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Enantioselective Copper-Catalyzed Domino Reactions

1.1 Introduction

The combination of asymmetric metal catalysis [1] with the concept of domino reactions [2] has already allowed many chiral complex products to be synthesized with high enantioselectivities and good yields on the basis of simple and economic one-pot procedures, not requiring the purification of intermediates [3]. Taking advantage of the higher abundance and lower costs and toxicity of copper catalysts in comparison with other transition metals [4], more ecologic and economic enantioselective domino reactions have been developed in the last decade on the basis of asymmetric copper catalysis. Indeed, with the growing interest in using green chemistry to design cleaner organic reactions, mild, energy-efficient, and atom-economical processes, the asymmetric copper-catalyzed domino reactions represent a pivotal part in the development of modern chemistry. The goal of this chapter is to collect the advances in enantioselective copper-catalyzed domino reactions including multicomponent processes published in the last 13 years. Previously, this special field has been included in several reports dealing with more general (asymmetric) domino reactions [1e,f, 2h,o, 3a,b, 5]. This chapter is subdivided into two parts, dealing successively with two-component domino reactions and three-component domino processes. The first part is subdivided into five sections, according to the different types of domino reactions involved, such as reactions based on cyclizations, reactions initiated by Michael additions, reactions initiated by Friedel–Crafts reactions, reactions initiated by aldol reactions, and miscellaneous reactions. The second part of the chapter dedicated to the three-component processes is subdivided into six sections, dealing successively with reactions based on alkyne couplings, reactions initiated by Michael additions, reactions based on 1,3-dipolar cycloadditions, reactions based on addition reactions to alkenes, reactions based on alkene couplings, and miscellaneous reactions. Since 2006, a myriad of completely novel powerful asymmetric domino processes have been developed on the basis of asymmetric green copper catalysis, taking economic advantages, such as avoiding costly protecting groups and time-consuming purification procedures after each step.

Asymmetric Metal Catalysis in Enantioselective Domino Reactions, First Edition. Hélène Pellissier.

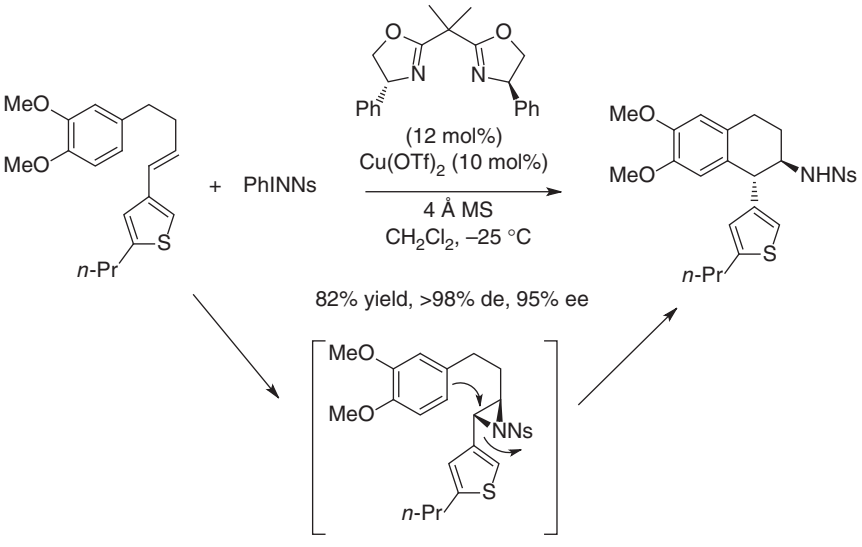
1.2 Two-Component Processes

1.2.1 Reactions Based on Cyclizations

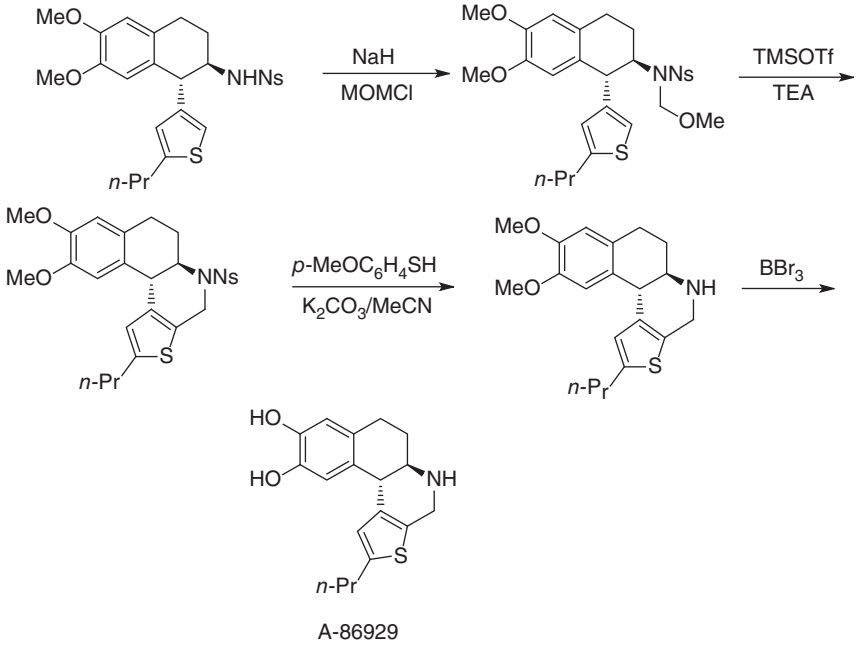
In the last 13 years, different types of asymmetric domino reactions based on cyclizations have been successfully catalyzed by chiral copper complexes. For example, in 2011 Hajra and Bar reported a copper-catalyzed enantioselective domino aziridination/Friedel–Crafts cyclization reaction [6]. In this process, a functionalized styrene reacted with PhINNs in the presence of a copper catalyst *in situ* generated from $Cu(OTf)_2$ and a chiral bisoxazoline ligand to afford the corresponding chiral bicyclic domino product in 82% yield, with an almost complete *trans*-diastereoselectivity (>98% de) and a high enantioselectivity of 95% ee. As depicted in Scheme 1.1, the starting styrene was converted in the first step into the corresponding chiral aziridine by reaction with PhINNs as the aziridinating agent. Then, this intermediate aziridine was submitted to a ring-opening through a Friedel–Crafts-type cyclization to give the final product. The utility of this methodology was demonstrated by its application in a total synthesis of the dopamine D1 agonist A-86929. Indeed, the domino product was converted into A-86929 through four additional steps, beginning with the reaction of its sodium salt generated by treatment with NaH with MOMCl, providing the corresponding methoxy methyl ether. The Pictet–Spengler-type cyclization of this compound using TMSOTf afforded a tetracyclic product, which was subsequently deprotected by treatment with *p*-methoxythiophenol and K_2CO_3 to give the corresponding secondary amine. The demethylation of the latter performed with BBr_3 finally accomplished the synthesis of A-86929 (Scheme 1.1).

In 2011, Toste and coworkers reported an enantioselective route to highly substituted furans based on a copper-catalyzed domino cycloisomerization/indole addition reaction [7]. As presented in Scheme 1.2, a preformed copper(II) catalyst derived from a chiral phosphine was found capable of promoting the intramolecular heterocyclization of a range of 2-(1-alkynyl)-2-alkene-1-ones followed by a nucleophilic attack of indoles, resulting in the formation of the corresponding tetracyclic domino products. The reaction showed a wide substrate scope since both aromatic and aliphatic alkynes reacted with high yields and enantioselectivities of up to 94% ee. Similarly, electronic variations in the aryl ring of the indole scaffold were tolerated, as both electron-donating and electron-withdrawing substituents led to the corresponding products in high yields and enantioselectivities. However, 2-methyl indole provided a low yield (16%).

In 2012, asymmetric domino amination/Heck-type reactions of γ-alkenylsulfonamides with vinylarenes were developed by Chemler and coworker [8]. The process was catalyzed by a combination of $Cu(OTf)_2$ and a chiral bisoxazoline in the presence of MnO_2 as oxidant, affording the corresponding 2-substituted chiral indolines in both good to high yields (65–85%) and enantioselectivities (71–91% ee). As shown in Scheme 1.3, *N*-arylsulfonylanilines led to the corresponding products with relatively higher enantioselectivities than the *N*-mesyl- and *N*-trimethylsilylethylsulfonyl analogs. On the other hand, the yields and enantioselectivities were relatively insensitive to the nature of the 4-substitution on the aniline. Concerning the vinylarenes, diphenylethylene

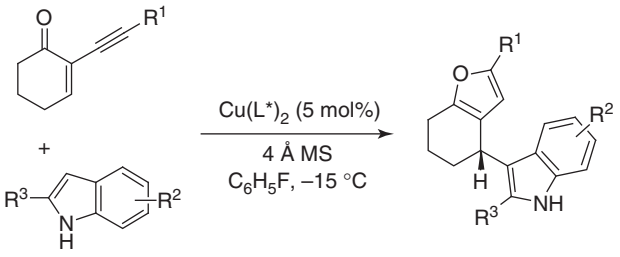


Synthesis of A-86929:

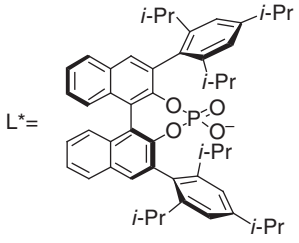


A-86929

Scheme 1.1 Domino aziridination/Friedel–Crafts cyclization reaction of a functionalized styrene with PhINNs and synthesis of A-86929.



R^1 = Ph, R^2 = R^3 = H: 92% yield, 91% ee
R^1 = *p*-$MeOC_6H_4$, R^2 = R^3 = H: 82% yield, 92% ee
R^1 = *p*-Tol, R^2 = R^3 = H: 85% yield, 90% ee
R^1 = *p*-*t*-BuC_6H_4, R^2 = R^3 = H: 85% yield, 90% ee
R^1 = Bn, R^2 = R^3 = H: 84% yield, 73% ee
R^1 = Cy, R^2 = R^3 = H: 85% yield, 94% ee
R^1 = Ph, R^2 = 5-Br, R^3 = H: 90% yield, 93% ee
R^1 = Ph, R^2 = 5-Cl, R^3 = H: 81% yield, 90% ee
R^1 = Ph, R^2 = H, R^3 = Me: 16% yield, 85% ee

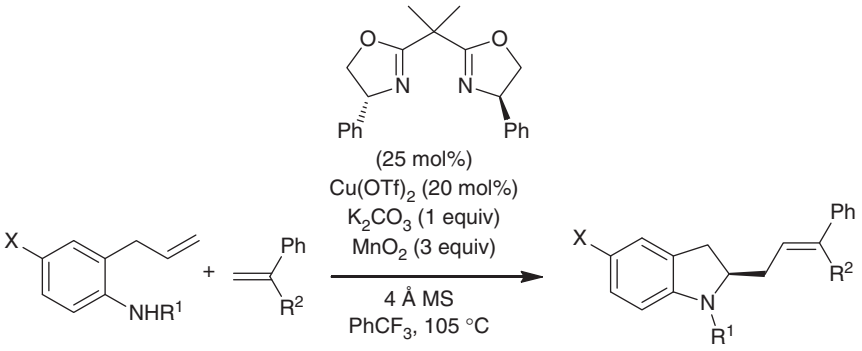


Scheme 1.2 Domino cycloisomerization/nucleophilic addition reaction of 2-(1-alkynyl)-2-alkene-1-ones with indoles.

(R^2 = Ph) was found to be the most reactive substrate. The authors have proposed a radical mechanism in which the vinylarene intercepted a chiral β-aminoalkyl radical **A** generated *in situ* from an enantioselective aminocupration of the γ-alkenylsulfonamide followed by C—Cu(II) homolysis (Scheme 1.3). In the presence of MnO_2, the resulting carbon radical coupling intermediate was oxidized to the final alkene.

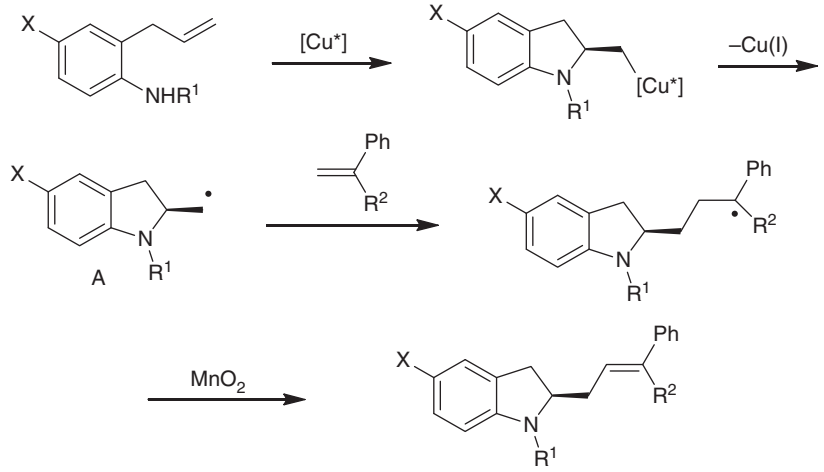
In addition, the scope of this methodology could be extended to relatively less reactive 4-pentenylsulfonamides, which required higher temperature (120 °C) to provide by reaction with diphenylethylene the corresponding chiral pyrrolidines diphenylethylene in good to high yields (62–88%) and moderate to high enantioselectivities (55–95% ee), as illustrated in Scheme 1.4 [8].

Related reaction conditions were applied by the same authors to asymmetric domino aminohalogenation/cyclization reactions of the same sulfonamide substrates with 2-iodopropane [9]. In this case, the chiral β-aminoalkyl radical intermediate **A** (Scheme 1.3) was intercepted with 2-iodopropane to provide chiral 2-iodomethylindolines (first equation) and 2-iodomethylpyrrolidines (second equation) starting respectively from the corresponding γ-alkenylsulfonamides and 4-pentenylsulfonamides. These functionalized heterocycles were obtained



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

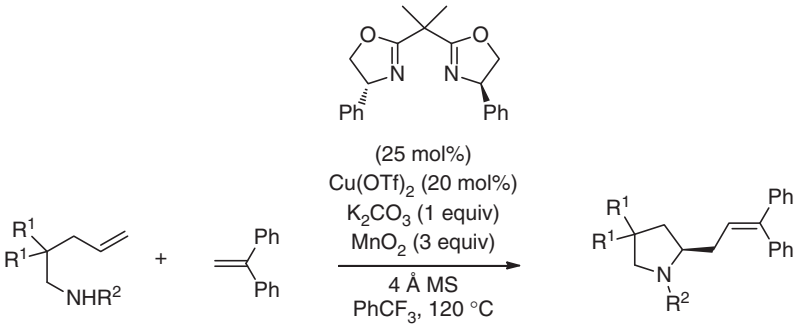
Proposed mechanism:



Scheme 1.3 Domino amination/Heck-type reaction of γ-alkenylsulfonamides with vinylarenes.

in 71–85% and 77–85% yields in combination with 15–90% and 43–93% ee, respectively (Scheme 1.5).

In another context, some enantioselective copper-catalyzed domino reactions have been initiated by arylations [10]. Among them, asymmetric copper-catalyzed domino arylation/cyclization reactions were developed by MacMillan

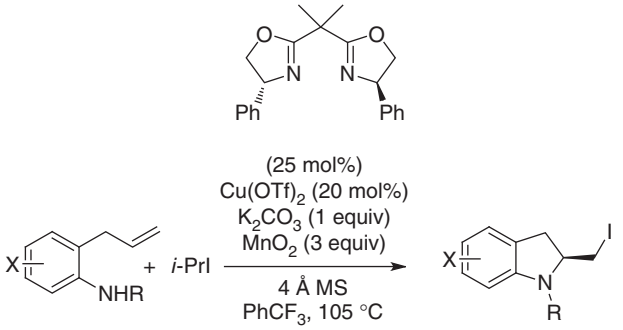


R^1 = Me, R^2 = Ts: 74% yield, 92% ee
R^1 = Me, R^2 = Ms: 88% yield, 55% ee
R^1 = Ph, R^2 = Ts: 68% yield, 95% ee
R^1 = Ph, R^2 = Ms: 68% yield, 90% ee
R^1 = H, R^2 = Ts: 62% yield, 80% ee

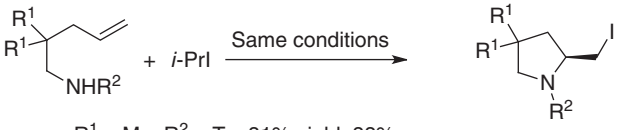
Scheme 1.4 Domino amination/Heck-type reaction of 4-pentenylsulfonamides with diphenylethylene.

and coworker in 2012, yielding biologically interesting C3-aryl pyrroloindolines [11]. Promoted by a chiral preformed bisoxazoline copper catalyst, the reaction of various indole acetamides with diphenyliodonium salt (Ar = X = Ph) evolved through an arylation followed by cyclization of the formed intermediates to give the corresponding chiral pyrroloindolines in high yields (80–98%) combined with excellent enantioselectivities (90–>99% ee), as depicted in Scheme 1.6 (X = Ph). The scope of this process was wide since a range of alkyl-protecting groups (R) of the indole acetamides were found compatible. Thus, *N*-methyl-, *N*-allyl-, and *N*-benzyl-substituted indole acetamides all provided excellent enantioselectivities (97–99% ee). Moreover, unsubstituted indole nitrogens were tolerated with low or no effect on the enantioselectivity of the reaction (90–95% ee). The scope of the methodology was also extended to the use of nonsymmetric aryliodonium salts (X = Ms) since a series of *ortho*-, *meta*-, and *para*-substituted aryl rings (Ar) with diverse steric and electronic properties readily reacted with methyl-protected indole benzylacetamide (R = Me, PG = Bn) to afford the corresponding chiral pyrroloindolines in uniformly high enantioselectivities (91–>99% ee) combined with moderate to high yields (55–92%) as illustrated in Scheme 1.6 (X = Ms).

In 2013, Shimizu and coworkers reported a novel asymmetric entry to 1*H*-isochromene skeletons based on sequential intramolecular oxycupration of allenes and subsequent asymmetric addition of the *in situ* generated allylcopper intermediates to carbonyl compounds [12]. As shown in Scheme 1.7, the reaction of various allenic alcohols with aldehydes in the presence of 10 mol% of MsCu combined with 11 mol% of a chiral biphosphine ligand, such as (*R*)-DTBM-Segphos and (*S,S*)-Ph-bpe, afforded the corresponding chiral 1*H*-isochromene derivatives in good to high yields (60–91% with

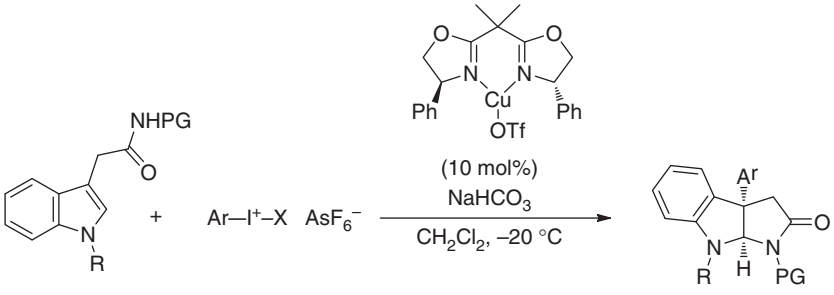


X = 4-Me, R = Ts: 85% yield, 90% ee
X = 4-CN, R = Ts: 85% yield, 84% ee
X = 4-F, R = Ts: 80% yield, 89% ee
X = 4-Cl, R = Ts: 83% yield, 87% ee
X = 4-OMe, R = Ts: 72% yield, 87% ee
X = 3-OMe, R = Ts: 71% yield, 88% ee
X = 2-OMe, R = Ts: 80% yield, 15% ee
X = H, R = Bs: 77% yield, 88% ee



R^1 = Me, R^2 = Ts: 81% yield, 88% ee
R^1 = Me, R^2 = Ms: 78% yield, 43% ee
R^1 = Me, R^2 = Ns: 80% yield, 60% ee
R^1 = Ph, R^2 = Ts: 85% yield, 93% ee
R^1 = H, R^2 = Ts: 77% yield, 73% ee
R^1 = H, R^2 = 3,5-*t*-$Bu_2C_6H_3SO_2$: 85% yield, 88% ee
R^1,R^1 = $CH_2OSi(t\text{-}Bu)_2OCH_2$, R^2 = Ts: 78% yield, 92% ee

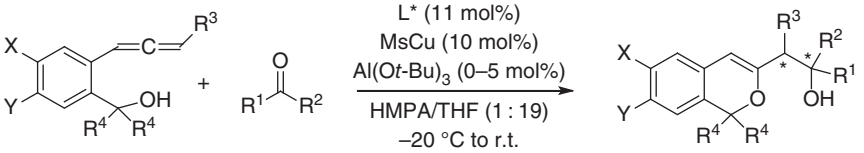
Scheme 1.5 Domino aminohalogenation/cyclization reactions of γ-alkenylsulfonamides and 4-pentenylsulfonamides with 2-iodopropane.



with Ar = Ph, X = Ph
R = Me, Bn, allyl, H
PG = Bn, Me, H:
80–98% yield, 90–>99% ee

with X = Ms, R = Me, PG = Bn
Ar = *p*-Tol, *p*-$MeOC_6H_4$, *p*-PhC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$F_3CC_6H_4$, *m*-$EtO_2CC_6H_4$, *m*-BrC_6H_4, 2-Naph, *o*-FC_6H_4, *o*-$MeOC_6H_4$, 2-thienyl:
55–92% yield, 91–>99% ee

Scheme 1.6 Domino arylation/cyclization reaction of indole acetamides with aryliodonium salts.

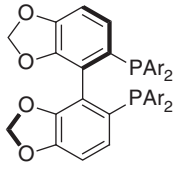


with L* = (*R*)-DTBM-Segphos:

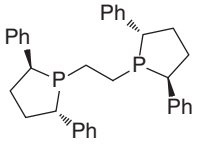
X = Y = R^2 = R^3 = R^4 = H, R^1 = Ph: 70% yield, 81% ee
X = Y = R^2 = R^3 = R^4 = H, R^1 = *t*-Bu: 77% yield, 91% ee
X = Y = R^2 = R^3 = R^4 = H, R^1 = Cy: 66% yield, 91% ee
X = Y = R^2 = R^3 = R^4 = H, R^1 = *c*-Pent: 60% yield, 89% ee
X = Y = R^2 = R^3 = R^4 = H, R^1 = *i*-Pent: 91% yield, 93% ee
X = Y = R^2 = R^3 = R^4 = H, R^1 = *c*-Pr: 78% yield, 84% ee
X = R^2 = R^3 = R^4 = H, Y = Cl, R^1 = Cy: 72% yield, 86% ee
X = R^2 = R^3 = R^4 = H, Y = Cl, R^1 = *i*-Pent: 76% yield, 91% ee
X = F, R^2 = R^3 = R^4 = H, Y = Cl, R^1 = *i*-Pent: 86% yield, 93% ee
X = Y = R^3 = R^4 = H, R^1 = Ph, R^2 = Me: 77% yield, 76% ee

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

X = Y = R^2 = R^3 = H, R^1 = Ph, R^4 = Me: 92% yield, 92% ee
X = Y = R^2 = R^3 = H, R^1 = *p*-$MeOC_6H_4$, R^4 = Me: 91% yield, 90% ee
X = Y = R^2 = R^3 = H, R^1 = *p*-(*t*-Bu)C_6H_4, R^4 = Me: 90% yield, 91% ee
X = Y = R^2 = R^3 = H, R^1 = *p*-FC_6H_4, R^4 = Me: 85% yield, 90% ee
X = R^2 = R^3 = H, Y = OMe, R^1 = Ph, R^4 = Me: 69% yield, 92% ee
X = Y = R^2 = H, R^1 = Ph, R^3 = R^4 = Me: 98% yield, 58% de, 97% ee and 82% ee
X = Y = R^2 = H, R^1 = R^4 = Ph, R^3 = Me: 99% yield, 30% de, 81% ee and 95% ee

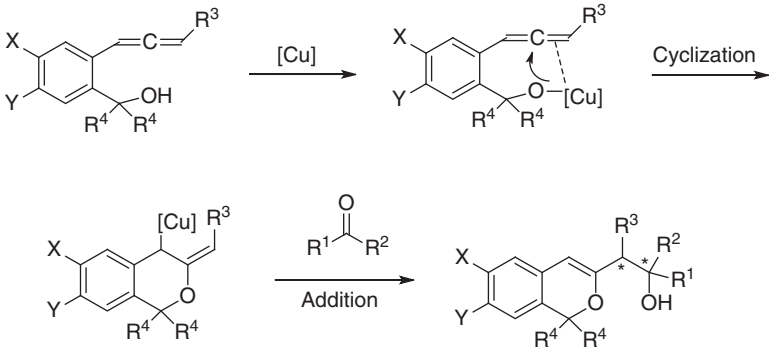


(*R*)-DTBM-Segphos
Ar = 3,5-*t*-Bu_2–4-MeO–C_6H_2



(*S,S*)-Ph-bpe

Proposed mechanism:



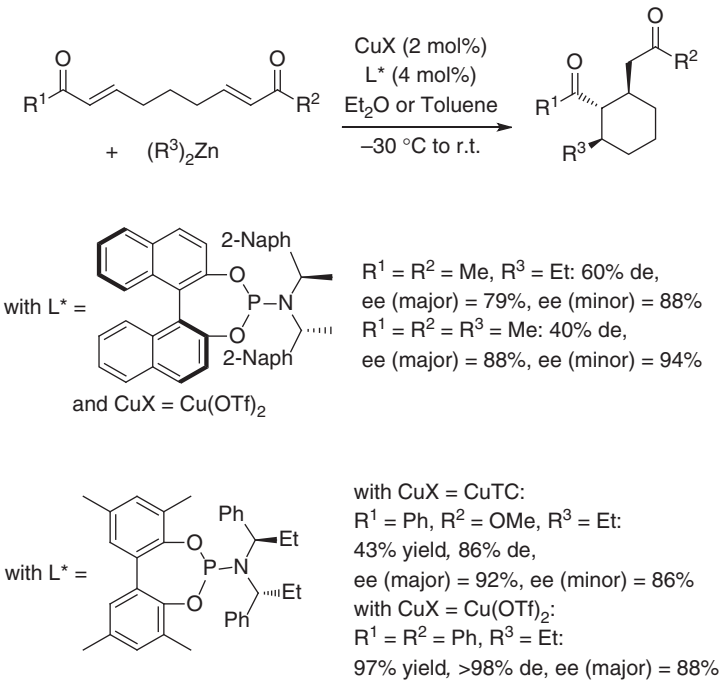
Scheme 1.7 Domino cyclization/addition reaction of allenic alcohols with carbonyl compounds.

(*R*)-DTBM-Segphos, 69–99% with (*S,S*)-Ph-bpe) combined with high enantioselectivities (84–93% ee with (*R*)-DTBM-Segphos, 81–97% ee with (*S,S*)-Ph-bpe). The use of $Al(O\textit{t}\text{-}Bu)_3$ as an additive was found essential to achieve a good reactivity. Both aromatic and aliphatic aldehydes were tolerated and, moreover, less reactive acetophenone (R^1 = Ph, R^2 = Me) also provided the desired product in good yield (77%) albeit with moderate enantioselectivity (76% ee). Concerning the allenic alcohols, those bearing an electron-withdrawing halogen substituent at the *meta*- or *para*-position of the allene moiety showed good reactivity, affording the corresponding products in high enantioselectivities (86–93% ee) while the presence of an electron-donating group (MeO) at the *para*-position of the allene moiety led to a slower reaction (69% yield); but the product (R^1 = Ph, $R^2 = R^3$ = X = H, R^4 = Me, Y = OMe) was still obtained with high enantioselectivity (92% ee).

1.2.2 Reactions Initiated by Michael Additions

Michael-type reactions can be considered as one of the most powerful tools for the stereocontrolled formation of carbon–carbon and carbon–heteroatom bonds [13], as has been demonstrated by the wide number of examples in which it has been applied as a key strategic transformation in total synthesis. Since the first catalytic domino Michael/aldol reaction reported by Noyori and coworkers in 1996 [14], there have been numerous examples of domino reactions initiated by a Michael addition [15]. Among them, a number of enantioselective domino reactions have been promoted by chiral copper catalysts, allowing the synthesis of many carbocycles but also heterocycles, such as indoles, benzoxazoles, and quinoxalines. An example was reported by Alexakis and coworker in 2007, involving the copper-catalyzed enantioselective conjugate addition of dialkylzinc to bis-α,β-unsaturated carbonyl compounds, followed by the intramolecular trapping of the intermediate zinc enolate through a second intramolecular conjugate addition in the presence of chiral phosphoramidite ligands [16]. This domino double Michael process produced the corresponding chiral cyclic and heterocyclic products exhibiting three stereogenic centers as mixtures of two diastereomers with moderate to high diastereoselectivities (40–>98% de) and enantioselectivities (79–94% ee), as presented in Scheme 1.8. The stereochemistry was determined to be *trans*, *trans* for the major products and *trans*, *cis* for the minor ones.

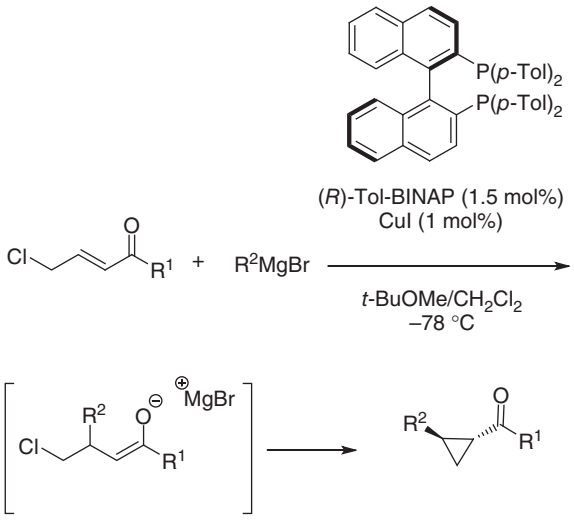
In 2010, Feringa and coworkers reported another type of enantioselective copper-catalyzed Michael-initiated domino reaction [17]. It dealt with the copper-catalyzed conjugate addition of Grignard reagents to 4-chloro-α,β-unsaturated esters, thioesters, and ketones, followed by enolate trapping through intramolecular alkylation reaction to provide the corresponding *trans*-1-alkyl-2-substituted cyclopropane esters, thioesters, and ketones, respectively, in moderate to excellent yields (56–>95%) and uniformly high enantioselectivities (84–98% ee), as shown in Scheme 1.9. The reaction was promoted by a chiral catalyst *in situ* generated from (*R*)-Tol-BINAP as chiral ligand and CuI as precatalyst. The utility of this novel methodology was demonstrated by the



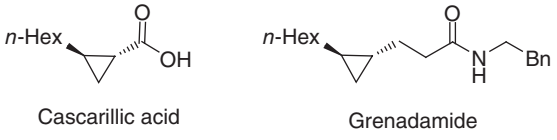
Scheme 1.8 Domino double Michael reaction of bis-α,β-unsaturated carbonyl compounds with dialkylzinc reagents.

synthesis of key intermediates for the total syntheses of the natural products cascarillic acid and grenadamide.

The reductive Michael/aldol reaction of α,β-unsaturated carbonyl compounds with saturated carbonyl compounds promoted by catalytic amounts of transition-metal complexes and reducing agents constitute a powerful tool for the stereocontrol of carbon–carbon bond formation. In this reaction, the enantioselectivity of the product depends on the second addition of the generating metal enolate with chiral ligands to electrophiles. So far, excellent progress has been achieved in the area of copper-catalyzed domino reductive Michael/aldol reactions for the construction of several contiguous stereocenters [18]. As an example, in 2008 Lipshutz et al. described the first enantioselective catalytic one-pot hydrometallative intramolecular cycloreduction leading to three new contiguous stereocenters [19]. As shown in Scheme 1.10, the enantioselective domino reductive Michael/intramolecular aldol reaction of acyclic β,β-disubstituted ketoenones with diethoxymethylsilane as the reductant formed the corresponding functionalized cyclohexanols **1a–f** as single diastereomers in good to quantitative yields (66–98%) and high enantioselectivities (84–97% ee). The generation of the three contiguous stereocenters was achieved by using a combination of $Cu(OAc)_2$ and a chiral biphosphine as catalyst system. In this process, the initial conjugate hydride addition generated an intermediate chiral copper enolate, which subsequently underwent an intramolecular aldol addition



R^1 = SEt, R^2 = *n*-Hex: 87% yield, 94% ee
R^1 = SEt, R^2 = Me: 56% yield, 87% ee
R^1 = SEt, R^2 = Et: 67% yield, 95% ee
R^1 = SEt, R^2 = $(CH_2)_3O$*t*-Bu: >95% yield, 96% ee
R^1 = SEt, R^2 = $BnCH_2$: 92% yield, 84% ee
R^1 = *n*-$C_{11}H_{23}$, R^2 = $BnCH_2$: 75% yield, 96% ee
R^1 = *n*-$C_{11}H_{23}$, R^2 = Me: 87% yield, 98% ee
R^1 = OMe, R^2 = $BnCH_2$: 68% yield, >95% ee



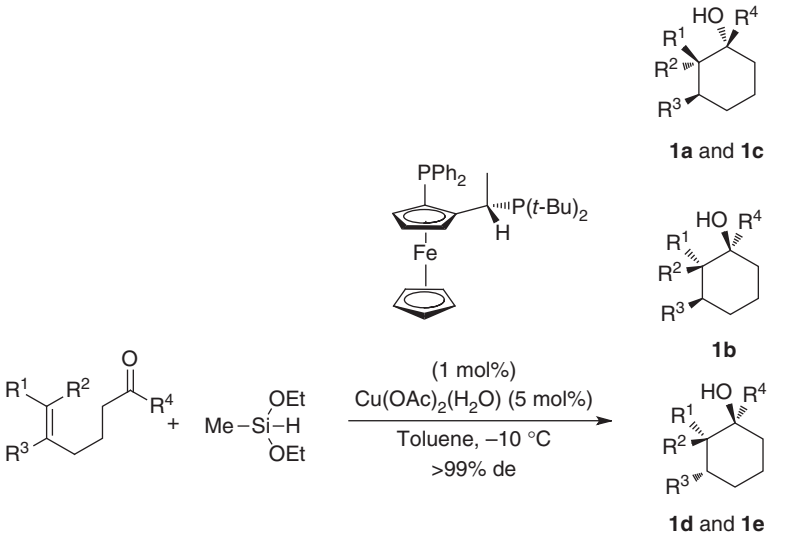
Cascarillic acid

Grenadamide

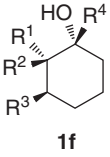
Scheme 1.9 Domino Michael/intramolecular alkylation reaction of 4-chloro-α,β-unsaturated esters/thioesters/ketones with Grignard reagents.

to ketones. Further transmetalation of the resulting copper alkoxide with a particular stoichiometric silane regenerated the ligated CuH.

Only a few methodologies of domino reductive Michael/aldol reactions have described the synthesis of bi- and tricyclic compounds. One example was reported by Riant and coworker in 2009, who developed a versatile methodology for the diastereo- and enantioselective domino reductive aldol cyclization reaction of functionalized α,β-unsaturated *tert*-butyl esters into the corresponding bicyclic domino products in moderate to good yields (70–85%) and enantioselectivities (66–97% ee), as illustrated in Scheme 1.11 [20]. The reaction was catalyzed by a copper(I) complex of a chiral biphosphine, such as a Taniaphos ligand, in the presence of phenylsilane as the reductive agent. The *cis*-product was produced as the major diastereomer with moderate to complete diastereoselectivities



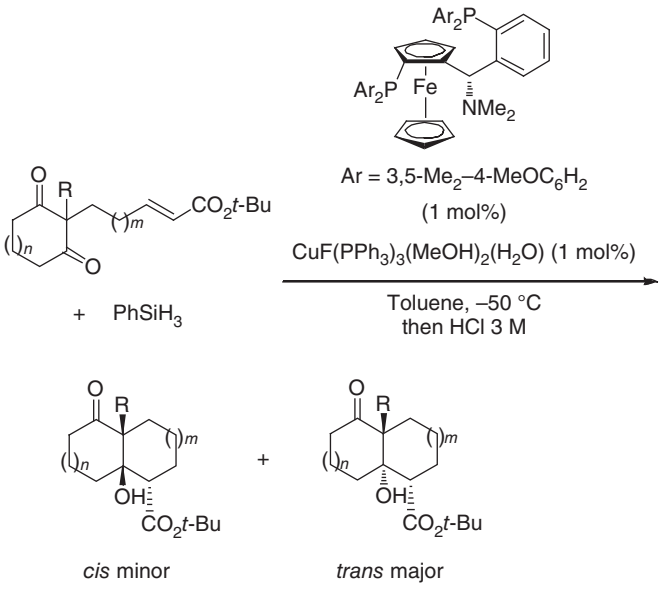
1a: R^1 = Ac, R^2 = H, R^3 = R^4 = Me: 91% yield, 96% ee
1b: R^1 = H, R^2 = Ac, R^3 = R^4 = Me: 88% yield, 96% ee
1c: R^1 = Ac, R^2 = H, R^3 = Me, R^4 = Ph: 77% yield, 97% ee
1d: R^1 = H, R^2 = Ac, R^3 = Me, R^4 = Ph: 75% yield, 97% ee
1e: R^1 = H, R^2 = CO(*i*-Pr), R^3 = *i*-Pr, R^4 = Me: 66% yield, 84% ee
1f: R^1 = Bz, R^2 = H, R^3 = R^4 = Me: 98% yield, 85% ee



Scheme 1.10 Domino reductive Michael/aldol reaction of β,β-disubstituted ketoenones with diethoxymethylsilane.

(*cis*/*trans* = 89 : 11 to >99 : 1). It was found that the stereoselectivity of the process was increased with the steric hindrance of the ester moiety, since the best results were obtained with *t*-butyl esters. Moreover, increasing the steric bulkiness around the phosphorus atoms of the ligand allowed further improvement of both the enantioselectivity and the *cis*/*trans* ratio.

Later in 2012, the same authors extended the scope of this methodology to the synthesis of other chiral highly functionalized bicyclic derivatives [21]. As shown in Scheme 1.12, the reaction of various diketoesters with phenylsilane performed in the presence of the same catalyst system led to the corresponding bicyclic chiral domino products in good yields (70–85%). The latter were obtained as major *cis*-diastereomers with moderate to complete diastereoselectivities (44–>99% de) and uniformly high enantioselectivities (84–97% ee). The Taniaphos ligand in which the phosphorus atom was sterically hindered was selected as optimal among a range of other chiral diphosphanes, including BINAP, MeO–BIPHEP, Josiphos, Walphos, Xyl-P-Phos, and Mandyphos. The scope of the methodology was found wide since a range of bicyclic products bearing various ring sizes and substitutions could be easily synthesized with homogeneous yields and enantioselectivities. However, the diastereoselectivity

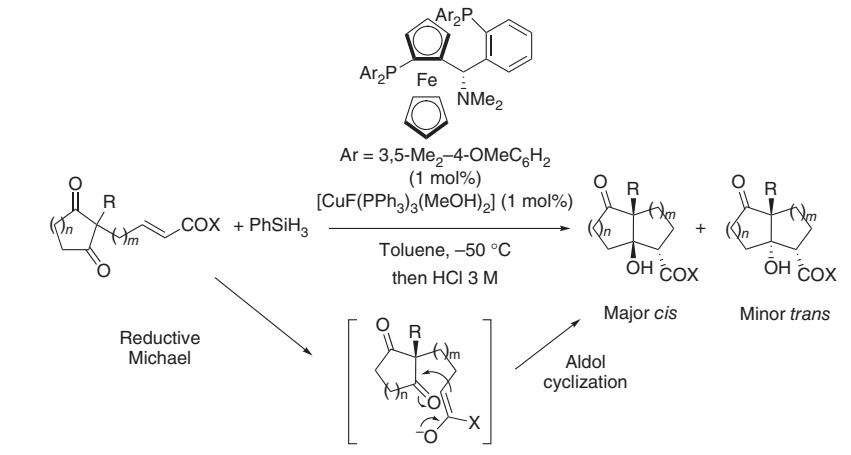


R = Me, n = 1, m = 0 : 85% yield, *cis*/*trans* = 94 : 6,
ee (*cis*) = 80%, ee (*trans*) = 85%
R = Me, n = 0, m = 1 : 80% yield, *cis*/*trans* = 89 : 11,
ee (*cis*) = 97%, ee (*trans*) = 72%
R = Me, n = m = 0 : 85% yield, *cis*/*trans* >99 : 1, ee (*cis*) = 66%
R = Me, n = 2, m = 1 : 85% yield, *cis*/*trans* >99 : 1, ee (*cis*) = 94%
R = allyl, n = m = 1 : 70% yield, *cis*/*trans* >99 : 1, ee (*cis*) = 94%

Scheme 1.11 Domino reductive Michael/aldol reaction of functionalized α,β-unsaturated esters with phenylsilane.

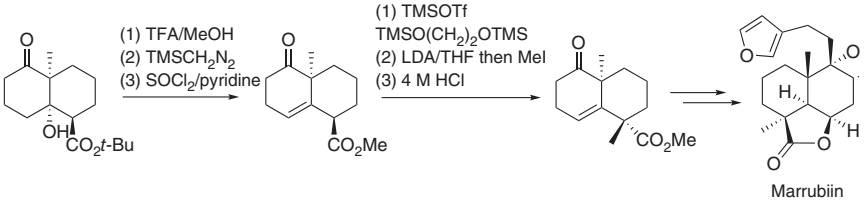
of the reaction was found influenced by the nature of the ester moiety on the diketoester, increasing from 44 to 64 and >99% de from methyl, ethyl to *t*-butyl esters (with $n = m = 2$). In addition, the reductive Michael/aldol cyclization process of a diketoenone (X = R = Me, $n = m = 2$) afforded the corresponding domino product as a single *cis*-diastereomer in good yield (75%) albeit with moderate enantioselectivity (65% ee). The utility of this novel methodology was demonstrated in the synthesis of a key intermediate of the natural diterpene marrubiin. As depicted in Scheme 1.12, a domino product (R = Me, X = O*t*-Bu, $n = m = 2$) was submitted to dehydration by successive treatments with TFA, $TMSOCH_2N_2$, and $SOCl_2$ to produce the corresponding nonconjugated cyclohexenone. The latter was then methylated in the presence of LDA and methyl iodide to yield the corresponding bicyclic ester after required protection of the ketone group as dioxolane. This compound constituted a crucial intermediate in the synthesis of marrubiin previously reported [22].

In 2012, Chiu and coworkers reported asymmetric copper-catalyzed reductive Michael aldol cyclizations of enethioate derivatives of 1,3-diones with phenylsilane [23]. The reactions were promoted by a chiral catalyst *in situ* generated from 5 mol% of $Cu(OAc)_2(H_2O)$ and the same quantity of a related chiral Taniaphos



R = Me, X = OMe, *n* = *m* = 2: 75% yield, 44% de, 84% ee (*cis*)
R = Me, X = OEt, *n* = *m* = 2: 80% yield, 64% de, 92% ee (*cis*)
R = Me, X = O*t*-Bu, *n* = *m* = 2: 80% yield, >99% de, 95% ee (*cis*)
R = Me, X = OEt, *n* = 1, *m* = 2: 78% yield, 76% de, 92% ee (*cis*)
R = Me, X = O*t*-Bu, *n* = 1, *m* = 2: 80% yield, 78% de, 97% ee (*cis*)
R = Me, X = O*t*-Bu, *n* = 3, *m* = 2: 85% yield, >99% de, 95% ee (*cis*)
R = allyl, X = O*t*-Bu, *n* = *m* = 2: 70% yield, >99% de, 94% ee (*cis*)
R = Me, X = OEt, *n* = 1, *m* = 2: 78% yield, 76% de, 92% ee (*cis*)
R = Me, X = Me, *n* = *m* = 2: 75% yield, >99% de, 65% ee (*cis*)

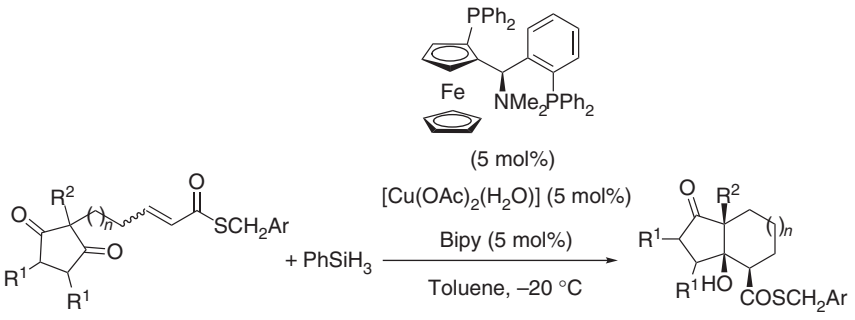
Formal synthesis of marrubiin:



Scheme 1.12 Domino reductive Michael/aldol cyclization reaction of diketoesters/diketoenone with phenylsilane and synthesis of marrubiin.

ligand in the presence of bipyridine (Bipy) as an additive. In these conditions, a variety of unsaturated thioesters produced the corresponding chiral bicyclic β-hydroxythioesters bearing three contiguous stereogenic centers having all substituents *cis*. They were obtained in moderate to high yields (56–94%), diastereoselectivities (56–>96% de), and enantioselectivities of up to 98% ee, as illustrated in Scheme 1.13. The lowest enantioselectivity (27% ee) was obtained in the formation of a five-membered ring ($n = 0$) while uniformly excellent enantioselectivities of 88–98% ee were obtained in the formation of six- and seven-membered rings.

In addition, Lam and coworkers developed enantioselective domino conjugate boration/aldol cyclization reactions of diketoenones in 2012 [24]. This process began with the enantioselective conjugate boration of enone diones with $B_2(Pin)_2$ performed in the presence of a combination of CuCl and a Josiphos ligand, followed by an aldol cyclization reaction that yielded the corresponding domino products. As shown in Scheme 1.14, a range of functionalized decalin-, hydrindane-, and diquinane-based chiral products exhibiting four contiguous



R^1 = H, R^2 = Me, n = 1, Ar = Ph: 84% yield, >96% de, 90% ee
R^1 = H, R^2 = Me, n = 1, Ar = p-t-BuC_6H_4: 94% yield, >96% de, 90% ee
R^1 = H, R^2 = Me, n = 1, Ar = 2,4,6-$Me_3C_6H_2$: 93% yield, >96% de, 93% ee
R^1,R^1 = $(CH{=}CH)_2$, R^2 = Me, n = 1, Ar = Ph: 71% yield, >96% de, 96% ee
R^1,R^1 = $(CH{=}CH)_2$, R^2 = allyl, n = 1, Ar = Ph: 71% yield, 74% de, 95% ee
R^1,R^1 = $(CH{=}CH)_2$, R^2 = CH_2(p-BrC_6H_4), n = 1, Ar = Ph: 65% yield, 56% de, 98% ee
R^1 = H, R^2 = Me, n = 2, Ar = Ph: 72% yield, >96% de, 93% ee
R^1 = H, R^2 = Me, n = 2, Ar = p-t-BuC_6H_4: 86% yield, 80% de, 88% ee
R^1 = H, R^2 = Bn, n = 2, Ar = Ph: 65% yield, >96% de, 93% ee
R^1 = H, R^2 = Me, n = 0, Ar = Ph: 56% yield, >96% de, 27% ee

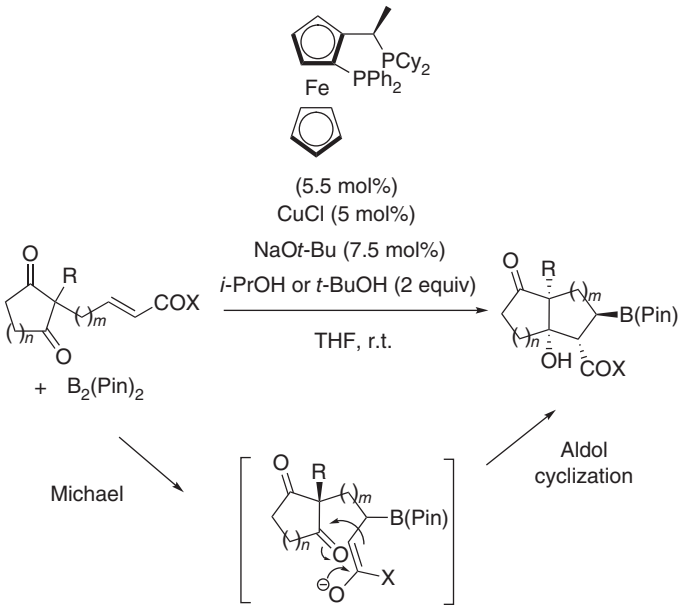
Scheme 1.13 Domino reductive Michael/aldol reaction of unsaturated diketothioesters with phenylsilane.

stereocenters, with two of them being quaternary, were synthesized in moderate to high yields (52–>95%), very high diastereoselectivity of >90% de in most cases, and uniformly excellent enantioselectivities (92–>99% ee). The presence of stoichiometric amounts of hindered alcohol additives, such as *i*-PrOH or *t*-BuOH, was found essential to obtain high diastereo- and enantioselectivities. The optimal Josiphos ligand was selected among various common chiral biphosphine ligands including BINAP, QUINOX, and Taniaphos ligands.

1.2.3 Reactions Initiated by Friedel–Crafts Reactions

While the Friedel–Crafts reaction constitutes a fundamental reaction in organic chemistry, enantioselective catalytic versions remain unexplored [25]. In 2013, Xiao and coworkers developed asymmetric copper-catalyzed domino Friedel–Crafts/N-hemiacetalization reactions of 3-substituted indoles with β,γ-unsaturated α-ketoesters [26]. Promoted by a chiral catalyst *in situ* generated from $Cu(OTf)_2$ and a chiral bisoxazoline ligand, the process enabled the synthesis of diversely functionalized chiral 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles. Indeed, a range of these substituted and functionalized chiral products were obtained in low to excellent enantioselectivities (27–>99% ee), moderate to quantitative yields (67–97%) and low to high diastereoselectivities (12–94% de), as presented in Scheme 1.15.

Later in 2015, these reactions were reinvestigated by Fu and coworkers in the presence of another chiral bisoxazoline ligand [27]. As illustrated in



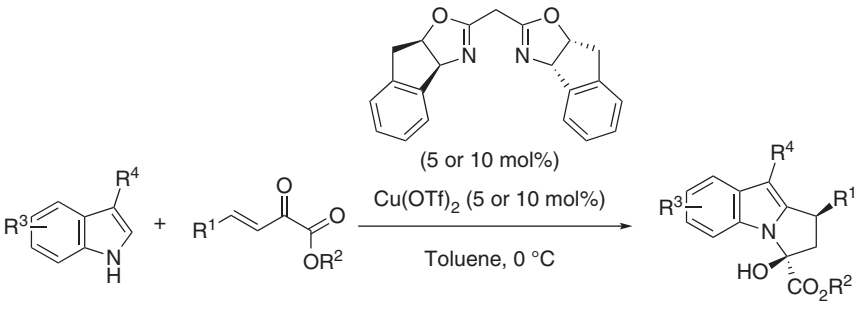
R = Me, X = Ph, $n = m = 2$: 71% yield, >90% de, 95% ee
R = Me, X = *p*-ClC_6H_4, $n = m = 2$: 74% yield, >90% de, 94% ee
R = Me, X = *p*-$MeOC_6H_4$, $n = m = 2$: 82% yield, >90% de, >99% ee
R = allyl, X = Ph, $n = m = 2$: 70% yield, >90% de, 95% ee
R = Me, X = $(CH_2)_2OBn$, $n = m = 2$: 52% yield, >90% de, 92% ee
R = Me, X = OBn, $n = m = 2$: 79% yield, >90% de, 93% ee
R = Me, X = Ph, $n = 1$, $m = 2$: >95% yield, >90% de, 97% ee
R = Me, X = *p*-ClC_6H_4, $n = 1$, $m = 2$: 82% yield, >90% de, 93% ee
R = Me, X = *p*-$MeOC_6H_4$, $n = 1$, $m = 2$: >95% yield, >90% de, 92% ee
R = Et, X = Ph, $n = 1$, $m = 2$: 89% yield, >90% de, 96% ee
R = Me, X = Ph, $n = 2$, $m = 1$: 90% yield, 58% de, 99% ee
R = Me, X = Ph, $n = m = 1$: 79% yield, 20% de, 92% ee

Scheme 1.14 Domino conjugate boration/aldol cyclization reaction of diketoenones with $B_2(Pin)_2$.

Scheme 1.16, using this heteroarylidene-tethered bisoxazoline ligand in combination with the same precatalyst $Cu(OTf)_2$ allowed a range of enantiomeric functionalized pyrroloindoles to be obtained starting from the corresponding 3-methyl indoles and β,γ-unsaturated α-ketoesters. Moderate to high yields of 54–95% and diastereoselectivities (58–92% de) combined with uniformly high enantioselectivities (87–98% ee) were achieved for this domino Friedel–Crafts/N-hemiacetalization reaction.

1.2.4 Reactions Initiated by Aldol Reactions

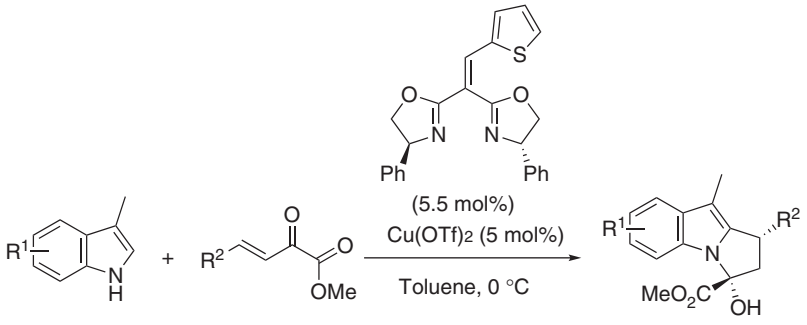
The direct catalytic asymmetric aldol reaction is a powerful and atom-economical method for synthesizing chiral β-hydroxy carbonyl compounds. Many metals and organocatalysts have already been applied to these reactions in the past decade [28]. In 2015, Matsunaga, Kanai, and coworkers involved a chiral copper



67–97% yield, 12–94% de, 27–>99% ee

R^1 = Ph, *p*-Tol, *p*-$MeOC_6H_4$, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *m*-BrC_6H_4, *o*-FC_6H_4, 2-thiophenyl, (*E*)-PhCH=CH, CO_2Et, Cy, $(MeO)_2CH$, *n*-Pr
R^2 = Me, Et, Bn, *i*-Pr
R^3 = H, 4-Me, 5-Me, 6-Me, 5-MeO, 5-BnO, 5-F, 5-Cl, 5-Br, 6-Cl, 6-F
R^4 = Me, Et, *i*-Pr, Cy, Bn, Ph, CH_2CO_2Me, $(CH_2)_2OTBS$, $(CH_2)_2NPhth$

Scheme 1.15 Domino Friedel–Crafts/N-hemiacetalization reaction of 3-substituted indoles with β,γ-unsaturated α-ketoesters.

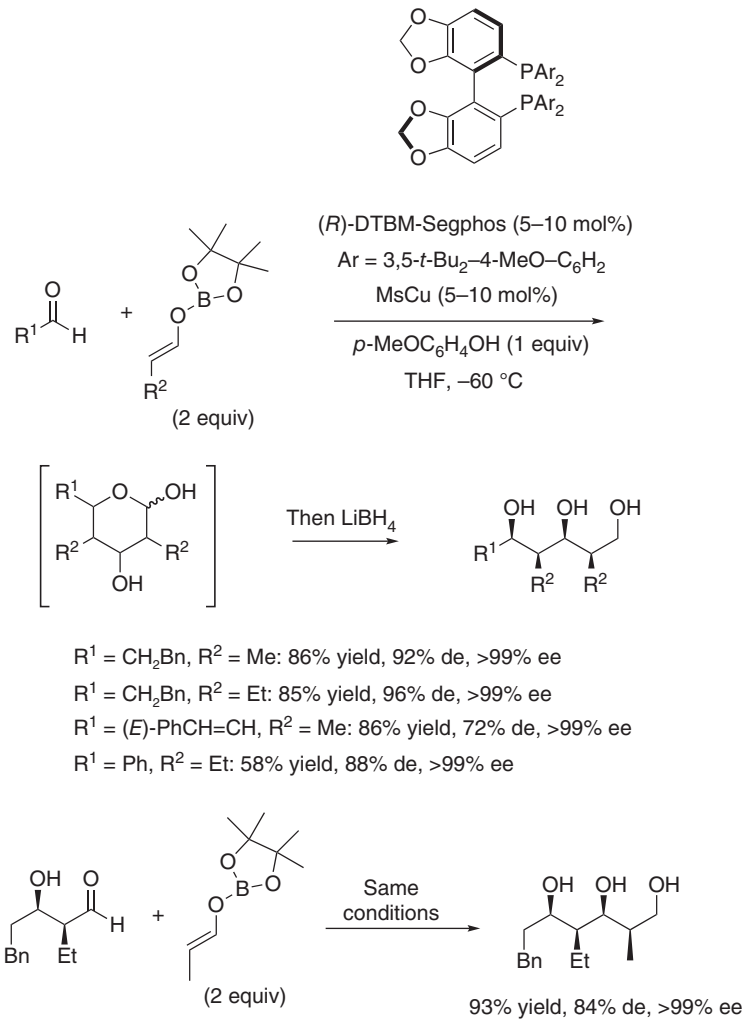


54–95% yield, 58–92% de, 87–98% ee

R^1 = H, 5-Me, 5-MeO, 5-F, 5-Cl, 5-Br, 6-F, 4-MeO, 7-F
R^2 = Ph, *p*-Tol, *p*-$MeOC_6H_4$, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-$F_3CC_6H_4$, *m*-Tol, *m*-FC_6H_4, *m*-BrC_6H_4, *o*-FC_6H_4, 2-furyl, 2-thienyl, (*E*)-PhCH=CH, CO_2Et, Cy, $(MeO)_2CH$, *n*-Pr

Scheme 1.16 Domino Friedel–Crafts/N-hemiacetalization reaction of 3-methyl indoles with β,γ-unsaturated α-ketoesters.

catalyst *in situ* generated from MsCu as precatalyst and (*R*)-DTBM-Segphos as ligand in an asymmetric domino double aldol reaction of aldehydes with boron enolates [29]. Performed in the presence of a stoichiometric amount of 4-methoxyphenol, the reaction led to the corresponding cyclized hemiacetals, which were directly reduced by treatment with $LiBH_4$ to form the corresponding final enantiopure triols (>99% ee) in uniformly high yields (58–93%) and good to high diastereoselectivities (72–96% de), as shown in Scheme 1.17. This approach



Scheme 1.17 Domino double aldol reactions of aldehydes with boron enolates.

could be extended to more than double-aldol reactions, such as triple and quadruple asymmetric domino aldol reactions, which yielded chiral 1,3-polyols with comparable excellent enantioselectivities of up to >99% ee.

In 2015, Wang and coworkers reported an unprecedented copper-catalyzed asymmetric domino vinylogous Mukaiyama-type/Michael reaction of 2-silyloxyfurans with azoalkenes, providing a novel and direct entry to chiral fused biologically interesting butyrolactones [30]. The optimal catalyst was *in situ* generated from $Cu(OTf)_2$ and a chiral bisoxazoline and employed HFIPA as stoichiometric additive. Performed at 0 °C in dichloromethane as solvent, the reaction of variously substituted 2-silyloxyfurans with azoalkenes yielded the corresponding fused chiral butyrolactones (X = O) as almost single

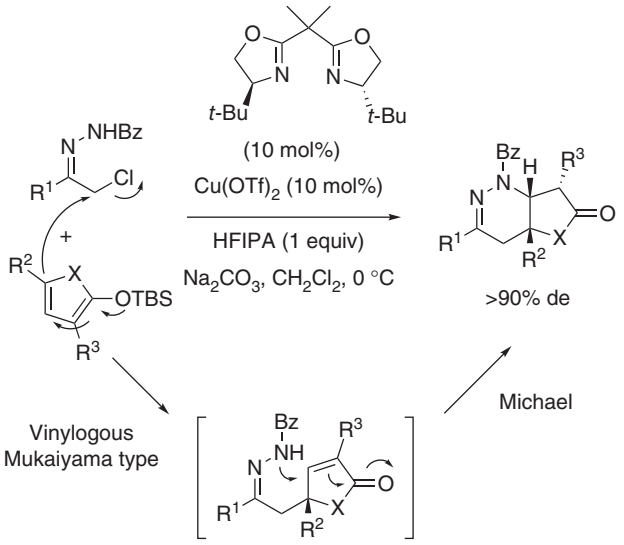
diastereomers (>90% de) in good yields (75–88%) and enantioselectivities (71–98% ee), as shown in Scheme 1.18. The substrate scope of the azoalkenes revealed that the substitution pattern of the phenyl group (R^1 = Ph) had little effect on the reactivity and enantioselectivity of the reaction since *para*-, *meta*-, and *ortho*-substituted hydrazones were all tolerated. Moreover, the electronic nature of substituents on this phenyl group had no influence on the results. Only in the case of one substrate, a moderate enantioselectivity of 71% ee was obtained in the reaction of an alkenyl-substituted hydrazine (R^1 = (*E*)-PhCH=CH, R^2 = R^3 = H, X = O). Furthermore, the scope of the methodology was extended to a pyrrole-based dienoxysilane (X = *N*-Boc), which reacted with azoalkenes to afford the corresponding butyrolactams in both high yields (80–92%) and enantioselectivities (90–98% ee), as shown in Scheme 1.18.

1.2.5 Miscellaneous Reactions

In 2016, Batra and coworkers combined CuI with a chiral proline-derived organocatalyst to cooperatively catalyze enantioselective domino reactions occurring between terminal alkynes and 1-formyl-9*H*-β-carbolines [31]. This multicatalyst system opened a novel route for achieving biologically interesting chiral 5,6-dihydrocanthin-4-ones in moderate to high yields (57–92%) and enantioselectivities (68–>99% ee), as illustrated in Scheme 1.19. 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 mechanism is depicted in Scheme 1.19, which began with the reaction of the aldehyde with the chiral pyrrolidine catalyst to give the corresponding iminium ion **B**, which then reacted with the *in situ* generated copper-coordinated alkyne **C** to give intermediate **D**. The latter subsequently underwent an intramolecular aza-Michael addition to provide the final domino product after hydrolysis.

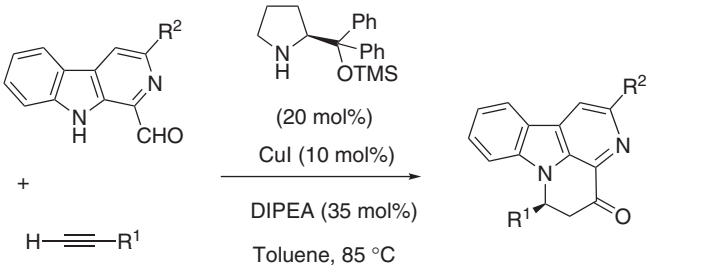
In 2016, Quintard, Rodriguez, and coworkers combined 6.5 mol% of an achiral iron tricarbonyl complex with 8 mol% of a chiral proline-derived organocatalyst in the presence of 5 mol% of $Cu(acac)_2$ to promote enantioselective domino oxidation/Michael/reduction/Claisen fragmentation reactions of 1,3-diketones with allylic alcohols (Scheme 1.20) [32, 33]. The multicatalyst system employed at 25 °C in Xylenes as solvent allowed the corresponding chiral 3-alkylpentanols to be achieved in good yields (66–85%) and uniformly high enantioselectivities (87–96% ee). The mechanism of the domino reaction shown in Scheme 1.20 began with the iron-catalyzed oxidation of the allylic alcohol into the corresponding α,β-unsaturated aldehyde **E**, which subsequently underwent a Michael addition with the 1,3-diketone through iminium catalysis from the chiral organocatalyst to afford the chiral intermediate **F**. A chemoselective aldehyde reduction of the latter led to alcohol intermediate **G**, which further cyclized into lactol **H**. Then, intermediate **H** was submitted to a Claisen fragmentation to give intermediate **I**, which led after protonation to the final chiral product.

Later in 2018, the same authors applied a related multicatalyst system to develop another type of enantioselective domino reactions [34]. As shown in Scheme 1.21, the use of a multicatalytic system composed of 6.5 mol% of the same achiral iron tricarbonyl complex, 13 mol% of a chiral proline-derived



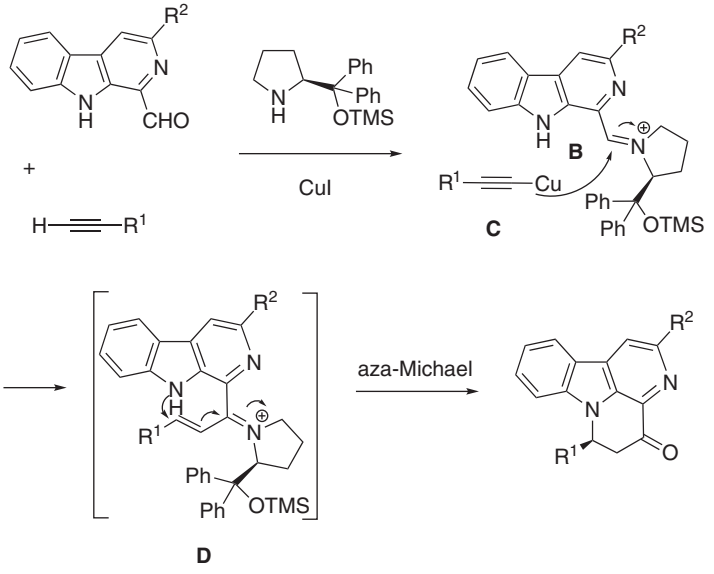
R^1 = Ph, R^2 = R^3 = H, X = O: 85% yield, 97% ee
R^1 = *p*-BrC_6H_4, R^2 = R^3 = H, X = O: 86% yield, 94% ee
R^1 = *p*-ClC_6H_4, R^2 = R^3 = H, X = O: 88% yield, 94% ee
R^1 = *m*-ClC_6H_4, R^2 = R^3 = H, X = O: 81% yield, 91% ee
R^1 = *o*-FC_6H_4, R^2 = R^3 = H, X = O: 86% yield, 93% ee
R^1 = *p*-Tol, R^2 = R^3 = H, X = O: 80% yield, 96% ee
R^1 = *p*-$MeOC_6H_4$, R^2 = R^3 = H, X = O: 87% yield, 94% ee
R^1 = *m*-Tol, R^2 = R^3 = H, X = O: 78% yield, 92% ee
R^1 = 2-Naph, R^2 = R^3 = H, X = O: 88% yield, 94% ee
R^1 = (*E*)-PhCH=CH, R^2 = R^3 = H, X = O: 83% yield, 71% ee
R^1 = Ph, R^2 = H, R^3 = Me, X = O: 82% yield, 97% ee
R^1 = *p*-ClC_6H_4, R^2 = H, R^3 = Me, X = O: 75% yield, 96% ee
R^1 = *p*-$F_3CC_6H_4$, R^2 = H, R^3 = Me, X = O: 83% yield, 97% ee
R^1 = *p*-Tol, R^2 = H, R^3 = Me, X = O: 78% yield, 93% ee
R^1 = *m*-Tol, R^2 = H, R^3 = Me, X = O: 75% yield, 93% ee
R^1 = Ph, R^2 = Me, R^3 = H, X = O: 81% yield, 97% ee
R^1 = *p*-BrC_6H_4, R^2 = Me, R^3 = H, X = O: 86% yield, 95% ee
R^1 = *p*-ClC_6H_4, R^2 = Me, R^3 = H, X = O: 84% yield, 96% ee
R^1 = *p*-Tol, R^2 = Me, R^3 = H, X = O: 80% yield, 94% ee
R^1 = *m*-Tol, R^2 = Me, R^3 = H, X = O: 76% yield, 96% ee
R^1 = Ph, R^2 = R^3 = H, X = NBoc: 92% yield, 90% ee
R^1 = *p*-BrC_6H_4, R^2 = R^3 = H, X = NBoc: 87% yield, 95% ee
R^1 = *o*-FC_6H_4, R^2 = R^3 = H, X = NBoc: 82% yield, 97% ee
R^1 = *p*-Tol, R^2 = R^3 = H, X = NBoc: 80% yield, 98% ee
R^1 = *p*-BrC_6H_4, R^2 = R^3 = H, X = NBoc: 87% yield, 95% ee

Scheme 1.18 Domino vinylogous Mukaiyama-type/Michael reaction of 2-silyloxyfurans/pyrrole-based dienoxysilane with azoalkenes.



R^1 = Ph, *p*-*t*-BuC_6H_4, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-Tol, *p*-MeOC_6H_4, *m*-FC_6H_4, *m*-Tol, 2-pyridyl, 2-cyclohexenyl, *n*-Bu, CO_2Me, 2-thienyl, *p*-*n*-BuC_6H_4, *p*-PhOC_6H_4, *p*-MeO(2-Naph), 3,4-$Cl_2C_6H_3$
R^2 = CO_2Me, H

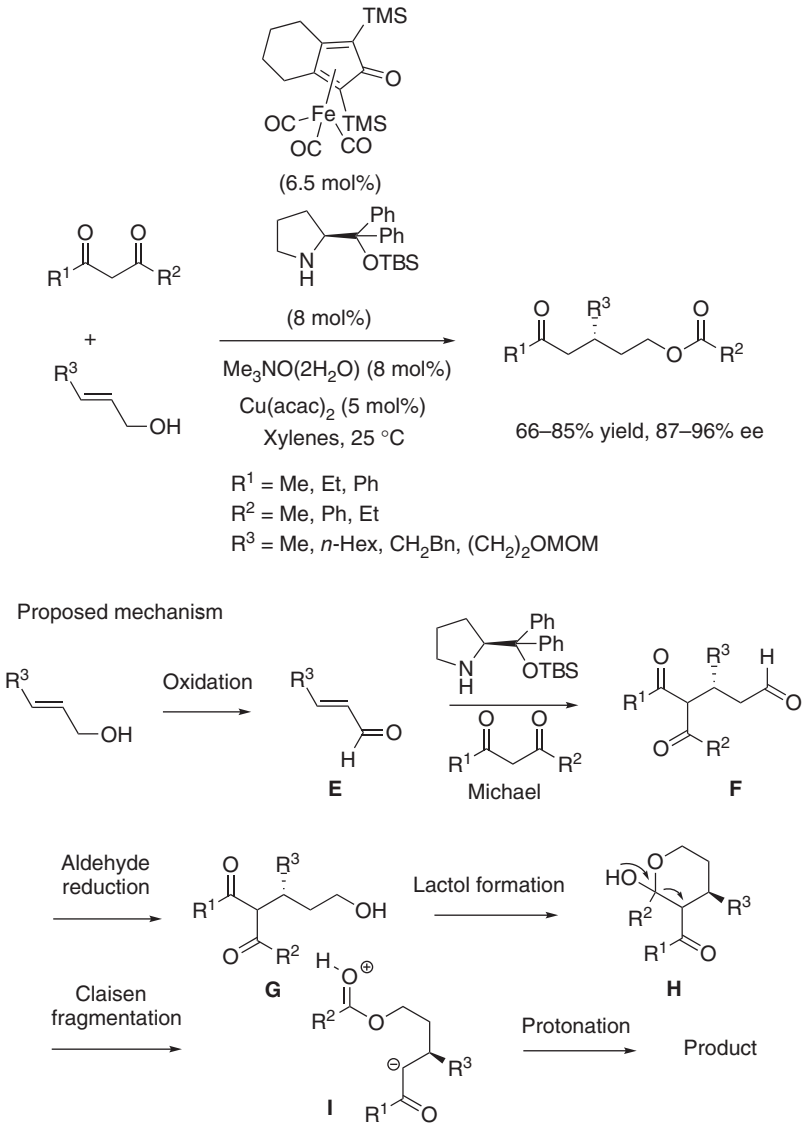
Proposed mechanism:



Scheme 1.19 Multicatalytic domino condensation/aza-Michael reaction of terminal alkynes with 1-formyl-9*H*-β-carbolines.

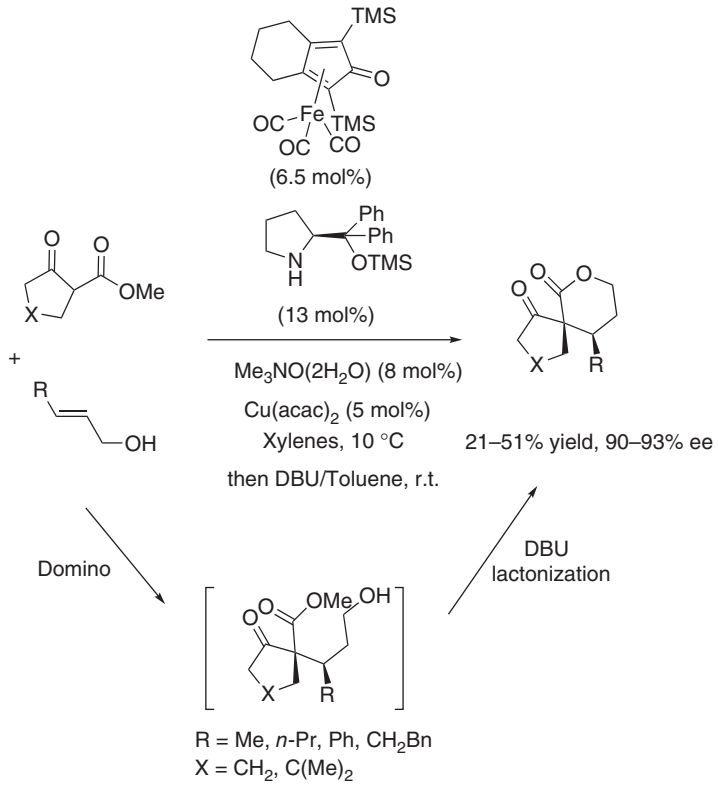
organocatalyst, and 5 mol% of $Cu(acac)_2$, allowed enantioselective domino oxidation/Michael/reduction reactions between cyclic β-keto esters and allylic alcohols to occur in Xylenes at 10 °C. The domino products were subsequently submitted to lactonization by treatment with DBU at room temperature in Toluene to give the corresponding chiral δ-lactones in low to moderate yields (21–51%) combined with high enantioselectivities (90–93% ee).

In 2018, Enders and coworkers reported the first copper-catalyzed highly chemo-, regio-, diastereo-, and enantioselective domino Kinugasa/Michael



Scheme 1.20 Multicatalytic domino oxidation/Michael/reduction/Claisen fragmentation reaction of 1,3-diketones with allylic alcohols.

reaction for the desymmetrization of prochiral cyclohexadienones [35]. As illustrated in Scheme 1.22, in the presence of a chiral copper catalyst *in situ* generated from $Cu(OTf)_2$ and a chiral bisoxazoline ligand, alkyne-tethered cyclohexadienones reacted with nitrones in the presence of a base, such as *i*-Bu_2NH, in acetonitrile at 0 °C to give the corresponding chiral spirocyclic lactams. These highly functionalized domino products exhibiting four contiguous stereocenters were obtained in moderate to high yields (55–94%), good to high diastereoselectivities (72–>90% de), and uniformly high enantioselectivities



Scheme 1.21 Multicatalytic domino oxidation/Michael/reduction reaction of cyclic β-keto esters with allylic alcohols followed by lactonization.

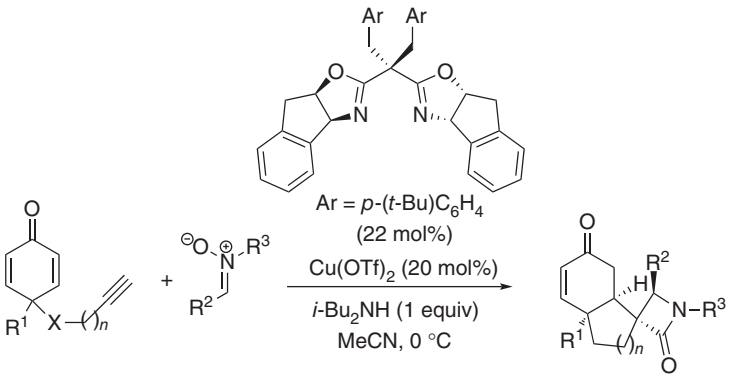
(82–97% ee). The process exhibited high functional-group tolerance and a broad substrate scope with various substituents on the two substrates. Especially, the diastereoselectivity was almost complete (>90% de) in all cases of substrates with three exceptions for cyclohexadienones bearing a longer alkyl chain (R^1 = *n*-Bu, *n*-Pent, *n*-Hex), which reacted with lower diastereoselectivity levels (72–82% de).

1.3 Three-Component Processes

1.3.1 Reactions Based on Alkyne Couplings

1.3.1.1 Reactions of Alkynes, Aldehydes, and Amines

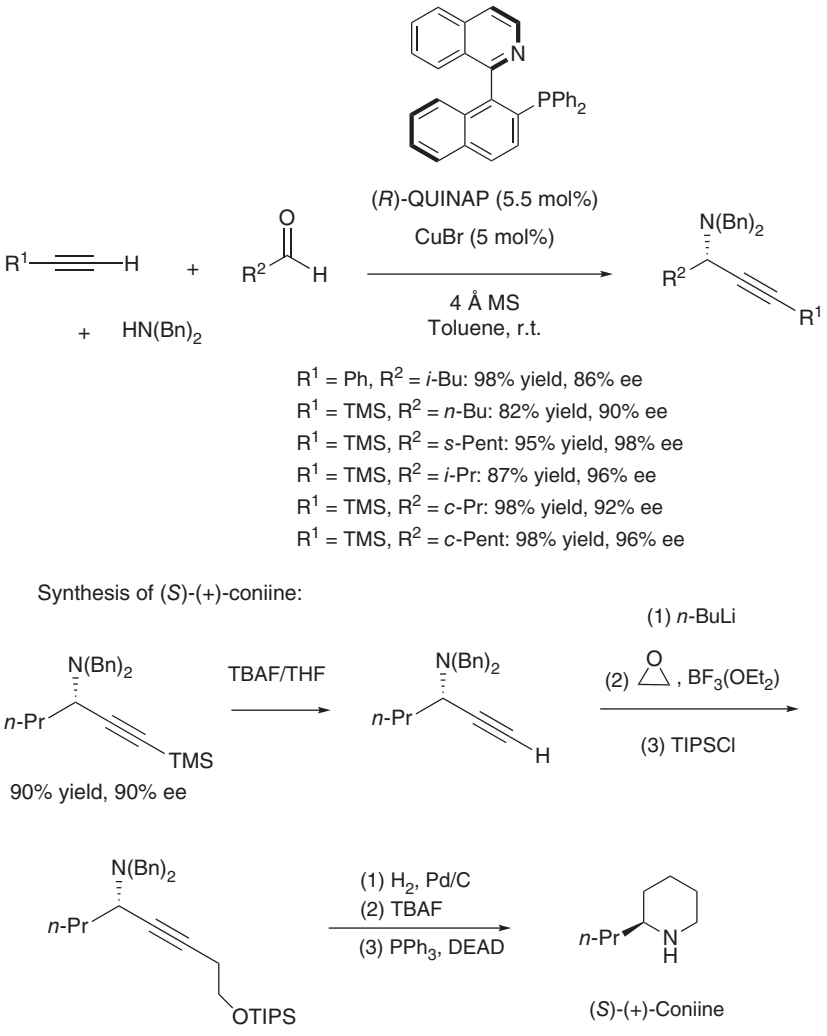
Multicomponent reactions are defined as domino processes involving more than two starting reagents that form a single product containing the essential parts of the starting materials [2]. These reactions involve the simultaneous addition of reactants, reagents, and catalyst at the beginning of the reaction and do not require adjustment of the reaction conditions throughout the process



X = O, CH_2
n = 1–2
R^1 = Ph, Me, Et, n-Pr, n-Bu, n-Pent, n-Hex, Br, OMe
R^2 = Ph, p-$MeOC_6H_4$, p-ClC_6H_4, m-BrC_6H_4, p-Tol, 2-furyl
R^3 = Ph, p-Tol, p-FC_6H_4, p-BrC_6H_4

Scheme 1.22 Domino Kinugasa/Michael reaction of alkyne-tethered cyclohexadienones with nitrones.

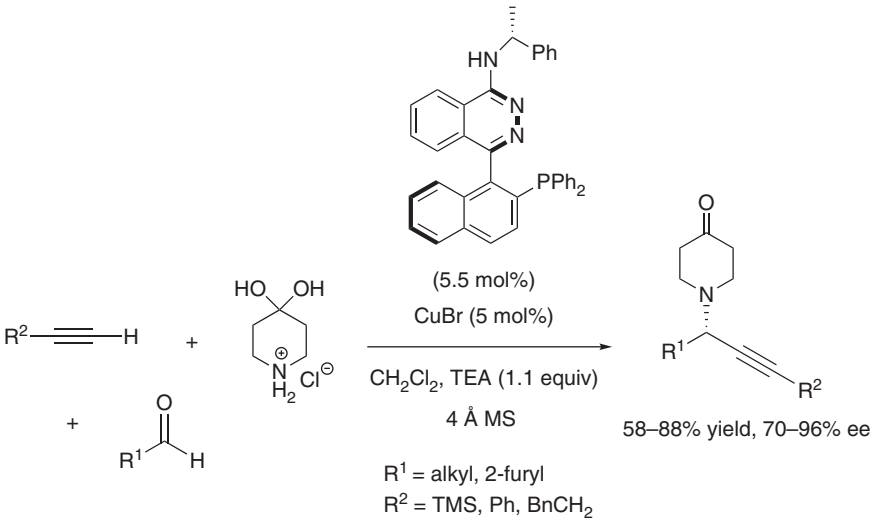
in conformity with the concept of domino reactions. They represent a pivotal step in the development of modern chemistry and have already been used in the synthesis of a range of biologically important products. Although most of the established metal-catalyzed multicomponent reactions are based on the use of copper or palladium catalysts, the search for new multicomponent products has resulted in the increasing development of novel catalytic systems. Especially, with the growing interest in green chemistry, multicomponent reactions promoted by green copper catalysts represent a challenge in organic chemistry. Among these reactions, the copper-catalyzed three-component reaction among terminal alkynes, aldehydes, and amines, producing chiral propargylamines, has been investigated by several groups. In 2006, Knochel and coworker employed a combination of CuBr as precatalyst with (*R*)-QUINAP as ligand to promote the reaction with secondary amines, such as dibenzylamine, which led to the corresponding propargylamines in both excellent yields (82–98%) and enantioselectivities (86–98% ee) [36]. As shown in Scheme 1.23, the best results were obtained for silylated propargylamines. The applicability of these products in the synthesis of natural products was demonstrated in a total synthesis of the alkaloid (*S*)-(+)-coniine. As depicted in Scheme 1.23, one domino product (R^1 = TMS, R^2 = n-Pr) could be converted into (*S*)-(+)-coniine through six steps. In the first step, the latter was desilylated by treatment with TBAF to give the corresponding alkyne, which was subsequently deprotonated with n-BuLi and then alkylated with ethylene oxide. After silylation of the resulting alcohol with TIPSCl, the corresponding TIPS ether was formed. Then, the latter was



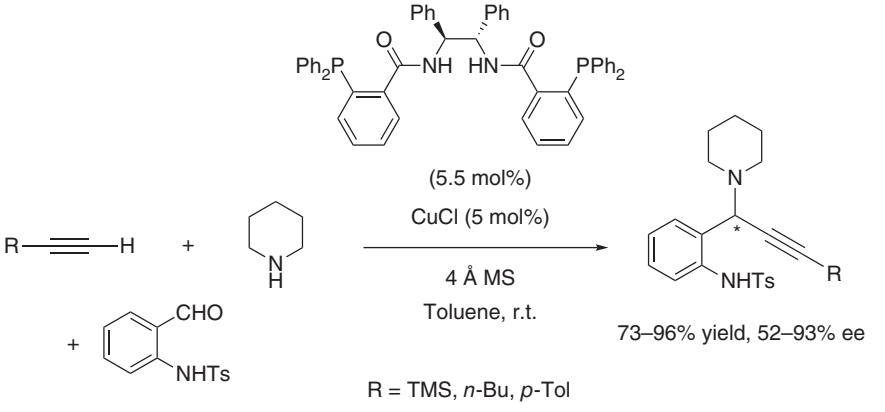
Scheme 1.23 Three-component reaction of alkynes, aldehydes, and dibenzylamine and synthesis of (*S*)-(+)-coniine.

successively submitted to hydrogenation on Pd/C, desilylation with Bu_4NF, and intramolecular Mitsunobu reaction to finally yield (*S*)-(+)-coniine.

In the same area, Carreira and coworkers developed in the same year the enantioselective three-component reaction of aldehydes and alkynes with 4-piperidone hydrochloride hydrate, which led to the corresponding tertiary propargylamines in both moderate to high yields (58–88%) and enantioselectivities (70–96% ee), as illustrated in Scheme 1.24 [37]. The reaction employed a (*R,R*)-*N*-PINAP as the chiral ligand of CuBr. It was found that use of 4-piperidone as the amine component not only provided access to a useful building block but also highlighted the excellent chemoselectivity of the process.



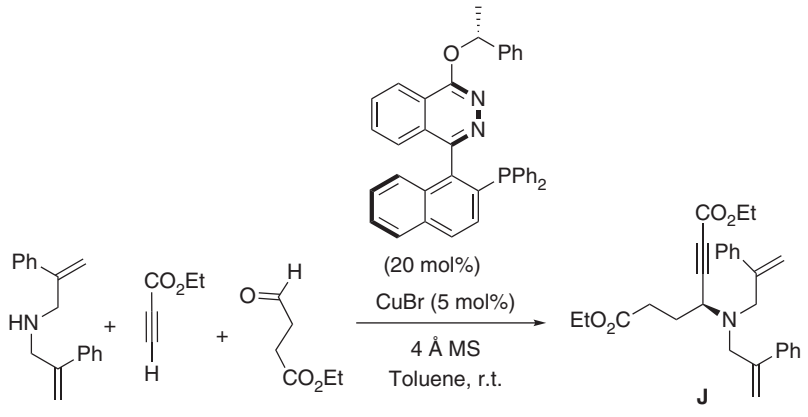
Scheme 1.24 Three-component reaction of alkynes, aldehydes, and 4-piperidone hydrochloride hydrate.



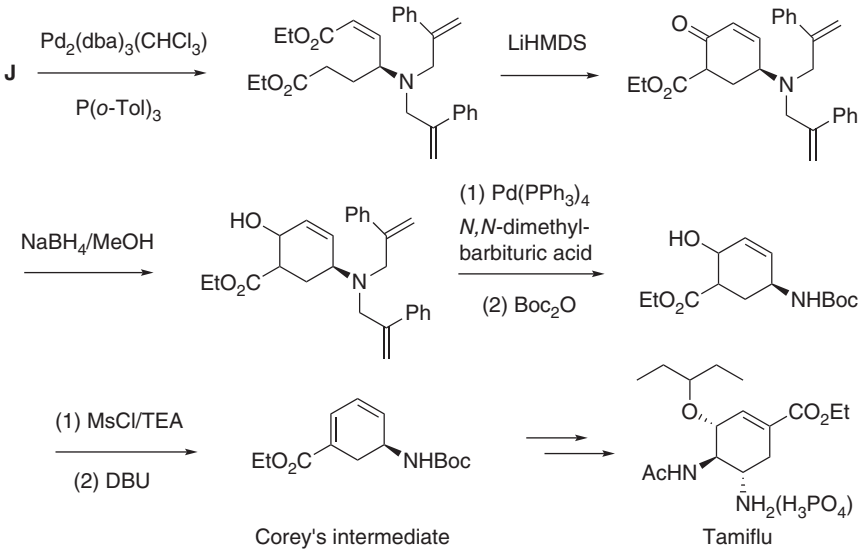
Scheme 1.25 Three-component reaction of alkynes, *N*-(2-formylphenyl)-4-methylbenzenesulfonamide, and piperidine.

Later in 2010, Gevorgyan and coworkers developed an efficient synthesis of chiral 3-aminoindolines, the key step of which was the enantioselective copper-catalyzed three-component reaction of piperidine, alkynes, and *N*-(2-formylphenyl)-4-methylbenzenesulfonamide (Scheme 1.25) [38]. This reaction was promoted by a combination of CuCl with Trost's C_2-symmetric biphosphine ligand, providing the corresponding key propargylamines in good yields (73–96%) and moderate to high enantioselectivities (52–93% ee). These products were subsequently transformed into the expected chiral indolines through desilylation followed by copper-catalyzed cyclization.

In 2013, Watanabe, Shibasaki, and coworkers developed an enantioselective copper-catalyzed three-component reaction of bis(2-phenylallyl)amine, ethyl propiolate, and an aldehyde as the key step of a total synthesis of oseltamivir phosphate (Tamiflu) [39]. The reaction was promoted by a chiral copper catalyst *in situ* generated from CuBr and a (*R,R*)-*O*-PINAP as ligand. As shown in Scheme 1.26, the desired Corey's intermediate **J** was achieved in 84% yield and moderate enantioselectivity (76% ee) by catalyzing the domino reaction with a combination of CuBr and a chiral (*R,R*)-*O*-PINAP ligand. Compound



Synthesis of Tamiflu:

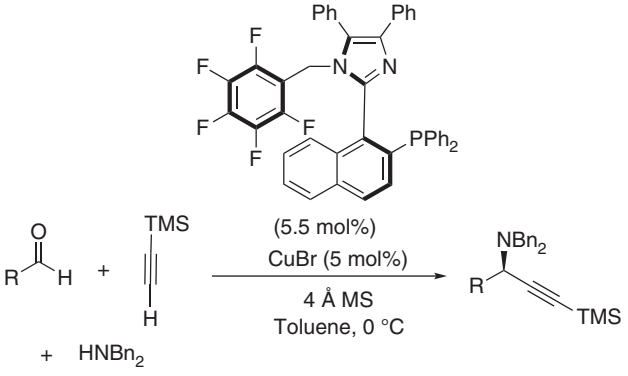


Scheme 1.26 Three-component reaction of ethyl propiolate, an aldehyde, and bis(2-phenylallyl)amine and synthesis of Tamiflu.

J was converted through a seven-step sequence into Corey's intermediate for the total synthesis of Tamiflu. The first step of the sequence dealt with the poisoned palladium-catalyzed hydrogenation of the domino product **J** into the corresponding triene followed by Dieckmann condensation in the presence of LiHMDS to give the corresponding six-membered compound. The ketone functionality of the latter was further reduced with $NaBH_4$ to form the corresponding alcohol. Then, the two 2-phenylallyl groups of this alcohol were removed by allylic substitution in the presence of $Pd(PPh_3)_4$ and *N,N*-dimethylbarbituric acid as nucleophile, which was followed by the introduction of the Boc group to yield the corresponding *N*-Boc-protected amine. Finally, mesylation of the latter followed by subsequent β-elimination afforded Corey's intermediate for the total synthesis of Tamiflu.

In 2013, another chiral P,N-ligand was employed by Aponick and coworkers to promote comparable reactions among dibenzylamine, aldehydes, and trimethylsilylacetylene [40]. As shown in Scheme 1.27, the domino reaction led to a range of chiral propargylamines with low to high yields (15–95%) and uniformly high enantioselectivities (89–97% ee). The best yields (92–95%) were achieved in the reaction of aliphatic aldehydes while (hetero)aromatic aldehydes provided the corresponding products in lower yields (15–80%). On the other hand, the enantioselectivities were found to be homogeneously excellent for all types of aldehydes.

In 2014, Ma and coworkers investigated the use of tetrahydroisoquinolines as the amine partners in these reactions [41]. The three-component reaction of

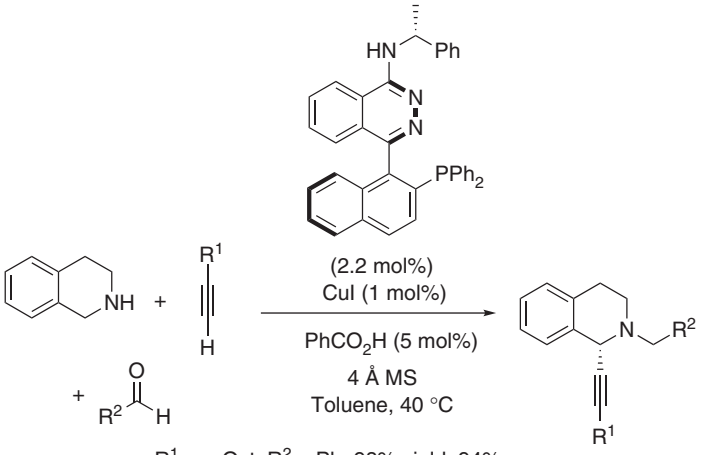


R = Cy: 95% yield, 97% ee
R = *i*-Pr: 92% yield, 95%ee
R = *n*-Pr: 92% yield, 89% ee
R = Ph: 80% yield, 94% ee
R = *p*-$MeOC_6H_4$: 77% yield, 94% ee
R = 2-thienyl: 60% yield, 94% ee
R = *p*-$F_3CC_6H_4$: 15% yield, 95% ee
at 22 °C (24 h):
R = *p*-$F_3CC_6H_4$: 70% yield, 92% ee

Scheme 1.27 Three-component reaction of trimethylsilylacetylene, aldehydes, and dibenzylamine.

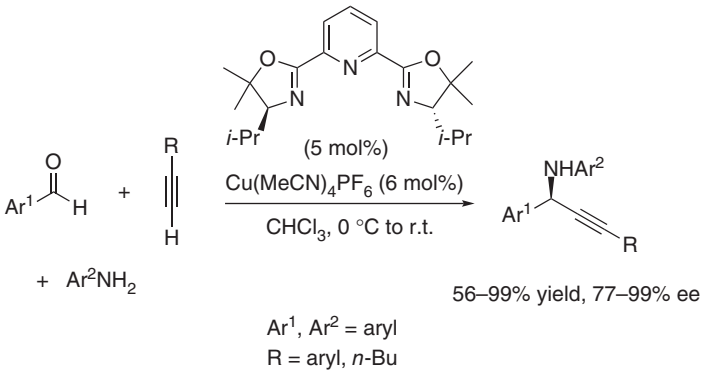
unsubstituted tetrahydroisoquinoline, aldehydes, and alkynes produced the corresponding chiral tetrahydroisoquinoline-alkaloid derivatives. When the process was promoted by a combination of only 1 mol% of CuI and 2.2 mol% of another chiral N,P-ligand, such as a (*R,R*)-*N*-PINAP ligand, in the presence of benzoic acid as an additive, a range of chiral α-alkynylated tetrahydroisoquinolines were obtained in both excellent yields (80–98%) and enantioselectivities (91–95% ee), as illustrated in Scheme 1.28. All types of alkynes including (functionalized) aliphatic and aromatic ones provided comparable excellent results. Concerning the scope of the aldehydes, aliphatic, aromatic, as well as heteroaromatic ones also provided comparable excellent yields and enantioselectivities. It must be noted that this methodology presents the advantage of employing a low catalyst loading, combined with broad scope and efficiency.

Comparable reactions have also been performed with primary amines. For example, in 2006 Singh and coworker reported the same type of three-component reaction with anilines in the presence of a combination of $Cu(I)PF_6$ and a chiral C_2-symmetric Pybox ligand [42]. This process could be applied to a wide variety of aromatic aldehydes, leading to the corresponding aromatic alkynylamines with good to excellent yields (56–99%) and enantioselectivities (77–99% ee), as shown in Scheme 1.29. It must be noted that Benaglia and coworkers also



R^1 = *n*-Oct, R^2 = Ph: 98% yield, 94% ee
R^1 = Cy, R^2 = Ph: 94% yield, 95% ee
R^1 = CH_2CO_2Me, R^2 = Ph: 91% yield, 91% ee
R^1 = $(CH_2)_2OTBS$, R^2 = Ph: 96% yield, 93% ee
R^1 = R^2 = Ph: 94% yield, 95% ee
R^1 = *p*-FC_6H_4, R^2 = Ph: 95% yield, 94% ee
R^1 = *p*-$MeOC_6H_4$, R^2 = Ph: 97% yield, 93% ee
R^1 = *n*-Oct, R^2 = *p*-Tol: 95% yield, 94% ee
R^1 = *n*-Oct, R^2 = *p*-FC_6H_4: 97% yield, 95% ee
R^1 = *n*-Oct, R^2 = 2,6-$Cl_2C_6H_3$: 89% yield, 93% ee
R^1 = *n*-Oct, R^2 = *N*-Ts-indole-3-: 80% yield, 92% ee

Scheme 1.28 Three-component reaction of alkynes, aldehydes, and unsubstituted tetrahydroisoquinoline.

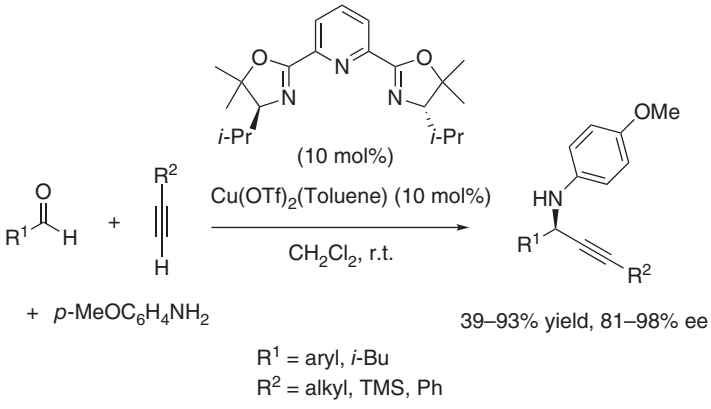


Scheme 1.29 Three-component reaction of alkynes, aldehydes, and anilines.

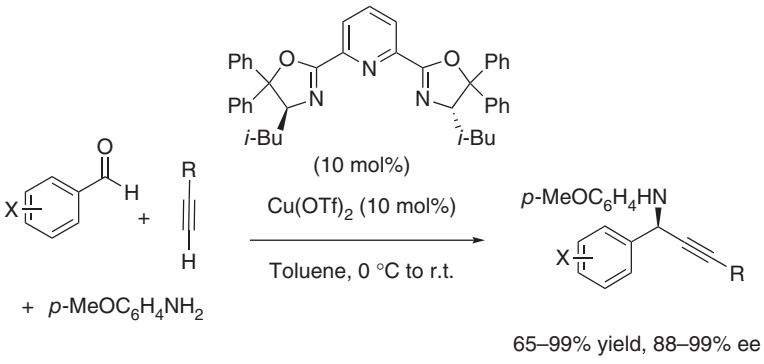
studied the three-component reaction of phenylacetylene with anilines and aldehydes upon catalysis by copper complexes of chiral bis-imines [43]. The best enantioselectivities of ≤75% ee were obtained by using a chiral bis-imine readily prepared from commercially available binaphthyl diamine. In addition, comparable levels of enantioselectivity (≤74% ee) were reported by Chan and coworkers for the three-component reaction of ethyl glyoxylate, *p*-anisidine, and aliphatic, aromatic alkynes catalyzed by a combination of $CuOTf(C_6H_6)_{0.5}$ with another chiral Pybox ligand [44].

In 2010, Nakamura et al. extended the scope of this type of reaction to the use of various aliphatic terminal alkynes [45]. The reaction of the latter with a range of aldehydes and *p*-anisidine afforded, in the presence of a catalytic amount of a combination of $Cu(OTf)_2$ with the same chiral C_2-symmetric Pybox ligand, the corresponding chiral amines in moderate to high yields (39–93%) and high enantioselectivities (81–98% ee), as illustrated in Scheme 1.30.

In 2012, Singh and coworker reported the asymmetric three-component reaction of alkynes, benzaldehydes, and *p*-anisidine catalyzed by 10 mol% of a combination of $Cu(OTf)_2$ with a more sterically hindered chiral Pybox ligand



Scheme 1.30 Three-component reaction of alkynes, aldehydes, and *p*-anisidine.



R = Ph, *n*-Bu, *p*-Tol, *p*-$MeOC_6H_4$, *p*-BrC_6H_4, *p*-(*n*-Pent)C_6H_4, CH_2Bn
X = H, 4-F, 2-Cl, 2,4-Me_2

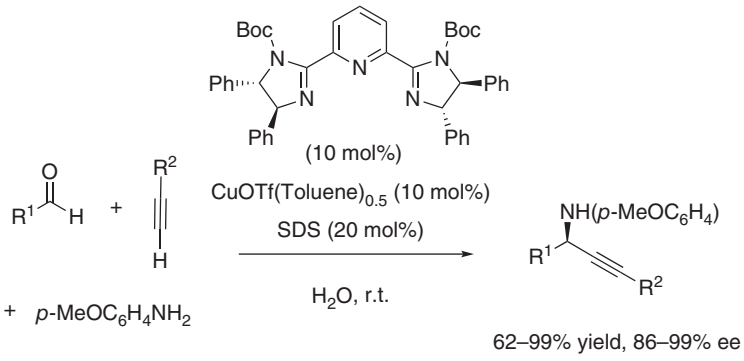
Scheme 1.31 Three-component reaction of alkynes, benzaldehydes, and *p*-anisidine.

in Toluene [46]. As shown in Scheme 1.31, a range of chiral aromatic as well as aliphatic propargylamines were formed in good yields (65–99%) and uniformly high enantioselectivities (88–99% ee) for all substituted alkynes investigated.

Later in 2014, these reactions were reinvestigated by Nakamura and coworkers by employing a related tuned Pybox-derived ligand bearing a hydrophobic substituent, allowing these reactions to be performed in water [47]. The use of 10 mol% of this sterically hindered ligand in combination with the same quantity of $CuOTf(Toluene)_{0.5}$ as precatalyst in water at room temperature in the presence of SDS as surfactant in this domino reaction provided a range of chiral propargylamines in high enantioselectivities (86–99% ee) and moderate to quantitative yields (62–99%), as shown in Scheme 1.32. In addition to its simple and environmentally friendly conditions, this process offered a remarkably wide scope, allowing a range of aliphatic as well as aromatic alkynes and aldehydes to react smoothly.

With the aim of finding other environmentally friendly conditions for this type of reactions, Su and coworker reported in 2015 their development under solvent-free high-vibration ball-milling conditions [48]. As shown in Scheme 1.33, the solvent-free three-component reactions of benzaldehydes, alkynes, and anilines catalyzed by a combination of $Cu(OTf)_2$ and a more simple chiral Pybox ligand by ball-milling were achieved within 60 minutes, yielding a wide range of chiral propargylamines in uniformly excellent yields (90–99%) and enantioselectivities (83–99% ee) starting from aromatic aldehydes, anilines, and aliphatic as well as aromatic alkynes. Another advantage of this original process was that the catalyst system could be easily recovered and reused five times without losing its performance.

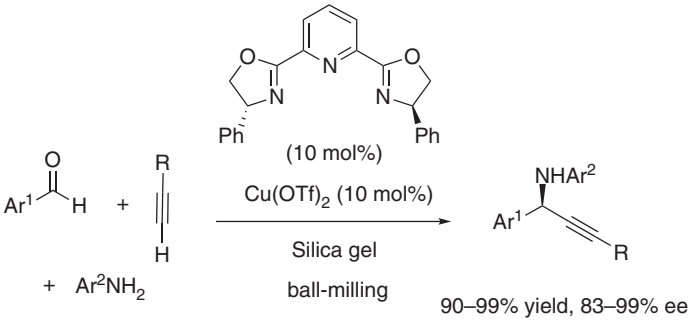
In order to develop a general catalytic system for the direct synthesis of diversely substituted chiral isoindolinones exhibiting biological importance, Singh and coworkers reported in 2014 an unprecedented asymmetric three-component domino alkynylation/lactamization reaction (Scheme 1.34) [49]. This process occurred among *o*-formyl methyl benzoates, alkynes, and arylamines



R^1 = Ph, Cy, *p*-$MeOC_6H_4$, *o*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *o*-ClC_6H_4, *p*-ClC_6H_4, *m*-ClC_6H_4, 1-Naph
R^2 = CH_2Bn, *n*-Pr, *n*-Bu, *n*-Hex, *n*-Oct, Cy, *c*-Pent, *c*-Pr, $(CH_2)_2Br$, $(CH_2)_2OH$, $C(CH_2)_2OH$, Ph

SDS, sodium dodecyl sulfate

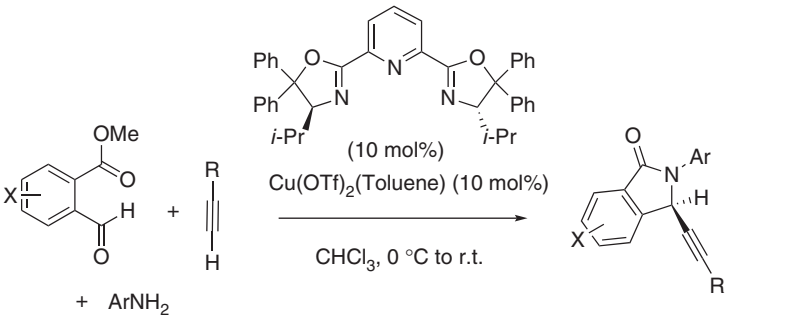
Scheme 1.32 Three-component reaction of alkynes, aldehydes, and *p*-anisidine in water.



Ar^1 = Ph, *p*-Tol, 3,4-$Me_2C_6H_3$, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *m*-Tol, *m*-ClC_6H_4, *p*-$MeOC_6H_4$, *p*-$O_2NC_6H_4$, *m*-$O_2NC_6H_4$, 1-Naph
Ar^2 = Ph, *p*-Tol, *p*-EtC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-$MeOC_6H_4$
R = Ph, *p*-Tol, *c*-Pr, *n*-Pent

Scheme 1.33 Three-component reaction of alkynes, benzaldehydes, and anilines under solvent-free high-vibration ball-milling.

in the presence of a chiral copper complex derived from a highly substituted Pybox ligand in chloroform. After alkynylation of the *in situ* formed imine, subsequent lactamization of the propargylamine intermediate occurred to give the final isoindolinone. The best results were obtained by using aniline and *p*-anisidine as amines of choice, and aldehydes bearing no substituent at the *ortho* position (X = H). Concerning the alkyne partners, a wide range of



Ar = Ph, *p*-$MeOC_6H_4$, *p*-$MeSC_6H_4$
R = *p*-Tol, *p*-$MeOC_6H_4$, *p*-FC_6H_4, 3,4-$(MeO)_2C_6H_3$, *n*-Bu, *n*-Hex, *n*-Oct, Ph, H, MeO
X = H, 5-Br, 5-Ph, 5-NO_2, 5-CN, 4,5-$(MeO)_2$, 3,5-$(MeO)_2$, 3,4,5-$(MeO)_3$, 2,3-$(MeO)_2$

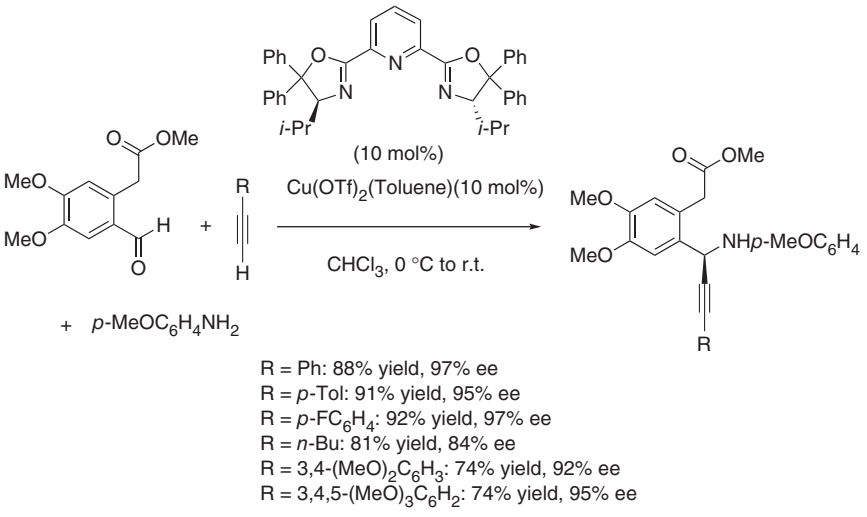
Scheme 1.34 Three-component domino alkynylation/lactamization reaction of alkynes, *o*-formyl methyl benzoates, and anilines.

alkynes bearing an aromatic ring or an aliphatic side chain were tolerated with high enantioselectivities. Notably, alkynes with aromatic rings containing both electron-donating and electron-withdrawing groups afforded the domino products with high enantioselectivities of up to >99% ee. Even with aliphatic terminal alkynes, the process provided uniformly high enantioselectivities (82–90% ee).

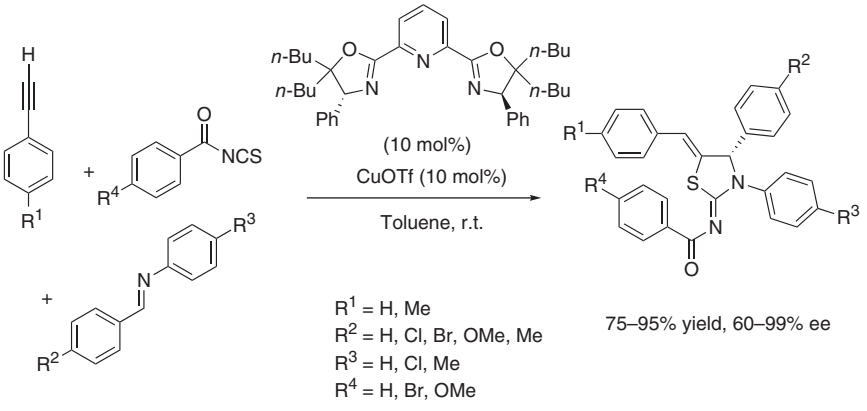
With the aim of extending the scope of this methodology to the synthesis of C1-substituted isoquinolinones for the construction of various synthetically important tetrahydroisoquinolines, the authors further investigated the reaction of methyl (6-formyl-3,4-dimethoxyphenyl)acetate with *p*-methoxyphenylamine and various alkynes under the same reaction conditions [49]. However, the results were disappointing since only uncyclized products were produced, but in fairly good yields (74–92%) and with uniformly high enantioselectivities (84–97% ee), as presented in Scheme 1.35.

1.3.1.2 Other Alkyne Couplings

In 2015, Dethe and coworkers reported an enantioselective copper-catalyzed three-component reaction among terminal aromatic alkynes, aryl imines, and aryl isothiocyanates, allowing the synthesis of chiral five-membered thiazolidine-2-imines to be achieved [50]. The process was promoted in Toluene at room temperature by a chiral copper catalyst *in situ* generated from 10 mol% of CuOTf and the same quantity of a sterically hindered Pybox ligand. It produced a range of chiral thiazolidine-2-imines with moderate to excellent enantioselectivities (60–99% ee) and good yields (75–95%), as shown in Scheme 1.36. The reaction began with the addition of the alkyne to the chiral copper catalyst-activated iminium ion to generate a propargylamine, which further reacted with the isothiocyanate through an addition/intramolecular hydrothiolation sequence in which the isothiocyanate played a dual role as an electrophile and nucleophile to construct a thiazolidine-2-imine.



Scheme 1.35 Three-component reaction of alkynes, an *o*-formyl methyl benzoate, and *p*-anisidine.



Scheme 1.36 Three-component reaction of alkynes, imines, and isothiocyanates.

1.3.2 Reactions Initiated by Michael Additions

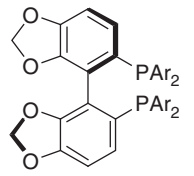
The first example of enantioselective copper-catalyzed three-component domino reductive Michael/aldol reactions was reported by Shibasaki and coworkers in 2006 [51]. While copper-catalyzed reductive Michael/aldol reactions between acetophenone and methyl acrylate, performed in the presence of pinacolborane as the reducing agent, provided the corresponding tertiary alcohol in only moderate enantioselectivities (≤30% ee) in all cases of chiral ligands investigated, reductive Michael/aldol reactions between symmetric ketones and β-disubstituted α,β-unsaturated esters afforded selectively the corresponding α-products in low to good enantioselectivities (29–80% ee) when catalyzed by a copper complex derived from (*R*)-Tol-BINAP. Moreover, high enantioselectivities

of up to 99% ee were obtained in the reaction of allenic ethyl ester with ketones (Scheme 1.37, first equation). When catalyzed by a copper(I) complex derived from (*R*)-DTBM-Segphos, the process was γ-*cis*-selective since the corresponding tertiary alcohols were obtained as single products in both high yields (80–96%) and enantioselectivities (88–99% ee), as illustrated in Scheme 1.37 (first equation). Surprisingly, the α- or γ-selectivity of the reaction could be switched depending on the structure of the chiral diphosphine ligands employed. For example, the use of a copper(I) complex of Taniaphos ligands rendered the reaction α-selective and provided the corresponding tertiary alcohols in high yields (86–91%) and enantioselectivities (66–84% ee), as shown in Scheme 1.37.

In 2006, Riant and coworkers employed other chiral Taniaphos-based ligands to promote the copper(I)-catalyzed domino reductive Michael/aldol reaction of methyl acrylate with aldehydes using phenylsilane as the reducing agent [52]. In spite of a high chemoselectivity, the process provided moderate *syn*-diastereoselectivities (≤76% de). On the other hand, good to excellent enantioselectivities of up to 97% ee were obtained in the reaction of a variety of cyclic aliphatic, aromatic, and heteroaromatic aldehydes (Scheme 1.38, first equation). A related methodology was applied to the reductive Michael/aldol reactions of methyl acrylate with ketones [53]. Thus, the reaction of ketones with methyl acrylate and phenylsilane evolved chemoselectively by using a closely related chiral Taniaphos ligand (Scheme 1.38, second equation) to yield the corresponding tertiary alcohols as mixtures of *erythro*- and *threo*-diastereomers. The major *erythro*-isomers were formed in good to high enantioselectivities (82–95% ee) combined with moderate to good diastereoselectivities (72–84% de).

In 2009, Fukuzawa and coworkers reported an enantioselective three-component domino reductive Michael/aldol reaction among ketones, methyl acrylate, and phenylsilane catalyzed by 1 mol% of a copper(I)–ClickFerrophos complex in Toluene at −50 °C [54]. It yielded the corresponding chiral tertiary alcohols in low to excellent yields (36–93%) and good to high enantioselectivities (73–85% ee). These domino products were formed as major *erythro*-diastereomers with uniformly high diastereoselectivity levels (82–98% de), as shown in Scheme 1.39.

In 2007, Shibasaki and coworkers described the synthesis of chiral highly functionalized δ-lactones through enantioselective three-component domino Michael/aldol/lactonization reactions between dialkylzincs, allenic ethyl ester, and unactivated ketones (Scheme 1.40) [55]. The processes were performed in the presence of a combination of $Cu(OAc)_2$ as precatalyst and (*R*)-DIFLUORPHOS as ligand. The reaction began with the conjugate addition of an alkyl-copper species to the allenic ester to give a highly active copper enolate. The latter subsequently underwent an asymmetric aldol addition to the ketone followed by lactonization, leading to the final lactone in moderate to high yields (67–92%) and uniformly excellent enantioselectivities (92–98% ee), as presented in Scheme 1.40. The use of an additive, such as DMSO, HMPA, or $Ph_2S{=}O$, was found significant for obtaining high yields, with suppression of the undesired α-addition pathway. Later in 2009, the same authors reported an enantioselective three-component domino reductive Michael/aldol reaction occurring between 3-phenyl-2-cyclohexen-1-one, benzaldehyde, and pinacolborane [56]. In the



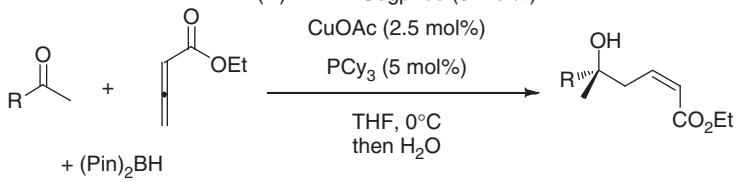
Ar = 4-MeO–3,5-(*t*-Bu)$_2$C$_6$H$_2$

(*R*)-DTBM-Segphos (5 mol%)

CuOAc (2.5 mol%)

PCy$_3$ (5 mol%)

THF, 0°C
then H_2O

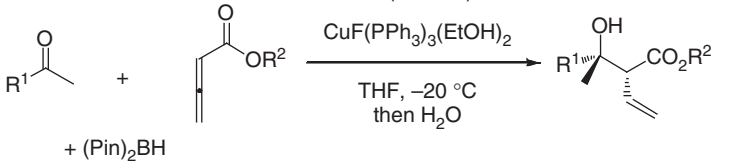


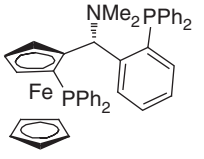
R = Ph: 96% yield, 99% ee
R = *p*-ClC$_6$H$_4$: 93% yield, 98% ee
R = *p*-Tol: 90% yield, 97% ee
R = *m*-ClC$_6$H$_4$: 90% yield, 99% ee
R = Bn: 70% yield, 96% ee
R = *n*-Bu: 86% yield, 88% ee
R = *i*-Pr: 80% yield, 98% ee

L* (5 mol%)

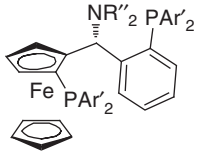
CuF(PPh$_3$)$_3$(EtOH)$_2$

THF, –20 °C
then H_2O



with L* = 

: R^1 = Ph, R^2 = Et: 86% yield, 66% ee

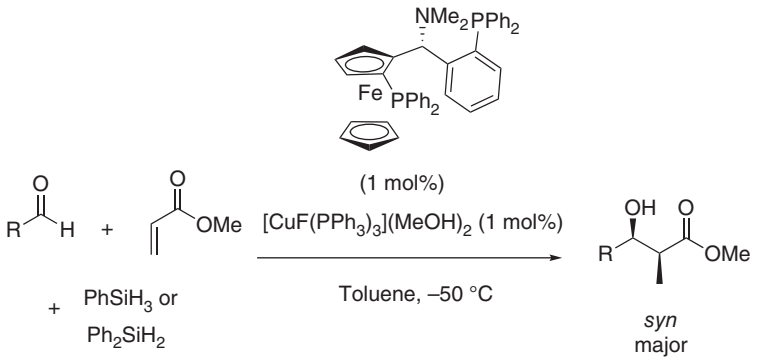
with L*= 

:

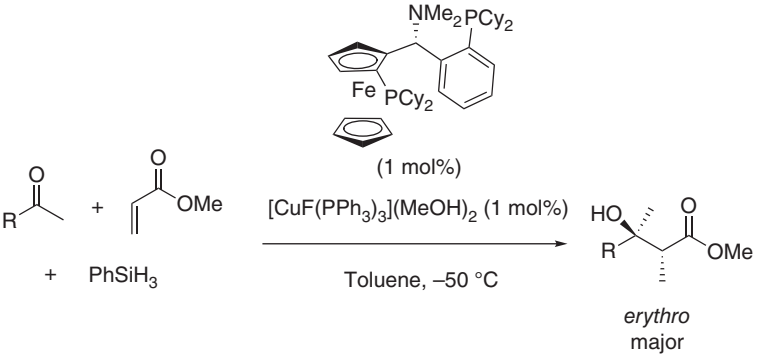
R^1 = Ph, R^2 = Me: 90% yield, 84% ee
R^1 = *p*-ClC$_6$H$_4$, R^2 = Me: 89% yield, 83% ee
R^1 = *m*-ClC$_6$H$_4$, R^2 = Me: 89% yield, 82% ee
R^1 = *p*-IC$_6$H$_4$, R^2 = Me: 86% yield, 84% ee
R^1 = 2-Naph, R^2 = Me: 91% yield, 84% ee

R″$_2$ = (CH$_2$)$_2$O(CH$_2$)$_2$–,
Ar′ = 3,5-xylyl

Scheme 1.37 Three-component domino reductive Michael/aldol reactions of ketones, allenic esters, and pinacolborane.



R = Cy: 99% conversion, *syn*/*anti* = 88 : 12, ee (*syn*) = 97%
R = *p*-FC_6H_4: 99% conversion, *syn*/*anti* = 44 : 56, ee (*syn*) = 86%
R = *p*-ClC_6H_4: 99% conversion, *syn*/*anti* = 44 : 56, ee (*syn*) = 85%
R = *p*-$MeOC_6H_4$: 99% conversion, *syn*/*anti* = 60 : 40, ee (*syn*) = 68%

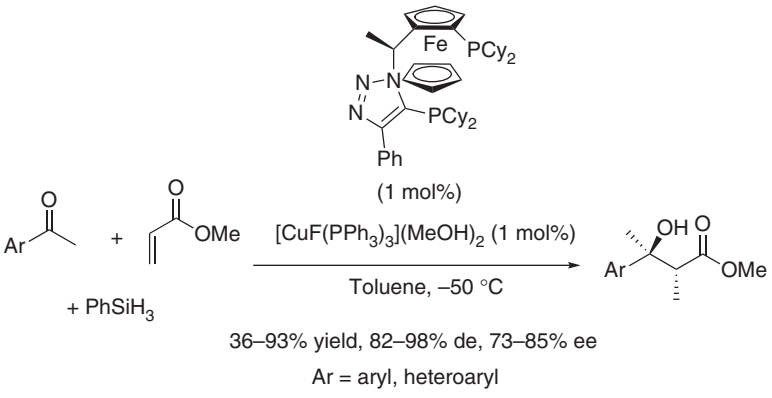


R = Ph: 98% yield, chemoselectivity >99%, *erythro*/*threo* = 92 : 8, ee (*erythro*) = 95%
R = *p*-FC_6H_4: 88% yield, chemoselectivity = 94%, *erythro*/*threo* = 91 : 9, ee (*erythro*) = 92%
R = *p*-$MeOC_6H_4$: 31% yield, chemoselectivity = 97%, *erythro*/*threo* = 92 : 8, ee (*erythro*) = 90%
R = *p*-ClC_6H_4: 95% yield, chemoselectivity = 95%, *erythro*/*threo* = 86 : 14, ee (*erythro*) = 90%
R = *m*-ClC_6H_4: 70% yield, chemoselectivity = 89%, *erythro*/*threo* = 88 : 12, ee (*erythro*) = 82%

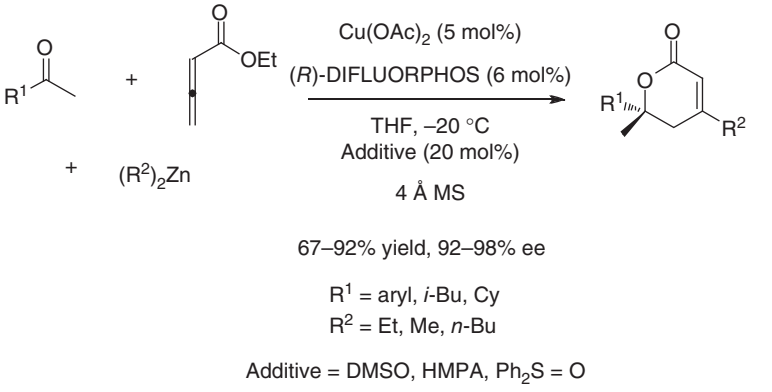
Scheme 1.38 Three-component domino reductive Michael/aldol reactions of aldehydes/ketones, methyl acrylate, and phenylsilane.

presence of a copper complex of a chiral diphosphine, the conjugate boration of the enone, followed by aldol condensation onto benzaldehyde, led to the corresponding chiral tertiary organoboric ester, which was directly oxidized into the corresponding diol in moderate yield (71%) and diastereoselectivity (74% de) combined with a high enantioselectivity (91% ee).

In 2008, Yus and coworkers reported the synthesis of enantiopure β-amino ketones on the basis of another type of Michael-initiated three-component domino reactions, such as a domino Michael/Mannich reaction occurring among dialkyl zinc reagents, cyclic enones, and chiral *N*-*tert*-butanesulfinimines and catalyzed by a copper complex of a chiral phosphoramidite ligand [57].



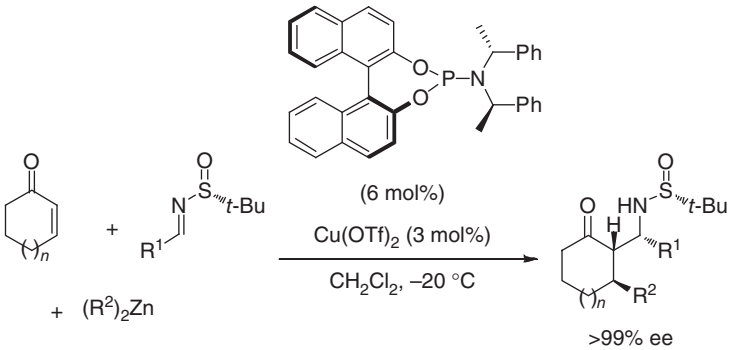
Scheme 1.39 Three-component domino reductive Michael/aldol reaction of ketones, methyl acrylate and phenylsilane.



Scheme 1.40 Three-component Michael/aldol/lactonization reaction of unactivated ketones, allenic ethyl ester, and dialkylzincs.

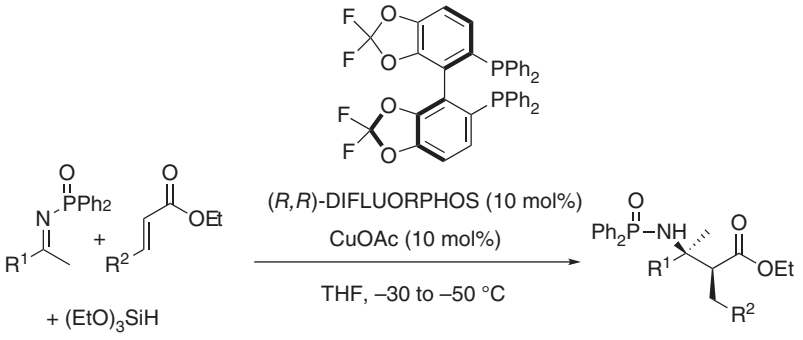
Three contiguous stereocenters could be generated in this process with excellent stereocontrol through a double asymmetric induction, arising from the chiral ligand and the chiral *N-tert*-butanesulfinimine, as shown in Scheme 1.41. The authors assumed that whereas the enantioselection at the cycle stereocenters was governed by the phosphoramidite auxiliary, in the case of the aminic α-C-stereocenter the asymmetric induction came from the *tert*-butylsulfinyl moiety. The enantiopure products were formed in moderate to excellent yields (65–95%), as shown in Scheme 1.41.

In 2008, a chiral copper(I) complex derived from (*R*)-DIFLUORPHOS was used by Shibasaki and coworkers to promote the first catalytic enantioselective reductive Michael/Mannich reaction of ketimines [58]. As illustrated in Scheme 1.42, the three-component reaction of ketimines, α,β-unsaturated esters, and $(EtO)_3SiH$ as the reducing agent led to the corresponding amines,



R^1 = Ph, R^2 = Et, *n* = 1 : 65% yield
R^1 = Ph, R^2 = Et, *n* = 2 : 66% yield
R^1 = *n*-Oct, R^2 = Et, *n* = 2 : 95% yield
R^1 = $BnCH_2$, R^2 = Et, *n* = 1 : 86% yield
R^1 = $BnCH_2$, R^2 = Me, *n* = 1 : 86% yield
R^1 = *n*-Oct, R^2 = *n*-Bu, *n* = 1 : 90% yield
R^1 = $(CH_2)_3CO_2Me$, R^2 = Et, *n* = 1 : 82% yield
R^1 = $(CH_2)_3CO_2Me$, R^2 = Et, *n* = 2 : 85% yield

Scheme 1.41 Three-component domino Michael/Mannich reaction of cyclic enones, chiral *N-tert*-butanesulfinimines, and dialkylzincs.



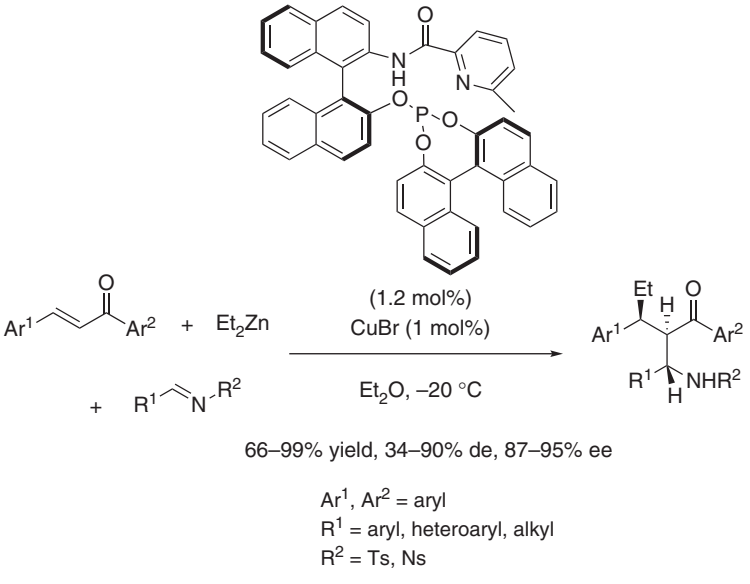
R^1 = Ph, *p*-ClC_6H_4, 2-Naph, 1-cyclohexenyl
R^2 = H, CO_2Et

Scheme 1.42 Three-component domino reductive Michael/Mannich reaction of ketimines, α,β-unsaturated esters, and $(EtO)_3SiH$.

containing contiguous tetra- and trisubstituted carbons, in both moderate to high yields (47–95%) and diastereoselectivities (50–94% de) combined with high enantioselectivities (82–93% ee). Interestingly, this methodology constituted the first entry to the catalytic asymmetric synthesis of $\beta^{2,3,3}$-amino acid derivatives.

In 2010, Huang and coworkers developed a highly diastereo- and enantioselective construction of three contiguous acyclic stereogenic centers through

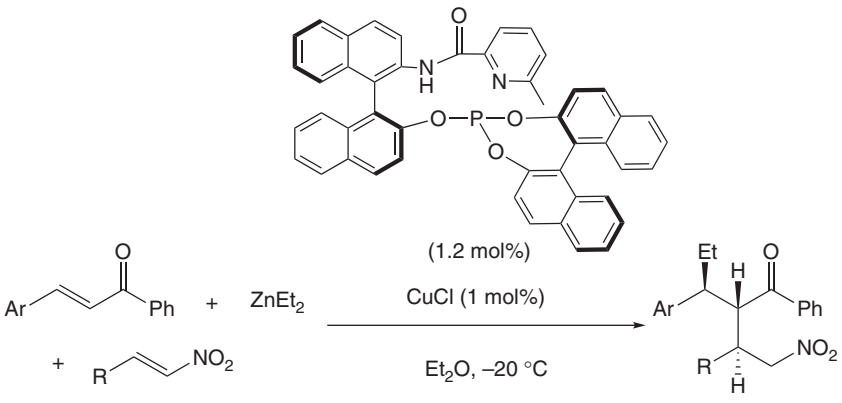
a copper-catalyzed three-component domino Michael/Mannich reaction occurring between acyclic α,β-unsaturated ketones, *N*-sulfonyl aldimines, and $ZnEt_2$ (Scheme 1.43) [59]. The process was catalyzed by a combination of CuBr as precatalyst with a chiral phosphite ligand and produced the corresponding β-aminocarbonyl derivatives in moderate to quantitative yields (66–99%), uniformly high enantioselectivities (87–95% ee), and low to high diastereoselectivities (34–90% de). The scope of the reaction was broad since both aromatic and aliphatic imines provided high enantioselectivities.



Scheme 1.43 Three-component domino Michael/Mannich reaction of *N*-sulfonyl aldimines, acyclic enones and diethylzinc.

In another area, Huang and coworkers developed in 2011 highly diastereo- and enantioselective three-component double Michael reactions, allowing a range of chiral functionalized pyrrolidines bearing three stereocenters to be achieved (Scheme 1.44) [60]. The process involved diethylzinc, α,β-unsaturated ketones and nitroalkenes as substrates, and was catalyzed by a combination of CuCl as precatalyst and the same chiral phosphite ligand. As shown in Scheme 1.44, the domino products were formed in both remarkable diastereo- (>90–>98% de) and enantioselectivities (94–97% ee), combined with moderate to high yields (55–88%). The dramatic effect of neutral copper in the domino reaction was disclosed, which provided evidence that the electrophilic nature of the catalyst precursor played a crucial role in the control of the stereoselectivity. This efficient methodology cumulates several advantages, such as the employment of a low catalyst loading of 1 mol%, a broad scope, and general excellent levels of diastereo- and enantioselectivities achieved in the control of three contiguous stereocenters.

The Henry reaction has been often associated to the Michael reaction in many successful asymmetric domino sequences [61]. For example, a novel highly



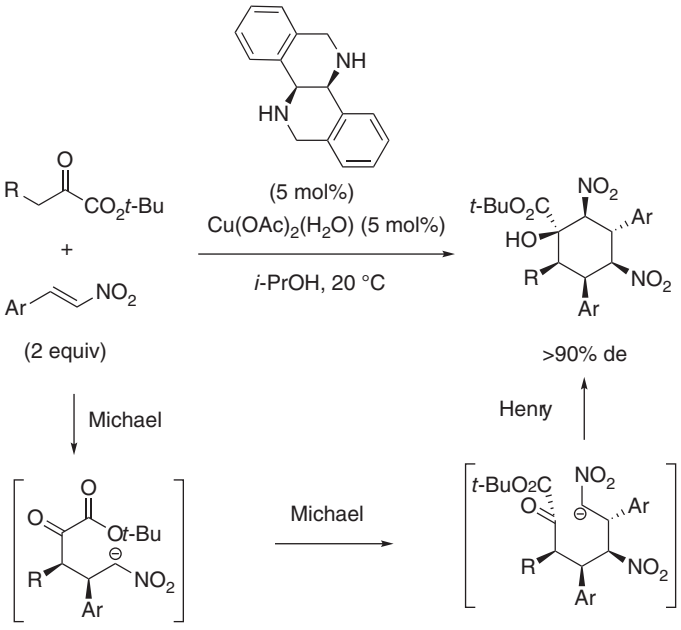
Ar = R = Ph: 82% yield, >98% de, 97% ee
Ar = Ph, R = *p*-BrC_6H_4: 80% yield, >90% de, 96% ee
Ar = Ph, R = *p*-FC_6H_4: 72% yield, >90% de, 97% ee
Ar = Ph, R = *p*-Tol: 78% yield, >90% de, 96% ee
Ar = Ph, R = *p*-$MeOC_6H_4$: 66% yield, >90% de, 95% ee
Ar = Ph, R = 1-Naph: 59% yield, >90% de, 97% ee
Ar = Ph, R = 2-furyl: 69% yield, >90% de, 96% ee
Ar = Ph, R = Cy: 55% yield, >90% de, 96% ee
Ar = Ph, R = AcNH: 68% yield, >90% de, 94% ee
Ar = Ph, R = (*E*)-PhCH=CH: 55% yield, >90% de, 97% ee
Ar = *p*-$MeOC_6H_4$, R = Ph: 64% yield, >90% de, 95% ee
Ar = *p*-ClC_6H_4, R = Ph: 87% yield, >90% de, 96% ee
Ar = *p*-FC_6H_4, R = Ph: 88% yield, >90% de, 97% ee
Ar = *p*-$MeOC_6H_4$, R = *p*-BrC_6H_4: 81% yield, >90% de, 95% ee

Scheme 1.44 Three-component domino double Michael reaction of α,β-unsaturated ketones, nitroalkenes, and diethylzinc.

enantio- and diastereoselective copper-catalyzed domino Michael/Michael/Henry reaction was reported by Huang and coworkers in 2012 [62]. This pseudo-three-component reaction involved 2 equiv of nitroalkenes and α-ketoesters, which afforded the corresponding highly functionalized cyclohexane carboxylates, exhibiting six stereogenic centers including one quaternary, in uniformly excellent diastereo- (>90% de) and enantioselectivities (94–98% ee) combined with moderate to excellent yields (42–95%) (Scheme 1.45). This formal [2+2+2]-annulation provided the best results when catalyzed by a combination of $Cu(OAc)_2(H_2O)$ and a chiral 1,2-diamine ligand. The performance of this remarkable process was situated in the excellent general levels of diastereo- and enantioselectivities obtained to control six contiguous stereocenters in one step under mild conditions.

1.3.3 Reactions Based on 1,3-Dipolar Cycloadditions

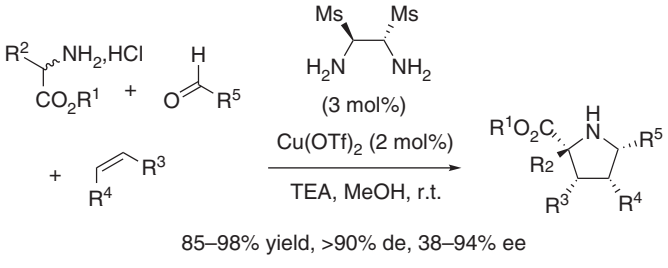
The 1,3-dipolar cycloaddition [63] between a dipolarophile and a 1,3-dipolar compound allows the production of important five-membered heterocycles to



Scheme 1.45 Pseudo-three-component domino Michael/Michael/Henry reaction of 2 equiv of nitroalkenes with α-ketoesters.

be achieved [64]. Among the metals used to catalyze these reactions [65], copper has been widely employed. As an example, Aron and coworkers developed in 2013 enantioselective copper-catalyzed three-component domino azomethine ylide formation/1,3-dipolar cycloaddition reactions of activated olefins with α-chelating aldehydes and amino acid esters [66]. These reactions employed low catalyst loadings of a commercially available chiral 1,2-diamine ligand (3 mol%), such as (*S,S*)-1,2-bismesitylene-1,2-ethylene-diamine and $Cu(OTf)_2$ (2 mol%), at room temperature in methanol as solvent. Chelating aldehydes, such as 4-substituted-2-picolinaldehydes and 4-methylthiazole-2-carboxaldehyde, reacted with a range of unprotected aminoesters derived from serine, methionine, tyrosine, tryptophan, and lysine to yield the corresponding intermediate azomethine ylides, which further underwent 1,3-dipolar cycloaddition with activated olefins, such as acrylonitrile, methyl acrylate, and dimethyl maleate, to afford the corresponding highly substituted chiral pyrrolidines bearing up to

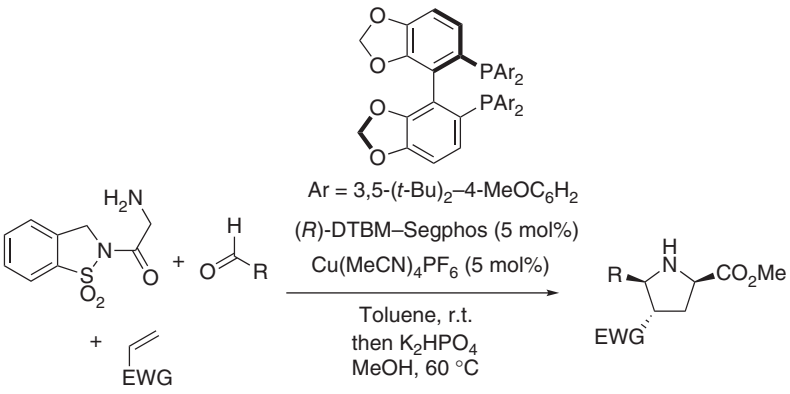
four stereogenic centers as almost single diastereomers (>90% de) in high yields (85–98%) and moderate to high enantioselectivities (38–94% ee), as presented in Scheme 1.46. It was found that nonaromatic and nonchelating aldehydes, such as benzaldehyde, 4-picolinaldehyde, and pivaldehyde, reacted sluggishly. On the other hand, the reaction displayed an excellent substrate scope with regard to the amino acid ester since a wide range of (functionalized) substituents (R^2) were compatible as well as bulky *tert*-butyl esters ($R^1 = t$-Bu).



Scheme 1.46 Three-component domino azomethine ylide formation/1,3-dipolar cycloaddition reaction of activated olefins, α-chelating aldehydes, and amino acid esters.

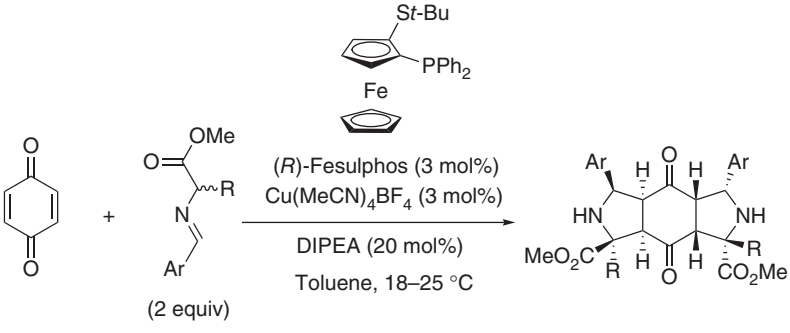
In 2014, Garner and coworkers reported asymmetric copper-catalyzed three-component domino azomethine ylide formation/1,3-dipolar cycloaddition reactions of activated olefins, aliphatic aldehydes, and glycyl sultam [67]. The process involved the *in situ* generation of azomethine ylides starting from the enolizable unbranched aliphatic aldehydes and the glycyl sultam, which subsequently reacted with the activated olefins through 1,3-dipolar cycloaddition to afford the corresponding chiral substituted pyrrolidines in moderate to good yields (46–85%), and good to complete diastereoselectivities (86–>98% de) and enantioselectivities (76–>98% ee), as shown in Scheme 1.47. The process was promoted in Toluene at room temperature by a chiral catalyst *in situ* generated from 5 mol% of $Cu(MeCN)_4PF_6$ and the same quantity of (*R*)-DTBM-Segphos as ligand. To simplify the purification of the products, the cycloadducts were subsequently converted by treatment with K_2HPO_4 into their corresponding methyl esters.

Earlier in 2012, Waldmann and coworkers described the development of an asymmetric pseudo-three-component synthesis of highly structurally complex chiral molecular architectures through two consecutive 1,3-dipolar cycloadditions of azomethine ylides derived from imines with *p*-benzoquinone [68].



Scheme 1.47 Three-component domino azomethine ylide formation/1,3-dipolar cycloaddition reaction of activated olefins, aliphatic aldehydes, and a glycyl sultam.

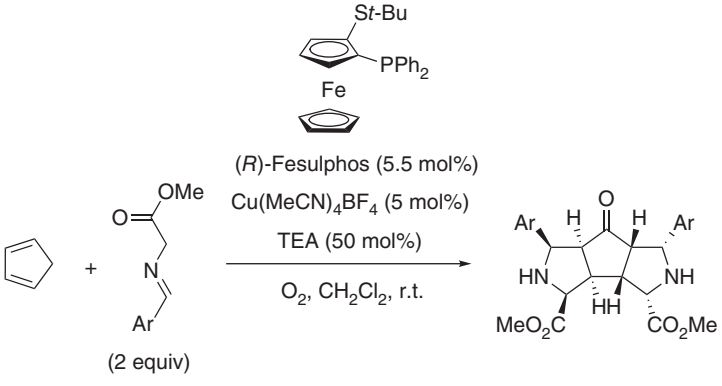
The domino reaction was promoted in Toluene at 18–25 °C by 3 mol% of a chiral catalyst *in situ* generated from $Cu(MeCN)_4BF_4$ and (*R*)-Fesulphos as ligand. In this remarkable domino reaction performed under mild reaction conditions, four new carbon–carbon bonds and eight stereogenic centers were produced with very high regio-, diastereo- and enantioselectivities, allowing the highly selective formation of one stereomer among 512 possible isomers. As shown in Scheme 1.48, the reactions of variously substituted imines led to a



Scheme 1.48 Pseudo-three-component domino double 1,3-dipolar cycloaddition reaction of 1,4-benzoquinone with 2 equiv of α-iminoesters.

range of chiral tricyclic products as almost single diastereomers (>90% de) in uniformly excellent enantioselectivities (96–99% ee) combined with moderate to good yields (38–84%). Notably, the enantioselectivity was consistently excellent and not affected by the position, the electronic nature, and the number of the substituents of imines.

Later in 2015, these authors applied the same catalyst system to the asymmetric copper-catalyzed pseudo-three-component domino oxidation/double 1,3-dipolar cycloaddition reaction of cyclopentadiene with 2 equiv of α-iminoesters [69]. The domino process 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 reaction with 2 equiv of azomethine ylides derived from glycine ester imines to provide the corresponding chiral 5,5,5-tricyclic domino products bearing eight stereogenic centers as almost single diastereomers (>90% de) with uniformly excellent enantioselectivities (95–98% ee) and moderate to good yields (60–78%), as shown in Scheme 1.49. One disadvantage of this methodology was related to the limitation of its scope since only halogenated aromatic α-iminoesters reacted with the position of the halogens (*ortho*, *meta*, or *para*) on the phenyl ring of the imines not influencing yield and enantioselectivity. The use of methyl and ester substituents on the phenyl ring led to decreased yields (35–74%), and glycine ester imines derived from heteroaromatic or aliphatic aldehydes did not react at all.



60–78% yield, >90% de, 95–98% ee

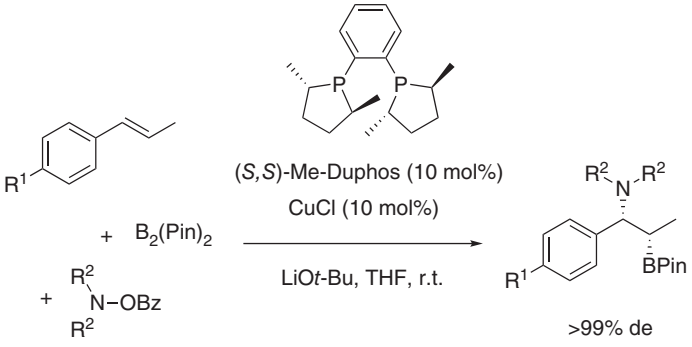
Ar = *o*-BrC_6H_4, *p*-FC_6H_4, *m*-FC_6H_4, *o*-FC_6H_4, *p*-$F_3CC_6H_4$, 3,4-Cl_2–C_6H_3, 2,3-Cl_2–C_6H_3, 3,4-Br_2–C_6H_3

Scheme 1.49 Pseudo-three-component domino oxidation/double 1,3-dipolar cycloaddition reaction of cyclopentadiene with 2 equiv of α-iminoesters.

1.3.4 Reactions Based on Addition Reactions to Alkenes

Organoborons constitute an important class of compounds in organic synthesis because of their high utilities for carbon–carbon and carbon–heteroatom

bond formation [70]. In 2013, Hirano and coworkers reported an asymmetric three-component copper-catalyzed aminoboration of styrenes with $B_2(Pin)_2$ and *O*-benzoyl-*N,N*-dialkylhydroxylamines [71]. As presented in Scheme 1.50, the reaction occurred regio- and diastereoselectively at room temperature in the presence of 10 mol% of a chiral copper catalyst *in situ* generated from CuCl and (*S,S*)-Me-Duphos as ligand in THF, producing the corresponding chiral aminoborated products as single *syn*-diastereomers in moderate to good yields (51–83%) and good enantioselectivities (80–86% ee).

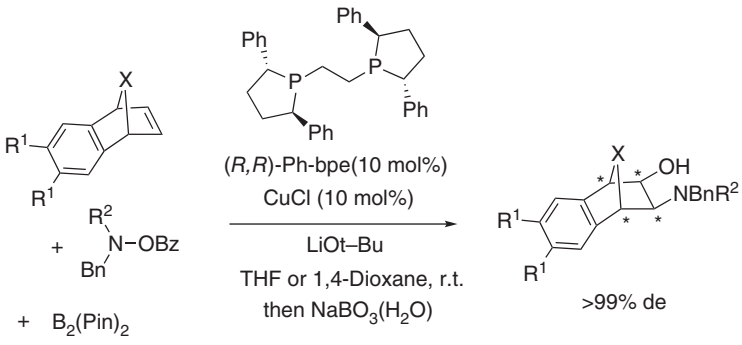


R^1 = H, R^2 = Et: 83% yield, 84% ee
R^1 = H, R^2 = Bn: 72% yield, 86% ee
R^1 = OMe, R^2 = Bn: 51% yield, 80% ee

Scheme 1.50 Three-component aminoboration reaction of styrenes, $B_2(Pin)_2$, and *O*-benzoyl-*N,N*-dialkylhydroxylamines.

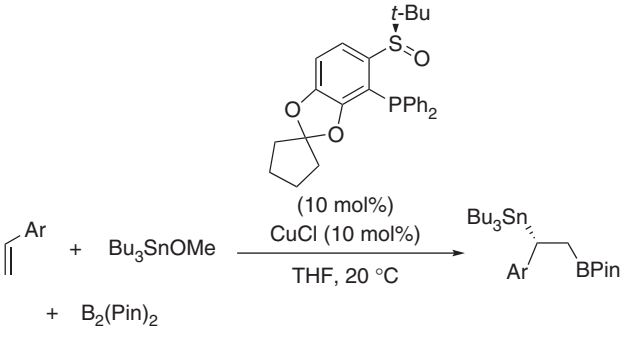
Later in 2015, the same authors employed another chiral biphosphine ligand, such as (*R,R*)-Ph-bpe, under related reaction conditions to promote the enantioselective copper-catalyzed three-component aminoboration reaction of bicyclic alkenes [72]. As shown in Scheme 1.51, the reaction of these alkenes with $B_2(Pin)_2$ and *O*-benzoyl-*N,N*-dialkylhydroxylamines provided the corresponding chiral aminoborated products as single diastereomers with good to high enantioselectivities (78–92% ee) combined with low to moderate yields (17–66%). The process was compatible to bicyclic oxa- and azabenzonorbornadienes as well as to methylene-bridged analogs, yielding the corresponding *exo*-products with comparable complete diastereoselectivity and comparable enantioselectivities.

Other functionalizations of alkenes, such as asymmetric borylstannations, were described by Liao and coworkers in 2015 [73]. Indeed, an enantioselective copper-catalyzed three-component reaction among styrenes, $B_2(Pin)_2$, and Bu_3SnOMe was performed in THF at 20 °C in the presence of a combination of a chiral sulfinylphosphine ligand and CuCl as precatalyst (Scheme 1.52). The process yielded the corresponding chiral α-aryl-β-borylstannanes in high enantioselectivities (86–96% ee) combined with moderate to quantitative yields (63–99%). It was found that the stereoelectronic properties of aryl groups (Ar) of alkenes had minimal effect on the enantioselectivity (86–96% ee). Electron-withdrawing aryl groups facilitated the borylstannation process with



R^1 = H, R^2 = Bn, X = O: 43% yield, 88% ee
R^1 = F, R^2 = Bn, X = O: 39% yield, 92% ee
R^1 = H, R^2 = Me, X = O: 17% yield, 88% ee
R^1 = H, R^2 = Bn, X = NBoc: 35% yield, 78% ee
R^1 = H, R^2 = Bn, X = CH_2: 66% yield, 88% ee

Scheme 1.51 Three-component aminoboration reaction of bicyclic alkenes, $B_2(Pin)_2$ and *O*-benzoyl-*N,N*-dialkylhydroxylamines.



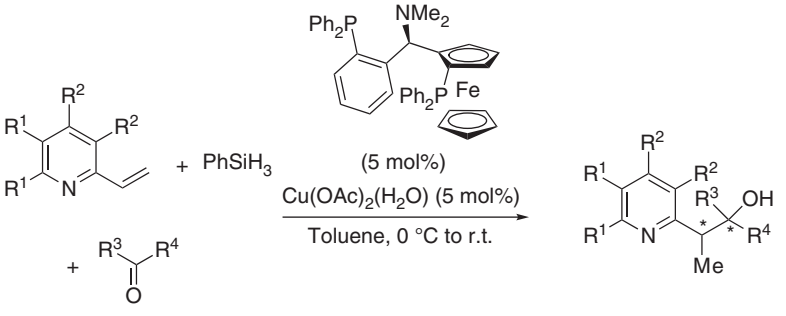
Ar = *o*-BrC_6H_4: 99% yield, 93% ee
Ar = *o*-ClC_6H_4: 94% yield, 94% ee
Ar = *o*-Tol: 93% yield, 95% ee
Ar = *o*-$MeOC_6H_4$: 63% yield, 86% ee
Ar = *m*-ClC_6H_4: 96% yield, 94% ee
Ar = *o*-$TfOC_6H_4$: 90% yield, 87% ee
Ar = *p*-BrC_6H_4: 75% yield, 95% ee
Ar = *p*-ClC_6H_4: 99% yield, 94% ee
Ar = *p*-FC_6H_4: 90% yield, 93% ee
Ar = *p*-(*t*-Bu)C_6H_4: 82% yield, 96% ee
Ar = *p*-Tol: 86% yield, 91% ee
Ar = *p*-$BzOC_6H_4$: 90% yield, 93% ee
Ar = 2-Naph: 64% yield, 92% ee
Ar = 1-Naph: 57% yield, 92% ee

Scheme 1.52 Three-component borylstannation reaction of alkenes, $B_2(pin)_2$ and Bu_3SnOMe.

full conversion of olefins while electron-rich styrenes were slightly less reactive. The reaction also enabled the synthesis of α-naphthyl-β-borylstannanes in lower yields (57–64%) albeit with comparable high enantioselectivity of 92% ee. It must be highlighted that this novel methodology constituted the first copper-catalyzed synthesis of chiral α-aryl-β-borylstannanes.

1.3.5 Reactions Based on Alkene Couplings

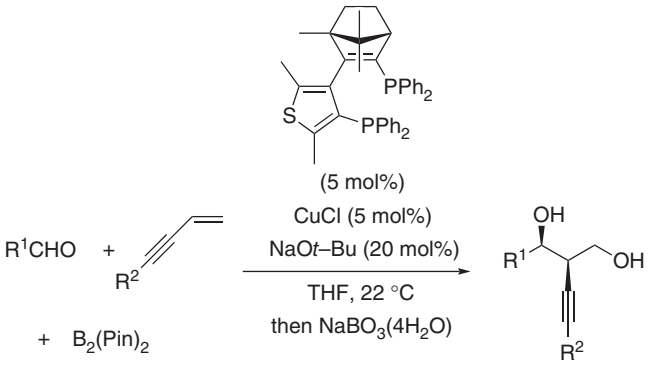
In 2012, Lam and coworkers reported the first examples of highly enantioselective copper-catalyzed reductive coupling reactions of alkenylazaarenes with ketones using phenylsilane as reducing agent [74]. Among a range of biphosphine ligands investigated, including BINAP, MeO-BIPHEP, Me-Duphos, QUINOX-P*, Josiphos, and Taniaphos ligands, a Taniaphos-type ligand was found optimal when used in Toluene at 5 mol% of catalyst loading in combination with $Cu(OAc)_2(H_2O)$ as precatalyst (Scheme 1.53). Therefore, the three-component reaction of variously substituted alkenylazaarenes with dialkyl or alkyl (hetero)aryl ketones and $PhSiH_3$ afforded the corresponding chiral aromatic heterocycles bearing tertiary-alcohol-containing side chains in uniformly high enantioselectivities (89–>99% ee), good yields (60–82%), and moderate to high diastereoselectivities (34–>90% de).



R^1,R^1 = $(CH{=}CH)_2$, R^2 = H, R^3 = Me, R^4 = Ph: 60% yield, 60% de, 93% ee
R^1,R^1 = $(CH{=}CH)_2$, R^2 = H, R^3 = Ph, R^4 = Bn: 60% yield, 78% de, 96% ee
R^1 = R^2 = H, R^3 = Me, R^4 = Ph: 65% yield, 34% de, >99% ee
R^1 = H, R^2,R^2 = $(CH{=}CH)_2$, R^3 = Me, R^4 = *p*-$F_3CC_6H_4$: 82% yield, 80% de, >99% ee
R^1 = H, R^2,R^2 = $(CH{=}CH)_2$, R^3 = Me, R^4 = *o*-$MeOC_6H_4$: 78% yield, >90% de, 97% ee
R^1 = H, R^2,R^2 = $(CH{=}CH)_2$, R^3 = Me, R^4 = 2-furyl: 76% yield, 84% de, 89% ee

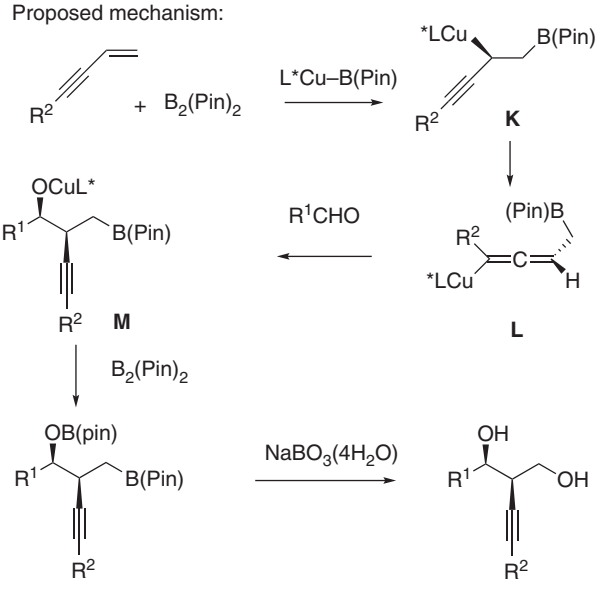
Scheme 1.53 Three-component reaction of vinylazaarenes, ketones, and phenylsilane.

In 2014, Hoveyda and coworkers developed enantioselective three-component reactions of 1,3-enynes with aldehydes and $B_2(Pin)_2$ performed at room temperature in the presence of a combination of another chiral biphosphine ligand combined with CuCl [75]. This process afforded after subsequent C—B oxidation the corresponding chiral *syn*-1,3-diols as major diastereomers with good to high diastereoselectivities (80–96% de) combined with moderate to high yields (66–94%) and enantioselectivities (70–96% ee), as shown in Scheme 1.54. Homogeneous results were achieved for aryl-, heteroaryl- as



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

Proposed mechanism:

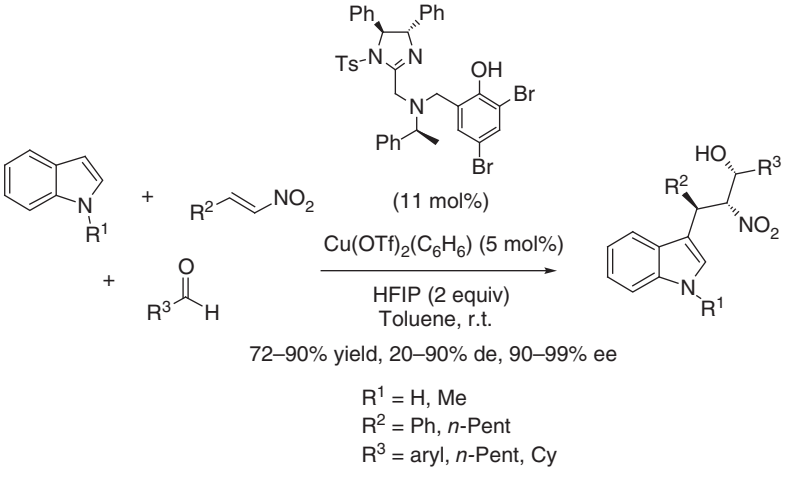


Scheme 1.54 Three-component reaction of 1,3-enynes, aldehydes, and $B_2(Pin)_2$.

well as alkenyl-substituted aldehydes in reaction with variously substituted enynes. The utility of these functionalized chiral products was enhanced by the presence of an alkyne group, allowing the preparation of fragments of the macrolide antibiotic natural products tylonolide and mycinolide IV to be achieved. The domino reaction began with the enantioselective addition of an *in situ* generated (ligand)Cu—B(Pin) species to the alkene of the 1,3-enyne, leading to propargyl-copper species **K**. The latter collapsed to the more energetically favorable trisubstituted allenyl complex **L**, which then added diastereoselectively to the aldehyde to give intermediate **M**, leading after oxidation to the final product (Scheme 1.54).

1.3.6 Miscellaneous Reactions

The asymmetric Friedel–Crafts reaction is one of the most powerful methods to synthesize chiral aromatic compounds and has been included in many enantioselective domino reactions. As an example, Arai et al. reported in 2008 the enantioselective multicomponent domino Friedel–Crafts–Henry reaction of indoles, nitroalkenes, and aldehydes catalyzed by a combination of $Cu(OTf)_2$ with a chiral imidazoline-aminophenol ligand [76]. The corresponding domino products bearing three contiguous stereocenters were obtained in good to high yields (72–90%), uniformly excellent enantioselectivities (90–99% ee), and low to high diastereoselectivities of up to (20–90% de), as illustrated in Scheme 1.55. These products were transformed into useful hydroxytryptamines.



Scheme 1.55 Three-component domino Friedel–Crafts/Henry reaction of indoles, nitroalkenes, and aldehydes.

1.4 Conclusions

Taking advantage 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. This chapter collects the advances in the field of enantioselective two- and three-component 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 domino processes have been developed, 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 domino reactions based on cyclizations, Michael-initiated processes, domino reactions initiated by Friedel–Crafts reactions, and domino reactions initiated by aldol condensations, among other two-component processes. Moreover, many enantioselective copper-catalyzed three-component reactions also encountered success, such as three-component reactions based on alkyne couplings, Michael-initiated three-component domino reactions, three-component domino reactions based on 1,3-dipolar cycloadditions, three-component reactions based on addition reactions to alkenes, and three-component reactions based on alkene couplings, among other three-component processes. Indeed, during the last 13 years, a myriad of novel powerful asymmetric processes have been developed in this field, allowing in some cases up to eight stereogenic centers to be generated in a single operation. Undoubtedly, there are still many enantioselective copper-promoted asymmetric domino reactions waiting to be discovered in this challenging and fascinating area of research. Therefore, the future direction in this field is to continue expanding the scope of enantioselective domino and multicomponent reactions through the combination of different types of reactions, in combination with the employment of novel chiral copper catalyst systems, and apply these powerful strategies to the synthesis of biologically active molecules and natural products.

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