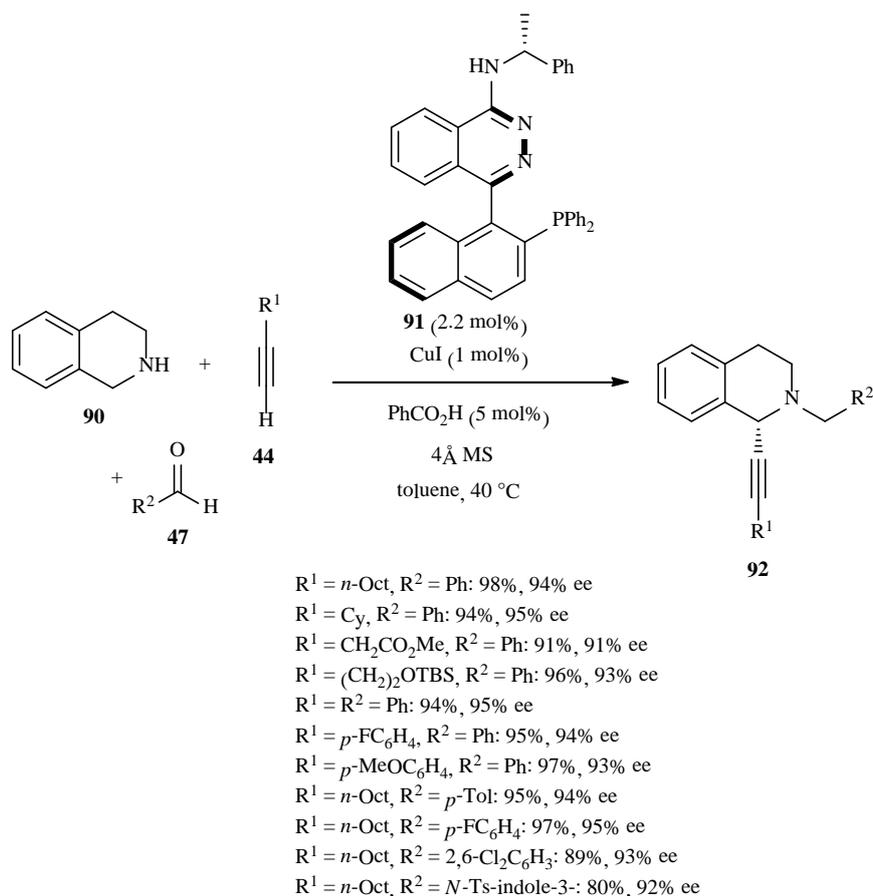
**Scheme 27.** Three-component reactions of *N*-(2-formylphenyl)-4-methylbenzenesulfonamide, alkynes and piperidine.

In 2013, bis(2-phenylallyl)amine **86** was used as other secondary amine by Watanabe and Shibasaki in the asymmetric copper-catalyzed three-component reaction involving ethyl propiolate **44b** and a functionalized aldehyde **87** as other substrates [35]. As shown in Scheme 28, the corresponding chiral domino product **88** was obtained in 84% yield and 76% ee in the presence of a combination of CuBr and chiral P,N-ligand **89**. This product was further converted into drug oseltamivir phosphate (Tamiflu).



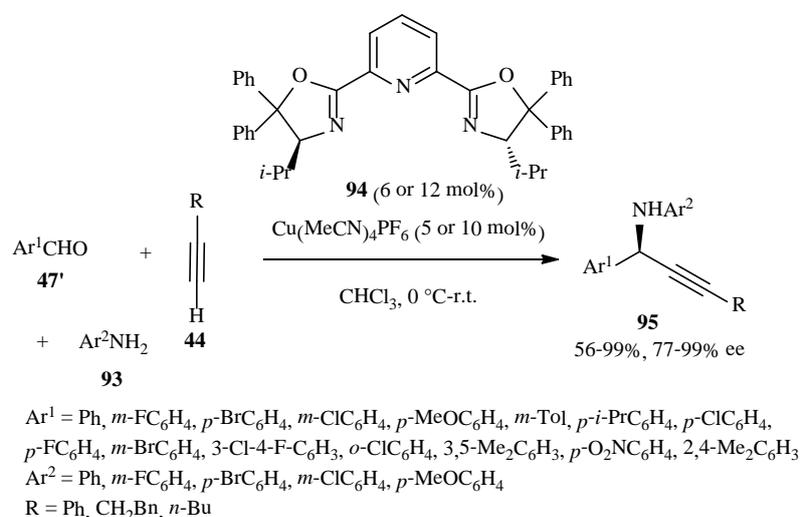
**Scheme 28.** Three-component reaction of an aldehyde, ethyl propiolate and bis(2-phenylallyl)amine.

In 2014, Ma et al. investigated tetrahydroisoquinoline **90** as the secondary amine partner in this type of reactions [36]. Promoted by only 1 mol% of CuI and 2.2 mol% of chiral N,P-ligand **91** in the presence of benzoic acid as additive, the enantioselective copper-catalyzed three-component reaction of unsubstituted tetrahydroisoquinoline **90**, aldehydes **47** and alkynes **44** provided the corresponding chiral  $\alpha$ -alkynylated tetrahydroisoquinolines **92** in both high yields (80-98%) and enantioselectivities (91-95% ee), as shown in Scheme 29. All types of alkynes including (functionalized) aliphatic and aromatic ones were compatible as well as aliphatic and (hetero)aromatic aldehydes.



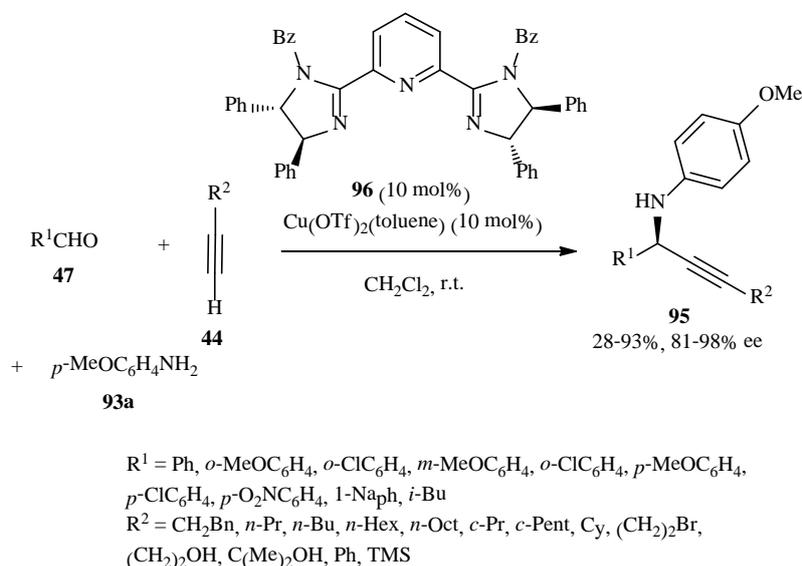
**Scheme 29.** Three-component reaction of aldehydes, alkynes and a tetrahydroisoquinoline.

Along with secondary amines, a range of primary amines have also been successfully involved in enantioselective copper-catalyzed three-component reactions with aldehydes and alkynes. For example, Singh and Bisai reported in 2006 the asymmetric three-component reaction of anilines **93** with aromatic aldehydes **47'** and aryl- or alkyl-substituted alkynes **44** catalyzed by a combination of Cu(MeCN)<sub>4</sub>PF<sub>6</sub> and chiral C<sub>2</sub>-symmetric Pybox ligand **94** [37]. This process provided the corresponding alkynylamines **95** with moderate to excellent yields (56-99%) and good to very high enantioselectivities (77-99% ee), as shown in Scheme 30. The same year, Benaglia et al. studied the enantioselective three-component reaction of phenylacetylene with primary amines and aldehydes catalyzed by copper complexes of BINOL-derived bis-imines, providing moderate enantioselectivities ( $\leq 75\%$  ee) [38].



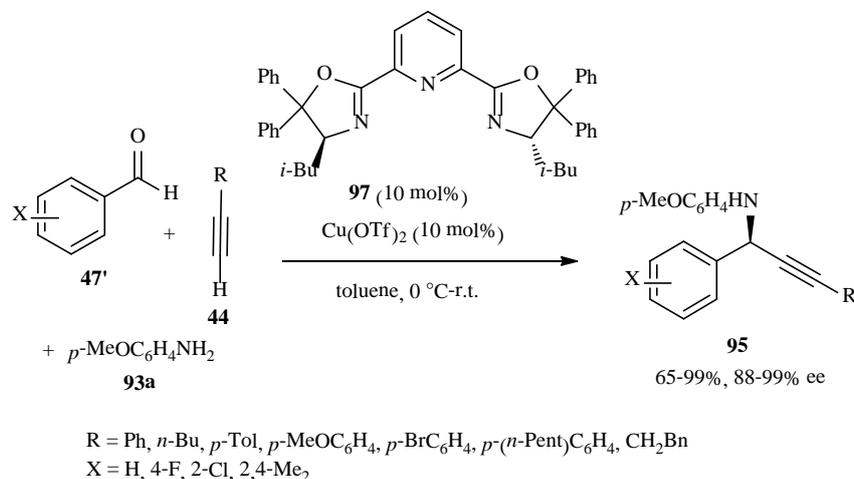
**Scheme 30.** Three-component reaction of aromatic aldehydes, alkynes and anilines.

In 2010, Nakamura et al. developed this type of domino reactions involving a range of aliphatic terminal alkynes **44** [39]. Their reaction with aromatic and aliphatic aldehydes **47** and *p*-anisidine **93a** afforded, in the presence of a combination of Cu(OTf)<sub>2</sub> with a related chiral C<sub>2</sub>-symmetric Pybox ligand **96**, the corresponding chiral amines **95** in low to high yields (28-93%) and good to excellent enantioselectivities (81-98% ee), as shown in Scheme 31.



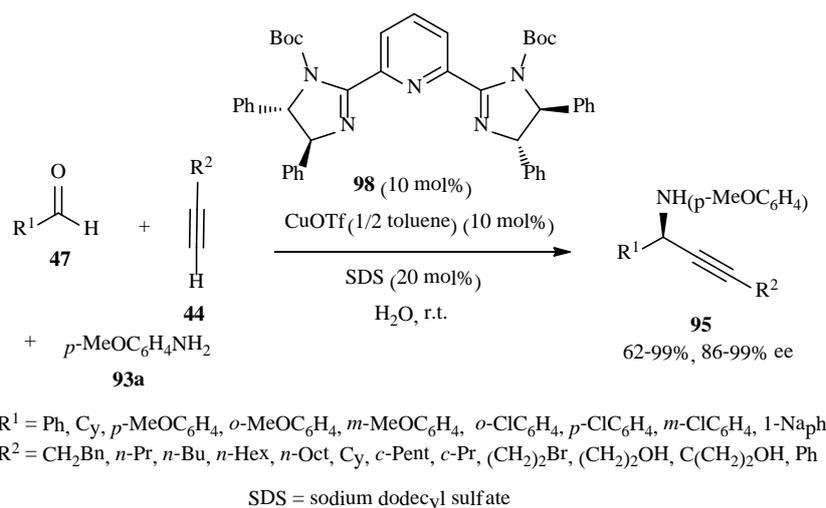
**Scheme 31.** Three-component reaction of aldehydes, aliphatic alkynes and *p*-anisidine.

In the same area, Singh and Bisai reported in 2012 the asymmetric three-component reaction of benzaldehydes **47'** with alkynes **44** and *p*-anisidine **93a** catalyzed by a combination of Cu(OTf)<sub>2</sub> with chiral Pybox ligand **97** [40]. As shown in Scheme 32, a range of chiral aromatic as well as aliphatic propargylamines **95** were achieved in good yields (65-99%) and uniformly high enantioselectivities (88-99% ee).



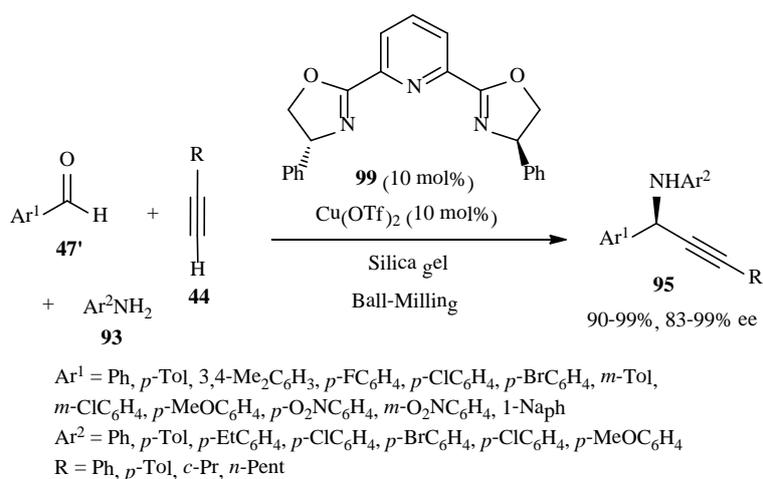
**Scheme 32.** Three-component reaction of benzaldehydes, alkynes and *p*-anisidine.

In 2014, Nakamura et al. reinvestigated these reactions by using a tuned Pybox-derived ligand **98** bearing a hydrophobic substituent, allowing these reactions to be performed in water instead of toluene [41]. In the presence of 10 mol% of this ligand combined with the same quantity of CuOTf(1/2toluene) as precatalyst in water at room temperature in the presence of sodium dodecyl sulfate (SDS) as surfactant, the domino reaction provided a range of chiral propargylamines **95** in moderate to quantitative yields (62-99%) and generally high enantioselectivities (86-99% ee), as shown in Scheme 33.



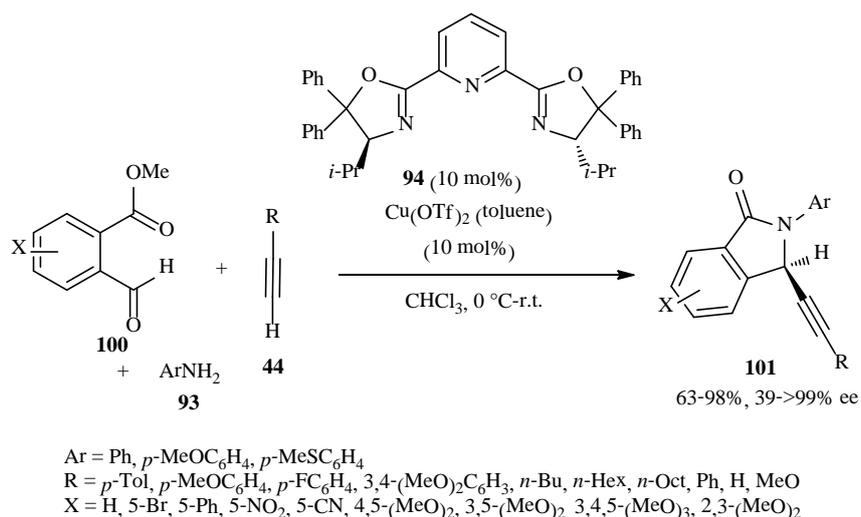
**Scheme 33.** Three-component reaction of aldehydes, alkynes and *p*-anisidine in water.

In 2015, Su et al. reported the development of these reactions under solvent-free high-vibration ball-milling conditions [42]. As shown in Scheme 34, the solvent-free three-component reaction of aromatic aldehydes **47'**, alkynes **44** and anilines **93** promoted by a chiral catalyst in situ generated from  $\text{Cu}(\text{OTf})_2$  and chiral Pybox ligand **99** by ball-milling provided the corresponding chiral propargylamines **95** in uniformly very high yields (90-99%) and enantioselectivities (83-99% ee) starting from aromatic aldehydes, anilines and aliphatic as well as aromatic alkynes. Notably, the catalyst system could be easily recovered and reused up to five times without losing its efficiency.



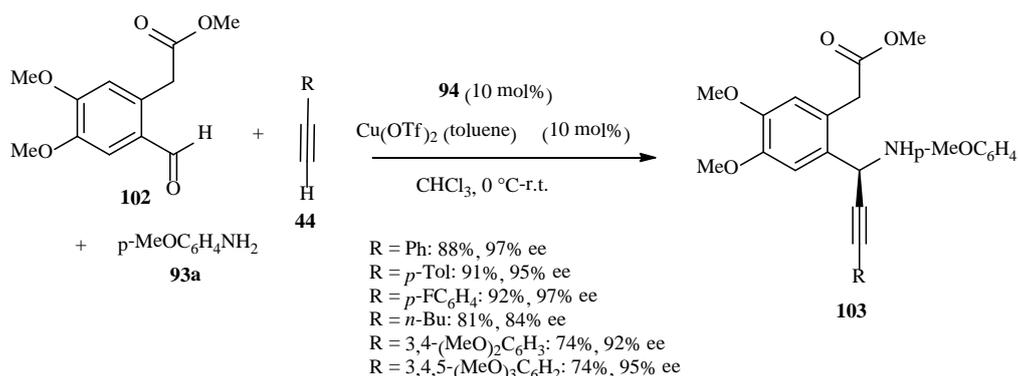
**Scheme 34.** Three-component reaction of aromatic aldehydes, alkynes and anilines under solvent-free high-vibration ball-milling.

In order to develop a practical route to synthesize diversely substituted and biologically important chiral isoindolinones, Singh et al. investigated in 2014 the three-component reaction of *o*-formyl methyl benzoates **100** with aromatic or aliphatic alkynes **44** and arylamines **93**, such as aniline and *p*-anisidine, in the presence of a chiral copper complex derived from highly substituted Pybox ligand **94** in chloroform [43]. The reaction evolved through a domino alkynylation/lactamization reaction to give the corresponding functionalized chiral isoindolinones **101** with moderate to high enantioselectivities (39->99% ee) and yields (63-98%), as shown in Scheme 35.



**Scheme 35.** Three-component domino imination/alkynylation/lactamization reaction of *o*-formyl methyl benzoates, alkynes and anilines.

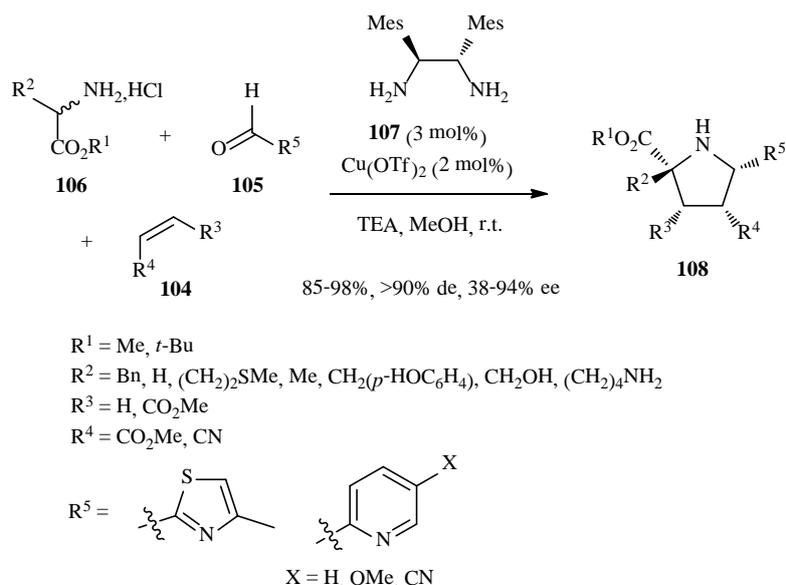
With the aim of extending the scope of this methodology to the synthesis of C1-substituted isoquinolinones to be further converted into synthetically important tetrahydroisoquinolines, the authors investigated the reaction of methyl (6-formyl-3,4-dimethoxyphenyl)acetate **102** with alkynes **44** and *p*-anisidine **93a** [43]. However, in this case no lactamization occurred since only uncyclized chiral products **103** were formed through domino imination/alkynylation reaction in good to high yields (74-92%) and enantioselectivities (84-97% ee), as shown in Scheme 36.



**Scheme 36.** Three-component reaction of an *o*-formyl methyl benzoate, alkynes and *p*-anisidine.

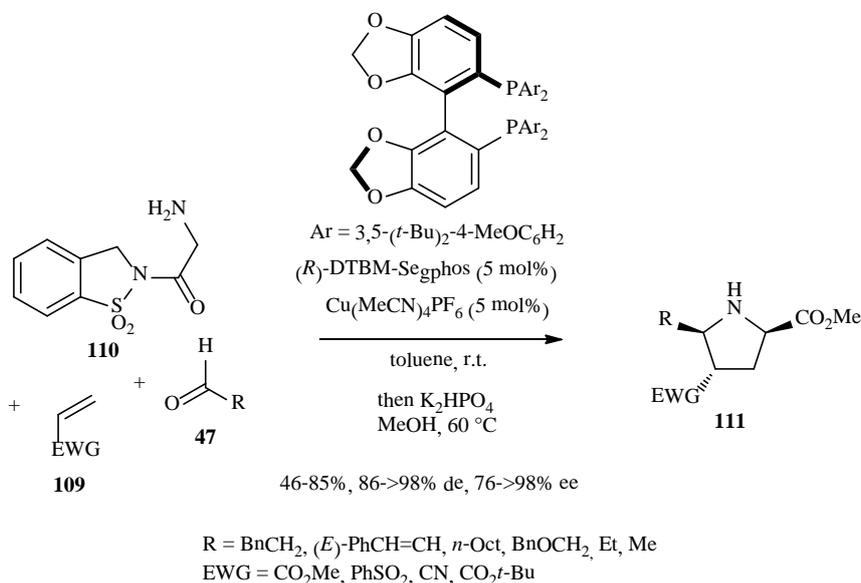
### 3.3. Three-Component Domino Reactions Based on 1,3-Dipolar Cycloadditions

The 1,3-dipolar cycloaddition [44] allows the synthesis of important five-membered heterocycles to be achieved [45]. Among metals employed as promoters of these reactions [46], copper has been widely used. In 2013, asymmetric copper-catalyzed three-component domino azomethine ylide formation/1,3-dipolar cycloaddition reactions of activated alkenes **104** with  $\alpha$ -chelating aldehydes **105** and amino acid esters **106** were reported by Aron et al. [47]. These reactions were catalyzed at room temperature by a chiral complex in situ generated from Cu(OTf)<sub>2</sub> and chiral diamine ligand **107** in methanol as solvent.  $\alpha$ -Chelating aldehydes **105**, such as 4-substituted-2-picolinaldehydes and 4-methylthiazole-2-carboxaldehyde, reacted with a range of unprotected aminoesters **106** derived from lysine, methionine, serine, tryptophan and tyrosine to provide the corresponding intermediate azomethine ylides, which further underwent 1,3-dipolar cycloaddition with alkenes **104**, such as acrylonitrile, dimethyl maleate and methyl acrylate, to afford the corresponding highly substituted chiral pyrrolidines **108** bearing up to four stereogenic centers as almost single diastereomers (>90% de) in high yields (85-98%) and moderate to high enantioselectivities (38-94% ee), as shown in Scheme 37.



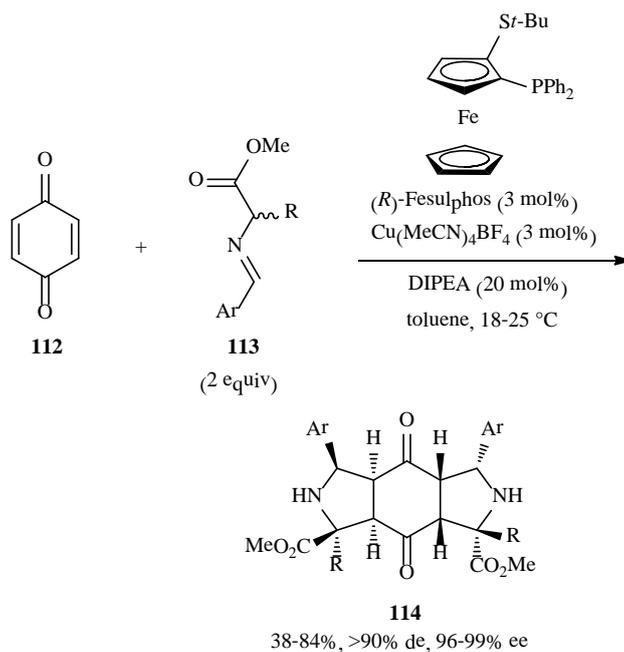
**Scheme 37.** Three-component domino azomethine ylide formation/1,3-dipolar cycloaddition reaction of activated alkenes,  $\alpha$ -chelating aldehydes and amino acid esters.

In 2014, enantioselective three-component domino azomethine ylide formation/1,3-dipolar cycloaddition reactions between activated olefins **109**, aliphatic aldehydes **47** and glycylic sultam **110** were developed by Garner et al. [48]. The processes afforded the corresponding chiral substituted pyrrolidines **111** in moderate to good yields (46-85%), good to complete diastereoselectivities (86->98% de) and good to excellent enantioselectivities (76->98% ee), as illustrated in Scheme 38. The catalyst was in situ generated from  $\text{Cu}(\text{MeCN})_4\text{PF}_6$  and (*R*)-DTBM-Segphos as ligand in toluene at room temperature. The domino chiral products were not isolated but directly converted by treatment with  $\text{K}_2\text{HPO}_4$  into their corresponding methyl esters.



**Scheme 38.** Three-component domino azomethine ylide formation/1,3-dipolar cycloaddition reaction of activated olefins, aliphatic aldehydes and a glycylic sultam.

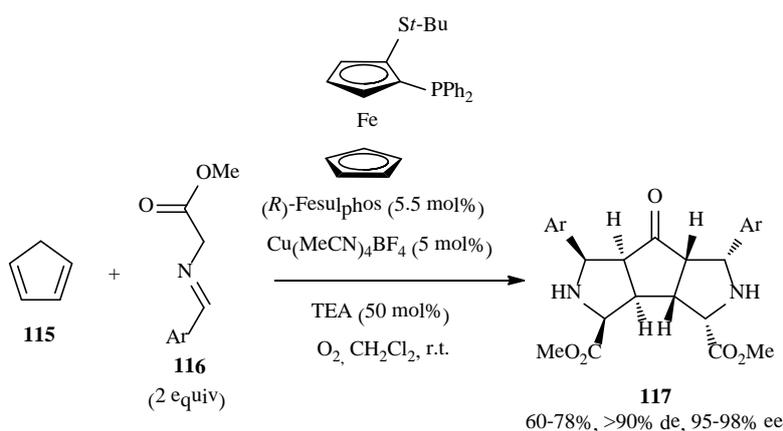
Earlier in 2012, an enantioselective copper-catalyzed pseudo-three-component domino double 1,3-dipolar cycloaddition reaction of 1,4-benzoquinone **112** with two equivalents of  $\alpha$ -iminoesters **113** was reported by Waldmann et al. [49]. As shown in Scheme 39, this process led to highly structurally complex chiral products **114** exhibiting eight stereogenic centers through two consecutive 1,3-dipolar cycloadditions of azomethine ylides derived from  $\alpha$ -iminoesters with *p*-benzoquinone. The reaction was catalyzed in toluene at 18-25 °C by a combination of  $\text{Cu}(\text{MeCN})_4\text{BF}_4$  and (*R*)-Fesulphos as chiral ligand. The chiral tricyclic products **114** were regioselectively obtained as almost single diastereomers (>90% de) in uniformly remarkable enantioselectivities (96-99% ee) combined with moderate to good yields (38-84%).



Ar = *p*-BrC<sub>6</sub>H<sub>4</sub>, *p*-Tol, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, *m*-FC<sub>6</sub>H<sub>4</sub>,  
*o*-FC<sub>6</sub>H<sub>4</sub>, Ph, 2-Naph, 2-Cl-6-F-C<sub>6</sub>H<sub>3</sub>, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>  
 R = Me, H, Ph

**Scheme 39.** Pseudo-three-component domino double 1,3-dipolar cycloaddition reaction of 1,4-benzoquinone with  $\alpha$ -iminoesters.

Later in 2015, these authors applied the same catalyst system to the asymmetric pseudo-three-component domino oxidation/double 1,3-dipolar cycloaddition reaction of cyclopentadiene **115** with two equivalents of halogenated aromatic  $\alpha$ -iminoesters **116** depicted in Scheme 40 [50]. The domino reaction was initiated by the copper-catalyzed aerobic C–H oxidation of cyclopentadiene into cyclopentadienone which subsequently underwent a double catalytic asymmetric 1,3-dipolar cycloaddition with two equivalents of azomethine ylides derived from glycine ester imines to afford the corresponding chiral tricyclic products **117** bearing eight stereogenic centers as almost single diastereomers (>90% de) with moderate to good yields (60-78%) and uniformly excellent enantioselectivities (95-98% ee).

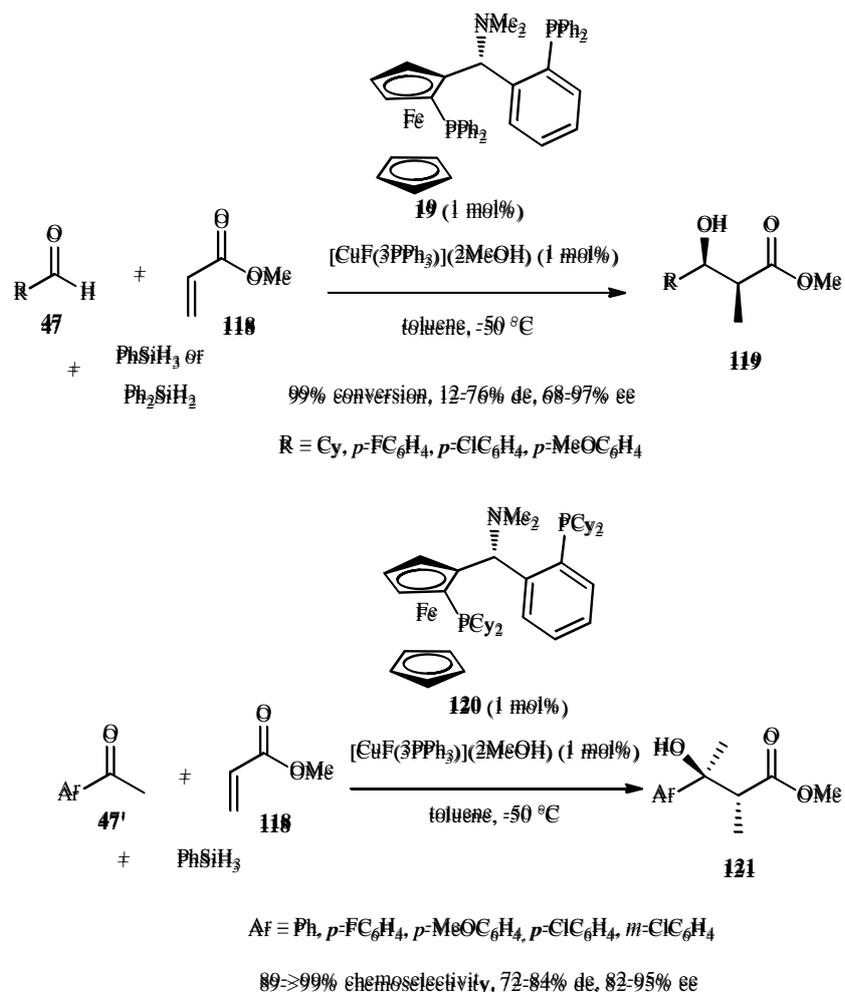


Ar = *o*-BrC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, *m*-FC<sub>6</sub>H<sub>4</sub>, *o*-FC<sub>6</sub>H<sub>4</sub>,  
*p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, 3,4-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>, 2,3-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>, 3,4-Br<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>

**Scheme 40.** Pseudo-three-component domino oxidation/double 1,3-dipolar cycloaddition reaction of cyclopentadiene with halogenated aromatic  $\alpha$ -iminoesters.

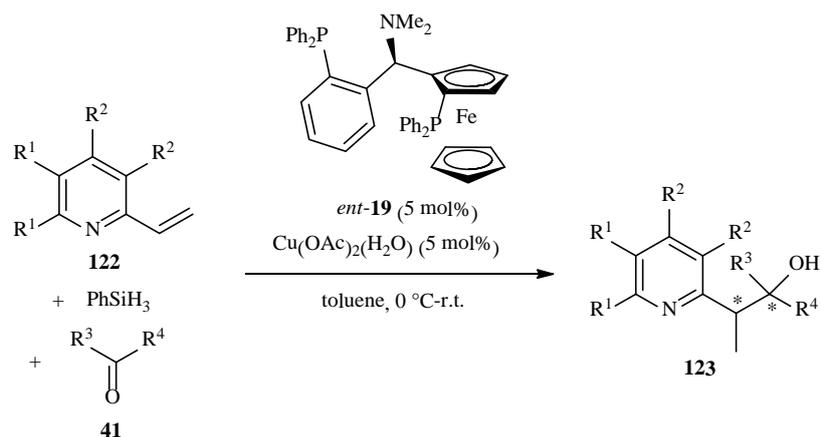
### 3.4. Miscellaneous Three-Component Domino Reactions

In 2006, Riant et al. reported enantioselective copper-catalyzed three-component domino reductive aldol reactions between aldehydes **47**, methyl acrylate **118** and phenylsilane as reducing agent [51]. When catalyzed by a chiral copper complex derived from Taniaphos chiral ligand **19** in toluene at -50 °C, the reaction led with low to moderate *syn*-diastereoselectivities (12-76% de) to the corresponding domino chiral products **119** in complete conversions and moderate to excellent enantioselectivities (68-97% ee), as shown in Scheme 41 (first equation). In addition, the authors showed that aromatic ketones **47'** were also compatible substrates when using a related chiral ligand **120** [52]. As illustrated in Scheme 41 (second equation), the domino reaction of these substrates with methyl acrylate **118** and phenylsilane afforded the corresponding *erythro*-tertiary alcohols **121** as major products with moderate to good diastereoselectivities (72-84% de), uniformly high yields (89->99%) and good to high enantioselectivities (82-95% ee).



**Scheme 41.** Three-component domino reductive aldol reactions of aldehydes and ketones, methyl acrylate and phenylsilane.

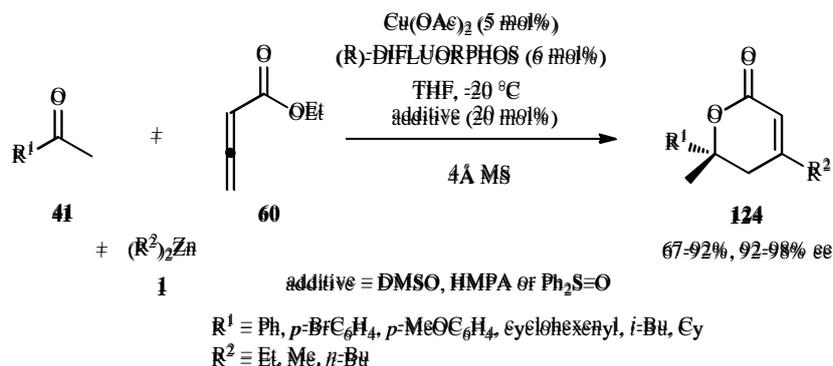
In 2012, Lam et al. reported the first examples of highly enantioselective copper-catalyzed reductive coupling reactions of alkenylazaarenes **122** with ketones **41** using phenylsilane as reducing agent [53]. The process was catalyzed by a chiral complex in situ generated from Cu(OAc)<sub>2</sub>(H<sub>2</sub>O) and Taniaphos-type ligand *ent*-**19**, affording the corresponding chiral aromatic heterocycles **123** bearing tertiary-alcohol-containing side chains in moderate to good yields (60-82%), low to high diastereoselectivities (34->90% de) and uniformly high enantioselectivities (89->99% ee), as shown in Scheme 42.



$\text{R}^1, \text{R}^2 = (\text{CH}=\text{CH})_2, \text{R}^3 = \text{H}, \text{R}^4 = \text{Ph}$ : 60%, 60% de, 93% ee  
 $\text{R}^1, \text{R}^2 = (\text{CH}=\text{CH})_2, \text{R}^3 = \text{H}, \text{R}^4 = \text{Bn}$ : 60%, 78% de, 96% ee  
 $\text{R}^1 = \text{R}^2 = \text{H}, \text{R}^3 = \text{Me}, \text{R}^4 = \text{Ph}$ : 65%, 34% de, >99% ee  
 $\text{R}^1 = \text{H}, \text{R}^2, \text{R}^2 = (\text{CH}=\text{CH})_2, \text{R}^3 = \text{Me}, \text{R}^4 = p\text{-F}_3\text{CC}_6\text{H}_4$ : 82%, 80% de, >99% ee  
 $\text{R}^1 = \text{H}, \text{R}^2, \text{R}^2 = (\text{CH}=\text{CH})_2, \text{R}^3 = \text{Me}, \text{R}^4 = o\text{-MeOC}_6\text{H}_4$ : 78%, >90% de, 97% ee  
 $\text{R}^1 = \text{H}, \text{R}^2, \text{R}^2 = (\text{CH}=\text{CH})_2, \text{R}^3 = \text{Me}, \text{R}^4 = 2\text{-furyl}$ : 76%, 84% de, 89% ee

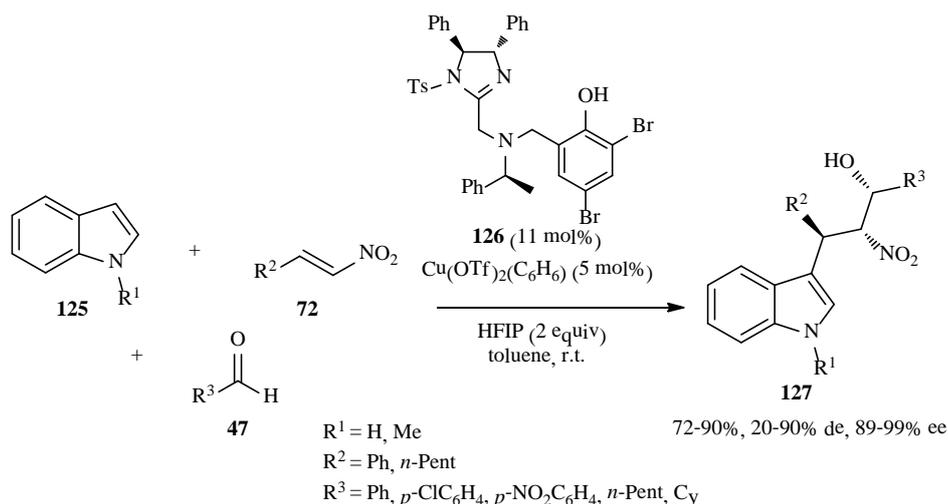
**Scheme 42.** Three-component domino reductive aldol reaction of vinylazaarenes, ketones and phenylsilane.

Earlier in 2007, Shibasaki et al. reported the enantioselective three-component reaction of ketones **41**, allenic ethyl ester **60** and dialkylzincs **1** promoted by a chiral catalyst in situ generated from  $\text{Cu}(\text{OAc})_2$  and (*R*)-DIFLUORPHOS as ligand, leading to the corresponding chiral  $\delta$ -lactones **124** in moderate to high yields (67-92%) and uniformly high enantioselectivities (92-98% ee), as shown in Scheme 43 [54].



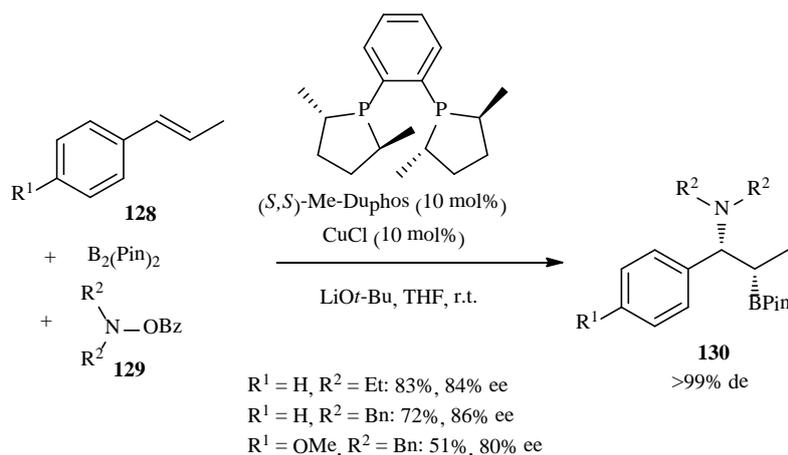
**Scheme 43.** Three-component domino alkylative aldol reaction of dialkylzincs, allenic ethyl ester and ketones.

In 2011, Arai et al. described the enantioselective three-component domino Friedel–Crafts/Henry reaction of nitroalkenes **72**, indoles **125** and aldehydes **47** catalyzed by a combination of  $\text{Cu}(\text{OTf})_2$  with chiral aminophenol ligand **126** [55]. The process led to the corresponding chiral indoles **127** exhibiting three contiguous stereocenters in moderate to high yields (72-90%), uniformly high enantioselectivities (89-99% ee) and low to high diastereoselectivities (20-90% de), as shown in Scheme 44.



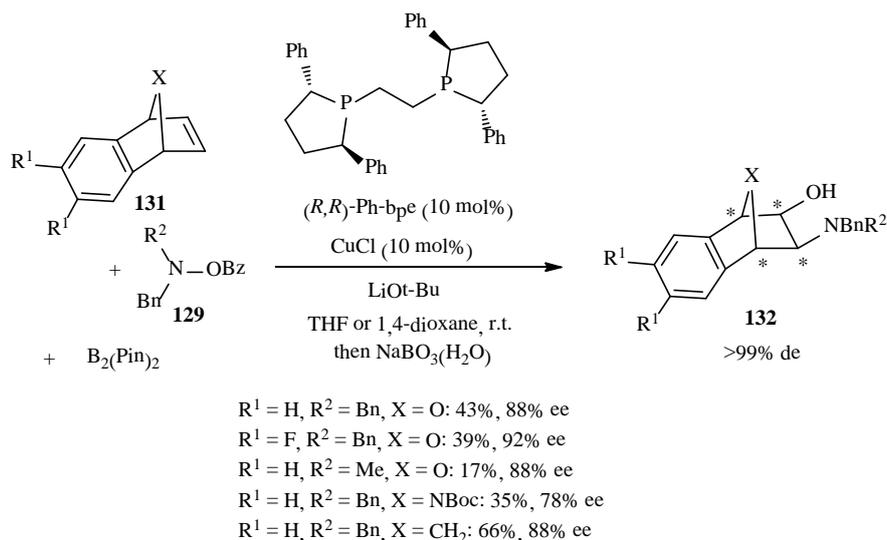
**Scheme 44.** Three-component domino Friedel–Crafts/Henry reaction of indoles, nitroalkenes and aldehydes.

In 2013, Hirano and Miura reported an enantioselective three-component copper-catalyzed aminoboration of styrenes **128** with *O*-benzoyl-*N,N*-dialkylhydroxylamines **129** and  $B_2(\text{Pin})_2$  [56]. As shown in Scheme 45, the reaction occurred regio- and diastereoselectively at room temperature in the presence of a chiral copper catalyst in situ generated from  $\text{CuCl}$  and (*S,S*)-Me-Duphos as ligand, leading to the corresponding chiral aminoborated products **130** as single *syn*-diastereomers in moderate to good yields (51–83%) and good enantioselectivities (80–86% ee).



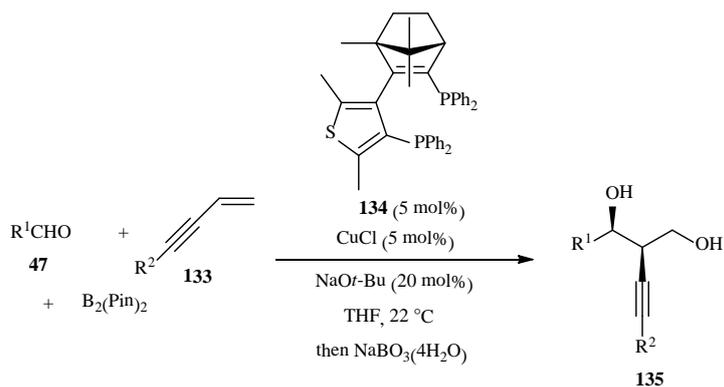
**Scheme 45.** Three-component domino boration/amination reaction of styrenes, *O*-benzoyl-*N,N*-dialkylhydroxylamines and  $B_2(\text{Pin})_2$ .

Later in 2015, the same authors employed another chiral biphosphine ligand, such as (*R,R*)-Ph-bpe, in another enantioselective copper-catalyzed three-component aminoboration reaction involving bicyclic alkenes **131** [57]. As shown in Scheme 46, the reaction of these alkenes with  $B_2(\text{Pin})_2$  and *O*-benzoyl-*N,N*-dialkylhydroxylamines **132** led to the corresponding chiral aminoborated products **133** as single diastereomers in low to moderate yields (17–66%) combined with good to high enantioselectivities (78–92% ee). Bicyclic oxo- and azabenzonorbornadienes as well as methylene-bridged analogues were tolerated, providing the corresponding *exo*-products with comparable diastereo- and enantioselectivities.



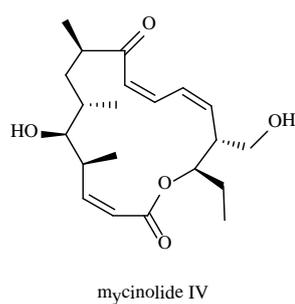
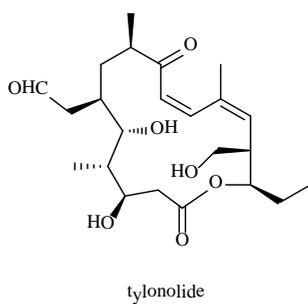
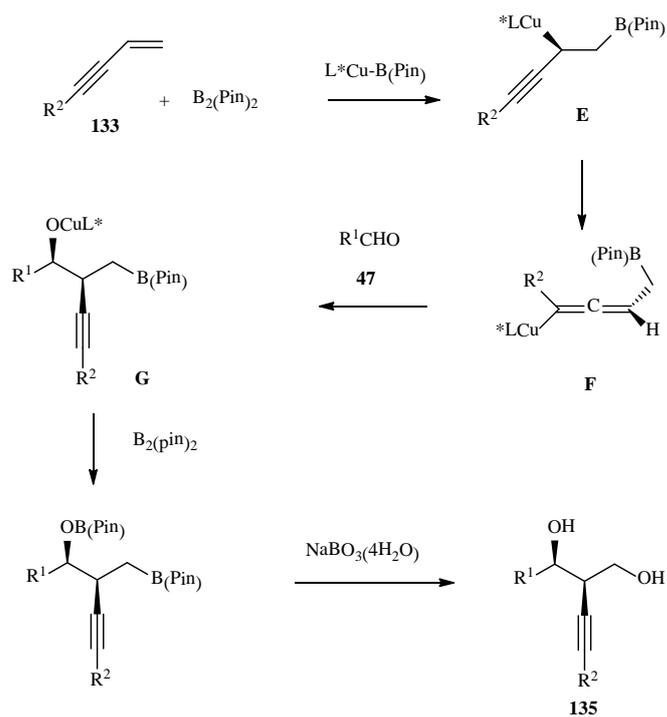
**Scheme 46.** Three-component domino boration/amination reaction of bicyclic alkenes, *O*-benzoyl-*N,N*-dialkylhydroxylamines and  $B_2(Pin)_2$ .

In 2014, asymmetric copper-catalyzed three-component reactions of 1,3-enynes **133** with  $B_2(Pin)_2$  and aldehydes **47** were developed by Hoveyda et al. in the presence of a combination of CuCl with chiral biphosphine ligand **134** [58]. They afforded at room temperature the corresponding chiral *syn*-1,3-diols **135** as major diastereomers in good to high diastereoselectivities (80-96% de) combined with moderate to high yields (66-94%) and enantioselectivities (70-96% ee), as shown in Scheme 47. Aryl-, heteroaryl- and alkenyl-substituted aldehydes reacted with variously substituted enynes with comparable results. The utility of this methodology was applied to the synthesis of fragments of macrolide antibiotic natural products tylonolide and mycinolide IV. A possible mechanism is depicted in Scheme 47, in which a first enantioselective addition of an in situ generated (ligand)Cu–B(Pin) species to the alkene moiety of the 1,3-enyne occurred, providing propargyl-copper species **E**. The latter was converted into the more energetically favorable trisubstituted allenyl complex **F**, which then added diastereoselectively to the aldehyde to give intermediate **G**, finally oxidized into to the final product **135**.



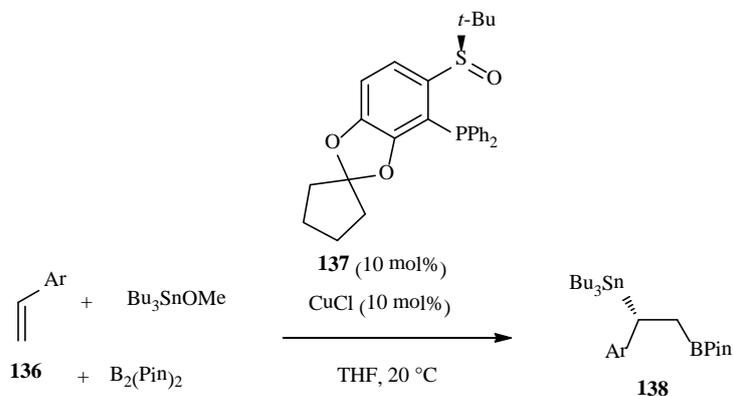
$R^1 = 1-Naph, R^2 = Ph$ : 94%, 96% de, 94% ee  
 $R^1 = o-Tol, R^2 = Ph$ : 83%, 84% de, 94% ee  
 $R^1 = p-MeOC_6H_4, R^2 = Ph$ : 70%, 80% de, 88% ee  
 $R^1 = p-FC_6H_4, R^2 = Ph$ : 87%, 84% de, 88% ee  
 $R^1 = (E)-PhCH=CH, R^2 = Ph$ : 66%, 92% de, 92% ee  
 $R^1 = (E)-PhCH=C(Me), R^2 = Ph$ : 86%, 88% de, 86% ee  
 $R^1 = CH_2Bn, R^2 = Ph$ : 80%, 96% de, 85% ee  
 $R^1 = Ph, R^2 = p-MeOC_6H_4$ : 69%, 90% de, 96% ee  
 $R^1 = Ph, R^2 = p-F_3CC_6H_4$ : 79%, 80% de, 84% ee  
 $R^1 = Ph, R^2 = 2-thienyl$ : 73%, 94% de, 92% ee  
 $R^1 = Ph, R^2 = SiEt_3$ : 83%, 88% de, 70% ee

proposed mechanism:



**Scheme 47.** Three-component reaction of 1,3-enynes,  $B_2(\text{Pin})_2$  and aldehydes.

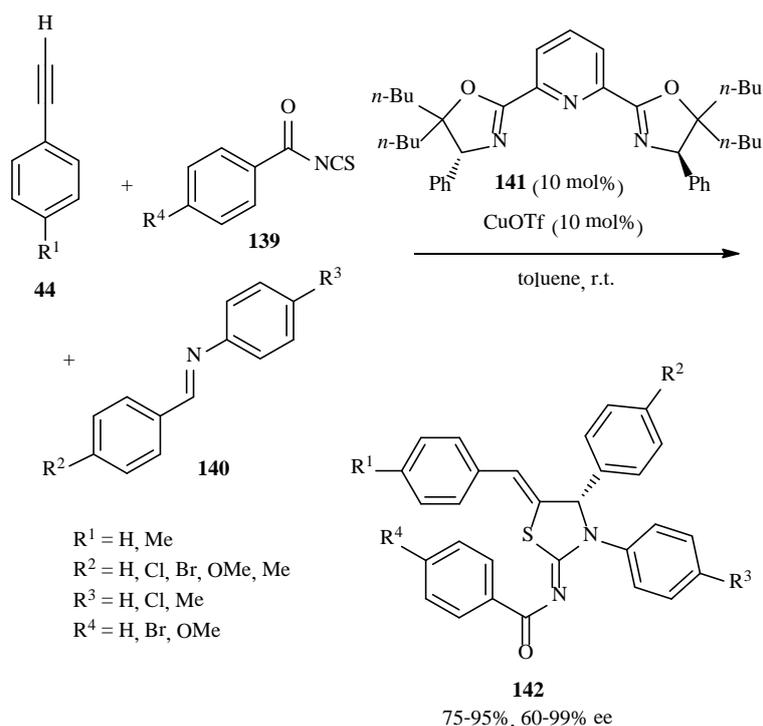
In 2015, asymmetric copper-catalyzed borylstannations of aromatic alkenes **136**,  $B_2(\text{Pin})_2$  and  $Bu_3\text{SnOMe}$  were developed by Liao et al., as shown in Scheme 48 [59]. Using a chiral catalyst in situ generated from  $\text{CuCl}$  and chiral sulfinylphosphine ligand **137**, the three-component reaction afforded the corresponding chiral  $\alpha$ -aryl- $\beta$ -borylstannanes **138** in moderate to quantitative yields (63-99%) and good to high enantioselectivities (86-96% ee). In addition to variously substituted styrenes, the reaction also enabled the synthesis of  $\alpha$ -naphthyl- $\beta$ -borylstannanes (Ar = 1-Naph, 2-Naph) in moderate yields (57-64%) and high enantioselectivity (92% ee).



Ar = *o*- $\text{BrC}_6\text{H}_4$ : 99%, 93% ee  
Ar = *o*- $\text{ClC}_6\text{H}_4$ : 94%, 94% ee  
Ar = *o*-Tol: 93%, 95% ee  
Ar = *o*- $\text{MeOC}_6\text{H}_4$ : 63%, 86% ee  
Ar = *m*- $\text{ClC}_6\text{H}_4$ : 96%, 94% ee  
Ar = *o*- $\text{TfOC}_6\text{H}_4$ : 90%, 87% ee  
Ar = *p*- $\text{BrC}_6\text{H}_4$ : 75%, 95% ee  
Ar = *p*- $\text{ClC}_6\text{H}_4$ : 99%, 94% ee  
Ar = *p*- $\text{FC}_6\text{H}_4$ : 90%, 93% ee  
Ar = *p*- $(t\text{-Bu})\text{C}_6\text{H}_4$ : 82%, 96% ee  
Ar = *p*-Tol: 86%, 91% ee  
Ar = *p*- $\text{BzOC}_6\text{H}_4$ : 90%, 93% ee  
Ar = 2-Naph: 64%, 92% ee  
Ar = 1-Naph: 57%, 92% ee

**Scheme 48.** Three-component borylstannation reaction of aromatic alkenes,  $B_2(\text{Pin})_2$  and  $Bu_3\text{SnOMe}$ .

The same year, a novel asymmetric synthesis of cyclic five-membered thiazolidine-2-imines was reported by Dethle et al. on the basis of an enantioselective copper-catalyzed three-component reaction between terminal aromatic alkynes **44**, aryl isothiocyanates **139** and aryl imines **140** [60]. The process was promoted by a chiral catalyst in situ generated from  $\text{CuOTf}$  and chiral Pybox ligand **141**, affording the corresponding chiral thiazolidine-2-imines **142** in good to high yields (75-95%) and moderate to excellent enantioselectivities (60-99% ee), as shown in Scheme 49. The reaction evolved through with the addition of the alkyne to the chiral copper catalyst-activated iminium ion to give a propargylamine which subsequently reacted with the isothiocyanate through an addition/intramolecular hydrothiolation sequence.



**Scheme 49.** Three-component reaction of alkynes, imines and isothiocyanates.

#### 4. CONCLUSIONS

This review collects for the first time enantioselective domino reactions promoted by chiral copper catalysts, covering the literature since the beginning of 2006. It shows that a wide variety of enantioselective copper-catalyzed two- and three-component domino processes have been developed in the last decade, becoming outstanding tools to synthesize complex and diversely functionalized cyclic as well as acyclic chiral products under green reaction conditions. Very high enantioselectivities have been described in enantioselective two-component reactions, including Michael-initiated processes, domino reactions based on cyclizations, domino reactions initiated by aldol-type condensations and Friedel–Crafts-initiated domino processes. Moreover, many enantioselective copper-catalyzed three-component reactions also encountered success, such as Michael-initiated three-component domino reactions, three-component reactions between alkynes, aldehydes and amines, three-component domino reactions based on 1,3-dipolar cycloadditions among other three-component reactions. Undoubtedly, other enantioselective copper-catalyzed asymmetric domino reactions will be discovered in the near future through the combination of different types of reactions, and the use of novel chiral environmentally benign copper catalyst systems.

#### CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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