Recent Developments in Enantioselective Multicatalyzed Tandem Reactions

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Abstract: This review updates the emerging field of enantioselective multicatalyzed tandem reactions published since the beginning of 2015. It illustrates how much the combination of different types of catalysts allows unprecedented enantioselective one-pot reactions of many types to be achieved, allowing a direct access to a variety of very complex chiral molecules.

Keywords: asymmetric tandem reactions; asymmetric domino reactions; asymmetric synthesis; multicatalysis; organocatalysts; transition metals

1 Introduction

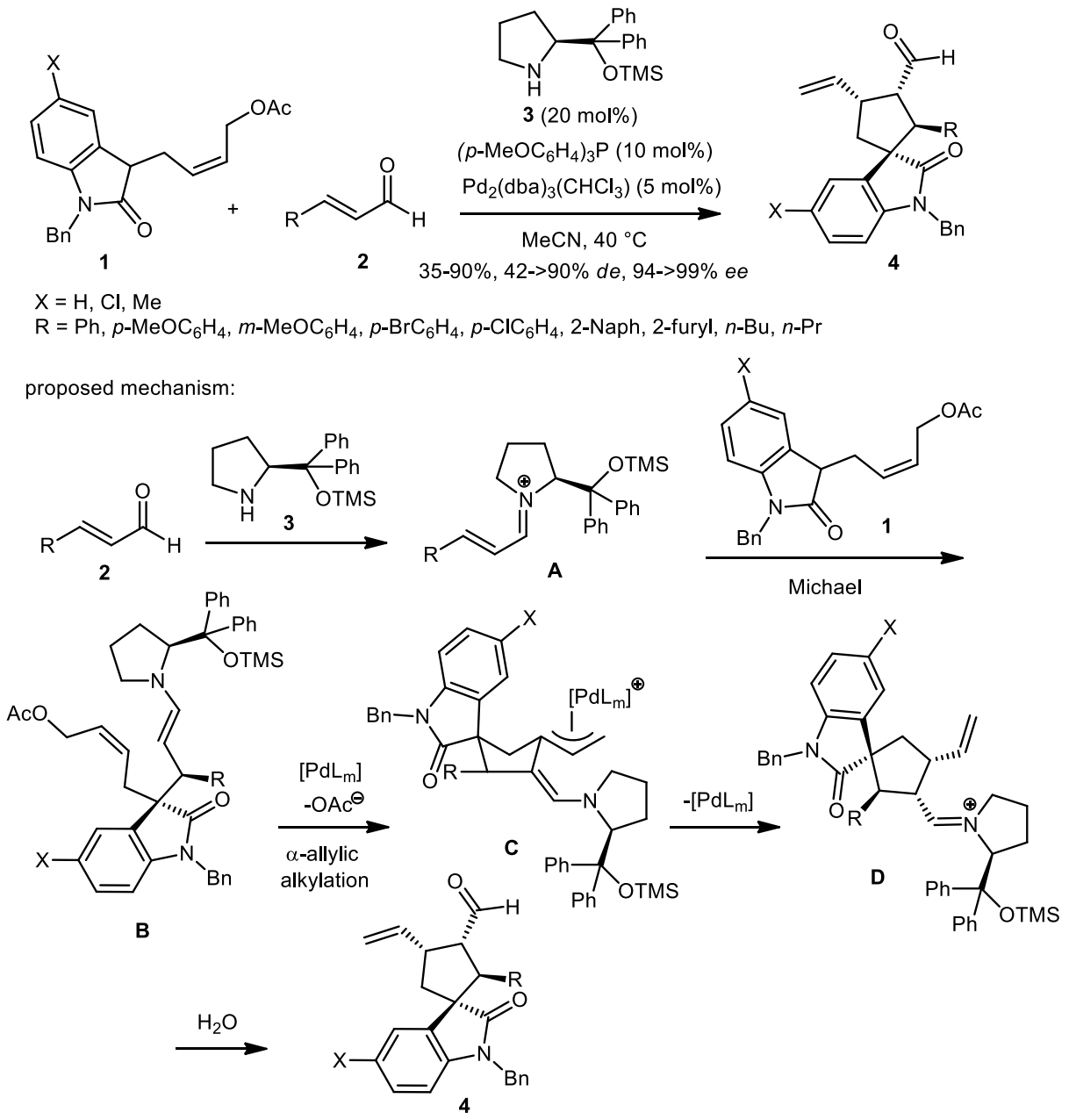
The quest for discovering novel one-pot methodologies to directly generate complex organic molecules has become increasingly popular, since these simple tandem reactions allow economy of time and energy by avoiding purifications, improving dramatically the synthetic efficiency.[1] Especially, multicatalyst-promoted asymmetric tandem reactions enable the synthesis of very complex chiral molecules, including natural and/or biologically active products, from simple starting materials often under mild conditions. Tandem catalysis refers to the synthetic strategies of modular combination of catalytic reactions into a single synthetic operation with minimum workup or change in conditions. Indeed, in comparison with stepwise synthesis, tandem catalysis allows reducing the usage of chemicals and circumvents the yield losses associated with the purification of intermediates, saves energy and time, alleviates the generation of waste, and maximizes synthetic efficiency. Moreover, handling of unstable or toxic intermediates is avoided in these reactions. In the last decade, a number of multicatalytic systems have been developed to promote these multistep processes. In these systems, the compatibility of the different catalysts as well as that between them and other reagents, solvent and intermediates. For example, while organocatalysts are generally compatible and robust, chiral metal catalysts are more sensitive to coordinate to other species present in the reaction medium. In case of incompatibility, it is possible to add successively the catalysts to the reaction media to avoid their interaction (sequential catalysis). Among tandem reactions are powerful domino processes which consist in one-step, two or more bond-forming transformations occurring under strictly the same reaction conditions.[2] The most employed multicatalytic concept, based on combining metal catalysis with organocatalysis, was introduced in 2003 by Krische.[3] Ever since, this emerging field has attracted great attention in the synthetic community, allowing unprecedented tandem reactions to be achieved with high chemo- and stereoselectivities, which were not possible so far by using single catalytic systems.[4] The goal of this review is to collect the very recent advances in enantioselective multicatalyzed tandem reactions published since the beginning of 2015 since this emerging field was most recently reviewed this year by a book published by Zhou.[4aa] Moreover, the special field of enantioselective cooperative catalysis applied to all types of transformations was the subject of a report in 2015 by Patil et al.[4z] In the same year, a perspective article on orthogonal tandem catalysis was published by Marks and Lohr, covering the literature until 2014.[4y] In 2016, the cooperative combination of aminocatalysts with metals was reviewed by Cordova and Afewerki but it included only nine references of asymmetric tandem reactions reported in 2015-2016.[4ac] Furthermore, a short highlight including only ten references ≥2015 was published by Loh et al. in 2018, focusing on multicatalyst-promoted asymmetric relay reactions.[4ad] In 2019, I published a review dealing with enantioselective metal-catalyzed domino reactions including only six references focusing on dual metal/organocatalysis.[2y]The present review is divided into three parts, dealing successively with enantioselective tandem reactions catalyzed by a combination of metals and organocatalysts, reactions catalyzed by two metals, and reactions catalyzed by multiple organocatalysts. The first part is subdivided into eight sections based on the nature of the metal combined with organocatalysts, such as palladium, iron, copper, rhodium, silver, gold, iridium and others. The second part of the review is subdivided into two sections according to the type of bimetallic catalysis involved, including relay catalysis and sequential catalysis. It must be remembered that in cooperative catalysis, both the two catalysts are present at the onset of the reaction, and share the same catalytic cycle, activating two different functional groups cooperatively to achieve the bond-formation steps. However, in relay or sequential catalysis, the substrate first reacts with one catalyst to give an intermediate through a first catalytic cycle. Then, this former intermediate reacts with the second catalyst to provide through a second catalytic cycle the final product or an intermediate for subsequent transformations. The difference between relay and sequential catalysis consists in the presence or not of the two catalysts at the onset of the reaction. Thus, relay as well as sequential catalysis involves a set of reactions independently catalyzed by two catalysts in a consecutive manner; but, while in relay catalysis the two compatible catalysts are both present from onset; in sequential catalysis, the addition of the second catalyst during the course of the reaction is necessary to avoid incompatibility.

2 Enantioselective Tandem Reactions Catalyzed by an Organocatalyst and a Metal Catalyst

In spite of the common drawbacks of metals, such as moisture sensitivity, recoverability, and sometimes toxicity,[5] metal catalysis still attracts a great attention.[6] On the other end, organocatalysts present the advantages to be robust, inexpensive, readily available, and non-toxic.[2e,7] Moreover, they have the ability of promoting a wide variety of transformations through different activation modes. Organocatalysts are usually Lewis bases, such as amines, carbenes, and tertiary phosphines, while metal catalysts have an empty coordination site to interact and activate a substrate. The challenge in combining an organocatalyst and a metal catalyst is to avoid the deactivation of catalyst by Lewis acid/base interaction. When the two catalysts are incompatible, the tandem reaction can nevertheless be performed by adding them successively to the reaction media (sequential catalysis). In spite of these difficulties, there are, however, many beautiful examples of asymmetric tandem reactions based on the use of combinations of organocatalysts with various types of metal complexes, acting through cooperative, relay as well as sequential catalysis.[4d,f-g,h-l,n,r,t,v-x,z,ac]

2.1 Organo- and Palladium Catalysis

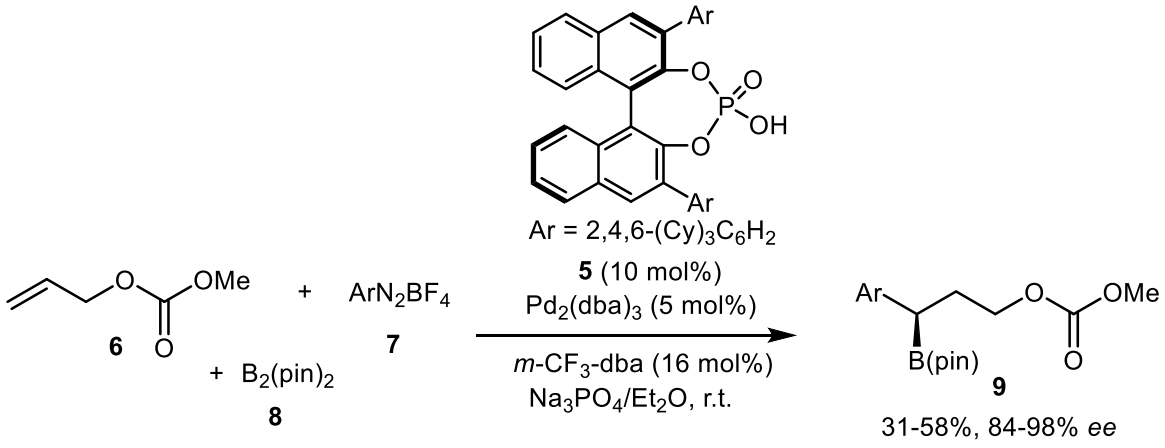
Among transition metals, palladium presents the advantage to be compatible with many functional groups.[8] Undoubtedly, this property has partly contributed to the development of many enantioselective palladium-catalyzed domino transformations by different groups.[2m,t-u] Especially, in the last few years palladium has been among the metals the most employed to promote asymmetric multicatalyzed domino reactions. It is known that the spirocyclic oxindole structural motif is found in many natural and unnatural products exhibiting important biological activities.[9] However, it must be recognized that a few methodologies have been disclosed to prepare these products enantiopure, particularly on the basis of organo- and metal catalysis. In this context, Cordova et al. reported a highly enantioselective domino Michael/α-allylic alkylation reaction of oxindoles **1** with α,β-unsaturated aldehydes **2** catalyzed by a combination of a racemic palladium complex, such as $Pd_2(dba)_3$, combined with an achiral triaryl phosphine ($(p\text{-}MeOC_6H_4)_3P$), and popular chiral proline-derived amine **3**.[10] This one-pot relay process afforded the corresponding chiral polysubstituted spirocyclic oxindoles **4** bearing four contiguous stereogenic centers, including the spiro all-carbon quaternary center. As shown in Scheme 1, these products were obtained in both moderate to high yields (35-90%) and diastereoselectivities (42->90% *de*) combined with uniformly excellent enantioselectivities (94->99% *ee*) when the reactions were performed at 40 °C in acetonitrile as the solvent with 20 mol% of chiral organocatalyst **3** combined with 5 mol% of $Pd_2(dba)_3$. The dual catalyst system tolerated aliphatic as well as aromatic α,β-unsaturated aldehydes. The lowest yield (35%) was observed in the reaction of a heteroaromatic aldehyde (R = 2-furyl) albeit combined with both excellent diastereo- and enantoselectivities (>90% *de*, 94% *ee*). The absolute and relative configuration of the chiral tricyclic products was determined by X-ray analysis. A mechanism based on relay catalysis is depicted in Scheme 1. The domino process began with the formation of chiral iminium **A** from the reaction between α,β-unsaturated aldehyde **2** and chiral amine catalyst **3**. Iminium **A** further underwent a Michael addition with oxindole **1** to give the corresponding enamine intermediate **B**, which subsequently provided in the presence of the palladium catalyst the corresponding π-allyl palladium complex **C**. A subsequent stereoselective intermolecular nucleophilic *Si*-facial attack by the chiral enamine via a five-membered transition state, followed by protonation and reductive elimination generated iminium intermediate **D** and released the palladium catalyst. Then, intermediate **D** was hydrolyzed to give final domino product **4** and regenerated organocatalyst **3**.



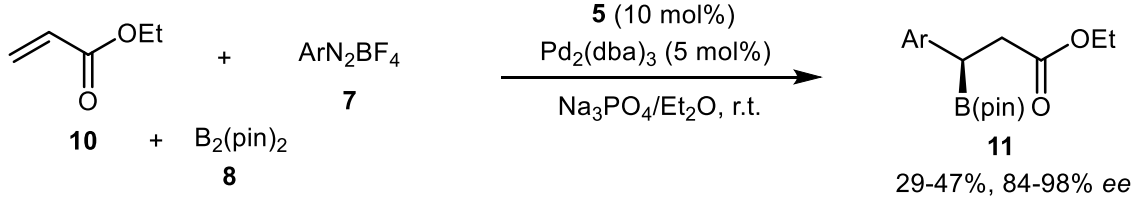
Scheme 1. Domino Michael/α-allylic alkylation reaction of α,β-unsaturated aldehydes with oxindoles.

In contrast with relay catalysis in which the organocatalyst and the metal catalyst perform two distinct catalytic cycles for the consecutive reactions, cooperative catalysis means that both the organocatalyst and the metal catalyst share the same catalytic cycle, working cooperatively to form the product. This type of catalysis was employed in 2015 by Toste et al. to promote an asymmetric three-component reaction between α-alkenes, aryldiazonium salts and bis(pinacolato)diboron.[11] Actually, the reaction involved a cooperative chiral anion phase transfer and palladium catalysis derived from the combined use of 10 mol% of chiral phosphoric acid **5** and 5 mol% of $Pd_2(dba)_3$ in diethyl ether as the solvent. For example, performed at room temperature in the presence of *m*-CF_3-dba as an additive and Na_3PO_4 as a base, the domino arylation/borylation reaction of allyl methyl carbonate **6** with aryldiazonium salts **7** and bis(pinacolato)diboron **8** led to the corresponding chiral benzylic boronic methyl carbonates **9** in moderate yields (31-58%) and uniformly high enantioselectivities (84-98% *ee*) whatever the electronic nature and position of the substituent born by the aryl group (Ar) of the

aryldiazonium salt (Scheme 2). Indeed, aryldiazonium salts with a methoxy, a vinyl or an alkyl group at the *meta*- or *para*-positions all provided excellent enantioselectivities. The same catalyst system was also applied to promote a related domino reaction of another type of α-alkenes, such as allyl ethyl ester **10**, which afforded by reaction with aryldiazonium salts **7** and bis(pinacolato)diboron **8** the corresponding chiral β,β-arylborylated esters **11** in moderate yields (29-47%) and uniformly high enantioselectivities (84-98% *ee*), as depicted in Scheme 2. In this case, the use of *m*-CF_3-dba as an additive was not required. Notably, the aryl moiety of the diazonium salt was found tolerant to substitution at the *para*-position with alkyl, vinyl or heteroatom functional groups.



Ar = *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-Tol, *p*-(*t*-Bu)C_6H_4, 3,5-$Me_2C_6H_3$, *m*-Tol, *p*-(Me_2C=CH)C_6H_4

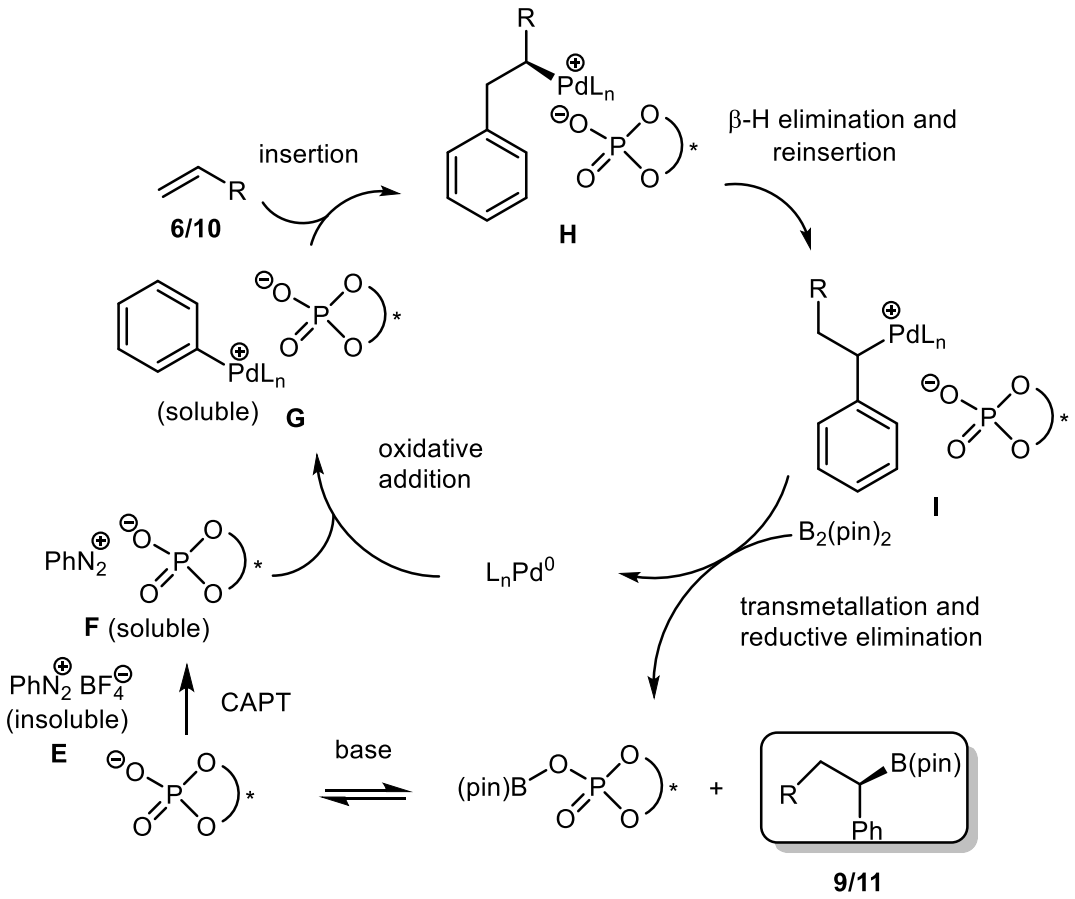


Ar = Ph, *p*-(PivO)C_6H_4, *p*-(*t*-Bu)C_6H_4, *p*-Tol, *p*-(Me_2C=CH)C_6H_4

Scheme 2. Three-component domino arylation/borylation reactions of α-alkenes, aryldiazonium salts and bis(pinacolato)diboron.

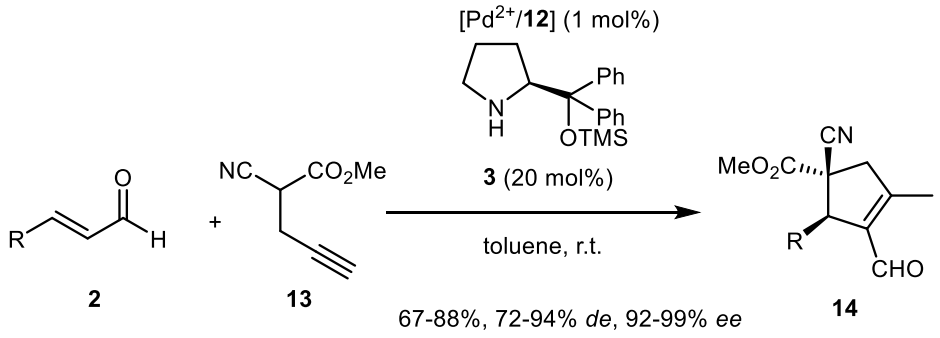
To explain the precedent results, the authors have proposed a chiral anion phase-transfer (CAPT) strategy, enabling the association of a chiral anion with Pd(II) intermediates involved in the enantio-determining step.[11] As illustrated in Scheme 3, insoluble aryldiazonium salt **E** underwent phase transfer to give soluble chiral ion pair **F**. Then, the oxidative addition of Pd(0) species to **G**, followed by migratory insertion of the α-alkene led to chiral palladium complex **H**. Subsequent β-hydride elimination and reinsertion yielded chiral benzylic palladium complex **I** that was poised to undergo transmetalation and subsequent reductive elimination to afford the final benzylic boronic ester. Notably, the non-cationic Pd(0) species generated in this process could be reoxidized by soluble diazonium chiral ion pair **F** to regenerate chiral intermediates **G**.

proposed dual catalytic cycle with Ar = Ph:



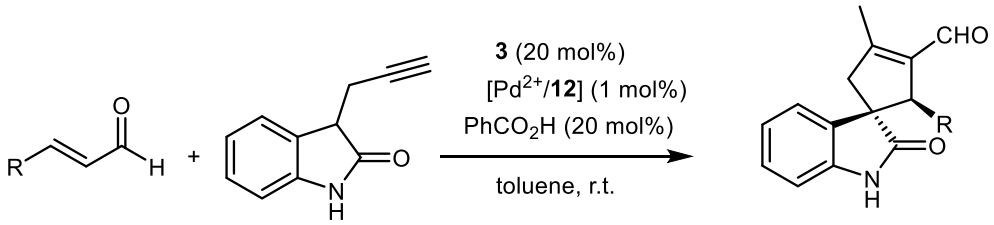
Scheme 3. Mechanism for three-component domino arylation/borylation reaction of α-alkenes, aryldiazonium salts and bis(pinacolato)diboron.

In 2015, Hedin et al. disclosed for the first time that a palladium(II) complex derived from a porous polyimine **12** could be an excellent catalyst for enantioselective cooperatively catalyzed cascade reactions.[12] Indeed, in combination with 20 mol% of chiral proline-derived organocatalyst **3**, only 1 mol% of palladium complex [Pd^{2+}/**12**] was found to promote enantioselective domino Michael/carbocyclization reactions of α,β-unsaturated aldehydes with carbon nucleophiles, such as methyl propargylcyanoacetate and propargyloxindole. As depicted in Scheme 4, the domino reaction of a range of α,β-unsaturated aldehydes **2** with methyl propargylcyanoacetate **13** performed at room temperature in toluene as the solvent led to the corresponding multisubstituted and functionalized chiral cyclopentenes **14** exhibiting an all-carbon quaternary stereocenter in uniformly excellent enantioselectivities (92-99% *ee*), combined with both good to high diastereoselectivities (72-94% *de*) and yields (67-88%). The same catalyst system was applied to promote enantioselective domino Michael/carbocyclization reactions of α,β-unsaturated aldehydes **2** with another type of nucleophiles, such as propargyloxindole **15**. As illustrated in Scheme 4, the reactions were performed in this case in the presence of benzoic acid as an additive, yielding the corresponding almost enantiopure (97->99% *ee*) spirocyclic oxindoles **16** bearing a quaternary stereogenic center in both good to high yields (69-83%) and diastereoselectivities (60-90% *de*). Notably, the presence of either electron-withdrawing or electron-donating groups on the β-aryl-substituted aldehydes had no incidence on the results.



67-88%, 72-94% *de*, 92-99% *ee*

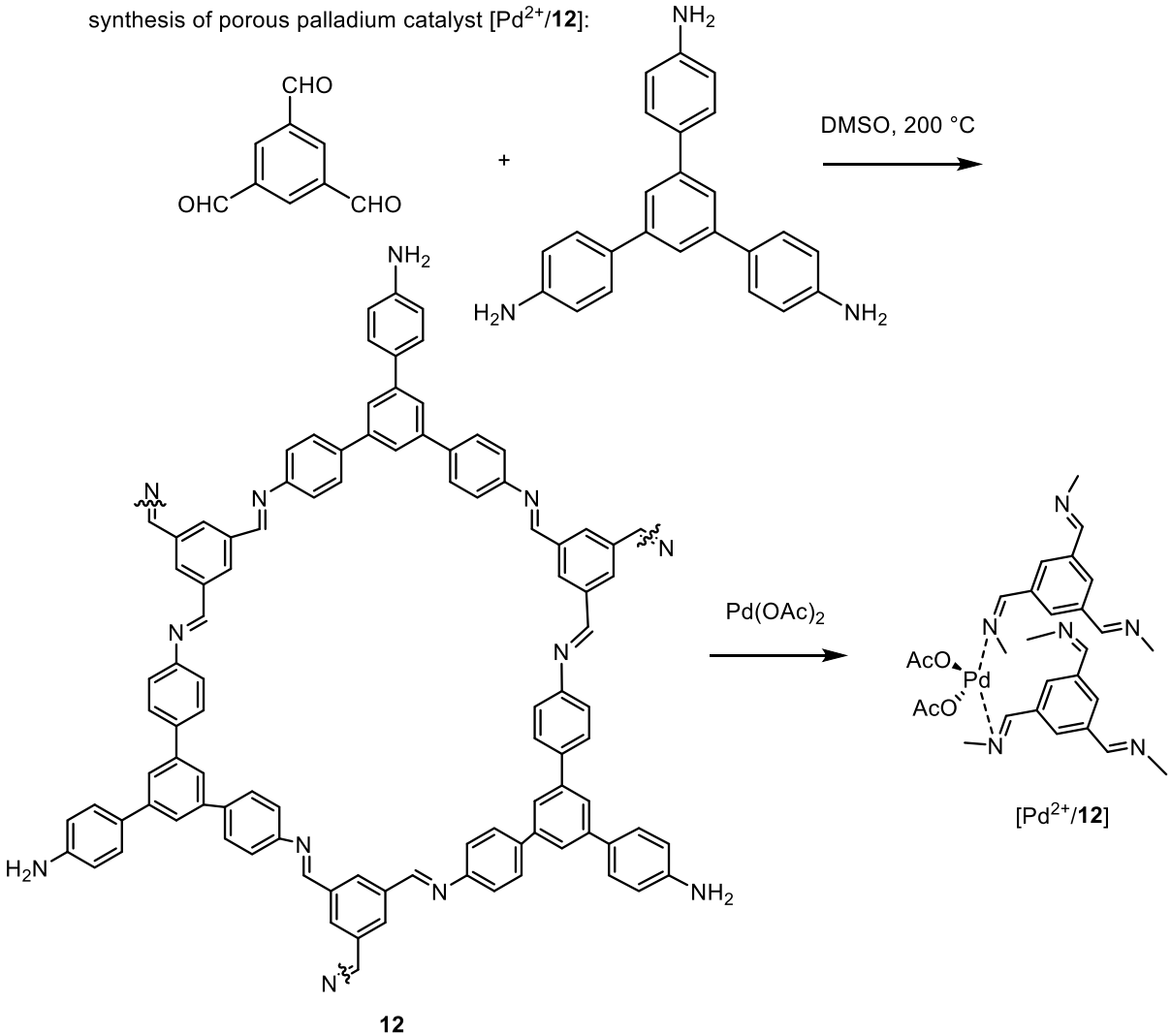
R = Ph, *p*-$O_2NC_6H_4$, *m*-$O_2NC_6H_4$, *p*-ClC_6H_4, *m*-ClC_6H_4, *o*-ClC_6H_4, *p*-BrC_6H_4, *p*-NCC_6H_4, *p*-$MeOC_6H_4$, *p*-Tol, 2-furyl, *n*-Bu



69-83%, 60-90% *de*, 97->99% *ee*

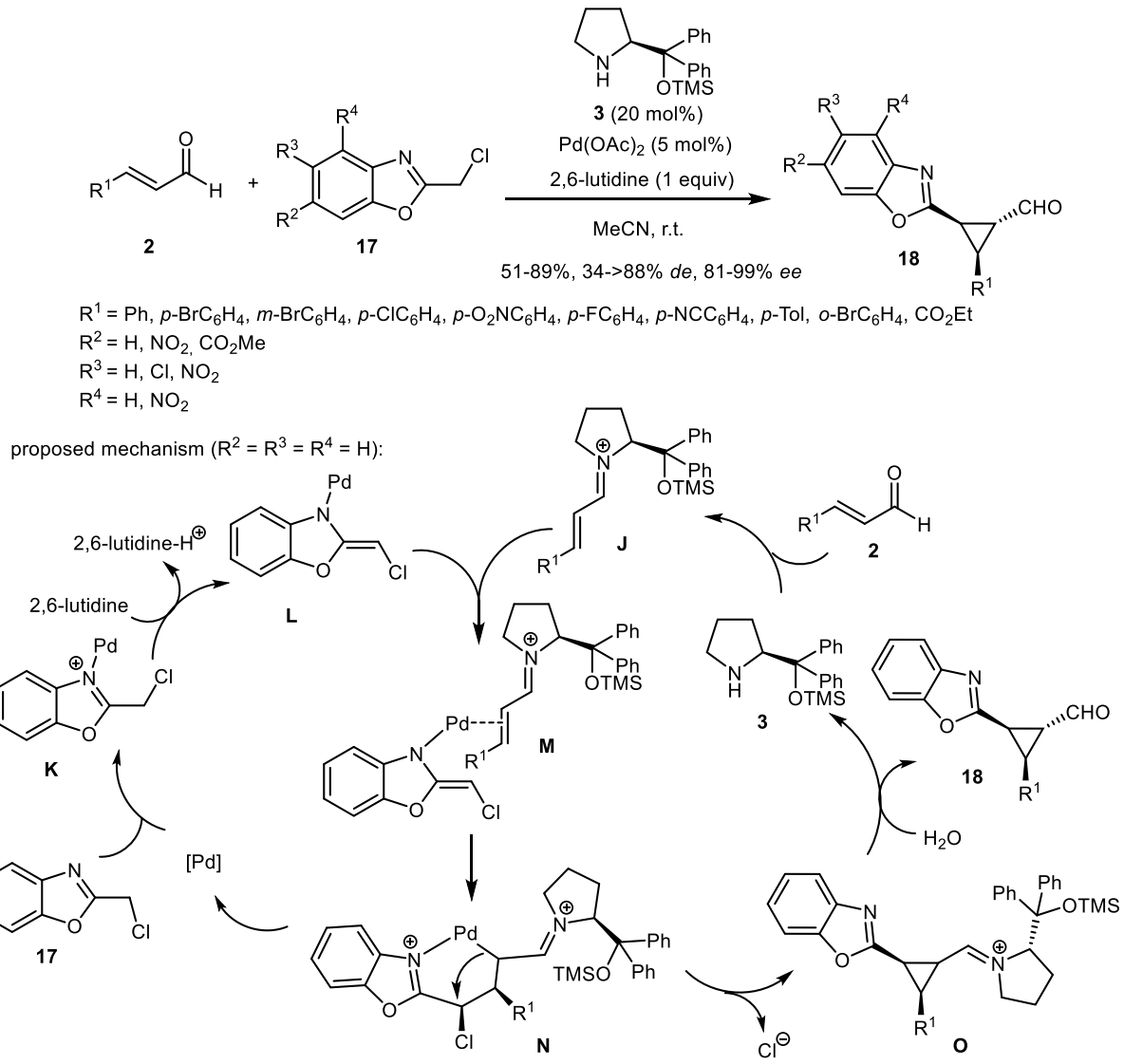
R = *p*-ClC_6H_4, *p*-Tol, *n*-Pr

synthesis of porous palladium catalyst [Pd^{2+}/**12**]:



Scheme 4. Domino Michael/carbocyclization reactions of α,β-unsaturated aldehydes with methyl propargylcyanoacetate/propargyloxindole.

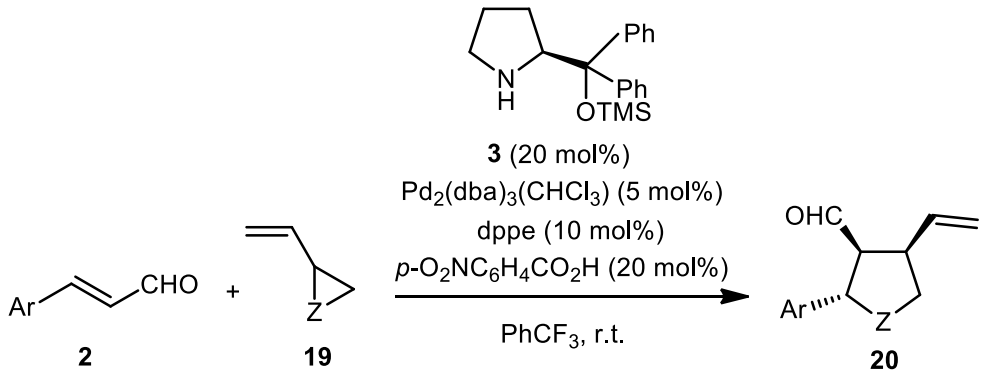
In 2016, Rios et al. reported another type of domino reactions based on cooperative palladium and organocatalysis, such as enantioselective domino Michael/alkylation reactions of α,β-unsaturated aldehydes **2** with benzoxazoles **17**.[13] The process consisted in the asymmetric cyclopropanation of α,β-unsaturated aldehydes with chloro-alkylbenzoxazoles performed at room temperature in acetonitrile as the solvent, which afforded the corresponding chiral cyclopropanes **18** in both moderate to high yields (51-89%) and diastereoselectivities (34->88% *ee*) combined with high enantioselectivities (81-99% *ee*). The reaction evolved through the activation of the azaarene with 5 mol% of $Pd(OAc)_2$ and the activation of the α,β-unsaturated aldehyde with 20 mol% of chiral proline-derived amine **3**. As shown in Scheme 5, the mechanism involved that the palladium Lewis acid interacted with the alkylbenzoxazole by coordinating to its nitrogen atom, increasing the acidity of the proton in the methylene position. The mechanism evolved through the stereoselective addition of palladium enolate **L** to chiral iminium intermediate **J**, followed by intramolecular cyclization. Indeed, in a first time, the coordination of the palladium to the benzoxazole occurred, followed by deprotonation by 2,6-lutidine as base, leading to intermediate **L**. At the same time, iminium intermediate **J** was generated from the reaction of the α,β-unsaturated aldehyde with the chiral amine organocatalyst **3**. Then, coordination between the palladium enolate and the double bond of the imine took place to form intermediate **M**. Subsequently, a *Si*-facial attack at the β-carbon occurred, providing intermediate **N**. Next, intramolecular alkylation between the new palladium enolate formed in α position of the iminium and the methylene chloride with inversion of configuration led to product exhibiting a *cis* configuration between the aryl ring and the benzoxazole. Then, hydrolysis of the latter yielded final product **18** and regenerated catalysts. The catalyst system was compatible with the presence of substituents on the aromatic ring of the α,β-unsaturated aldehyde, including electron-withdrawing groups (*p*-NO_2, *p*-CN, halides). Moreover, the α,β-unsaturated aldehyde derived from glyoxylate (R^1 = CO_2Et) also reacted smoothly albeit with a lower enantioselectivity (81% *ee*). Concerning the substrate scope of the benzoxazoles, it was found that the presence of electron-withdrawing groups (NO_2, CO_2Me) especially in the C1-position (R^2) of the azaarene ring was essential for the reactivity. Indeed, the only limitation of the substrate scope was that an electron-withdrawing group had to be present on the benzoxazole ring.



Scheme 5. Domino Michael/alkylation reaction of α,β-unsaturated aldehydes with chloro-alkylbenzoxazoles.

The synthesis of polysubstituted chiral cyclopentanes has received great attention from the chemical community because of the prominent presence of these scaffolds in many biologically active products.[14] In this context, Ratovelomanana-Vidal, Michelet and Vitale described in 2016 a novel diastereo- and enantioselective formal [3+2] cycloaddition of vinyl cyclopropanes **19** with α,β-unsaturated aldehydes **2** catalyzed by a combination of 5 mol% of $Pd_2(dba)_3 \cdot CHCl_3$ associated to 10 mol% of dppe as ligand and 20 mol% of proline-derived chiral amine catalyst **3**.[15] The process was performed at room temperature in the presence of *p*-nitrobenzoic acid as an additive in benzotrifluoride as the solvent, evolving through a domino Michael/cyclization reaction that afforded the corresponding enantiopure functionalized cyclopentanes **20** (>99% *ee*) with moderate to high yields (54-88%) and diastereoselectivities (72-80% *de*) when starting from 1,1-dicyano-2-vinyl cyclopropane (Z = $C(CN)_2$), as illustrated in Scheme 6. The same synergistic catalytic system also promoted the reaction of other vinyl cyclopropanes, such as 1,3-indanedione-derived vinyl cyclopropane, Meldrum's acid-derived vinyl cyclopropane and 1,3-dimethyl barbituric vinyl cyclopropane, which led to the corresponding enantiopure cyclopentanes **20** (>99% *ee*) with low to excellent yields (29-98%) and diastereoselectivities (24-82% *de*), as shown in Scheme 6. The authors have proposed the mechanism depicted in Scheme 6 that began with the ring-opening of the vinyl cyclopropane and generation of chiral zwitterionic intermediate **P**, which was susceptible to rapid

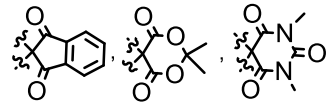
epimerization. On the other hand, in the presence of *p*-nitrobenzoic acid as an additive, α,β-unsaturated aldehyde **2** fast reacted with organocatalyst **3** to give chiral α,β-unsaturated iminium species **Q**, promoting the Michael addition rather than the polymerization of intermediate **P**. The reversibility of the Michael addition made that diastereomer **R** cyclized more promptly than its isomers because of the lower activation barrier associated with the corresponding chair-like transition state. Then, decomplexation of palladium(0) and hydrolysis of intermediate **S** allowed the final product to be achieved and the catalysts to be regenerated.



with Z = $C(CN)_2$

Ar = *p*-Tol, *m*-Tol, *o*-Tol, *p*-(*t*-Bu)C_6H_4, *p*-FC_6H_4, *p*-$F_3CC_6H_4$, *p*-ClC_6H_4, *m*-$MeOC_6H_4$, *m*-$MeO_2CC_6H_4$, 2-Naph

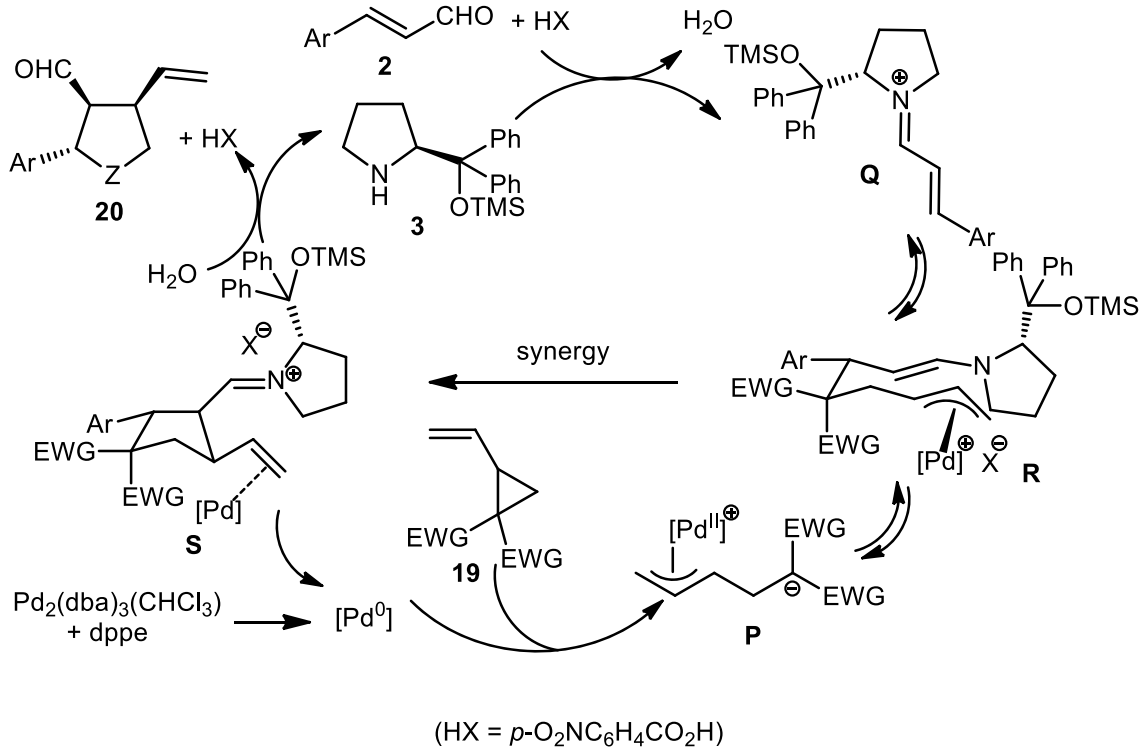
54-88%, 72-80% *de*, >99% *ee*

with Z = 

Ar = Ph, *p*-FC_6H_4, 2-Naph

29-98%, 24-82% *de*, >99% *ee*

possible mechanism:

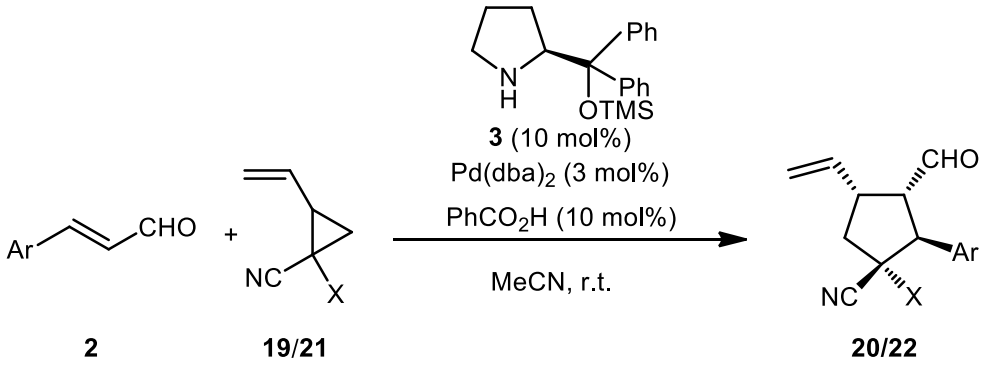


(HX = *p*-$O_2NC_6H_4CO_2H$)

Scheme 6. Domino Michael/cyclization reaction of α,β-unsaturated aldehydes with vinylcyclopropanes.

This type of reactions was also investigated at the same time by Jørgensen et al. by using a related catalyst system albeit employed at lower catalyst loadings.[16] Indeed, performed at room temperature in acetonitrile as the solvent and in the presence of only 10 mol% of organocatalyst **3** and 3 mol% of $Pd_2(dba)_3$, the domino Michael/cyclization reaction of α,β-unsaturated aldehydes **2** with vinylcyclopropanes **19**/**21** led to the corresponding chiral cyclopentanes **20**/**22** bearing up to four

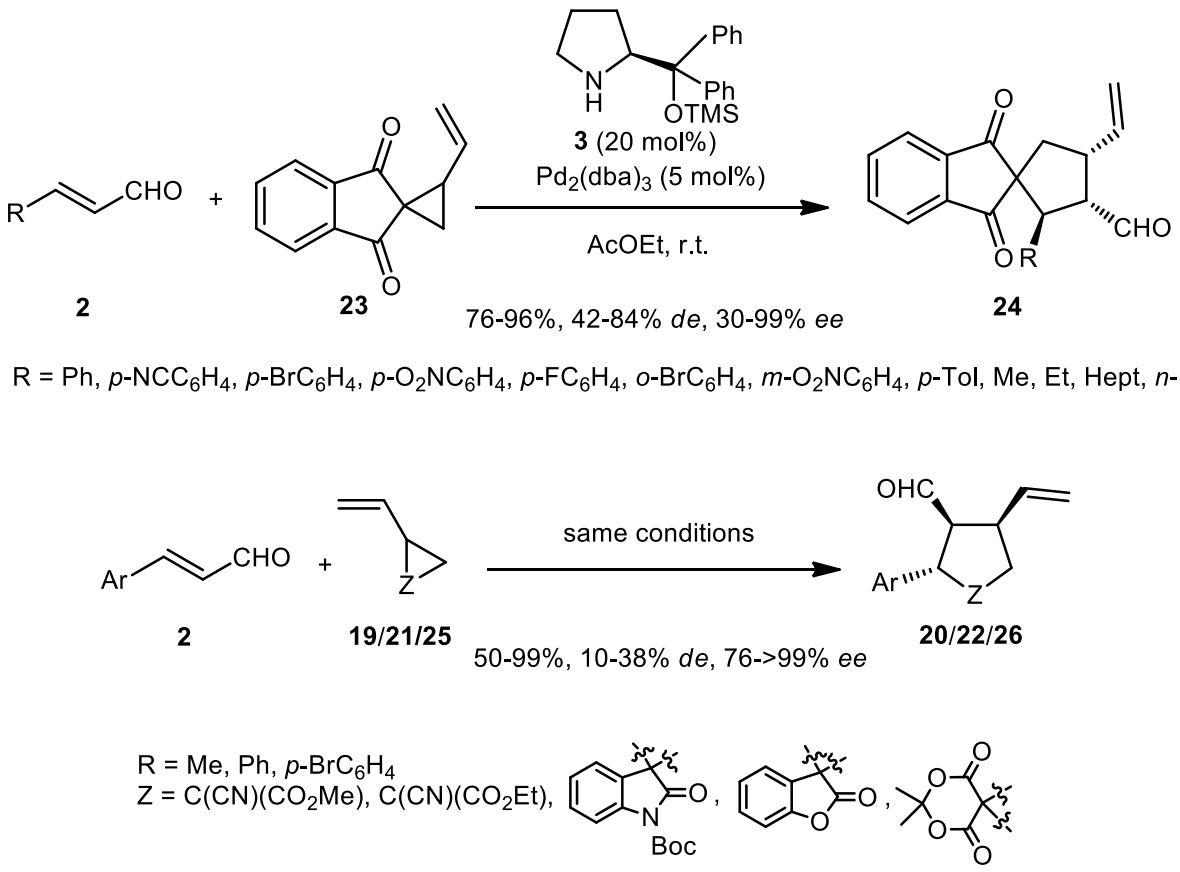
stereogenic centers including one quaternary with both uniformly high yields (80-97%) and enantioselectivities (91->99% *ee*) combined with moderate to high diastereoselectivities (42-82% *de*), as shown in Scheme 7. In addition to the vinyl cyclopropane **19** bearing two nitrile groups (X = CN), vinyl cyclopropanes exhibiting a methyl or a benzyl ester were also compatible as well as various aromatic α,β-unsaturated aldehydes. The domino process employed benzoic acid as an additive.



Ar = Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-$EtO_2CC_6H_4$
X = CN, CO_2Me, CO_2Bn
80-97%, 42-82% *de*, 91->99% *ee*

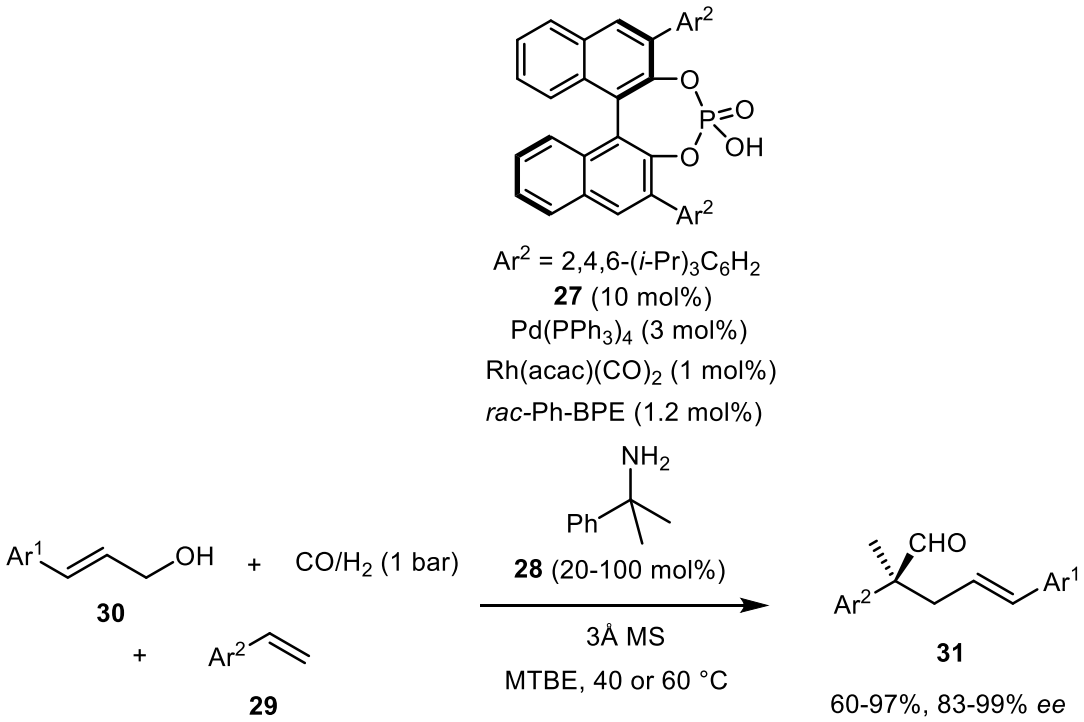
Scheme 7. Domino Michael/cyclization reaction of α,β-unsaturated aldehydes with vinylcyclopropanes.

These one-pot transformations were also studied by Rios and Meazza almost at the same time.[17] In this case, a combination of 20 mol% of the same organocatalyst **3** with 5 mol% of $Pd_2(dba)_3$ was used at room temperature as cooperative catalyst system in acetonitrile as the solvent. For example, the domino Michael/cyclization reaction of spirocyclic vinyl cyclopropane **23** with a range of either aromatic or aliphatic α,β-unsaturated aldehydes **2** afforded the corresponding chiral spirocyclic products **24** in high yields (76-96%) and both moderate to high diastereo- (42-84% *de*) and enantioselectivities (30-99% *ee*), as illustrated in Scheme 8. The scope of the reaction could be extended to other vinyl cyclopropanes **19**/**21**/**25** which led by reaction with aromatic α,β-unsaturated aldehydes **2** to the corresponding chiral cyclopentanes **20**/**22**/**26** in good to quantitative yields (50-99%) combined with low diastereoselectivities (10-38% *de*) and good to excellent enantioselectivities (76->99% *ee*), as illustrated in Scheme 8.

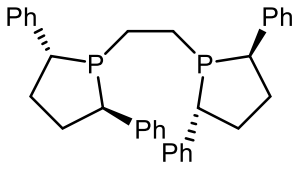


Scheme 8. Domino Michael/cyclization reactions of α,β-unsaturated aldehydes with vinylcyclopropanes.

In 2018, Gong and Han reported a novel relay multi-catalyst system consisting of a rhodium(I) complex, a palladium(0) complex, a chiral Brønsted acid catalyst and a tertiary achiral amine to promote a domino hydroformylation/allylation reaction of allylic alcohols with styrenes under CO/H_2 atmosphere.[18] As shown in Scheme 9, this three-component process was performed at 40 or 60 °C in MTBE as the solvent in the presence of 10 mol% of chiral phosphoric acid **27**, 3 mol% of $Pd(PPh_3)_4$ associated with 1.2 mol% of Ph-BPE as racemic ligand, 1 mol% of $Rh(acac)(CO)_2$ and 20 to 100 mol% of achiral amine **28**. Under these conditions, the reaction of styrenes **29** with aromatic allylic alcohols **30** under CO/H_2 atmosphere afforded the corresponding α-quaternary chiral aldehydes **31** in good to quantitative yields (60-97%) and uniformly high enantioselectivities (83-99% *ee*), as illustrated in Scheme 9. The multi-catalyst relay system was compatible with a wide range of cinnamyl alcohols bearing electron-donating or electron-withdrawing substituents at different positions of the arene moiety. It was found that allylic alcohols bearing electron-withdrawing groups generally provided higher yields than those with electron-donating substituents. Moreover, variously substituted styrenes were tolerated. It must be noted that these results could also be situated in section 2.4 dealing with enantioselective tandem reactions catalyzed by combinations of rhodium and organocatalysts.



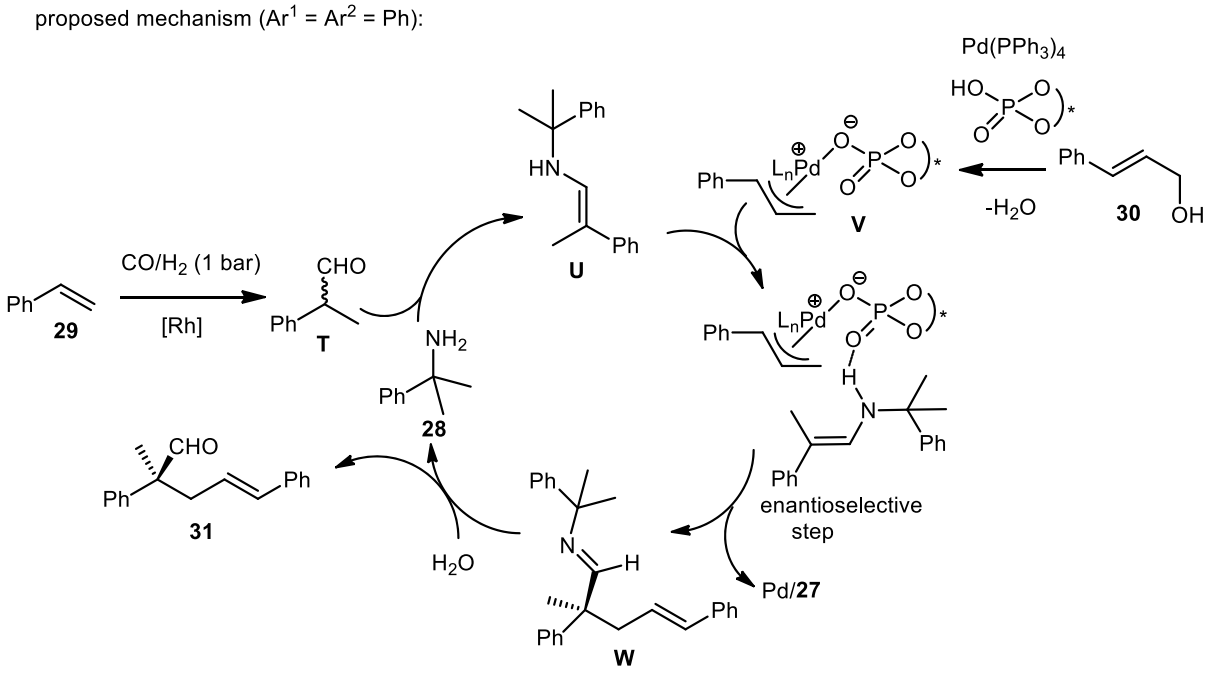
Ar^1 = *p*-NCC_6H_4, *p*-FC_6H_4, *p*-$F_3CC_6H_4$, *p*-ClC_6H_4, *p*-Tol, *p*-$MeOC_6H_4$, *o*-BrC_6H_4, *o*-$MeOC_6H_4$, *m*-ClC_6H_4, 2-furyl, *p*-$(HOCH_2)C_6H_4$, 3,4,5-$MeO_3C_6H_2$
Ar^2 = Ph, *p*-Tol, *p*-$MeOC_6H_4$, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *m*-FC_6H_4, *m*-BrC_6H_4, *o*-$MeOC_6H_4$, *m*-Tol, 3,5-$(F_3C)_2C_6H_3$



rac-Ph-BPE

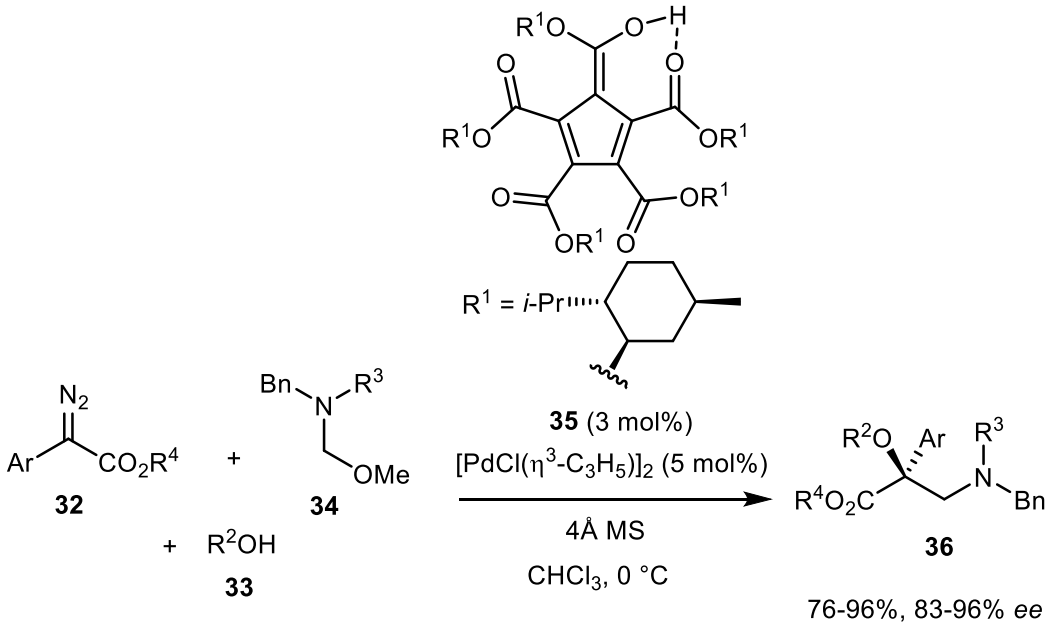
Scheme 9. Three-component domino hydroformylation/allylation reaction of styrenes, allylic alcohols and CO/H_2.

The authors proposed a relay multicatalysis which is detailed in Scheme 10.[18] In the presence of an achiral palladium catalyst and chiral phosphoric acid **27**, allylic alcohol **30** was converted into π-allyl palladium complex **V** bearing a chiral counter anion. In the same time, achiral amine **28** formed enamine intermediate **U** with α-branched aldehyde **T** derived from the hydroformylation of styrene **29**. Enamine species **U** subsequently reacted with π-allyl palladium complex **V** to give chiral imine **W** and regenerated catalysts. Subsequent hydrolysis yielded final chiral aldehyde **31** and released amine **28**.



Scheme 10. Proposed mechanism for three-component domino hydroformylation/allylation reaction of styrenes, allylic alcohols and CO/H_2.

In 2019, Xu and Hu described a novel enantioselective three-component aminomethylation reaction of aryldiazoesters **32**, alcohols **33** and α-aminomethyl ethers **34** performed at 0 °C in chloroform as the solvent, evolving through relay catalysis.[19] The reaction was catalyzed by a combination of 5 mol% of $[PdCl(\eta_3\text{-}C_3H_5)]_2$ and 3 mol% of chiral pentacarboxycyclopentadiene **35** as organocatalyst, leading to the corresponding chiral multifunctionalized β-amino acid derivatives **36** in both high yields (76-96%) and enantioselectivities (83-96% *ee*), as shown in Scheme 11. Aryldiazoesters bearing electron-withdrawing or electron-donating substituents were all compatible in addition to multisubstituted substrates. Moreover, a range of variously substituted benzyl alcohols reacted smoothly as well as alkyl alcohols and alcohols exhibiting alkynyl and alkenyl moieties.

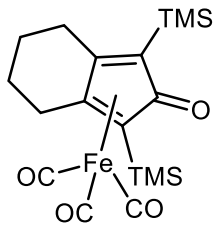


Ar = Ph, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-FC_6H_4, *p*-Tol, *p*-(*t*-Bu)C_6H_4, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, 3,4-$Me_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$
R^2 = Bn, *o*-$MeOC_6H_4CH_2$, *p*-$BrC_6H_4CH_2$, *p*-$MeOC_6H_4CH_2$, (2-furyl)CH_2, Me, Et, *i*-Pr, allyl, $HC{\equiv}C(CH_2)_2$, (*E*)-PhCH=CH-CH_2, $(Me)_2C$=CH-$(CH_2)_2$-(Me)C=CH-CH_2
R^3 = Bn, (*p*-Tol)CH_2, (*p*-ClC_6H_4)CH_2, (*p*-BrC_6H_4)CH_2
R^4 = Me, Bn

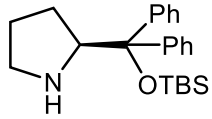
Scheme 11. Three-component aminomethylation reaction of aryldiazoesters, alcohols and α-aminomethyl ethers.

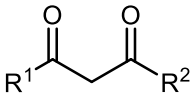
2.2 Organo- and Iron Catalysis

Related to the higher abundance and lower cost and toxicity of iron catalysts in comparison with other transition metals, economic and ecologic iron-catalyzed domino transformations represent a wide potential for future organic synthesis.[20] However, only few asymmetric versions of these reactions mediated by chiral iron catalysts have been described so far.[20b,d-e,21] Among them, an enantioselective domino oxidation/Michael/reduction/Claisen fragmentation reaction of 1,3-diketones **37** with allylic alcohols **38** was developed in 2016 by Quintard and Rodriguez on the basis of a multicatalyst system.[22] The latter consisted in a combination of 6.5 mol% of achiral iron tricarbonyl complex **39** with 13 mol% of chiral proline-derived organocatalyst **40** employed in the presence of 5 mol% of $Cu(acac)_2$ as an additive. As shown in Scheme 12, the use of this relay multicatalyst system at 25 °C in xylenes as a solvent allowed the corresponding chiral 3-alkylpentanols **41** to be synthesized in moderate to good yields (66-85%) and uniformly high enantioselectivities (87-96% *ee*). The mechanism of the domino process depicted in Scheme 12 began with the iron-catalyzed oxidation of allylic alcohol **38** into the corresponding α,β-unsaturated aldehyde **X** which subsequently underwent a Michael addition with 1,3-diketone **37** through iminium catalysis from chiral organocatalyst **40** to afford chiral intermediate **Y**. A chemoselective aldehyde reduction of the latter led to alcohol intermediate **Z** which further cyclized into lactol **AA**. Then, intermediate **AA** was submitted to a Claisen fragmentation to give novel intermediate **AB** which led after protonation to the final chiral domino product **41**.



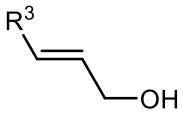
39 (6.5 mol%)





37

+



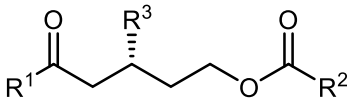
38

40 (13 mol%)

$Me_3NO(2H_2O)$ (8 mol%)

$Cu(acac)_2$ (5 mol%)

xylenes, 25 °C

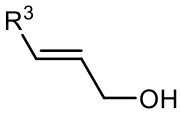


41

66-85%, 87-96% *ee*

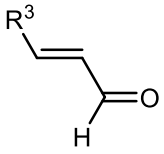
R^1 = Me, Et, Ph
R^2 = Me, Et, Ph
R^3 = Me, *n*-Hex, CH_2Bn, $(CH_2)_2OMOM$

proposed mechanism:

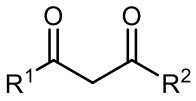


38

oxidation



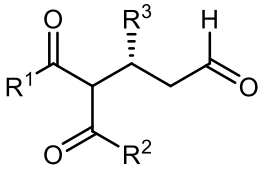
X



37

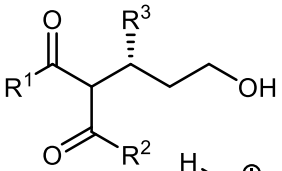
40

Michael



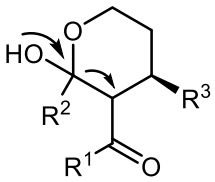
Y

aldehyde reduction



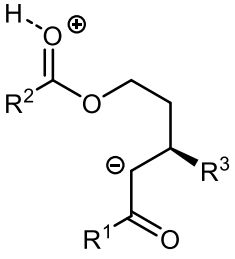
Z

lactol formation



AA

Claisen fragmentation



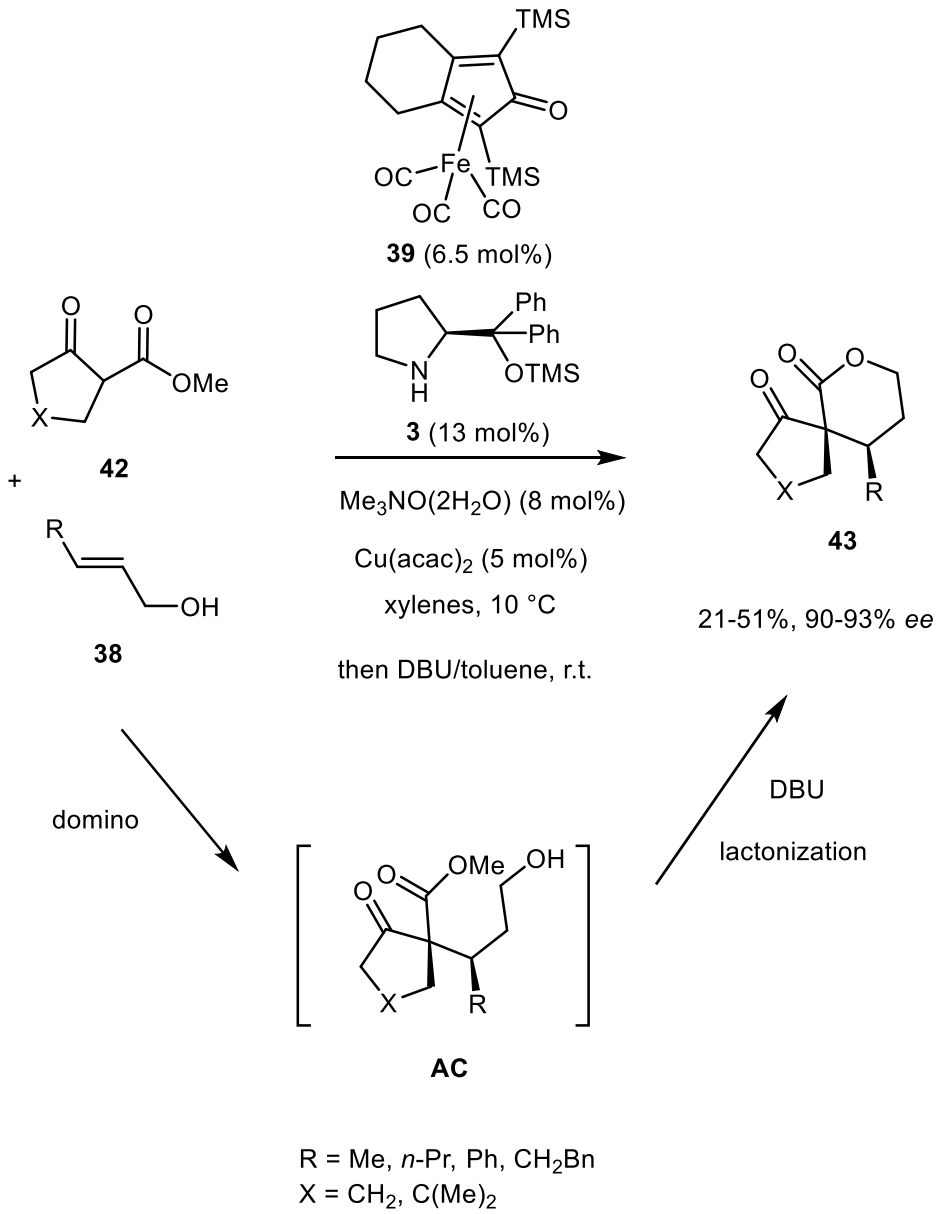
AB

protonation

41

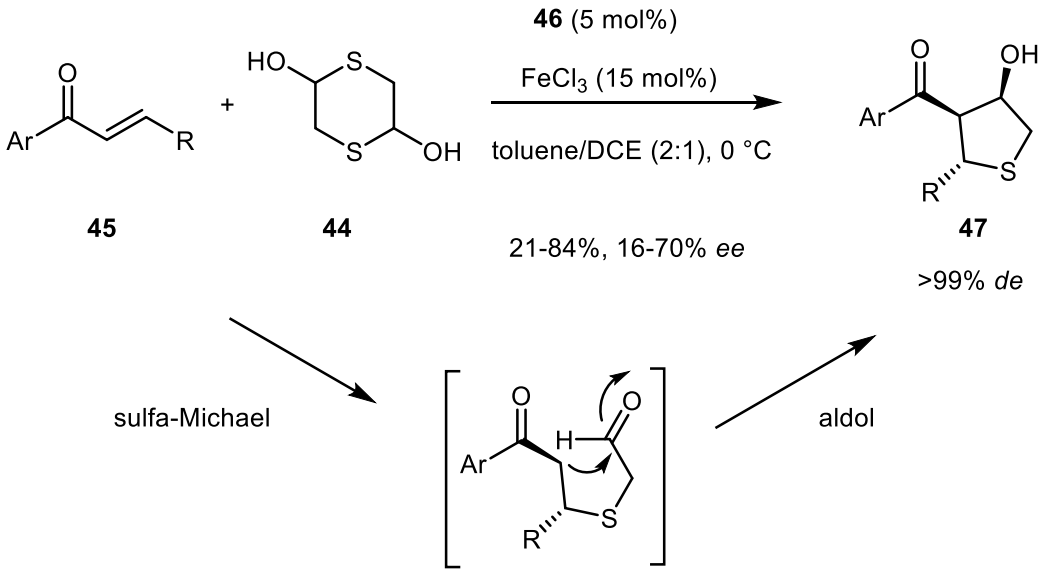
Scheme 12. Domino oxidation/Michael/reduction/Claisen fragmentation reaction of 1,3-diketones with allylic alcohols.

Later in 2018, the same authors applied a closely related relay multicatalyst system to develop another type of enantioselective domino reactions.[23] As shown in Scheme 13, the use of a multicatalytic system composed of 6.5 mol% of the same achiral iron tricarbonyl complex **39** and 13 mol% of chiral proline-derived organocatalyst **3** in the presence of 5 mol% of $Cu(acac)_2$ as an additive allowed enantioselective domino oxidation/Michael/reduction reactions between cyclic β-keto esters **42** and allylic alcohols **38** to occur in xylenes at 10 °C. The domino products **AC** were not isolated but subsequently submitted to lactonization by treatment with DBU at room temperature in toluene to give the corresponding chiral δ-lactones **43** in low to moderate yields (21-51%) combined with high enantioselectivities (90-93% *ee*).

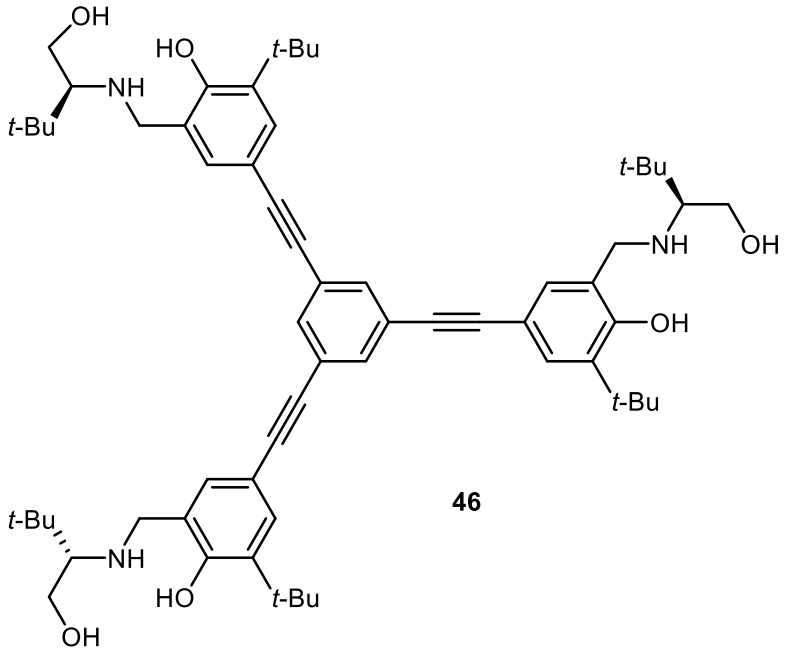


Scheme 13. Domino oxidation/Michael/reduction reaction of cyclic β-keto esters with allylic alcohols followed by lactonization.

In the same year, Punniyamurthy et al. described enantioselective iron-catalyzed domino sulfa-Michael/aldol reactions of 1,4-dithiane-2,5-diol **44** with aromatic α,β-unsaturated ketones **45**.[24] In this case, the multicatalyst system was composed by a combination of 15 mol% of $FeCl_3$ and 5 mol% of novel chiral dendrimer ligand **46**. Performed in a 2:1 mixture of toluene and DCE as the solvent, the domino reaction furnished the corresponding chiral tetrahydrothiophenes **47** as single diastereomers in low to high yields (21-84%) and low to moderate enantioselectivities (16-70% *ee*), as illustrated in Scheme 14. The chiral dendritic catalyst was recovered and reused for three runs. Notably, this study constituted the first example of a metal-catalyzed domino sulfa-Michael/aldol reaction of chalcones with 1,4-dithiane-2,5-diol.



Ar = Ph, *p*-$EtOC_6H_4$, *p*-EtC_6H_4, *p*-FC_6H_4
R = *o*-Tol, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-FC_6H_4, *p*-Tol, *p*-NCC_6H_4, 2-furyl, 2-thienyl, Cy, *i*-Pr, 2-Naph

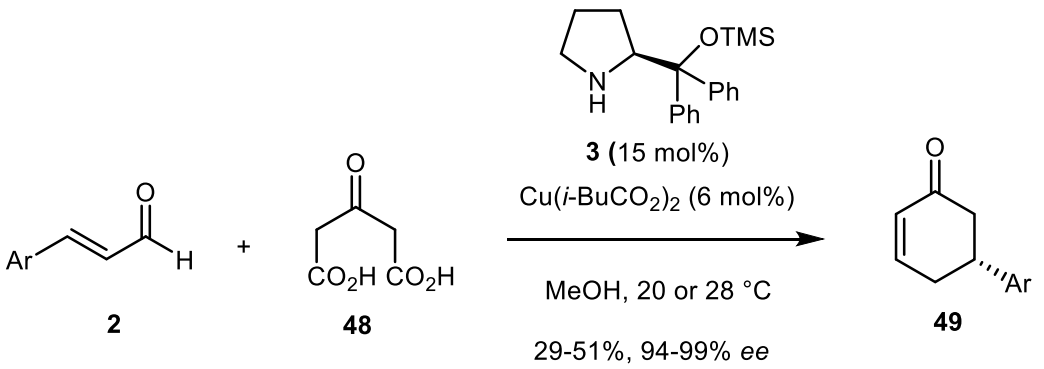


46

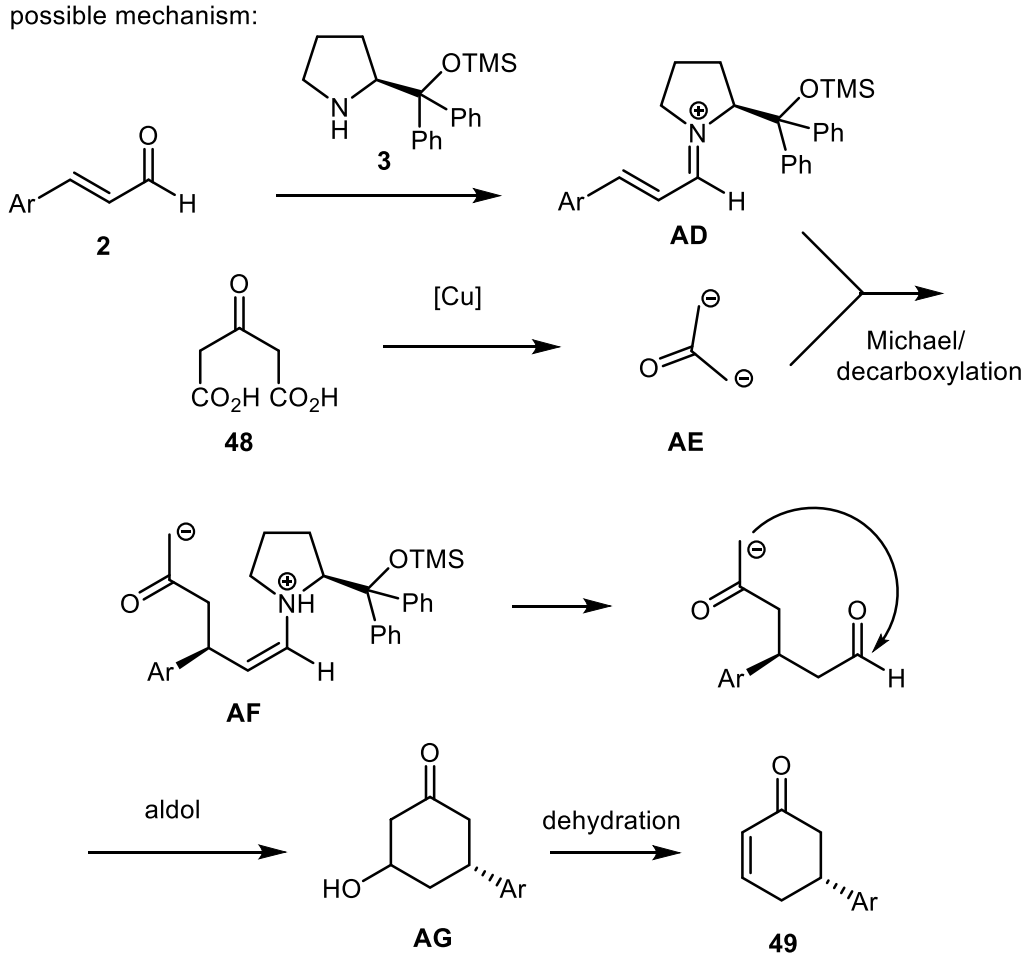
Scheme 14. Domino sulfa-Michael/aldol reaction of aromatic α,β-unsaturated ketones with 1,4-dithiane-2,5-diol.

2.3 Organo- and Copper Catalysis

Various types of asymmetric domino reactions have already been promoted by chiral copper catalysts.[25] As a recent example, Quintard and Rodriguez developed an enantioselective domino di-decarboxylative Michael/aldol/dehydration reaction of aromatic α,β-unsaturated aldehydes **2** with 1,3-acetonedicarboxylic acid **48** catalyzed by a combination of an achiral copper catalyst, such as $Cu(i\text{-}BuCO_2)_2$, and a chiral organocatalyst, such as proline-derived amine **3**.[26] Performed in methanol at 20 or 28 °C in the presence of 15 mol% of chiral amine catalyst **3** combined with 6 mol% of the copper complex, the domino reaction afforded chiral aryl-substituted cyclohexenones **49** in low to moderate yields (29-51%) and uniformly excellent enantioselectivities (94-99% *ee*), as depicted in Scheme 15. Electron-withdrawing as well as electron-donating groups were tolerated in all positions of the aromatic substituent of the α,β-unsaturated aldehyde. As illustrated in Scheme 15, the domino process began with the formation of iminium species **AD** from the reaction between α,β-unsaturated aldehyde **2** and the organocatalyst. In the same time, the copper catalyst activated 1,3-acetonedicarboxylic acid **48**, giving enolate **AE**, which then condensed onto iminium intermediate **AD** to afford chiral enamine **AF**. Then, an aldol reaction occurred to give chiral cyclohexanol **AG** which subsequently underwent dehydration to provide the final domino product. It must be noted that this is the first use of 1,3-acetonedicarboxylic acid **48** as a bis-nucleophile and a reactive acetone surrogate in asymmetric catalysis.



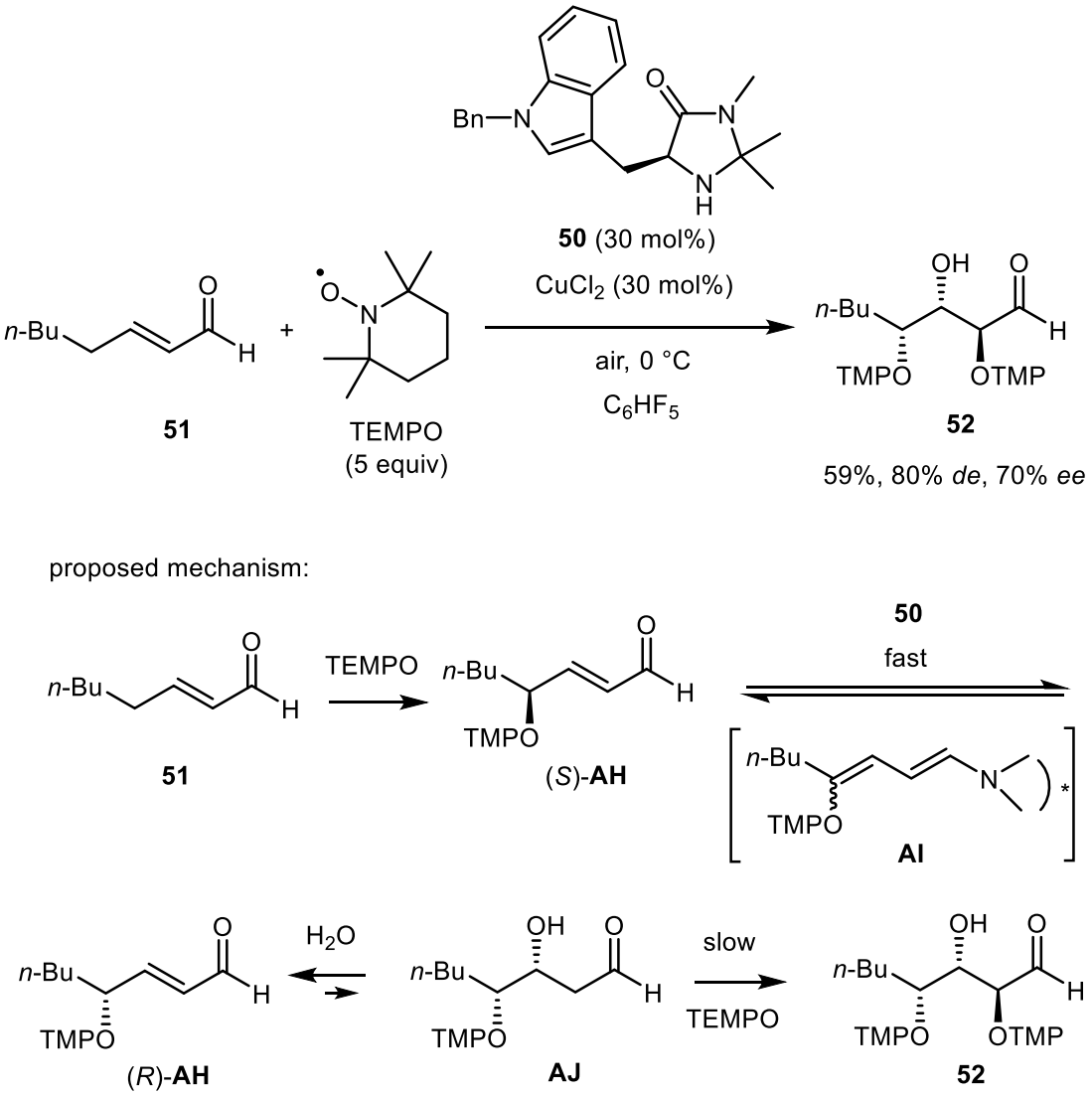
Ar = Ph, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-$O_2NC_6H_4$, *p*-$MeOC_6H_4$, *m*-$O_2NC_6H_4$, *o*-$O_2NC_6H_4$, *p*-$EtO_2CC_6H_4$



Scheme 15. Domino di-decarboxylative Michael/aldol/dehydration reaction of α,β-unsaturated aldehydes with 1,3-acetonedicarboxylic acid.

In 2015, Chen and Abeykoon reported the first α,β,γ-trifunctionalization cascade reaction of α,β-unsaturated aldehydes.[27] This domino α,β,γ-trioxygenation reaction was enantioselectively catalyzed by a combination of 30 mol% of tryptophan-derived imidazolidinone chiral organocatalyst **50** combined with the same quantity of $CuCl_2$. The process depicted in Scheme 16 was performed at 0 °C in pentafluorobenzene as the solvent. It occurred between α,β-unsaturated aldehyde **51** and five equivalents of TEMPO, delivering the corresponding chiral α,β,γ-trioxyaldehyde **52** in good yield (59%) and diastereoselectivity (80% *de*) associated with moderate enantioselectivity (70% *ee*). A

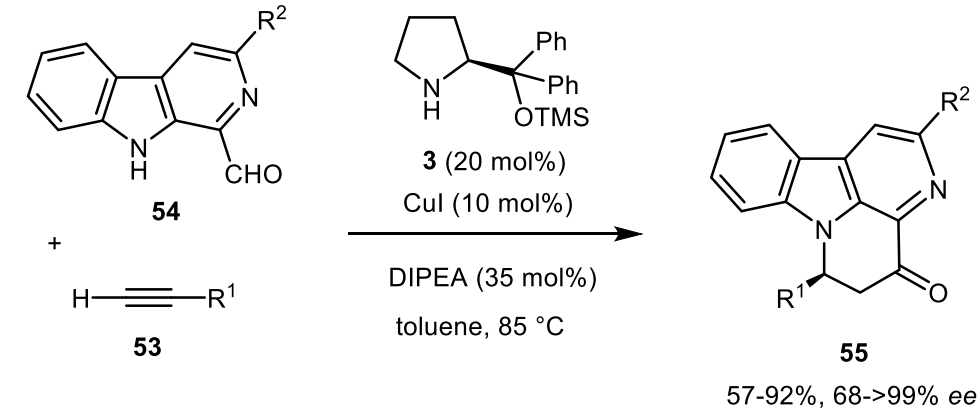
possible mechanism is outlined in Scheme 16, involving the initial formation of γ-oxyenal "(*S*)-**AH**" by incorporation of TEMPO. Then, intermediate "(*S*)-**AH**" underwent a rapid organocatalyzed racemization through dienamine intermediate **AI**. The latter was further submitted to a reversible Michael addition of water to give β,γ-dioxyaldehyde **AJ** which was thermodynamically unfavorable. However, this compound was in a sufficiently high concentration to undergo a final α-oxygenation with TEMPO to afford product **52**.



Scheme 16. Domino α,β,γ-trioxygenation reaction of an α,β-unsaturated aldehyde with TEMPO.

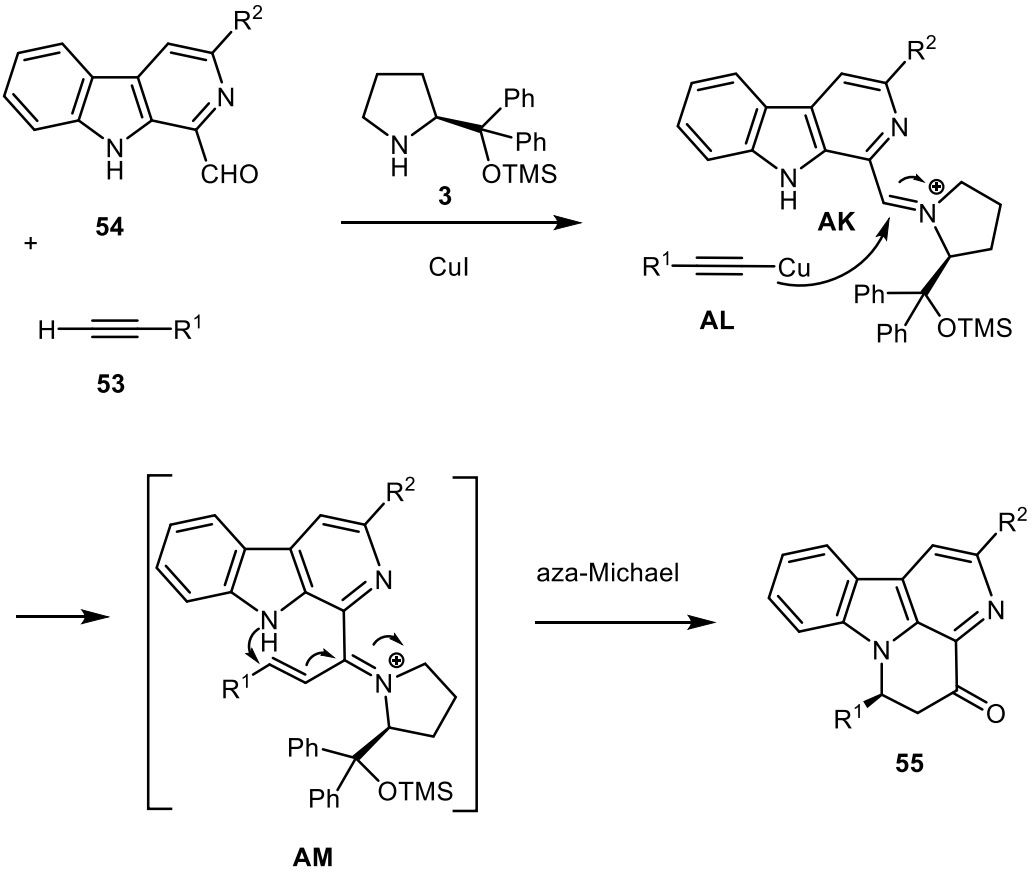
Later in 2016, Batra et al. developed an enantioselective domino condensation/aza-Michael reaction of terminal alkynes **53** with 1-formyl-9*H*-β-carbolines **54**.[28] The reaction was cooperatively multicatalyzed at 85 °C by 10 mol% of CuI and 20 mol% of chiral proline-derived organocatalyst **3** in toluene as the solvent in the presence of DIPEA as an additive. As illustrated in Scheme 17, the reaction of terminal alkynes **53** with 1-formyl-9*H*-β-carbolines **54** led to the corresponding biologically interesting chiral 5,6-dihydrocanthin-4-ones **55** in both moderate to high yields (57-92%) and enantioselectivities (68->99% *ee*). The catalyst system tolerated a range of variously substituted alkynes, with the highest enantioselectivities (84->99% *ee*) obtained in the case of (hetero)aromatic alkynes (R^1 = (hetero)aryl). A mechanism depicted in Scheme 17 proposed that the domino reaction began with the reaction of aldehyde **54** with chiral organocatalyst **3** to give iminium intermediate **AK**. The latter subsequently reacted with the *in situ* generated copper-coordinated alkyne **AL** to afford

intermediate **AM**. Then, **AM** underwent an intramolecular aza-Michael addition to provide the final domino product **55** after hydrolysis.



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

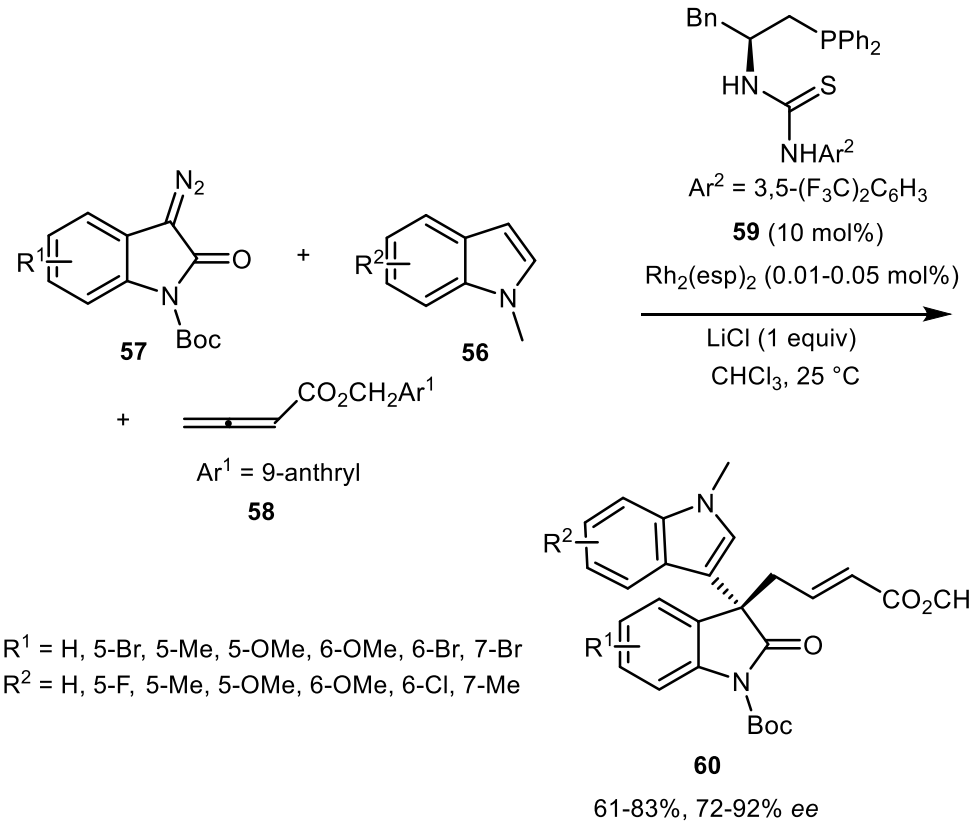
proposed mechanism:



Scheme 17. Domino condensation/aza-Michael reaction of terminal alkynes with 1-formyl-9*H*-β-carbolines.

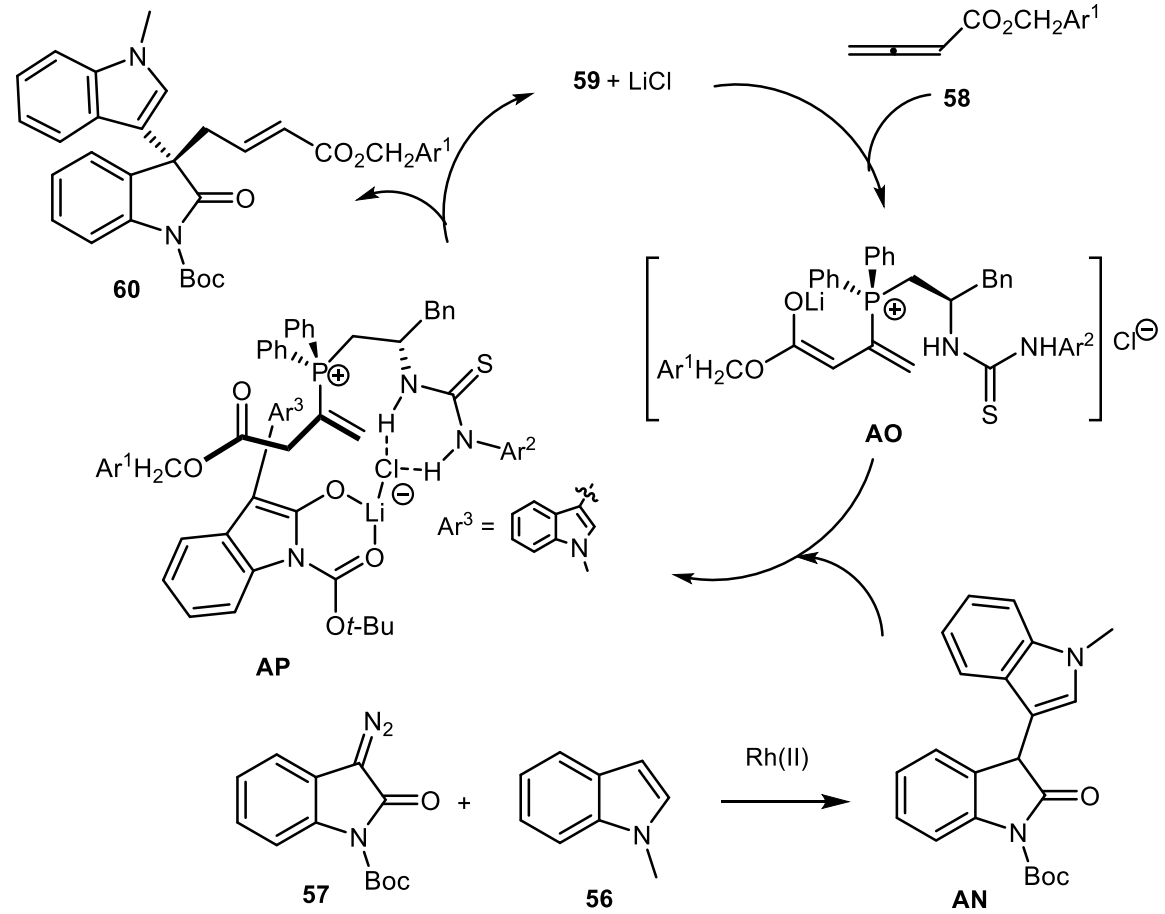
2.4 Organo- and Rhodium Catalysis

In 2015, Gong et al. developed combined catalyst systems constituted of Rh(II) complexes and amino acid-derived chiral phosphines that enabled highly enantioselective three-component domino C−H functionalization/allylation reaction between indoles **56**, 3-diazooxindoles **57** and allenoates **58**.[29] As shown in Scheme 18, the reaction catalyzed at 25 °C by 10 mol% of bifunctional chiral phosphine catalyst **59** and only 0.01-0.05 mol% of $Rh_2(esp)_2$ in chloroform as the solvent in the presence of one equivalent of LiCl afforded the corresponding chiral and biologically interesting 3,3'-indolyloxindoles **60** bearing a quaternary stereogenic center in good to high yields (61-83%) and enantioselectivities (72-92% *ee*). The substrate scope of the process was found wide since many substituents on either the indoles or 3-diazooxindoles were tolerated, providing high yields and enantioselectivities in most cases. The electronic nature of these substituents was found important in the reactivity. For example, substrates bearing electron-donating or electron-neutral substituents (R^1, R^2 = H, 5-Me, 5-OMe, 6-OMe, 7-Me: 64-83%) smoothly underwent the reaction in the presence of only 0.01 mol% of rhodium catalyst, while the reaction of those with electron-withdrawing substituents (R^1 = 5-Br, 7-Br, R^2 = H: 61-64%) required 0.05 mol% of $Rh_2(esp)_2$. Moreover, the presence of a substituent in C6- or C7-position of 3-diazooxindoles decreased the enantioselectivity (72-86% *ee* with R^1 = 6-OMe, 6-Br, 7-Br). A relay mechanism based on two catalytic cycles is shown in Scheme 18. It included an insertion reaction of rhodium carbene species to the C−H bond to provide intermediate **AN**. Moreover, during the domino process, a lithium-stabilized phosphonium enolate **AO** was generated, working as a strong base to facilitate the enolization of **AN**. Notably, LiCl in combination with the chiral phosphine catalyst constituted a ternary synergistic activation system, as shown in transition state **AP**, wherein the oxindole lithium enolate interacted with a chiral thiourea-chloride complex through Li-Cl coordination.



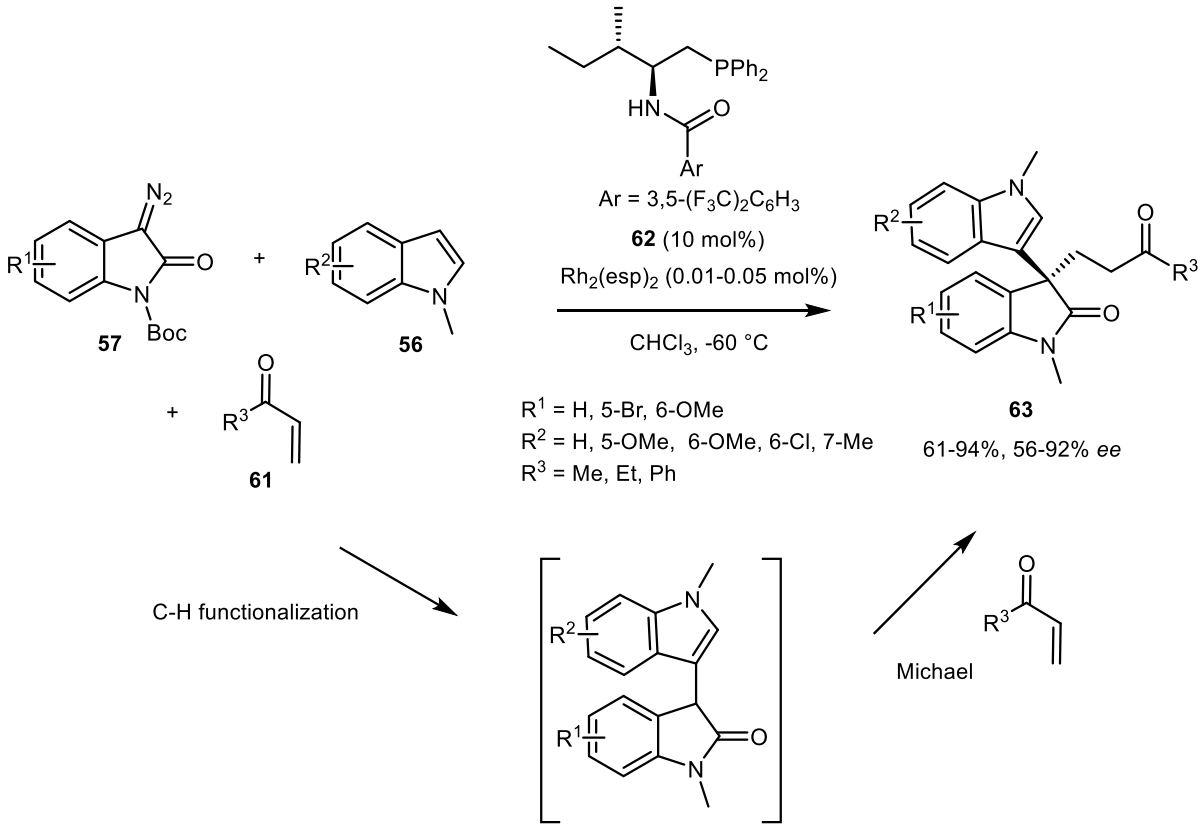
R^1 = H, 5-Br, 5-Me, 5-OMe, 6-OMe, 6-Br, 7-Br
R^2 = H, 5-F, 5-Me, 5-OMe, 6-OMe, 6-Cl, 7-Me

proposed mechanism (R^1 = R^2 = H):



Scheme 18. Three-component domino C−H functionalization/allylation reaction of indoles, 3-diazooxindoles and allenoates.

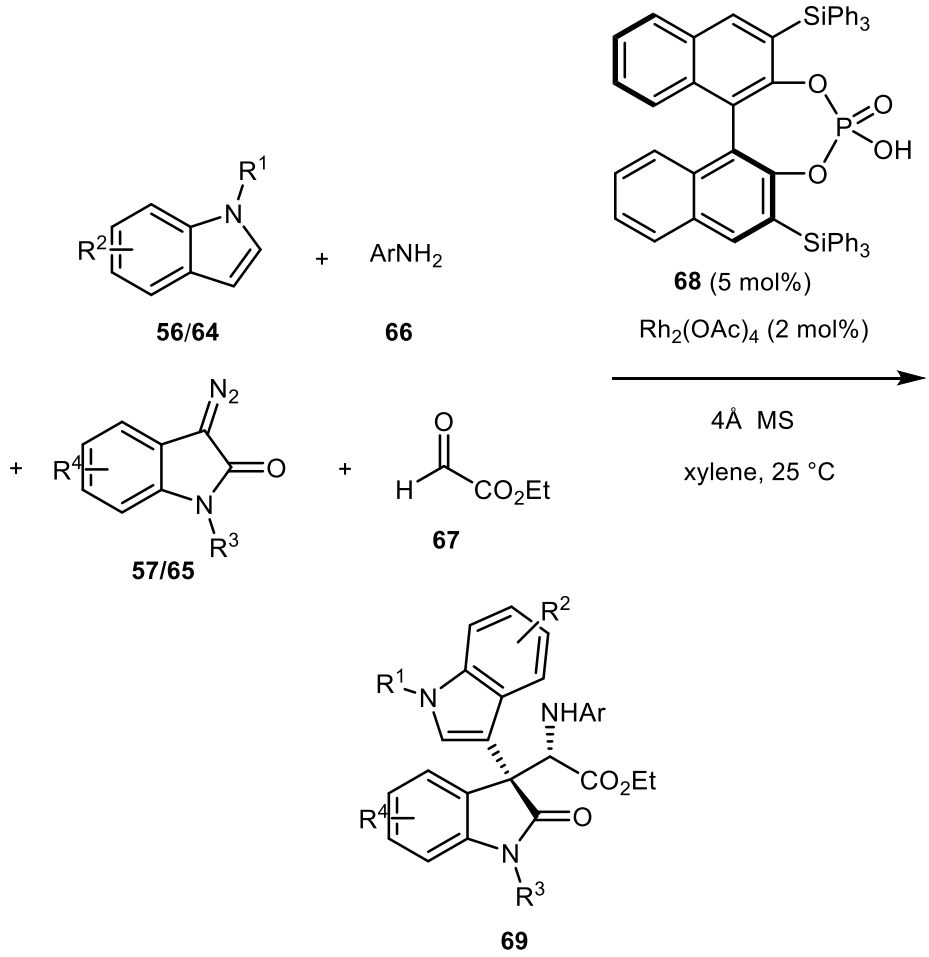
In the same study, the authors also investigated electrophiles other than allenoates **58**, such as vinyl ketones **61**. In this case, the three-component reaction of the latter with indoles **56** and 3-diazooxindoles **57** evolved through a domino C−H functionalization/Michael process.[29] It was catalyzed at -60 °C by a combination of 10 mol% of related chiral bifunctional phosphine **62** and 0.01-0.05 mol% of $Rh_2(esp)_2$ in chloroform as the solvent. As illustrated in Scheme 19, it yielded the corresponding chiral quaternary 3,3'-indolyloxindole derivatives **63** in moderate to excellent yields (61-94%) and enantioselectivities (56-92% *ee*). The presence of electron-donating substituents at the indole moiety generally provided higher enantioselectivities than those with electron-deficient substituents. Moreover, methyl-, ethyl- as well as phenyl vinyl ketones were compatible.



Scheme 19. Three-component domino C−H functionalization/Michael reaction of indoles, 3-diazooxindoles and vinyl ketones.

In the same context, Hu and Xing have described a novel route to other chiral 3,3-disubstituted 3,3'-indolyloxindole derivatives on the basis of an asymmetric four-component reaction of indoles **56**/**64**, 3-diazooxindoles **57**/**65**, anilines **66** and ethyl glyoxylate **67**.[30] The one-pot reaction involved a combination of 2 mol% of $Rh_2(OAc)_4$ and 5 mol% of chiral phosphoric acid **68** in xylene as the solvent. It afforded at 25 °C the corresponding chiral products **69** exhibiting a quaternary stereogenic center as single diastereomers (>90% *de*) in both good to excellent yields (49-94%) and enantioselectivities (49-98% *ee*), as illustrated in Scheme 20. The study of the substrate scope showed that a variety of substituted anilines were compatible with the catalyst system. While the reaction of electron-deficient anilines provided very good enantioselectivities (Ar = *p*-BrC_6H_4, *p*-ClC_6H_4, 3,4-

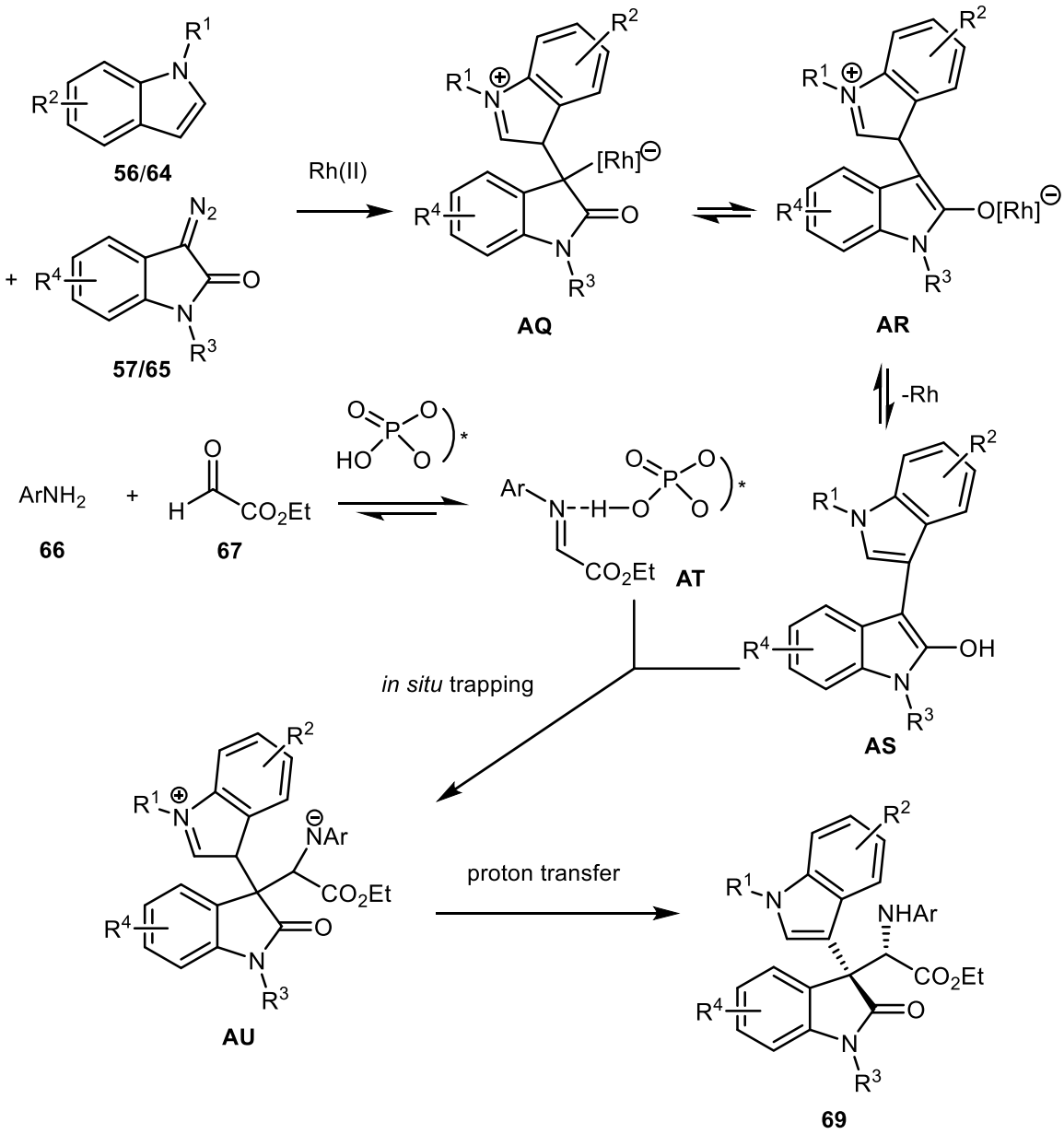
$Cl_2C_6H_3$, 3,5-$Cl_2C_6H_3$: 95-98% *ee*), that of electron-rich ones afforded the corresponding products in lower enantioselectivities (Ar = *p*-Tol: 49% *ee*). Concerning the scope of indoles, for C5-substituted ones, electron-withdrawing substituents gave higher enantioselectivities than electron-donating ones. The catalyst system was also compatible with C6- and C7-substituted indoles, giving the corresponding products with good yields and high enantioselectivities. Furthermore, *N*-Boc 3-diazooxindoles exhibiting substituents on the C5, C6 and C7 positions led to the corresponding products in good yields and high enantioselectivities (82-96% *ee*). In addition, different *N*-substituents on indoles and 3-diazooxindoles, such as *N*-benzyl, *N*-methyl and *N*-Boc groups, were tolerated.



R^1 = Bn, Me
R^2 = H, 5-Br, 5-OMe, 5-NO_2, 4-Br, 3-Me
R^3 = Boc, Bn
R^4 = H, 5-F, 5-Me, 4-F, 4-Cl
Ar = Ph, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-Tol, *p*-FC_6H_4, 3,4-$Cl_2C_6H_3$, 3,5-$Cl_2C_6H_3$

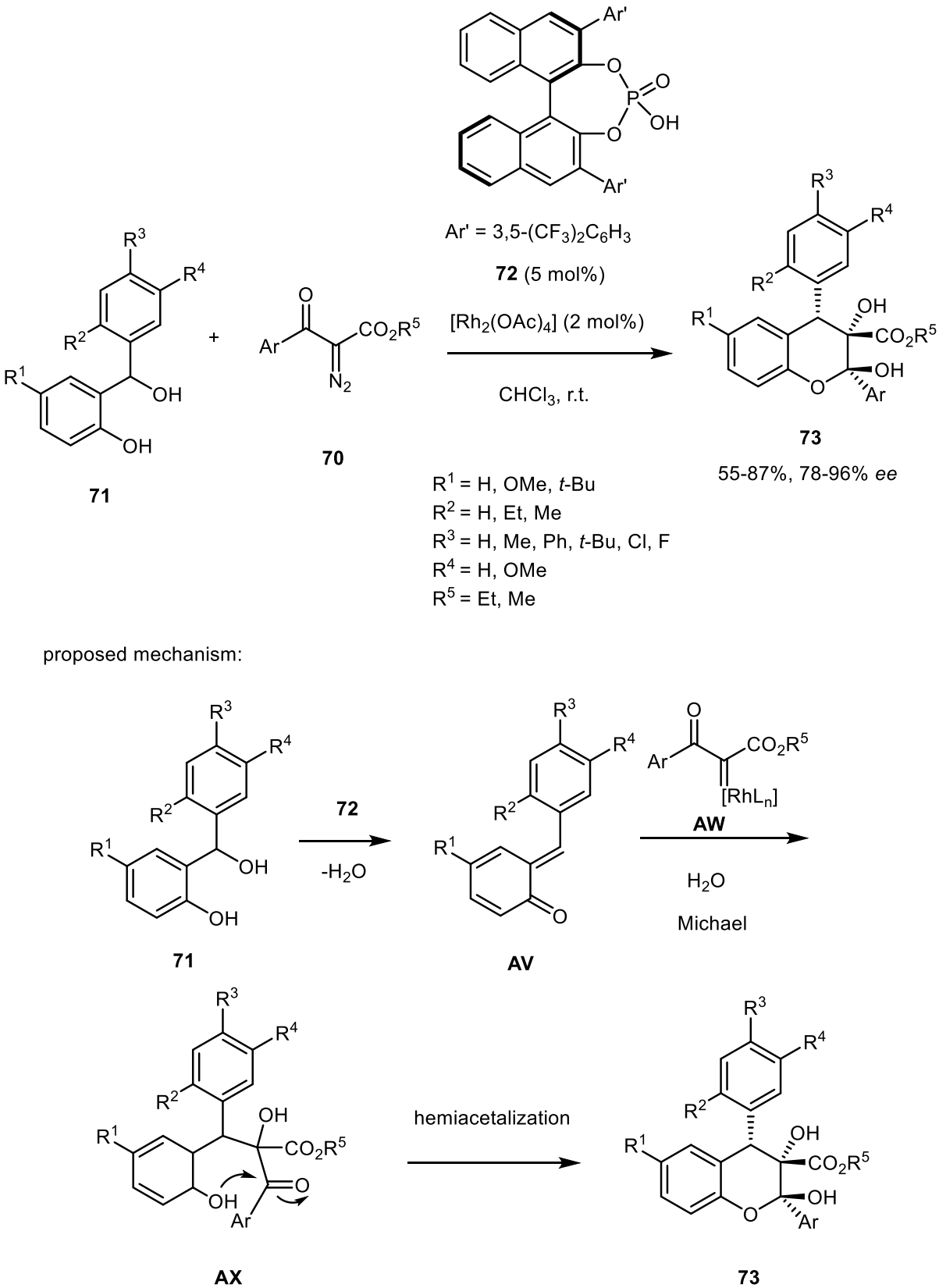
Scheme 20. Four-component reaction of indoles, 3-diazooxindoles, anilines and ethyl glyoxylate.

The process depicted in Scheme 20 was supposed to occur as shown in Scheme 21, zwitterionic intermediate **AQ** in equilibrium with **AR** was demetallated into enol **AS**, which further reacted with the phosphoric acid-activated iminoester **AT** to afford the final product after a proton transfer of intermediate **AU**.[30]



Scheme 21. Proposed mechanism for four-component reaction of indoles, 3-diazooxindoles, anilines and ethyl glyoxylate.

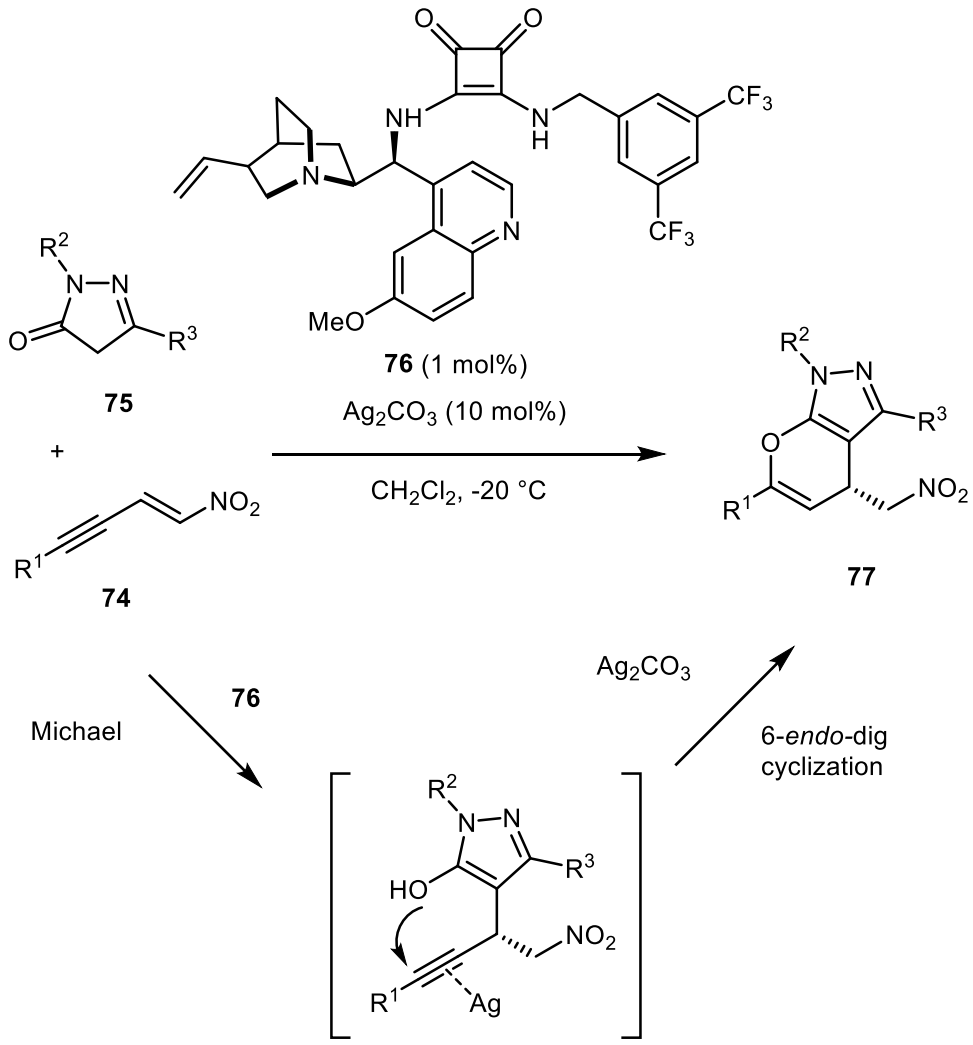
Later in 2016, an enantioselective domino Michael/hemiacetalization reaction between diazoesters **70** and *ortho*-hydroxy benzhydryl alcohols **71** was described by Schneider et al.[31] It involved a synergistic rhodium/phosphoric acid catalysis. As shown in Scheme 22, the process was performed at room temperature in the presence of a combination of 2 mol% of $Rh_2(OAc)_4$ and 5 mol% of chiral phosphoric acid **72** in chloroform as solvent, yielding the corresponding densely functionalized chiral chromans **73** bearing three contiguous stereogenic centers as single diastereomers in good to high yields (55-87%) and good to excellent enantioselectivities (78-96% *ee*). The process evolved through the *in situ* generation of *ortho*-quinone methides **AV** from the corresponding starting *ortho*-hydroxy benzhydryl alcohols **71** in the presence of the chiral phosphoric acid that trapped the rhodium carbene **AW** generated from the reaction of diazoester **70** with $Rh_2(OAc)_4$, resulting in the formation of intermediate **AX**. Then, the latter cyclized through hemiacetalization to give the final domino product.



Scheme 22. Domino Michael/hemiacetalization reaction of *ortho*-hydroxy benzhydryl alcohols with diazoesters.

2.5 Organo- and Silver Catalysis

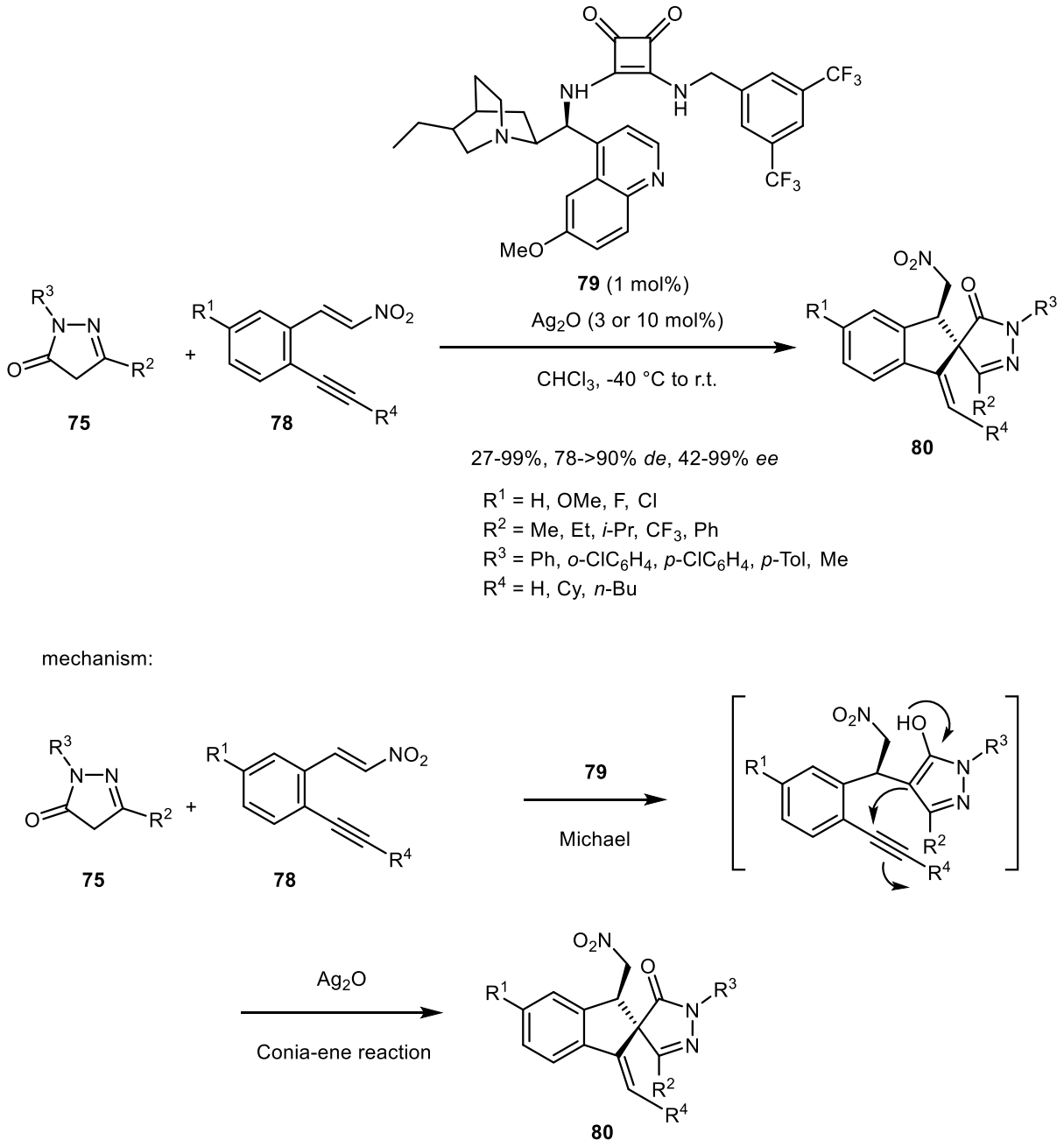
Silver has long been neglected in catalysis because of its moderate Lewis acidity. However, many efficient transformations,[32] such as asymmetric domino reactions,[33] are today available by using chiral silver catalysts. The first example of enantioselective silver-catalyzed domino reaction was reported in 1990 by Ito et al., dealing with a domino aldol/cyclization reaction of aldehydes with tosylmethyl isocyanide promotted by chiral ferrocenylphosphine/silver complexes with high enantioselectivity (86% *ee*).[34] Ever since, many other types of enantioselective silver-catalyzed domino reactions have been reported.[33,35] As a recent example, an asymmetric domino Michael/hydroalkoxylation reaction of alkyne-tethered nitroalkenes **74** with 5-pyrazolones **75** was disclosed by Enders et al., in 2015.[36] This process was based on a relay multicatalysis with cinchona-derived squaramide **76** and Ag_2CO_3. The reaction performed in dichloromethane at -20 °C afforded the corresponding chiral functionalized pyrano-annulated pyrazole derivatives **77** in moderate to excellent yields (48-95%) and high enantioselectivities (77-95% *ee*), irrespective of the steric or electronic nature of the substituents of alkynes (R^1) which could be (hetero)aromatic and aliphatic groups (Scheme 23). Only the alkynes bearing bulky substituents on the *ortho*-position (R^1 = *o*-BrC_6H_4, *o*-ClC_6H_4 or 1-naphthyl) gave slightly lower yields (74-77%). Interestingly, in all examples, a clean cyclization to the 6-*endo*-derived products was observed. Moreover, different pyrazolinones provided comparable results. The authors proposed a relay catalysis concept to explain this process in which the first Michael addition was organocatalyzed by **76**, and the second step promoted by the silver catalyst.



R^1 = Ph, *o*-BrC_6H_4, *p*-$F_3CC_6H_4$, *o*-ClC_6H_4, *m*-Tol, *m*-$MeOC_6H_4$, 3,4-$OCHOC_6H_3$, 1-Naph, 2-Naph, 1-furyl, 1-thienyl, *n*-Bu, *c*-Pent
R^2 = Ph, *o*-ClC_6H_4, *p*-ClC_6H_4, Me
R^3 = Me, CF_3
48-95%, 77-95% *ee*

Scheme 23. Domino Michael/hydroalkoxylation reaction of alkyne-tethered nitroalkenes with 5-pyrazolones.

Later in 2016, the same authors disclosed enantioselective silver-catalyzed domino Michael/Conia-ene reactions of 5-pyrazolones **75** with alkyne-tethered nitroalkenes **78** performed in chloroform as solvent.[37] The process was catalyzed at -40 °C to room temperature by a combination of 1 mol% of a cinchona-derived squaramide **79** as chiral organocatalyst with 3 or 10 mol% of Ag_2O, providing the corresponding chiral spiropyrazolones **80**. As shown in Scheme 24, the first step of the sequence was promoted by the organocatalyst while the second step by Ag_2O, according to a relay catalysis concept. The domino products were obtained in low to quantitative yields (27-99%) combined with moderate to excellent enantioselectivities (42-99% *ee*) and uniformly high diastereoselectivities (78->90% *de*) starting from variously substituted pyrazolones **75** and terminal alkynes **78**. It was found that sterically hindered nitroolefins provided the lowest yields (27-54%). Moreover, nitroalkenes with internal alkynes bearing aliphatic substituents (R^4 = Cy, *n*-Bu) were compatible, although requiring higher catalyst loadings in Ag_2O (10 mol% instead of 3 mol%).

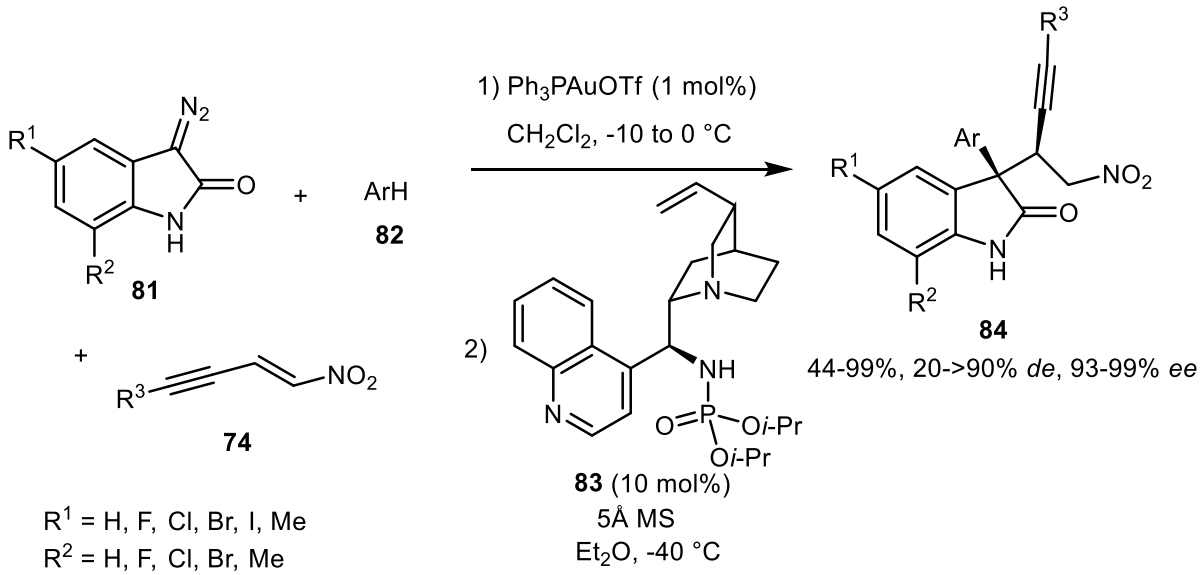


Scheme 24. Domino Michael/Conia-ene reaction of alkyne-tethered nitroalkenes with 5-pyrazolones.

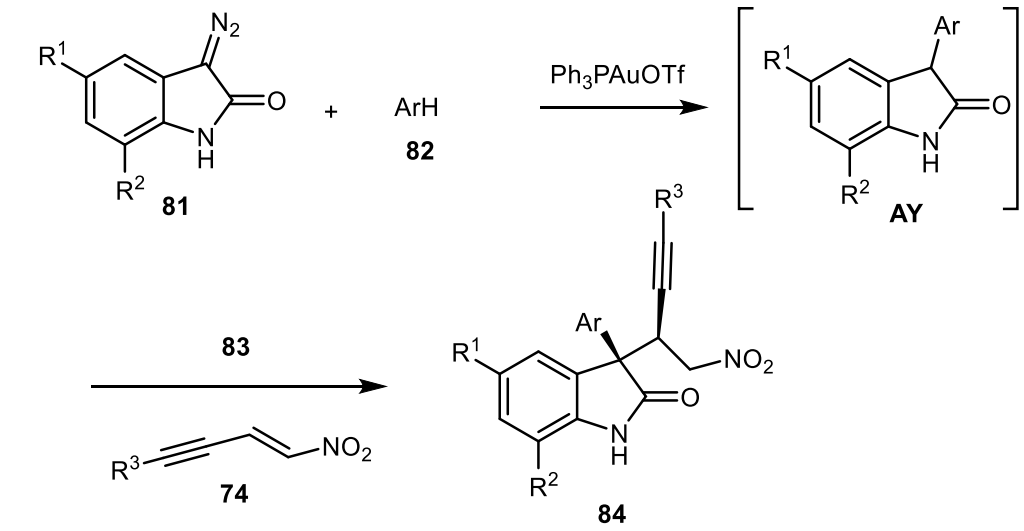
2.6 Organo- and Gold Catalysis

The combination of gold catalysis with organocatalysis has known a rapid growth in the last decade.[38] Whereas relay catalysis involves that there is no change in the reaction conditions and consequently both the two catalysts are present at the beginning of the reaction, in sequential catalysis the second catalyst is added after completion of the first catalytic cycle. In 2016, an example of novel asymmetric tandem sequential reaction catalyzed by a combination of gold and organocatalysis was described by Zhou et al.[39] It involved a C−H functionalization followed by a Michael reaction between diazooxindoles **81**, anisoles or thiophene **82**, and nitroenynes **74**. As depicted in Scheme 25, the process began with the gold-catalyzed C−H functionalization of the diazooxindole **76** with the anisole

or 3,4-dimethylthiophene **82** to give the corresponding 3-aryloxindole **AY** as intermediate which subsequently underwent a Michael addition to the nitroenyne **74** when cinchonidine-based bifunctional phosphoramide catalyst **83** was added to afford final 3,3-disubstituted chiral oxindole **84**. When performing this tandem C−H functionalization/Michael reaction with 1 mol% of $Ph_3PAuOTf$ in dichloromethane as the solvent at -10 to 0 °C, followed by addition of 10 mol% of organocatalyst **83** in diethylether at -40 °C, a range of chiral oxindoles **84** were synthesized in moderate to quantitative yields (44-99%), low to high diastereoselectivities (20->90% *de*) and uniformly excellent enantioselectivities (93-99% *ee*). The authors showed that the merging of the two catalytic reactions into one-pot operation was not possible. Indeed, it was found that dichloromethane had to be removed after the first step, since using diethylether as solvent was crucial to achieve a high diastereoselectivity in the Michael addition. The study of the substrate scope showed that the reaction conditions were compatible with differently substituted anisoles and nitroenynes. For example, the reaction of anisoles exhibiting a bromo or an iodo group as well as that of 3,4-dimethylthiophene (Ar = 3,4-$(Me)_2$-2-thienyl) all provided an excellent enantioselectivity (99% *ee*). Moreover, the alkyne substituent of nitroenynes could be an alkyl or aryl group as well as a trimethylsilyl group.



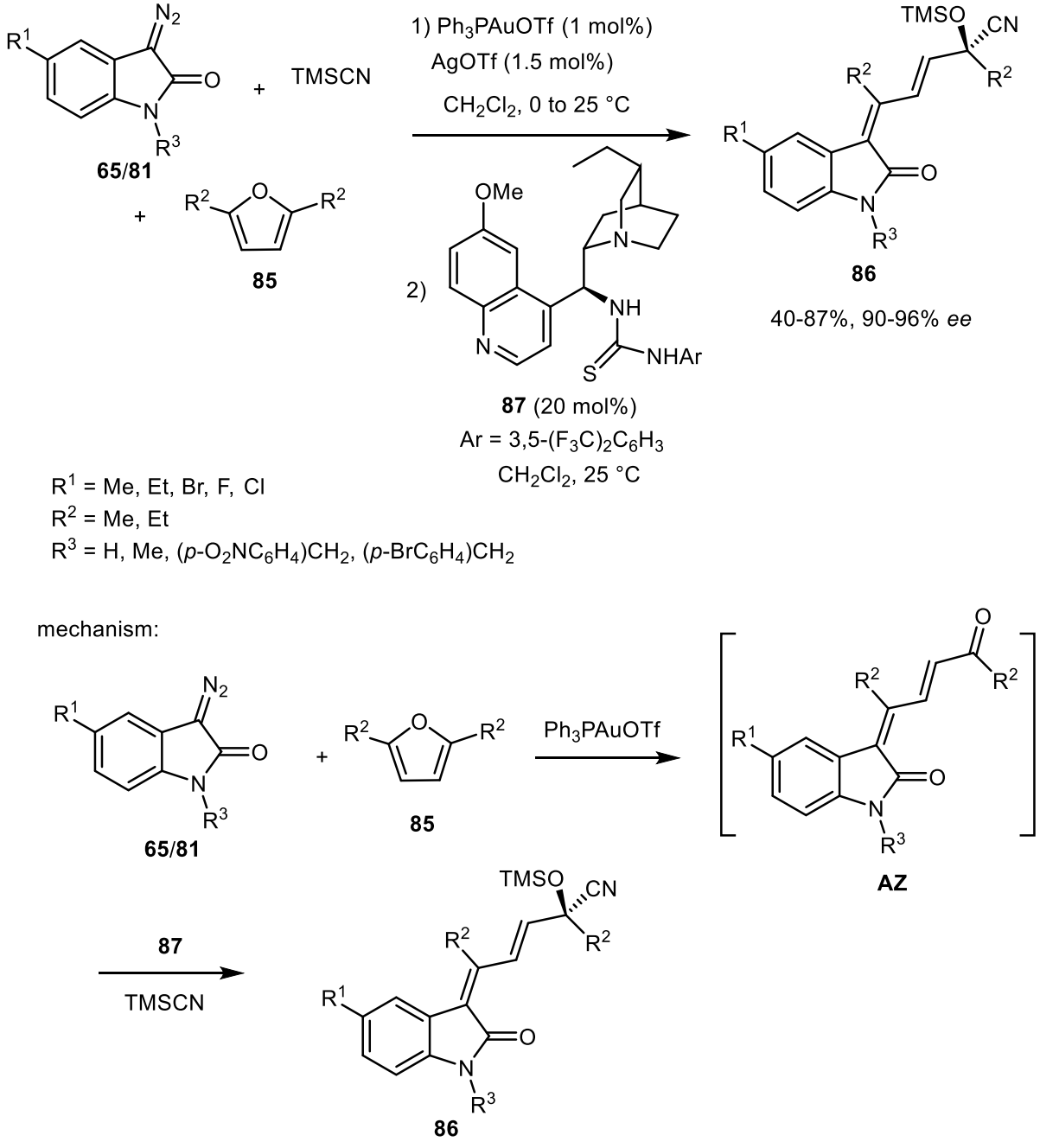
mechanism:



Scheme 25. Tandem C−H functionalization/Michael reaction of diazooxindoles, anisoles or 3,4-dimethylthiophene and nitroenynes.

The same authors also developed an unprecedented asymmetric sequential tandem enone formation/cyanosilylation reaction of diazooxindoles **65**/**81**, furans **85** and TMSCN, allowing the synthesis of optically active 3-alkenyloxindoles **81** that widely occur in bioactive compounds.[40] As illustrated in Scheme 26, the first step was catalyzed at 0 to 25 °C by 1 mol% of $Ph_3PAuOTf$ in dichloromethane as the solvent, followed by the addition of 20 mol% of hydroquinine-derived thiourea organocatalyst **87** in the same solvent at 25 °C. The first step consisted in the gold-catalyzed formation of enone **AZ** from the reaction between diazooxindole **65**/**81** and furan **85**, while the second step was an organocatalyzed cyanosilylation of this enone with TMSCN to yield the final chiral 3-alkenyloxindole **86** bearing a quaternary stereogenic center. A variety of these products were synthesized in moderate to high yields (40-87%) and uniformly excellent enantioselectivities (90-96%

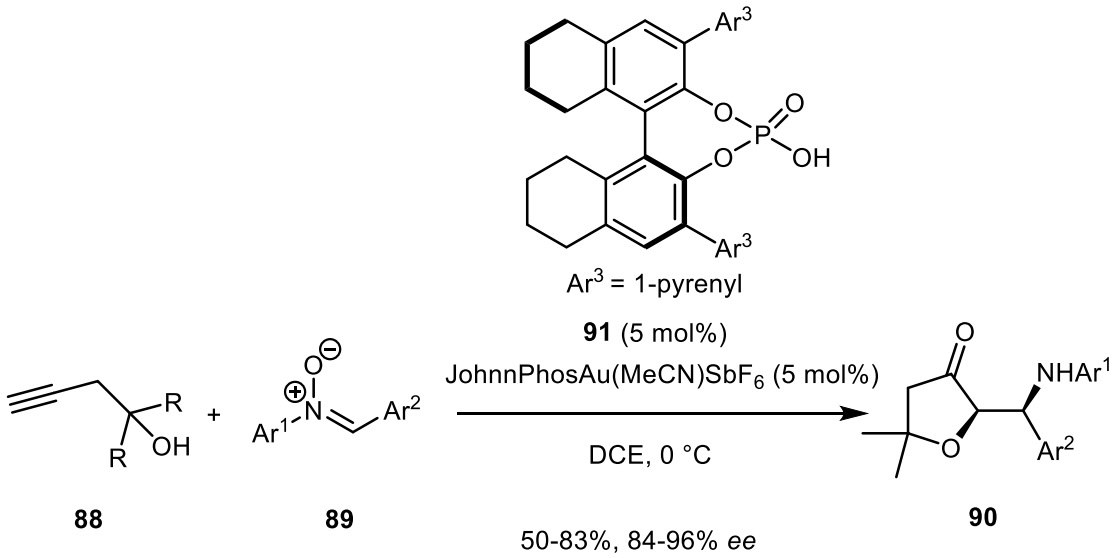
ee), as shown in Scheme 26. The process was compatible with unprotected diazooxindoles with different C5 substituents all providing the desired products in very high enantioselectivities (90-96% *ee*). However, due to the poor solubility of the enone intermediate in dichloromethane, some reactions could not achieve a full conversion, leading to lower yields (40% with R^1 = Br, R^2 = Me, R^3 = H vs 61-77%). On the other hand, *N*-protected diazooxindoles were more soluble, thus leading to the corresponding products with better yields (79-87%) along with comparable excellent enantioselectivities (92-95% *ee*).



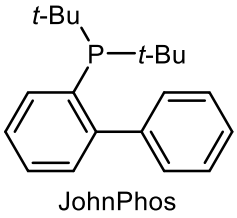
Scheme 26. Tandem enone formation/cyanosilylation reaction of diazooxindoles, furans and TMSCN.

In 2018, Hu and Xu reported an enantioselective domino oxidative/Mannich-type addition reaction of 3-butynols **88** with nitrones **89** to give the corresponding chiral dihydrofuran-3-ones **90**.[41] The

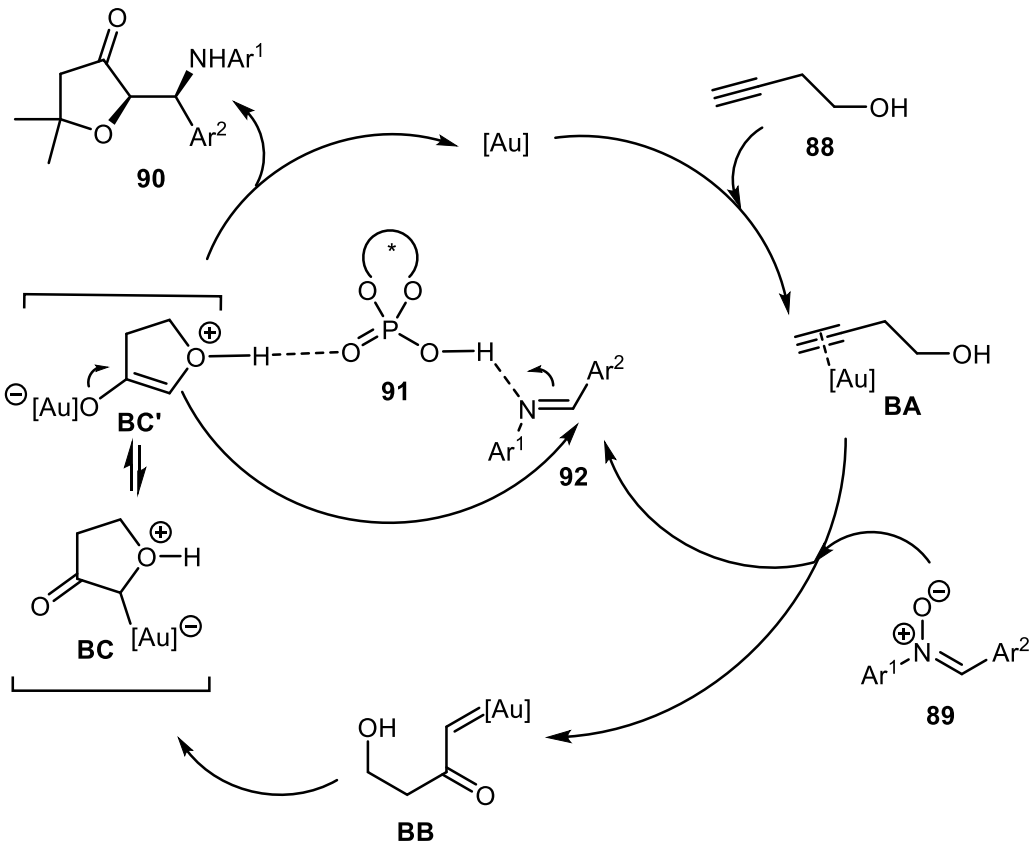
reaction evolved at 0 °C through cooperative catalysis involving 5 mol% of JohnPhosAu(MeCN)SbF_6 and the same quantity of chiral phosphoric acid **91** in DCE as the solvent. A wide variety of chiral products could be synthesized in uniformly high enantioselectivities (84-96% *ee*) and good to high yields (50-83%), as shown in Scheme 27. These good results were independent of the electronic character and steric hindrance of the substituents beared on the phenyl rings of nitrones. To explain the pathway of the domino process, the authors proposed the mechanism depicted in Scheme 27, beginning with gold-catalyzed alkyne oxidation in the presence of nitrone **89** to give gold carbene intermediate **BB** via gold alkyne complex **BA**. Then, intramolecular attack with the tethered hydroxy group of **BB** led to the formation of gold-oxonium ylide **BC** in equilibrium with its enolate form **BC'**. Subsequently, reaction of this intermediate with imine **92**, with the assistance of phosphoric acid organocatalyst through hydrogen bonding, yielded the final domino product **90** and regenerated the gold catalyst. The authors assumed that imine **92** was generated through N−O bond cleavage from nitrone **89**.



Ar^1 = Ph, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-Tol, *p*-$MeOC_6H_4$, *p*-$F_3CC_6H_4$, *p*-NCC_6H_4, *m*-BrC_6H_4
Ar^2 = Ph, *p*-FC_6H_4, *m*-FC_6H_4, *o*-BrC_6H_4, 2-thienyl, 2-furyl, *o*-$F_3CC_6H_4$, *m*-$F_3CC_6H_4$
R = H, Me



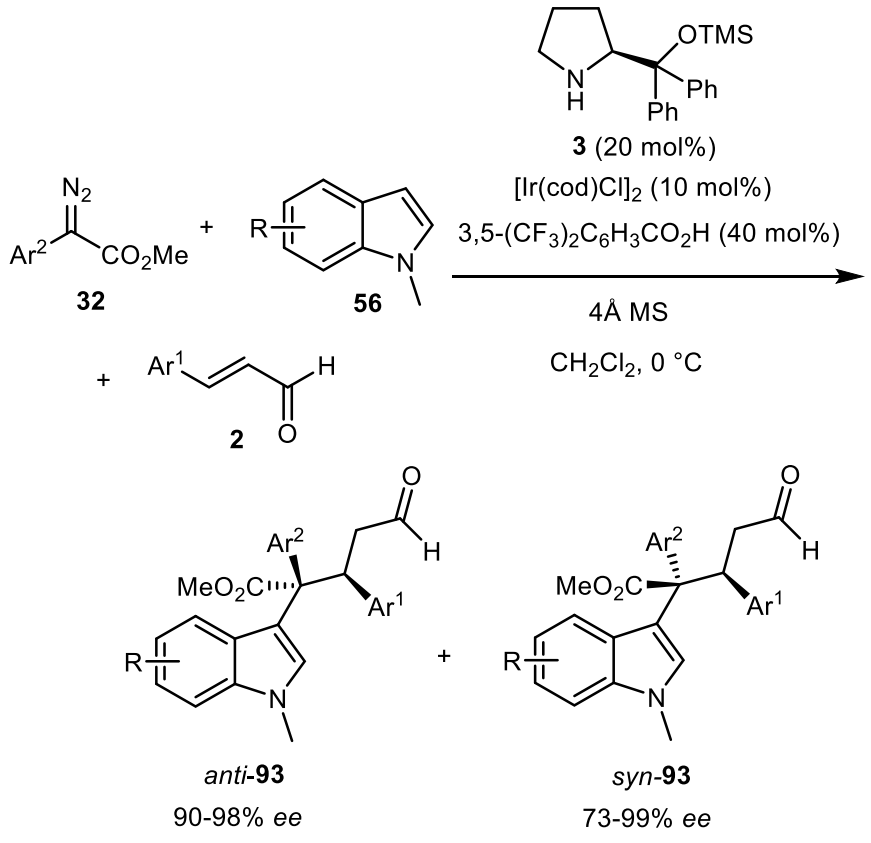
proposed mechanism (with R = H):



Scheme 27. Domino oxidative cyclization/Mannich-type addition reaction of 3-butynols and nitrones.

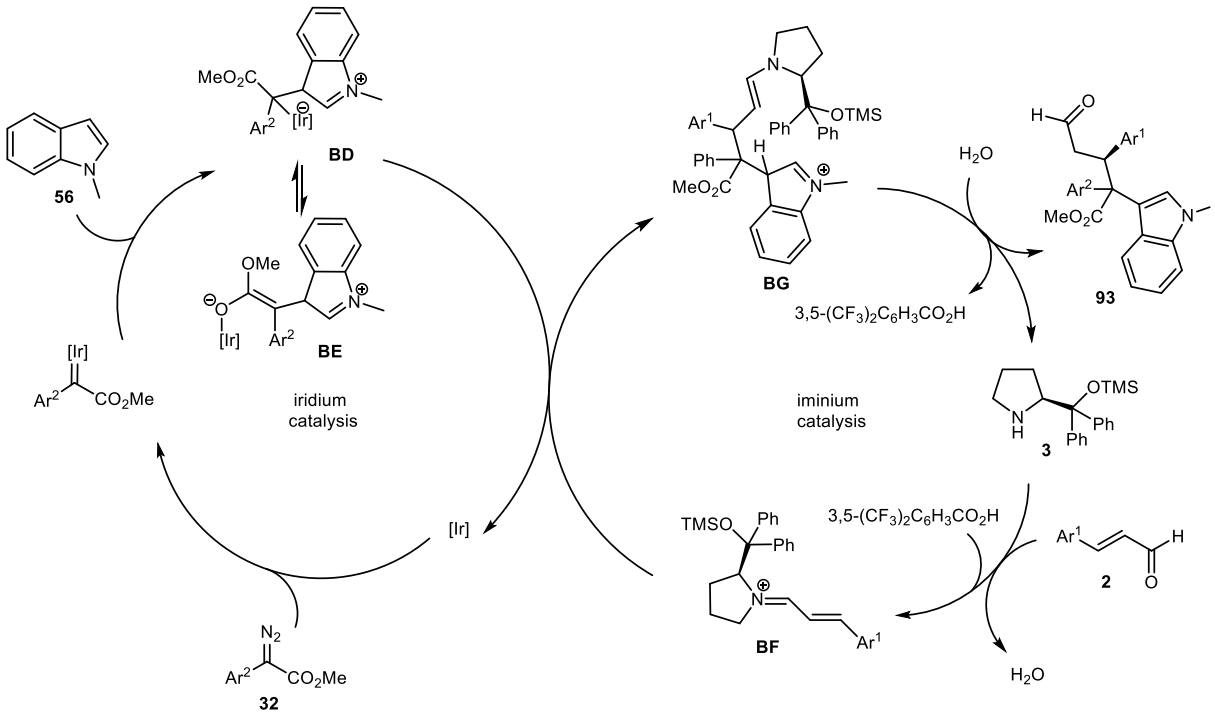
2.7 Organo- and Iridium Catalysis

In 2016, the first example of chiral secondary amine and iridium-catalyzed enantioselective three-component reaction of aryldiazoacetates **32**, indoles **56** and α,β-unsaturated aldehydes **2** was reported by Hu and Liu.[42] The domino reaction was performed in dichloromethane at 0 °C in the presence of a combination of 10 mol% of $[Ir(cod)Cl]_2$ and 20 mol% of proline-derived chiral amine **3** with a benzoic acid ($3,5\text{-}(CF_3)_2C_6H_3CO_2H$) as an additive. It afforded the corresponding chiral functionalized indole derivatives **93** as major *anti*-diastereomers with low to good diastereoselectivities (18-56% *de*). These products were obtained with low to high yields (34-80%) combined with uniformly excellent enantioselectivities (90-98% *ee*) for the major *anti*-products while the minor *syn*-indoles were obtained in good to excellent enantioselectivities (73-99% *ee*), as presented in Scheme 28. Generally, various substitutions on the (hetero)aromatic rings of α,β-unsaturated aldehydes, diazo compounds and indoles were tolerated. However, the process was found sensitive to the steric effect, since an *o*-bromo-substituted phenyl diazoacetate did not lead to the corresponding domino product whereas a *p*-bromo-substituted one gave the desired product.



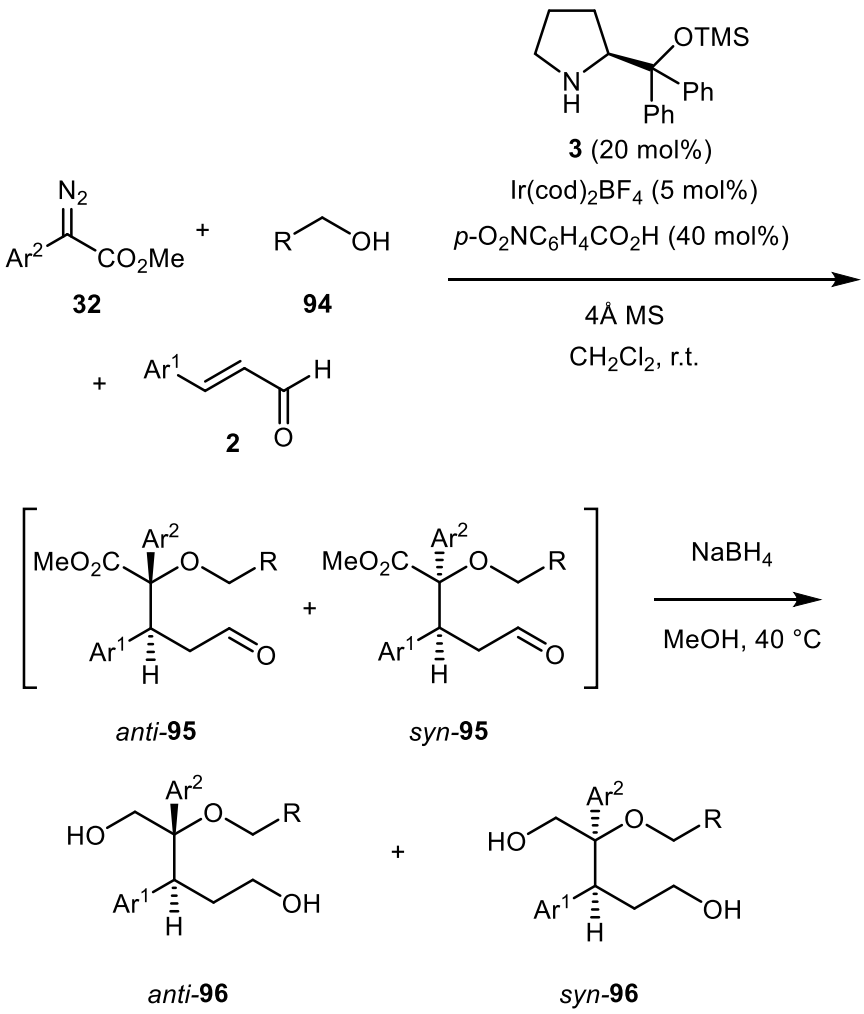
Scheme 28. Three-component reaction of aryldiazoacetates, indoles and α,β-unsaturated aldehydes.

The authors proposed the mechanism depicted in Scheme 29 to explain these results.[42] A zwitterionic intermediate **BD** or enolate **BE** was formed *in situ* from the iridium-catalyzed diazo decomposition of aryldiazoacetate **32** and indole **56**. For the iminium catalysis, the additive benzoic acid accelerated the formation of an iminium ion **BF**, which trapped the zwitterionic intermediate **BD**/**BE** to provide enamine **BG**. Then, hydrolysis of **BG** yielded the final domino product **93** and regenerated the organocatalyst.



Scheme 29. Mechanism for three-component reaction of aryldiazoacetates, indoles and α,β-unsaturated aldehydes.

Later in 2017, the same authors developed a related three-component reaction between aryldiazoacetates **32**, α,β-unsaturated aldehydes **2** and alcohols **94** (Scheme 30).[43] In this case, the domino reaction was performed at room temperature in dichloromethane as the solvent in the presence of a combination of 5 mol% of $Ir(cod)_2BF_4$ and 20 mol% of the same organocatalyst **3** in the presence of *p*-nitrobenzoic acid as an additive. Following a related mechanism, the reaction generally afforded a 1:1 mixture of the corresponding domino products *anti*-**95** and *syn*-**95** which were subsequently reduced by treatment with $NaBH_4$ to give a mixture of chiral 1,2,5-triol derivatives *anti*-**96** and *syn*-**96** obtained in moderate to quantitative yields (50-95%). In most cases, both the two diastereomers were achieved in excellent enantioselectivities (87-99% *ee*).



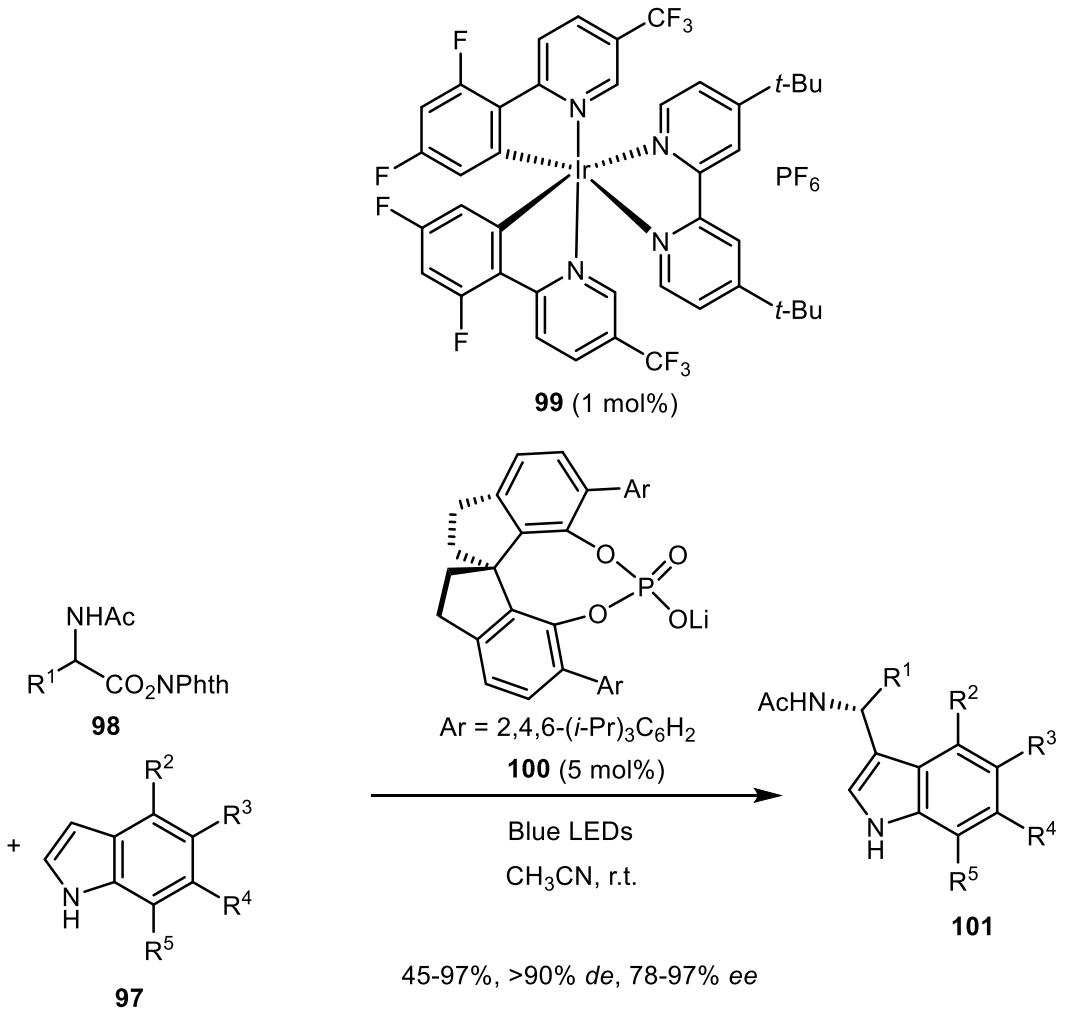
50-95%, *anti/syn* = 37:63-50/50
ee (*anti*) = 53-99%, *ee* (*syn*) = 95-99%

Ar^1 = Ph, *p*-$O_2NC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$MeOC_6H_4$, *p*-Tol, *m*-Tol
Ar^2 = Ph, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-Tol, *m*-$MeOC_6H_4$, *o*-BrC_6H_4
R = Ph, *p*-BrC_6H_4, *p*-$MeOC_6H_4$, *m*-BrC_6H_4, $TMSCH_2$

Scheme 30. Three-component reaction of aryldiazoacetates, alcohols and α,β-unsaturated aldehydes.

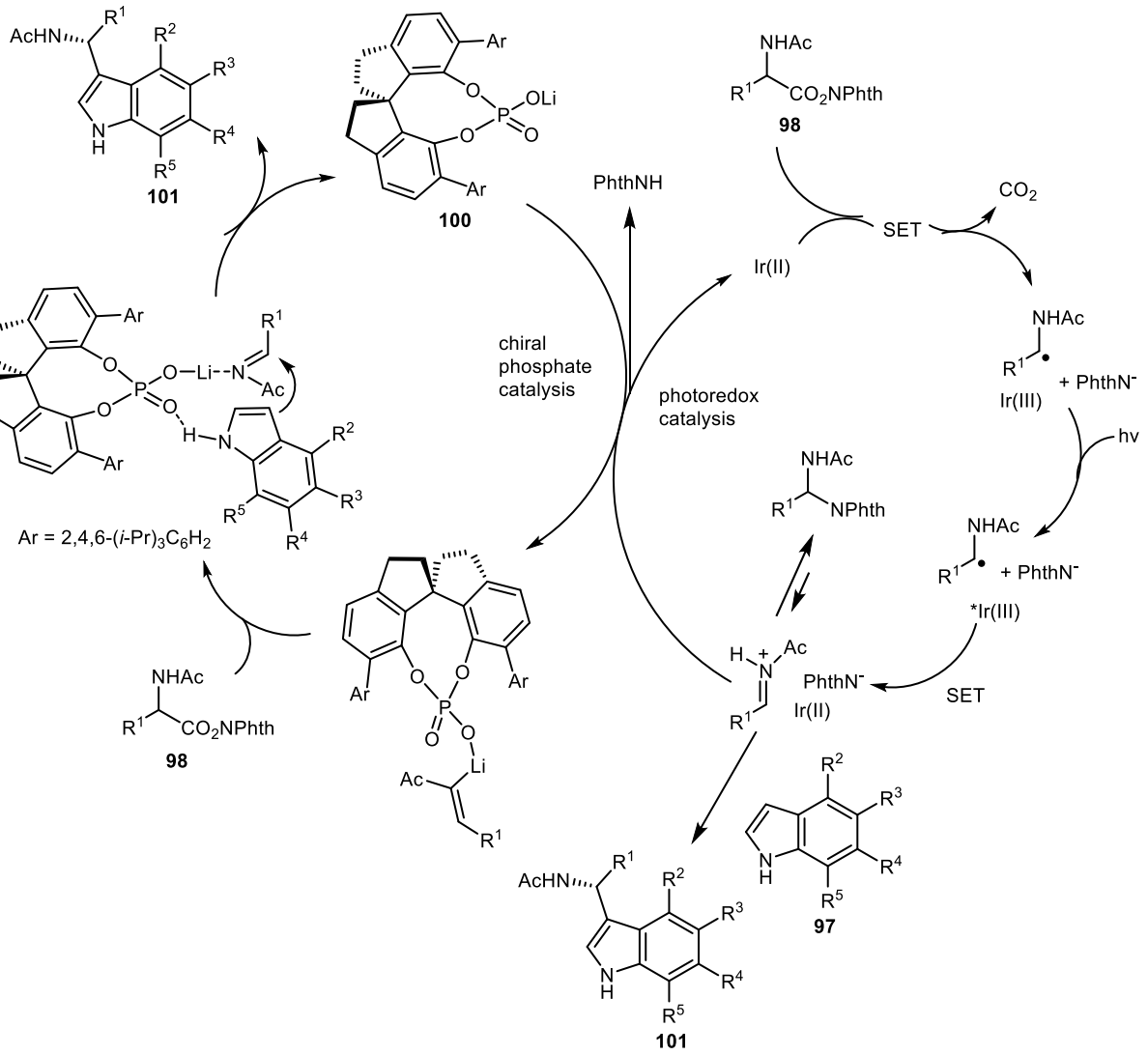
In 2019, Wang et al. developed an asymmetric domino *N*-acyl imine formation/Friedel−Crafts reaction of *N*-unsubstituted indoles **97** and *N*-acylated α-amino acids **98** based on visible-light photoredox iridium and chiral Brønsted acid combined catalysis.[44] The process was performed in acetonitrile at room temperature in the presence of 1 mol% of iridium photoredox catalyst **99** and 5 mol% of chiral phosphate **100**, as shown in Scheme 31. It afforded a range of chiral indolyl-1-alkylamine derivatives **101** in moderate to excellent yields (45-97%) combined with good to very high enantioselectivities (78-97% *ee*). Variously substituted indoles were compatible with the conditions, providing uniformly high enantioselectivities with either electron-donating or electron-withdrawing substituents. Moreover, a wide variety of nonaromatic α-amino acid-derived redox-active esters was tolerated. The authors proposed that *N*-acylated α-amino acids **98** generated the corresponding α-aminoalkyl radicals which were subsequently oxidized by the oxidative iridium photocatalyst to give the corresponding *N*-acyl

imines. The latter then underwent a Friedel−Crafts reaction with indoles **97** catalyzed by chiral phosphate catalyst **100**.



Scheme 31. Domino *N*-acyl imine formation/Friedel−Crafts reaction of indoles and *N*-acylated α-amino acids.

A plausible mechanism is detailed in Scheme 32, in which the irradiated Ir*(III) was quenched by indole **97**. Then, the corresponding reductive Ir(II) engaged in single-electron transfer (SET) with *N*-(acyloxy)-phthalimide, generating an α-aminoalkyl radical and Ir(III). The latter was reirradiated by blue light to regenerate oxidative Ir*(III), which further oxidized α-aminoalkyl radical to give protonated *N*-acyl imine or the corresponding aminal. The chiral phosphate was supposed to act as a bifunctional catalyst, including *N*-acyl imine activation and hydrogen bond formation with indole **97**, bringing them together in a chiral environment.

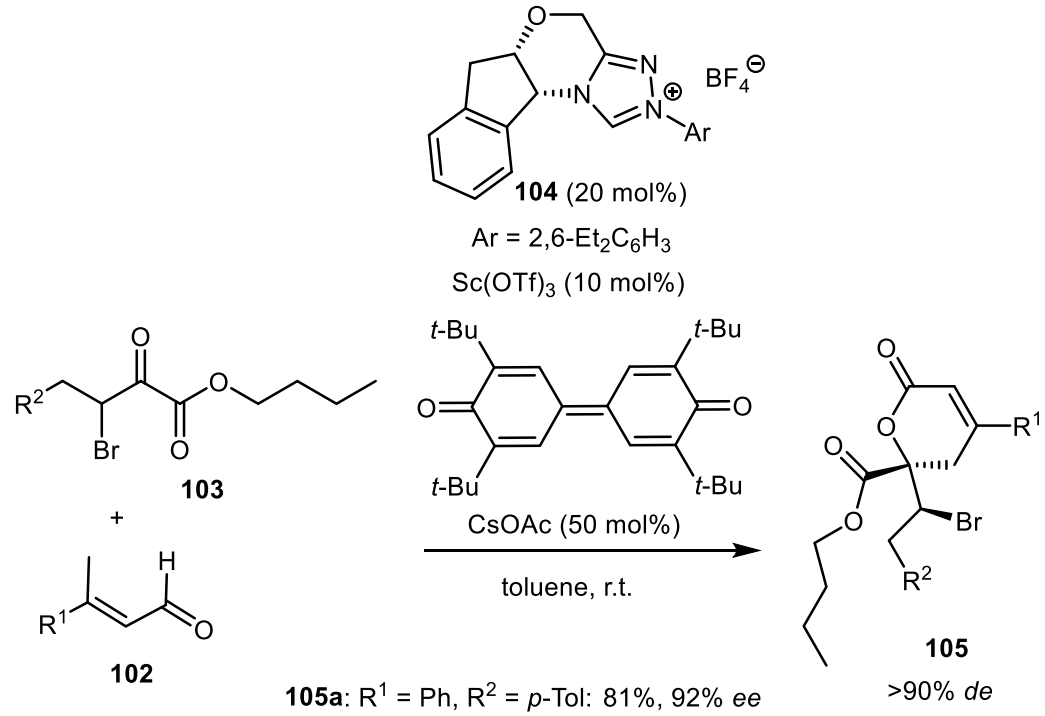


Scheme 32. Mechanism for domino *N*-acyl imine formation/Friedel−Crafts reaction of indoles and *N*-acylated α-amino acids.

2.8 Organo- and Other Metal Catalysis

While chiral catalysts based on p- or d-block metal elements have been widely investigated in asymmetric catalysis, the use of f-block elements has been much less studied so far.[45] However, in recent years chiral scandium catalysts have been successfully applied to promote enantioselective domino reactions.[46] Among them, a novel asymmetric domino γ-addition/cyclization reaction of α,β-unsaturated aldehydes **102** with β-bromo-α-ketoesters **103** was disclosed by Wang et al., in 2015 (Scheme 33).[47] This process was catalyzed by a combination of 20 mol% of chiral N-heterocyclic carbene (NHC) catalyst **104** with 10 mol% of $Sc(OTf)_3$ in toluene at room temperature in the presence of CsOAc as a base, leading to the corresponding chiral unsaturated δ-lactones **105** in moderate to high yields (67-88%), uniformly very high diastereoselectivity (>90% *de*) and moderate to excellent enantioselectivities (40-98% *ee*). Especially, the reaction of α,β-unsaturated aldehydes bearing various (hetero)aromatic substituents (R^1) provided good to high yields (70-88%) and uniformly high enantioselectivities (85-98% *ee*). An allyl-substituted substrate (R^1 = allyl) afforded the corresponding product **105v** in 83% yield, >90% *de* and 89% *ee* while the formation of product **105w** from a methyl-

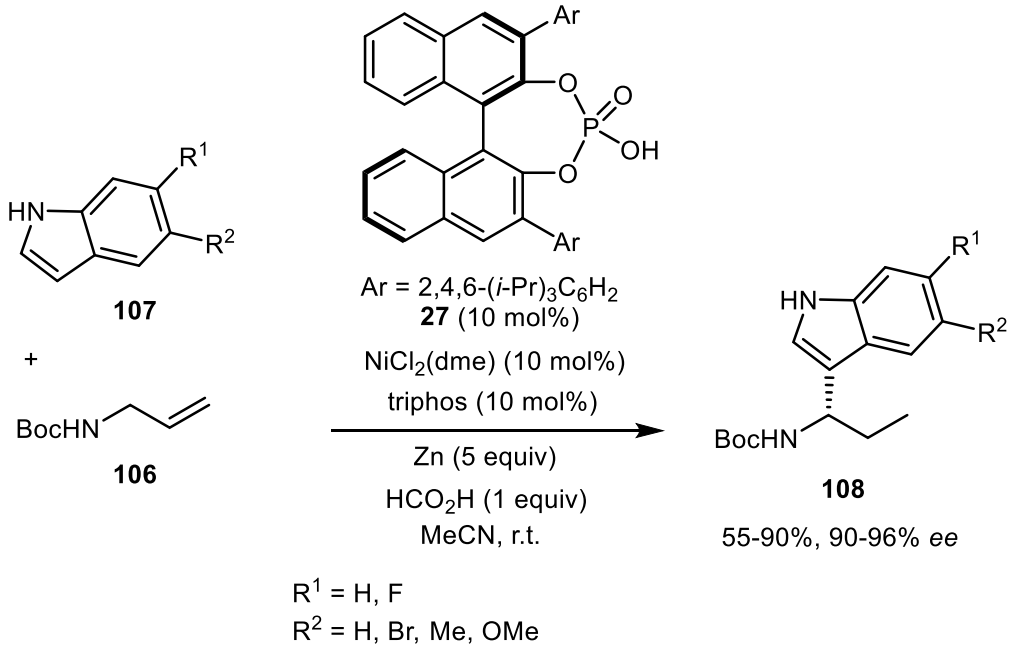
β-substituted α,β-unsaturated aldehyde resulted in a slow conversion (<10% at r.t., 67% yield at 50 °C) and a moderate enantioselectivity of 40% *ee* but always as almost single diastereomer (>90% *de*). On the other hand, the nature of the substituent (R^2) at the γ-position of β-bromo-α-ketoesters **103** had no influence on the results since they were homogeneous for aliphatic and (hetero)aromatic groups.



105a: R^1 = Ph, R^2 = *p*-Tol: 81%, 92% *ee*
105b: R^1 = Ph, R^2 = *p*-$MeOC_6H_4$: 80%, 85% *ee*
105c: R^1 = Ph, R^2 = *p*-FC_6H_4: 79%, 90% *ee*
105d: R^1 = Ph, R^2 = *p*-$CF_3C_6H_4$: 86%, 93% *ee*
105e: R^1 = Ph, R^2 = *m*-ClC_6H_4: 82%, 90% *ee*
105f: R^1 = Ph, R^2 = *o*-FC_6H_4: 80%, 92% *ee*
105g: R^1 = Ph, R^2 = 2-Naph: 83%, 90% *ee*
105h: R^1 = Ph, R^2 = 2-thienyl: 83%, 86% *ee*
105i: R^1 = Ph, R^2 = $CH{=}CH_2$: 70%, 87% *ee*
105j: R^1 = Ph, R^2 = Cy: 85%, 91% *ee*
105k: R^1 = Ph, R^2 = Et: 76%, 90% *ee*
105l: R^1 = Ph, R^2 = H: 77%, 91% *ee*
105m: R^1 = *p*-Tol, R^2 = Ph: 79%, 92% *ee*
105n: R^1 = *p*-$MeOC_6H_4$, R^2 = Ph: 70%, 94% *ee*
105o: R^1 = *p*-FC_6H_4, R^2 = Ph: 80%, 91% *ee*
105p: R^1 = *p*-ClC_6H_4, R^2 = Ph: 81%, 85% *ee*
105q: R^1 = *p*-BrC_6H_4, R^2 = Ph: 84%, 90% *ee*
105r: R^1 = *p*-$NO_2C_6H_4$, R^2 = Ph: 85%, 96% *ee*
105s: R^1 = 2-Naph, R^2 = Ph: 80%, 93% *ee*
105t: R^1 = 3-pyridyl, R^2 = Ph: 88%, 98% *ee*
105u: R^1 = 2-thienyl, R^2 = Ph: 75%, 90% *ee*
105v: R^1 = allyl, R^2 = Ph: 83%, 89% *ee*
105w: R^1 = Me, R^2 = Ph: 67%, 40% *ee* (50 °C)

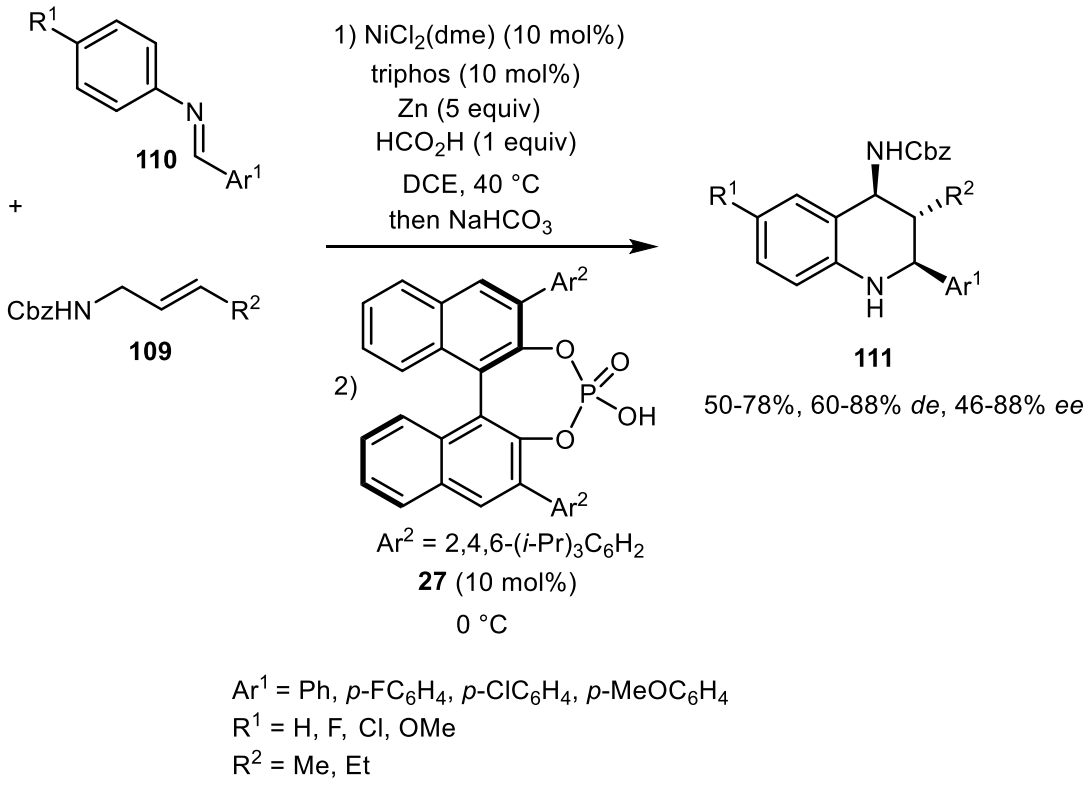
Scheme 33. Scandium-/organocatalyzed domino γ-addition/cyclization reaction of α,β-unsaturated aldehydes with β-bromo-α-ketoesters.

On the basis of the lower costs of nickel catalysts in comparison with many other transition metals and its wide range of oxidation states, enantioselective nickel-mediated transformations have blossomed in the last decade.[48] Among them, is an enantioselective domino isomerization/arylation reaction of *N*-Boc allylcarbamate **106** with unprotected indoles **107** described by Moran et al., in 2016.[49] The process was catalyzed by a combination of 10 mol% of $NiCl_2$(dme) and the same quantity of chiral phosphoric acid catalyst **27** in acetonitrile as solvent, as depicted in Scheme 34. It evolved through nickel-catalyzed isomerization of the *N*-Boc allylcarbamate in the presence of triphos (bis(diphenylphosphino-ethyl)phenylphosphine) as achiral ligand and zinc and formic acid as additives, followed by organocatalyzed enantioselective arylation of the resulting intermediate with an indole to yield the final chiral α-arylamine **108**. A range of domino products were synthesized in moderate to high yields (55-90%) and excellent enantioselectivities (90-96% *ee*).



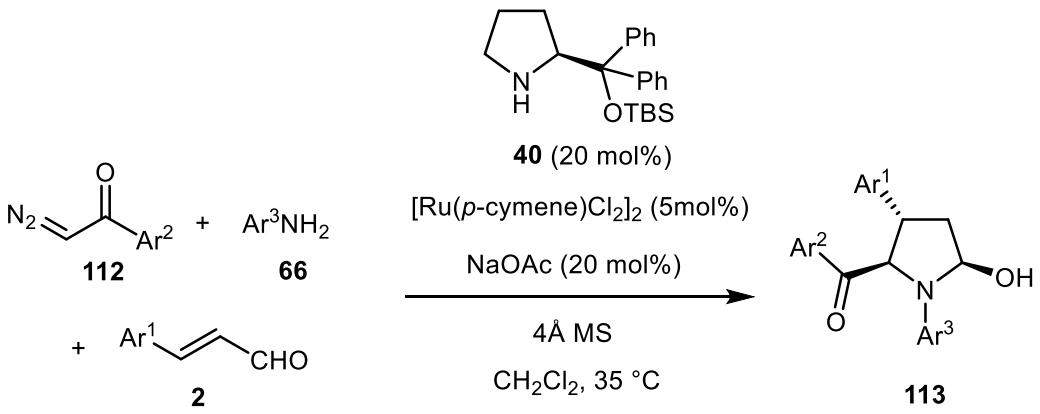
Scheme 34. Nickel-/organocatalyzed domino isomerization/arylation reaction of *N*-Boc allylcarbamate with indoles.

The same catalyst system was applied by these authors to promote a tandem reaction between *N*-Cbz allylcarbamates **109** and aromatic imines **110**.[49**Fehler! Textmarke nicht definiert.**] In this case, the catalysts were employed sequentially. In a first step, *N*-Cbz allylcarbamate **109** was isomerized in the presence of 10 mol% of $NiCl_2$(dme) in DCE at 40 °C to give an intermediate to which was added 10 mol% of organocatalyst **27** at 0 °C, triggering a Povarov reaction. The tandem isomerization/Povarov process afforded the corresponding chiral tetrahydroquinolines **111** in good yields (50-78%), combined with moderate to good diastereo-(60-88% *de*) and enantioselectivities (46-88% *ee*), as illustrated in Scheme 35.



Scheme 35. Nickel-/organocatalyzed tandem isomerization/Povarov reaction of *N*-Cbz allylcarbamates with aromatic imines.

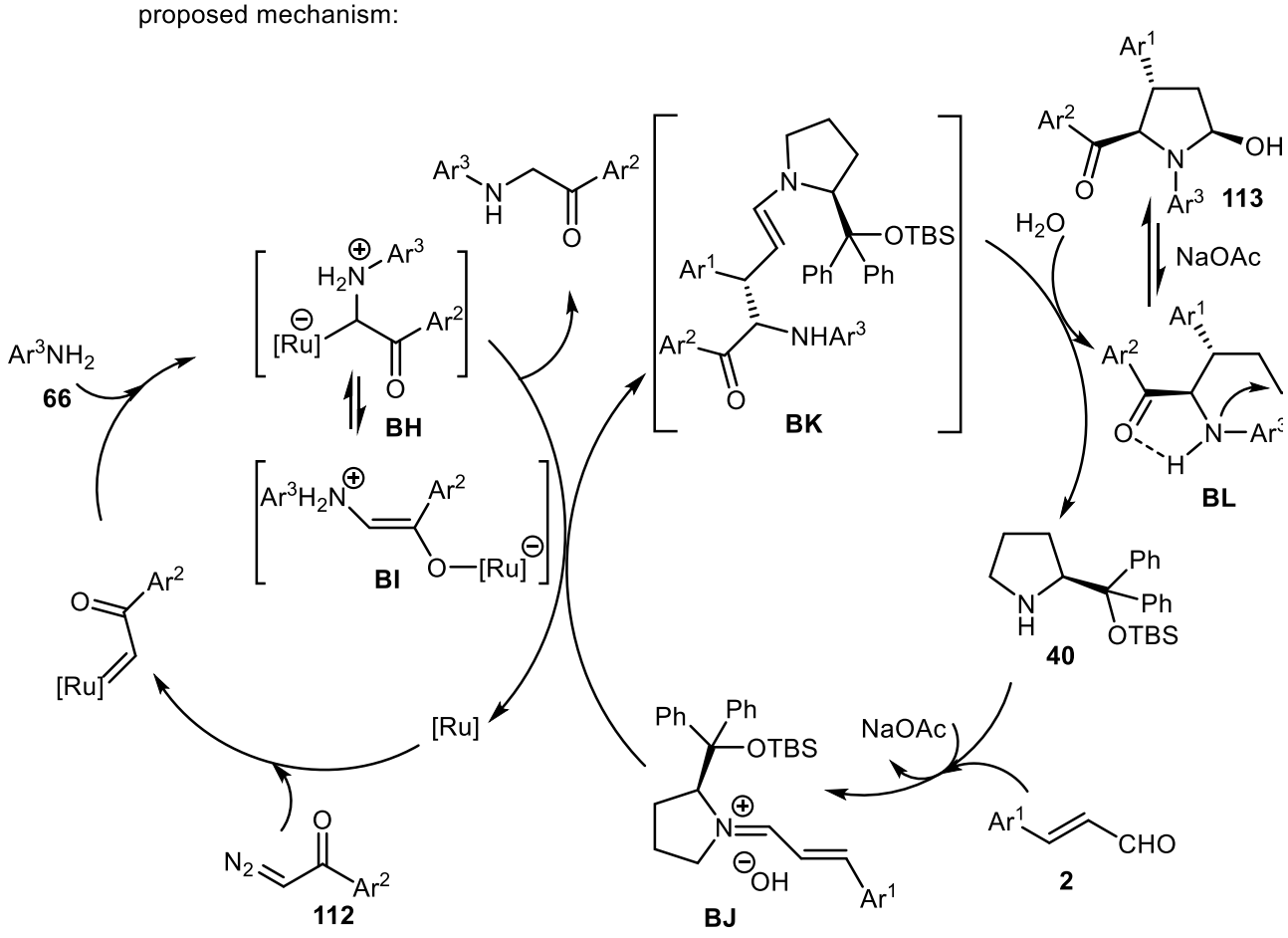
In 2017, the combination of rhutenium and iminium catalysis was applied by Hu and Liu to promote enantioselective three-component reaction of diazoacetophenones **112**, anilines **66** and α,β-unsaturated aldehydes **2**.[50] This formal [3+1+1] cycloaddition was performed at 35 °C in dichloromethane as the solvent in the presence of a combination of 5 mol% of [Ru(*p*-cymene)Cl_2]$_2$ with 20 mol% of proline-derived chiral amine **40** and 20 mol% of NaOAc as an additive. It led to the corresponding chiral multisubstituted pyrrolidines **113** in most cases as single diastereomers (>90% *de*) with moderate to good yields (40-65%) and uniformly high enantioselectivities (80-98% *ee*), as presented in Scheme 36. The authors proposed the mechanism depicted in this Scheme to explain the results. The ammonium ylide intermediate **BH** or enolate **BI** was *in situ* generated from the ruthenium-catalyzed diazo decomposition of aniline **66** and diazoacetophenone **112**. For NaOAc-promoted iminium catalytic cycle, α,β-unsaturated aldehydes **2** was activated by the organocatalyst to form iminium ion **BJ**, which trapped the ammonium ylide intermediate **BH** or **BI** to form enamine intermediate **BK**. Hydrolysis of the latter afforded intermediate **BL** and regenerated chiral organocatalyst **40**. Then, intermediate **BL** was submitted to an aza-aldol ring-closure to give the final product **113**.



40-65%, 34->90% *de*, 80-98% *ee*

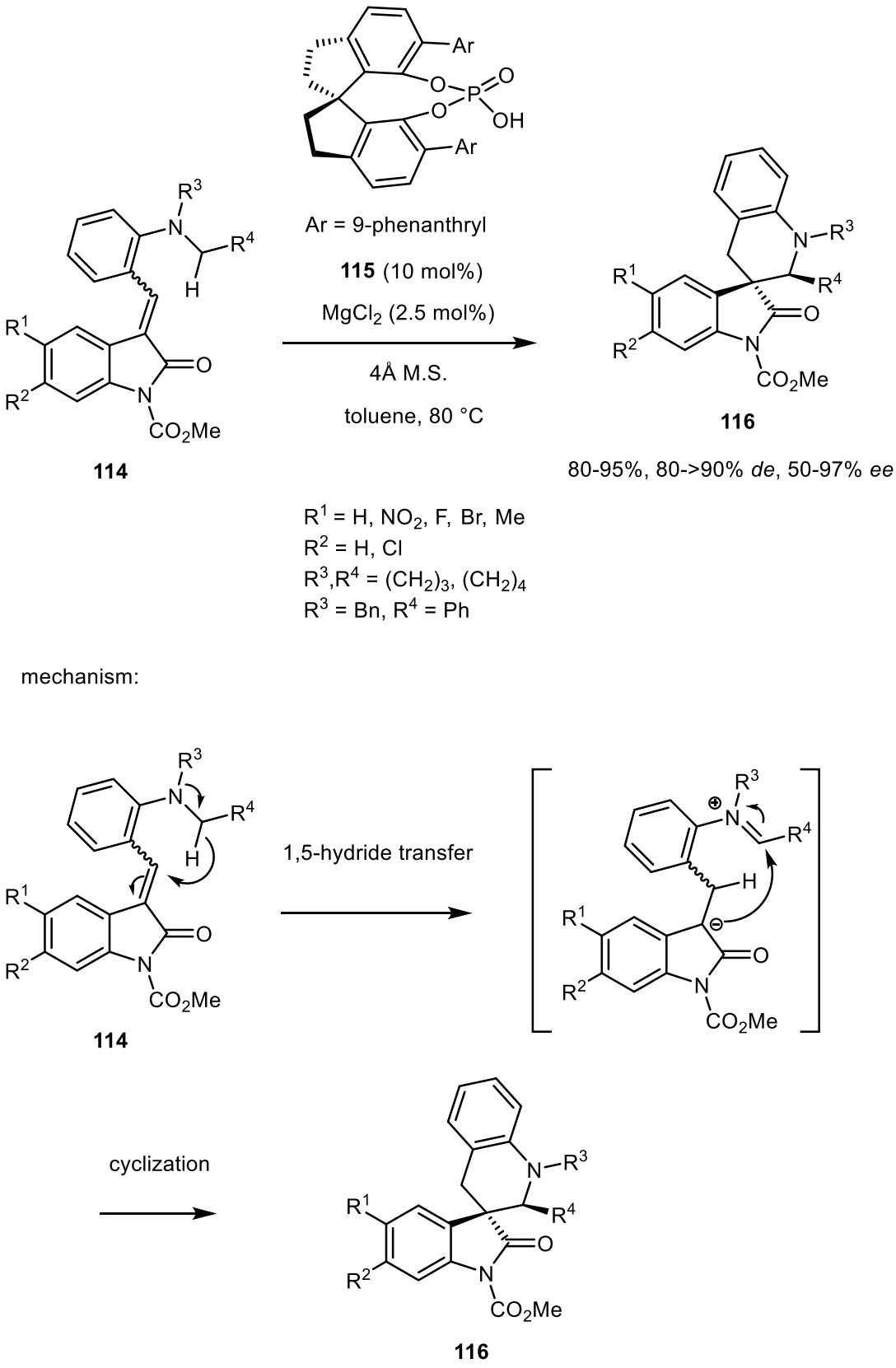
Ar^1 = Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-$O_2NC_6H_4$, *o*-$O_2NC_6H_4$, 2-furyl
Ar^2 = Ph, *p*-$MeOC_6H_4$, 3,4-$Cl_2C_6H_3$, *p*-ClC_6H_4, *m*-ClC_6H_4, *o*-ClC_6H_4, *p*-BrC_6H_4
Ar^3 = *p*-BrC_6H_4, Ph, 3,5-$Cl_2C_6H_3$, *p*-ClC_6H_4

proposed mechanism:



Scheme 36. Ruthenium-/organocatalyzed three-component reaction of diazoacetophenones, anilines and α,β-unsaturated aldehydes.

Alkaline earth metals, such as magnesium, are abundant, inexpensive and environmentally benign in contrast with traditional transition metals. Furthermore, due to their milder Lewis acidity in comparison to other transition metals, they exhibit a promising ability in the field of catalytic transformations.[51] Since the early reports by Corey in 1992,[52] many highly enantioselective green magnesium-catalyzed reactions have been developed, including the first asymmetric magnesium-catalyzed domino reactions disclosed only recently. As an example, Lin et al. described in 2016 an enantioselective intramolecular domino 1,5-hydride transfer/cyclization reaction of oxindole derivatives **114** promoted by a combination of 2.5 mol% of $MgCl_2$ and 10 mol% of chiral phosphoric acid **115**.[53] Performed in toluene at 80 °C, the domino reaction afforded the corresponding chiral spirooxindole tetrahydroquinolines **116** in both high yields (80-95%) and diastereoselectivities (80->90% *de*) combined with moderate to excellent enantioselectivities (50-97% *ee*), as illustrated in Scheme 37. The best enantioselectivities (93-97% *ee*) were achieved in the reaction of substrates bearing a strong electron-withdrawing group on the oxindole aromatic ring ($R^1 = NO_2$) while the lowest enantioselectivity (50% *ee*) was obtained in the reaction of a substrate bearing an electron-rich substituent (R^1 = Me).



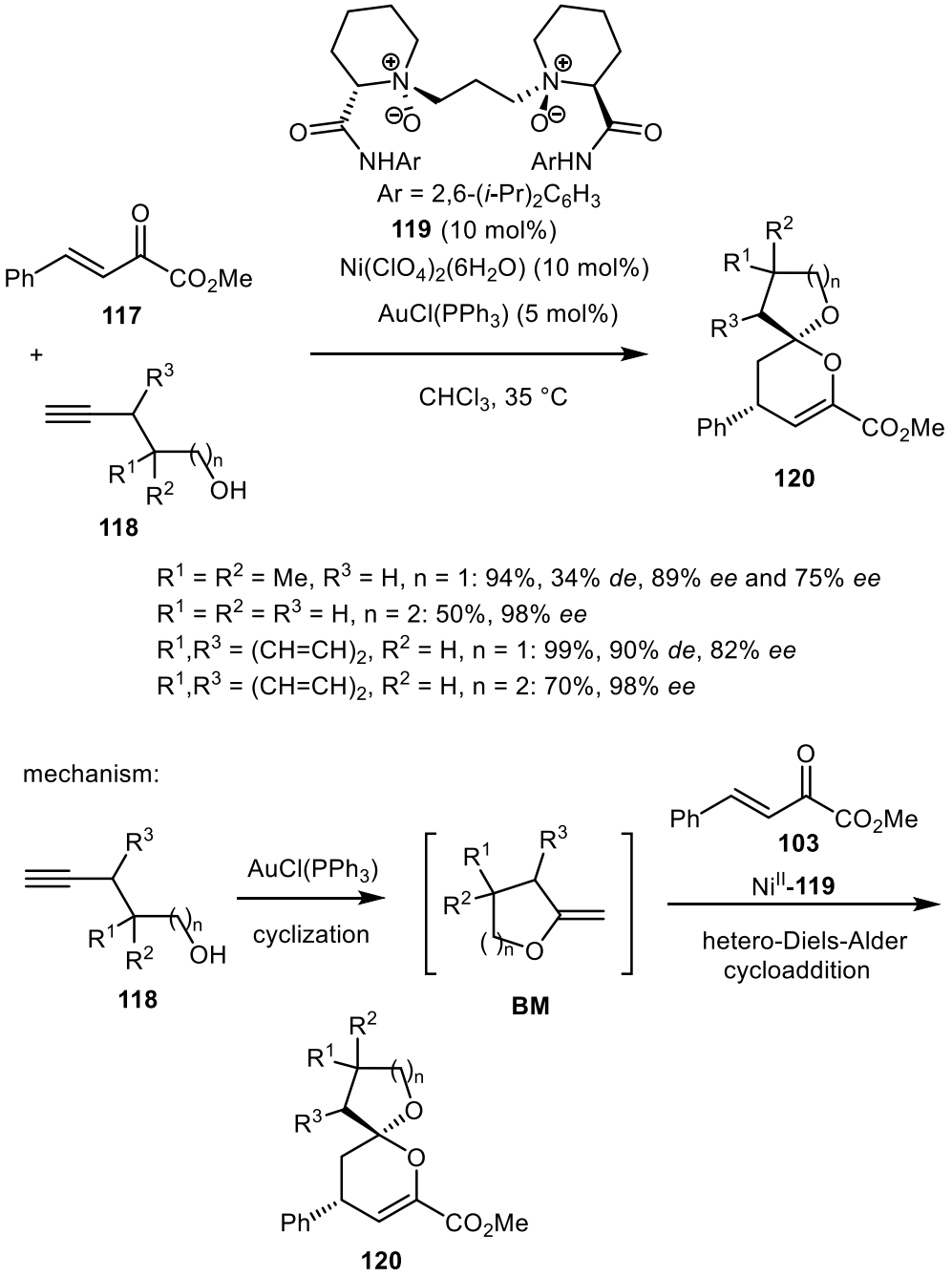
Scheme 37. Magnesium-/organocatalyzed domino intramolecular 1,5-hydride transfer/cyclization reaction of oxindole derivatives.

3 Enantioselective Tandem Reactions Catalyzed by Two Metals

In comparison with reactions multicatalyzed by combinations of organocatalysts and metal catalysts, the combined use of two metal catalysts is much less developed.[54] However, some advances have been achieved over the past few years, and the combination of two metals for cooperative, relay or sequential catalysis has become a promising area of research. Especially, the application of multimetallic catalytic systems to asymmetric catalysis is an emerging field in modern organic synthesis,[11,4u,55] probably owing to the fact that the presence of multiple metal catalysts leads to the competitive coordination of metals with the chiral ligand used, which makes the chiral environment unpredictable and unsuitable for a given transformation. Today, the bimetallic catalysis employs many different types of metals such as alkali metals, transition metals and lanthanides.

3.1 Relay Catalysis

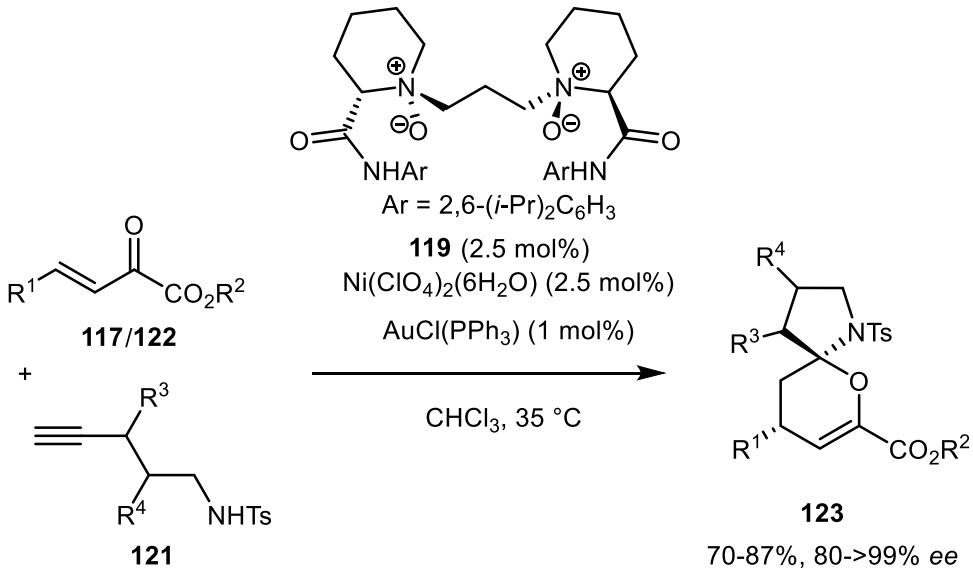
A recent example of bimetallic asymmetric relay catalysis based on the use of an achiral gold catalyst combined with a chiral nickel complex was reported by Feng and Liu, in 2016.[56] It involved an enantioselective gold- and nickel-catalyzed domino cycloisomerization/hetero-Diels−Alder reaction of an α-keto ester **117** with alkynyl alcohols **118** performed at 35 °C in chloroform as solvent. The catalyst system consisted of a combination of 5 mol% of $AuCl(PPh_3)$, which promoted the first cycloisomerization step of the alkynyl alcohol **118** into five-membered intermediate **BM**, and a chiral nickel catalyst *in situ* generated from 10 mol% of $Ni(ClO_4)_2{\cdot}6H_2O$ and the same quantity of a chiral *N,N'*-dioxide ligand **119**. The latter chiral nickel(II) complex catalyzed the following hetero-Diels−Alder cycloaddition with α-keto ester **117** to yield the corresponding functionalized chiral spiro-ketals **120** in moderate to quantitative yields (50-99%), low to high diastereoselectivities (34-90% *de*) and good to excellent enantioselectivities (75-98% *ee*), as illustrated in Scheme 38. Studying the substrate scope of the reaction, the authors found that a 2,2-disubstituted 4-pentynol (R^1 = R^2 = Me, R^3 = H, n = 1) provided both the lowest diastereoselectivity (34% *de*) and enantioselectivity (75% *ee*) while (2-ethynylphenyl)methanol (R^1,R^3 = $(CH{=}CH)_2$, R^2 = H, n = 2) reacted smoothly with an excellent diastereoselectivity (90% *de*). This result indicated that a bulkier phenyl substituent on the alkynyl alcohol was beneficial for the diastereoselectivity of the process.



Scheme 38. Gold- and nickel-catalyzed domino cycloisomerization/hetero-Diels−Alder reaction of an α-keto ester with alkynyl alcohols.

Encouraged by the precedent results obtained with alkynyl alcohols **118** as substrates, the same authors investigated the use of alkynyl amides **121** in comparable reactions multicatalyzed by the same catalyst system.[56] As illustrated in Scheme 39, these substrates reacted with a range of α-keto esters **117**/**122** through enantioselective gold- and nickel-catalyzed domino cycloisomerization/hetero-Diels−Alder reaction to give the corresponding chiral spiroaminals **123** as almost single diastereomers with good to high yields (70-87%) and uniformly high enantioselectivities (80->99% *ee*). In this case, only 2.5 mol% of the chiral nickel catalyst and 1 mol% of the gold catalyst were sufficient to promote the reactions in chloroform at 35 °C. Both aryl- and alkyl-substituted α-keto esters were compatible, giving comparable excellent results. Moreover, in the case of aryl-substituted α-keto esters, the steric

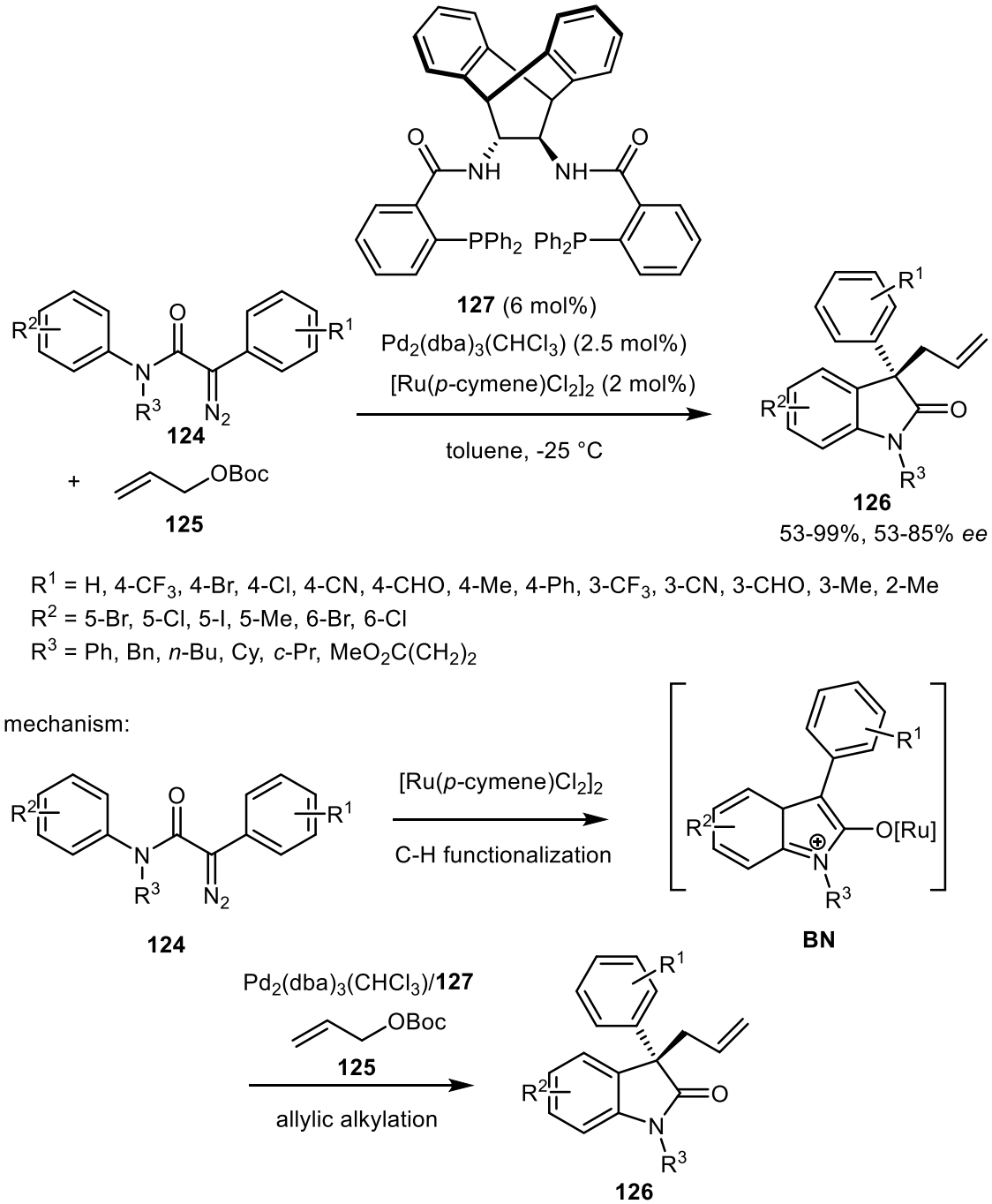
hindrance and electronic properties of the substituents born by the phenyl ring were found to have no effect on the efficiency of the process.



R^1 = Ph, *o*-Tol, *o*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *p*-Tol, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, 2,6-$Me_2C_6H_3$, 2-Naph, 2-thienyl, Cy, *n*-Bu
R^2 = Me, *i*-Pr, Bn
R^3 = R^4 = H
R^3,R^4 = $(CH=CH)_2$

Scheme 39. Gold- and nickel-catalyzed domino cycloisomerization/hetero-Diels−Alder reaction of α-keto esters with alkynyl amides.

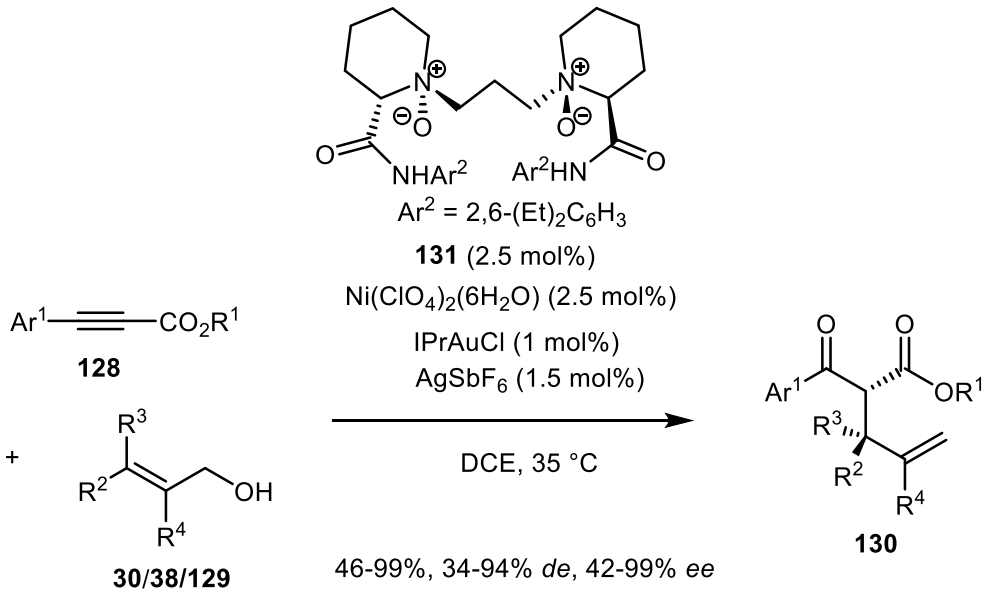
In 2016, Lautens et al. reported the first example of an enantioselective domino reaction involving a ruthenium carbenoid and a chiral allylpalladium complex to form two new C−C bonds and a chiral quaternary carbon center.[57] It concerned a ruthenium- and palladium-catalyzed domino C−H functionalization/allylic alkylation reaction of aryl α-diazoamides **124** with allyl *tert*-butyl carbonate **125**, providing at -25 °C in toluene as solvent the corresponding chiral 3-allyl-3-aryl oxindoles **126** in moderate to high yields (53-99%) and enantioselectivities (53-85% *ee*). As shown in Scheme 40, the process was catalyzed by 2 mol% of $[Ru(p\text{-cymene})Cl_2]_2$ combined with a chiral palladium catalyst *in situ* generated from 2.5 mol% of $Pd_2(dba)_3(CHCl_3)$ and 6 mol% of chiral biphosphine ligand **127**. The ruthenium catalyst promoted the C−H functionalization of the aryl α-diazoamide **124** to give intermediate **BN**, which subsequently underwent an asymmetric palladium-catalyzed allylic alkylation with allyl *tert*-butyl carbonate **125** to yield the final domino product **126**. The catalyst system was found compatible to a variety of diazo compounds. For example, both excellent enantioselectivities (76-82% ee) and yields (70-97%) were generally obtained in the reaction of substrates exhibiting an electron-withdrawing group (R^1) at the 4- or 3-position of the aryl ring attached to the diazo-bearing carbon while an incomplete reaction occurred with substrates exhibiting electron-neutral or electron-donating groups (R^1 = 4-H, 4-Me, 3-Me, 64-65%, 66-85% *ee*). The other aromatic group (R^2) exhibited halogen atoms at the 5- or 6-position. Concerning the substituents on the nitrogen atom, linear alkyl groups (R^3 = *n*-Bu) reacted smoothly while more sterically demanding substituents, (R^3 = Cy, *c*-Pr) decreased the reactivity, since the corresponding products were obtained in lower yields (53-70%).



Scheme 40. Ruthenium- and palladium-catalyzed domino C−H functionalization/allylic alkylation reaction of aryl α-diazoamides with allyl *tert*-butyl carbonate.

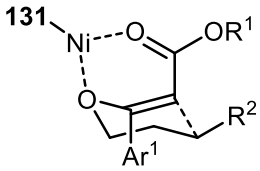
In another context, Feng and Liu described in 2017 an enantioselective gold- and nickel-catalyzed domino hydroalkoxylation/Claisen rearrangement reaction of alkynyl esters **128** with allylic alcohols **30**/**38**/**129** to give the corresponding chiral acyclic α-allyl β-keto esters **130**.[58] The process involved a hydroalkoxylation reaction catalyzed by 1 mol% of π-acidic gold(I) complex IPrAuCl followed by a Claisen rearrangement catalyzed by a chiral Lewis acidic nickel(II) complex *in situ* generated from 2.5 mol% of $Ni(ClO_4)_2$ and the same quantity of chiral *N,N'*-dioxide ligand **131**. The domino reaction was performed at 35 °C in DCE as solvent, allowing a wide range of chiral acyclic α-allyl β-keto esters

130 to be achieved in moderate to quantitative yields (46-99%), low to high diastereoselectivities (34-94% *de*) and moderate to excellent enantioselectivities (42-99% *ee*), as illustrated in Scheme 41. The study of the substrate scope showed that various alkynyl esters were compatible, including ethyl, methyl, benzyl and *tert*-butyl esters. Moreover, concerning the substituents born by the phenyl ring of the alkynyl esters, both steric hindrance and electronic properties had low impact on the results. Heteroaromatic substrates were also tolerated. A variety of aliphatic as well as aromatic allylic alcohols (R^2 = alkyl, (hetero)aryl) were compatible, providing comparable excellent enantioselectivities (90-98% *ee*). A transition state is proposed in Scheme 41.



Ar^1 = Ph, *o*-FC_6H_4, *m*-FC_6H_4, *p*-FC_6H_4, *o*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-NCC_6H_4, *p*-Tol, *p*-EtC_6H_4, *p*-PhC_6H_4, 3,4-$Me_2C_6H_3$, 1-Naph, 2-Naph, 2-thienyl
R^1 = Me, Bn, *t*-Bu, Et
R^2 = H, Me, Cy, *o*-$O_2NC_6H_4$, *o*-ClC_6H_4, *m*-ClC_6H_4, *p*-ClC_6H_4, *o*-Tol, *p*-Tol, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-$MeOC_6H_4$, 1-Naph, 2-Naph, 2-thienyl
R^3 = Ph, H, Me
R^4 = H, Me

possible transition state (R^3 = R^4 = H):

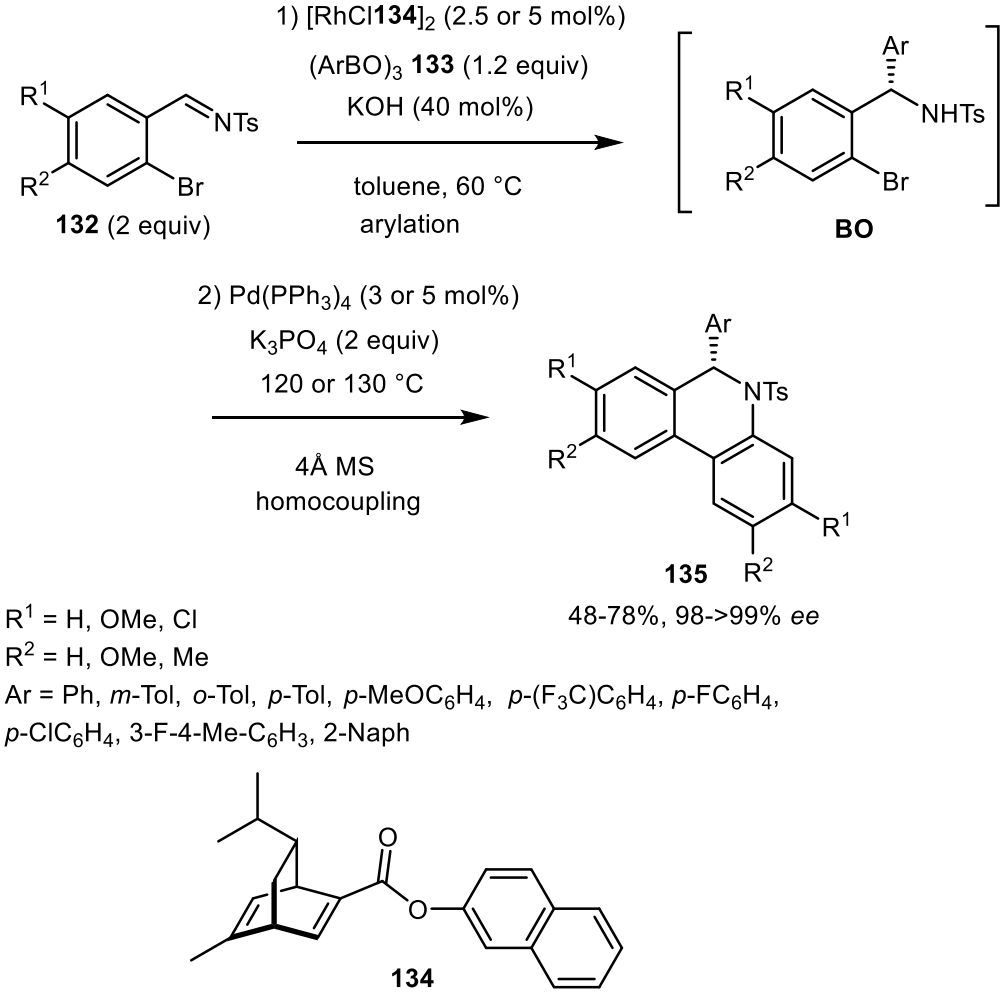


Scheme 41. Gold- and nickel-catalyzed domino hydroalkoxylation/Claisen rearrangement reaction of alkynyl esters with allylic alcohols.

3.2 Sequential Catalysis

In 2015, Lautens et al. reported an example of bimetallic rhodium/palladium sequential catalysis to promote enantioselective tandem arylation/homocoupling reactions of *o*-bromobenzaldimines **132** with arylboroxines **133**.[59] The process depicted in Scheme 42 was sequentially catalyzed by 2.5 or 5 mol% of a rhodium complex derived from chiral diene ligand **134**, and 3 or 5 mol% of $Pd(PPh_3)_4$. The

chiral rhodium catalyst promoted at 60 °C in toluene as solvent the asymmetric arylation of *o*-bromobenzaldimines **132** with arylboroxines **133** as nucleophiles to afford intermediates **BO** which subsequently underwent at 120 or 130 °C after addition of the palladium catalyst an homocoupling to yield the final biologically interesting chiral 6-aryl-substituted 5,6-dihydrophenanthridine derivatives **135** in moderate to high yields (48-78%) and uniformly excellent enantioselectivities (98->99% *ee*). Arylboroxines bearing electron-donating or electron-withdrawing groups all afforded the corresponding almost enantiopure products with moderate to good yields (53-78%) while lower yields (48-50%) were obtained in the reaction of sterically hindered 2-methylphenylboroxine and 1-naphthylboroxine.

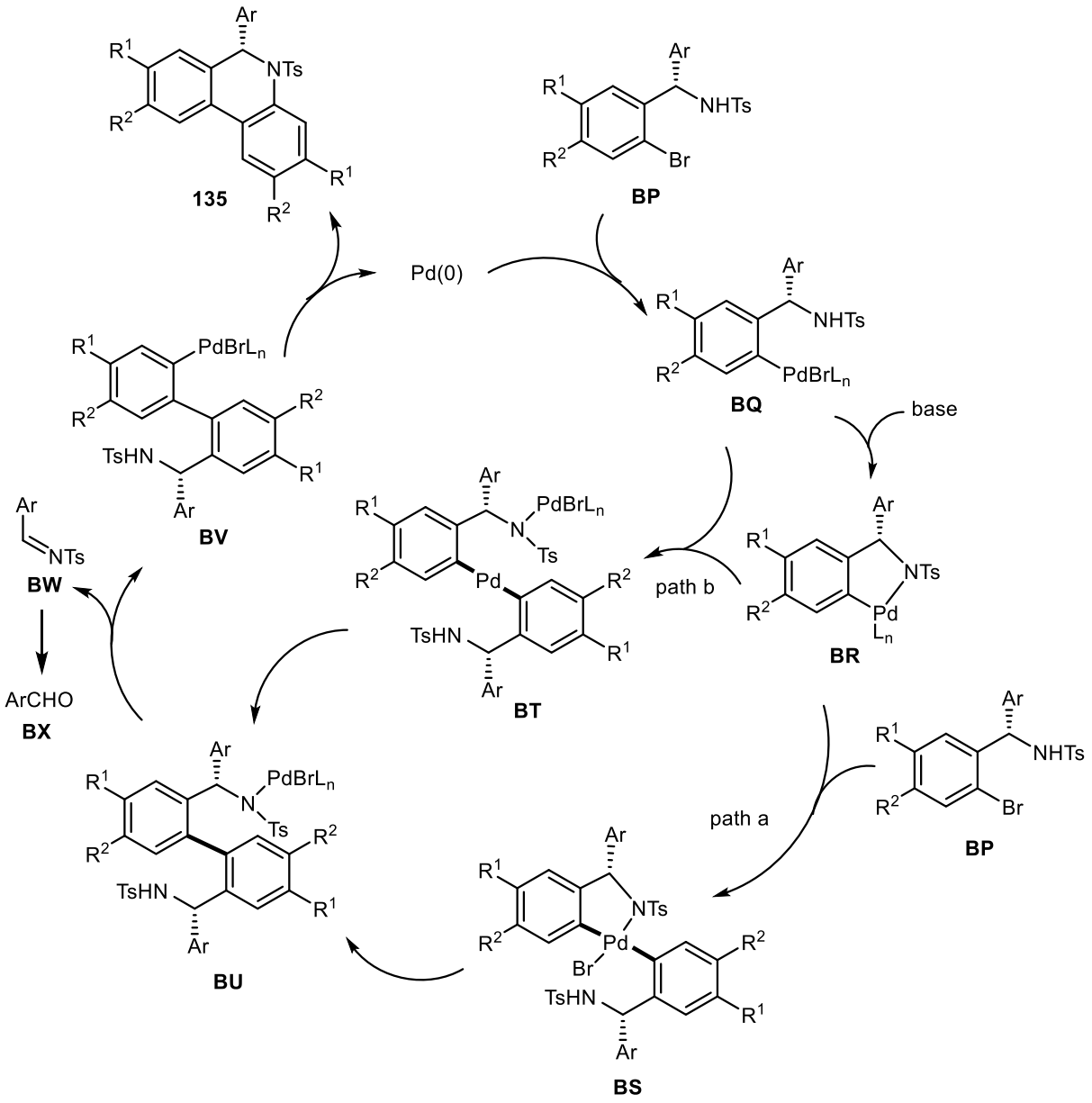


134

Scheme 42. Rhodium- and palladium-catalyzed tandem arylation/homocoupling reaction of *o*-bromobenzaldimines with arylboroxines.

A possible mechanism for the precedent reaction is depicted in Scheme 43.[59] First, oxidative addition of *o*-bromobenzylamine **BP** to Pd(0) generated intermediate **BQ** which was further deprotonated to give palladacycle **BR**. At this point, two pathways were possible for the generation of intermediate **BU**. In pathway a, palladacycle **BR** underwent oxidative addition with a second equivalent of *o*-bromobenzylamine **BP**, thus affording Pd(IV) species **BS**, which delivered intermediate **BU** through aryl−aryl reductive coupling. Alternatively, dinuclear Pd(II) complex **BT**, formed through a transmetalation-type reaction between palladacycle **BR** and palladium species **BQ**, could also lead to intermediate **BU** after reductive elimination, according to pathway b. Then, β-carbon elimination of

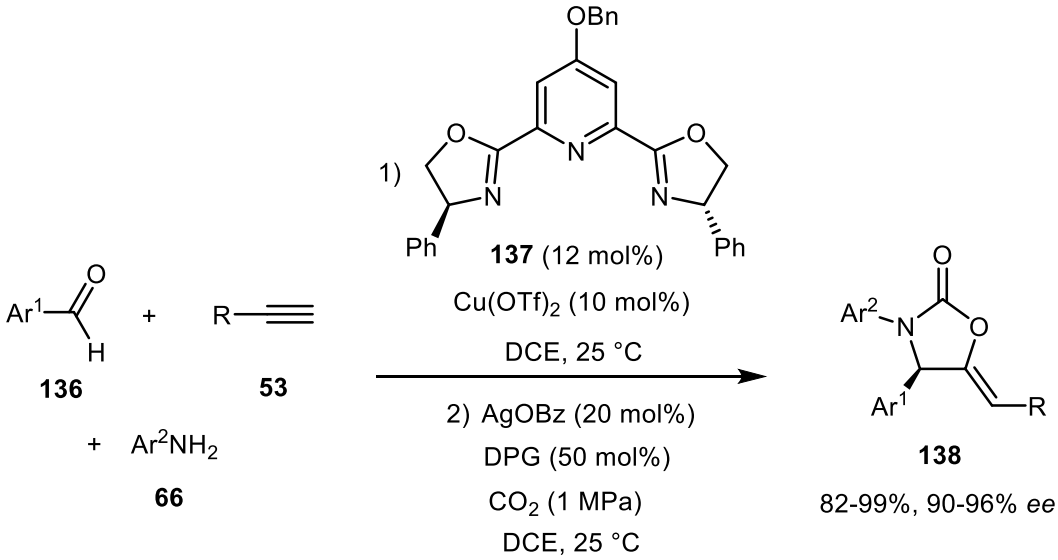
intermediate **BU** yielded aryl palladium species **BV** with concomitant formation of imine byproduct **BW** and its decomposition product **BX**. Then, Buchwald−Hartwig amination of intermediate **BV** produced the final product and regenerated the catalytically active Pd(0) species.



Scheme 43. Mechanism for rhodium- and palladium-catalyzed tandem arylation/homocoupling reaction of *o*-bromobenzaldimines.

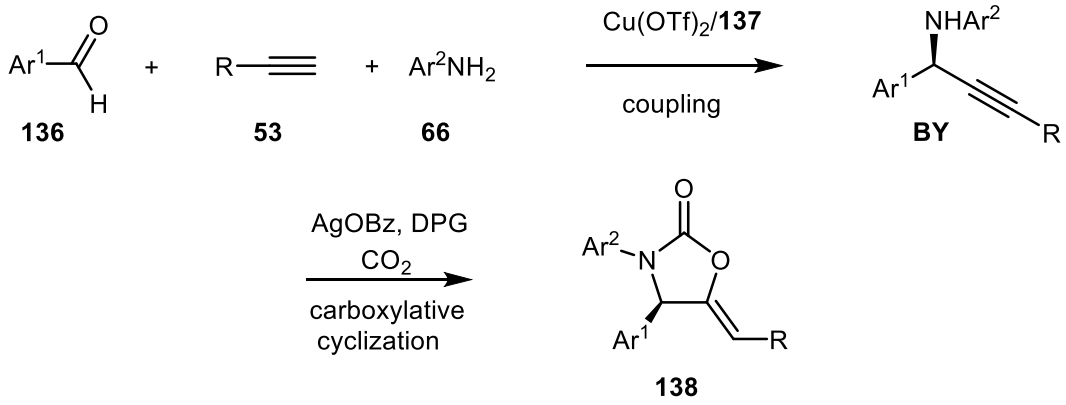
In 2017, Zhou, Wu and Zhou developed a novel route to chiral 2-oxazolidinones based on a multicatalyzed sequential tandem asymmetric coupling/carboxylative cyclization reaction between alkynes **53**, aromatic aldehydes **136**, aromatic amines **66** and CO_2.[60] The first step of the process involved at 25 °C in DCE as solvent a chiral copper catalyst *in situ* generated from 10 mol% of $Cu(OTf)_2$ and 12 mol% of chiral Pybox ligand **137** that promoted the coupling between alkyne **53**, aromatic aldehyde **122** and aromatic amine **66** to provide the corresponding chiral amine intermediate **BY**. Then, addition of 20 mol% of AgOBz and CO_2 under pressure in the presence of 1,3-

diphenylguanidine (DPG) as a base in DCE as solvent induced at 25 °C the second step of the sequence, dealing with the carboxylative cyclization of intermediate **BY** into final product **138**. This sequential bimetallic relay catalysis allowed a range of chiral *N*-aryl 2-oxazolidinones **138** to be synthesized in both uniformly high yields (82-99%) and enantioselectivities (90-96% *ee*), as illustrated in Scheme 44. Aromatic aldehydes with either electron-withdrawing or electron-donating substituents reacted smoothly to give the corresponding products in both high yields (82-97%) and enantioselectivities (90-96% *ee*). Even 2-naphthaldehyde (Ar^1 = 2-Naph) furnished the desired *N*-aryl 2-oxazolidinone in 90% yield and 91% *ee*. Concerning the alkyne partner, both aryl and alkyl alkynes were compatible, with aryl alkynes tolerating different substituents. Moreover, primary aromatic amines with electron-rich, electron-neutral and electron-deficient groups on the phenyl ring all provided excellent results.



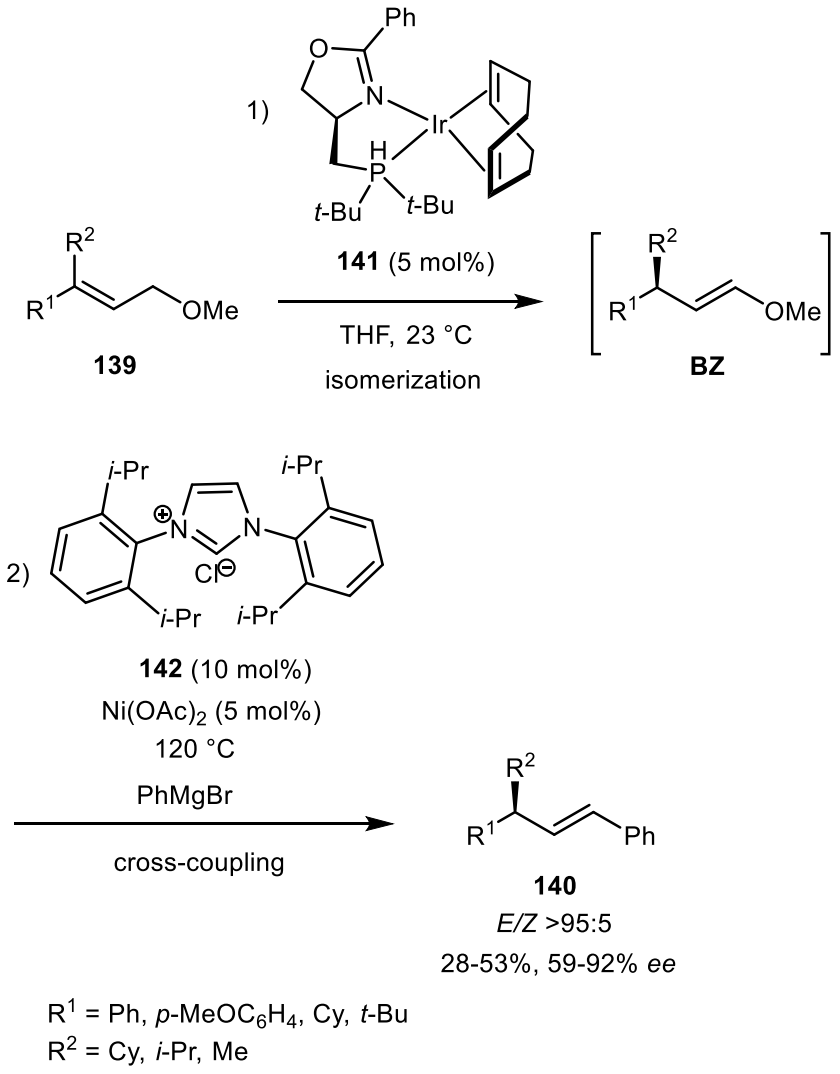
Ar^1 = Ph, *p*-Tol, *p*-EtC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-FC_6H_4, *m*-Tol, *o*-Tol, 3,4-$(Me)_2C_6H_3$, 2-Naph
R = Ph, *p*-$MeOC_6H_4$, *p*-Tol, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *m*-ClC_6H_4, *o*-ClC_6H_4, *n*-Pent
Ar^2 = Ph, *p*-$MeOC_6H_4$, *p*-Tol, *p*-EtC_6H_4, *m*-Tol, *m*-FC_6H_4, *m*-BrC_6H_4

mechanism:



Scheme 44. Copper- and silver-catalyzed tandem coupling/carboxylative cyclization reaction of alkynes, aromatic aldehydes, aromatic amines and CO_2.

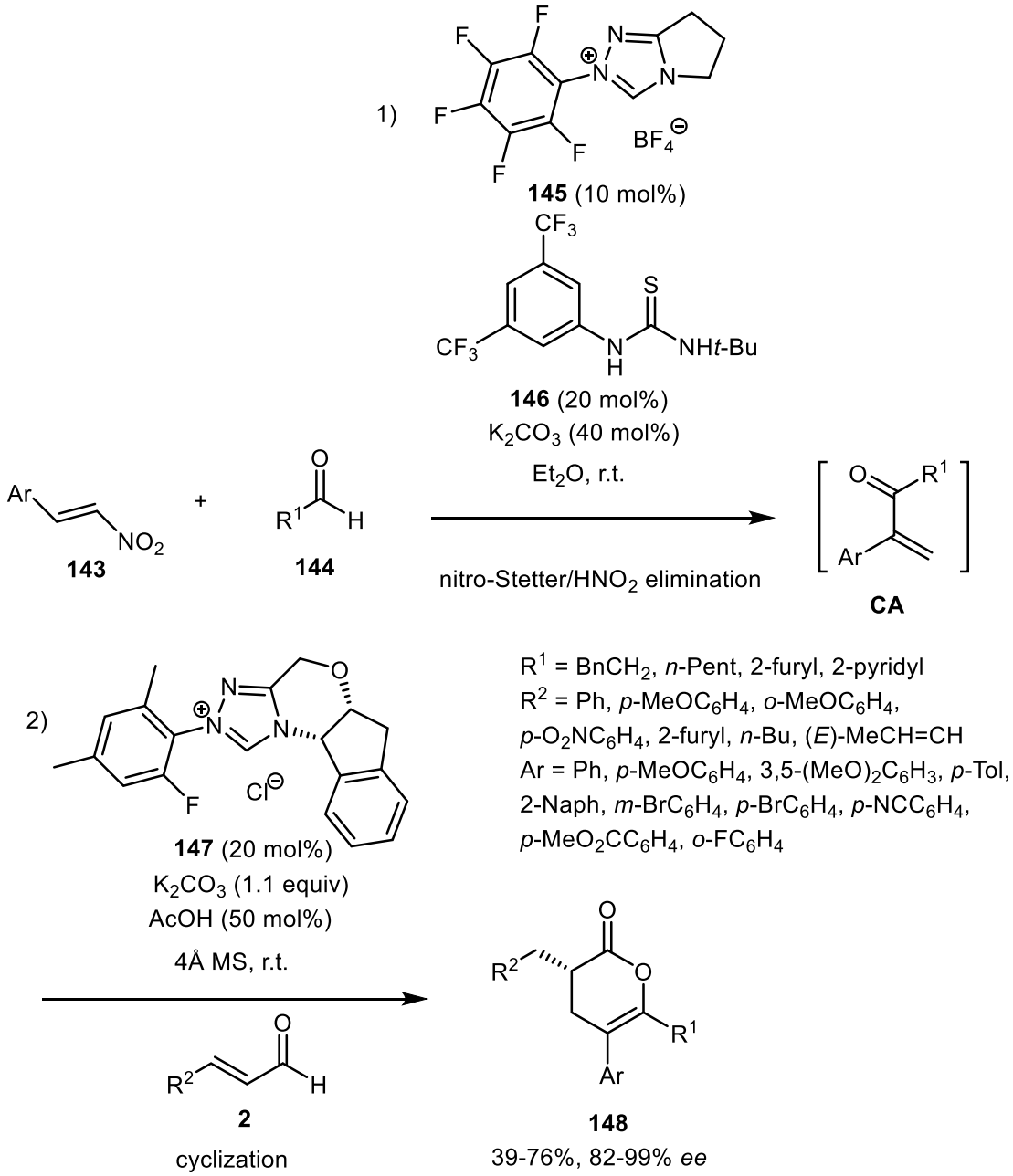
In 2018, Mazet and Romano reported another bimetallic sequential tandem reaction which was based on the use of iridium and nickel catalysts.[61] It concerned a tandem isomerization/cross-coupling reaction of allyl methyl ethers **139** with phenyl magnesium bromide, delivering the corresponding chiral alkenes **140** in low to moderate yields (28-53%), uniformly high diastereoselectivities (*E/Z* >95:5), and good to high enantioselectivities (59-92% *ee*), as illustrated in Scheme 45. The first step catalyzed at 23 °C by 5 mol% of chiral iridium complex **141** in THF as solvent involved the isomerization of allyl methyl ethers **139** into intermediate vinyl methyl ethers **BZ**. The subsequent addition of 5 mol% of $Ni(OAc)_2$ combined with 10 mol% of ligand **142** along with phenyl magnesium bromide as nucleophilic coupling partner at 120 °C triggered cross-coupling reaction which afforded the final substituted chiral alkenes **140**. The catalyst system was found compatible with variously substituted alkenes.



Scheme 45. Iridium- and nickel-catalyzed tandem isomerization/cross-coupling reaction of allyl methyl ethers with phenyl magnesium bromide.

4 Enantioselective Tandem Reactions Catalyzed by Multiple Organocatalysts

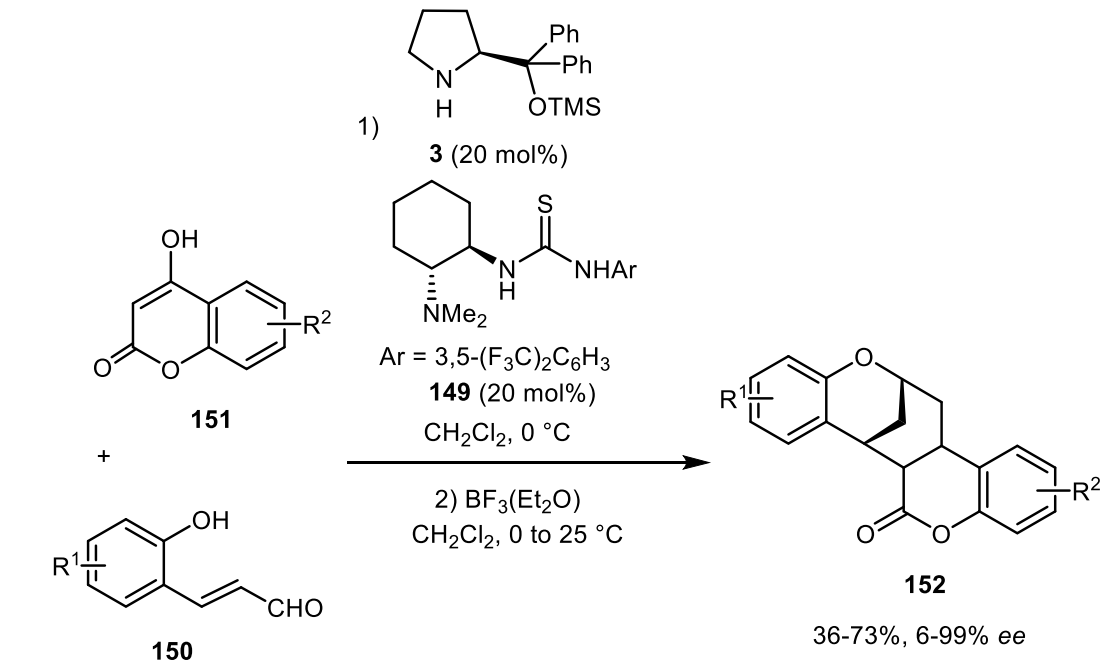
In addition to be easy to manipulate, robust and cheaper, organocatalysts present a significant advantage to be highly compatible in comparison with metal catalysts which are often expensive and toxic. Furthermore, many organocatalysts can promote various types of reactions through different activation modes. These attributes make multiple organocatalysis particularly versatile to design novel asymmetric tandem reactions.[4j,q,62] So far, many types of these one-pot transformations have been described with multiple organocatalysts interacting through either cooperative, relay or sequential manner.[4h,j,q] As a recent example, Zeitler and Fuchs developed a three-step tandem asymmetric reaction based on the sequential use of three organocatalysts, such as two different NHC catalysts and a thiourea catalyst.[63] The first step of the process consisted in a tandem nitro-Stetter/HNO_2 elimination reaction between aromatic nitroalkene **143** and aldehyde **144** to give the corresponding α,β-unsaturated ketone intermediate **CA**. It was multicatalyzed by a mixture of 10 mol% of achiral NHC catalyst **145** and 20 mol% of achiral thiourea catalyst **146** in diethylether at room temperature, as shown in Scheme 46. Then, the addition of the third partner of the reaction, such as α,β-unsaturated aldehyde **2**, along with 20 mol% of chiral NHC catalyst **147** triggered asymmetric lactonization of intermediate **CA** to afford the final chiral 3,5,6-trisubstituted 3,4-dihydropyranone **148**. Starting from a variety of substrates, a range of these products, the structure of which is prevalent within many natural and bioactive compounds, were readily synthesized in moderate to good yields (39-76%) and uniformly high enantioselectivities (82-99% *ee*). Studying the substrate scope, the authors showed that the reaction conditions were compatible with both aliphatic and heteroaromatic aldehydes while aromatic aldehydes did not react. Concerning the α,β-unsaturated aldehyde, electron-rich and electron-poor aromatic substrates were tolerated, providing the corresponding products with both good yields and high enantioselectivities. Notably, the efficiency of the process was not impeded by the presence of *o*-substituents on the phenyl group. Comparable good results were also obtained for α,β-unsaturated aldehydes bearing aliphatic and heteroaromatic substituents. Moreover, the reaction of a range of variously substituted nitrostyrenes provided uniformly excellent levels of enantioselectivity (94-99% *ee*), regardless of the electron-donating or electron-withdrawing nature of the phenyl substituents.



Scheme 46. Tandem nitro-Stetter/elimination/lactonization reaction of nitroalkenes, aldehydes and α,β-unsaturated aldehydes.

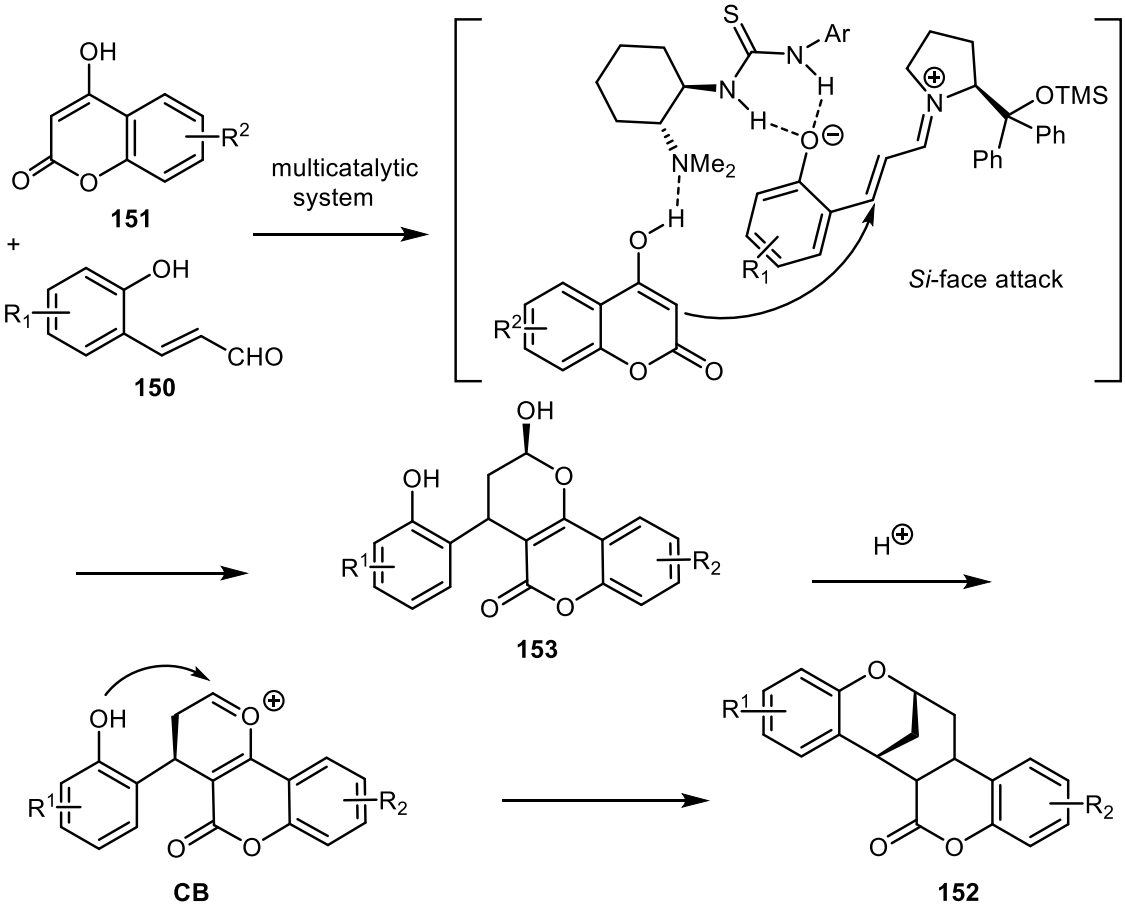
In 2020, Tan and Liu reported an asymmetric multicatalytic tandem Michael/cyclization reaction between 2-hydroxycinnamaldehydes and 4-hydroxycoumarins.[64] It involved as catalyst system a combination of 20 mol% of chiral diphenylprolinol trimethylsilyl ether **3** and chiral bifunctional tertiary amine-thiourea **149** in dichloromethane as solvent, followed by treatment with $BF_3(Et_2O)$. As depicted in Scheme 47, the sequential reaction of variously substituted 2-hydroxycinnamaldehydes **150** with 4-hydroxycoumarins **151** led to the corresponding chiral benzofused 2,8-dioxabicyclo[3.3.1]nonanes **152** in moderate to good yields (36-73%) and low to excellent enantioselectivities (6-99% *ee*). The reaction began with the combination of aminocatalyst **3** and 2-hydroxycinnamaldehyde **150** to give the corresponding iminium intermediate which after dehydration provided a zwitterionic intermediate. Then, bifunctional thiourea catalyst **149** served the dual function of activating the phenoxide anion through anion binding and the enolic 1,3-dicarbonyl substrate through acid–base interactions. As illustrated in Scheme 47, the multicatalysis promoted the Michael

addition of 4-hydroxycoumarin **151** to 2-hydroxycinnamaldehyde **150**, yielding hemiacetal **153**, in which the enolic Michael donor approached the active iminum ion from the *Si* face. Then, the acid-catalyzed cyclization via oxocarbenium ion **CB** afforded final product **152**. Studying the substrate scope of the reaction, the authors found that the presence of electron-withdrawing and electron-donating substituents at the 3-, 4-, and 5-positions of the phenyl ring of the 2-hydroxycinnamaldehyde was well tolerated, since uniformly high enantioselectivities were obtained (86-99% *ee*) with these substrates. In contrast, 6-substituted 2-hydroxycinnamaldehydes (R^1 = 6-Cl, 6-OMe) reacted very sluggishly to give the corresponding products with low enantioselectivities (6-23% *ee*). Concerning the scope of the 4-hydroxycoumarins, regardless of the electronic properties and position of substituents on the aromatic ring, the corresponding bridged bicyclic acetals were obtained with uniformly high enantioselectivities (82-97% *ee*).



R^1 = H, 3-F, 4-Cl, 5-MeO, 5-Br, 5-Cl, 5-F, 5-CO_2Et, 5-NO_2, 6-Cl, 6-MeO
R^2 = H, 3-Cl, 4-F, 4-MeO, 4-Me, 4-CN, 5-F, 5-Br, 5-Me, 6-Cl

proposed mechanism:



Scheme 47. Tandem Michael/cyclization reaction of 2-hydroxycinnamaldehydes and 4-hydroxycoumarins.

5 Conclusions

This review updates the recent advances in the field of enantioselective multicatalyzed tandem reactions, covering the literature since the beginning of 2015. It shows that this emerging field is in full bloom, allowing a one-pot access to complex functionalized chiral molecules from simple starting materials. In spite of a relatively short time covered (five years) by this review, it shows that an increasing number of combinations of different types of catalysts has already been applied to promote enantioselective tandem reactions of many classes. Undoubtedly, those combining a metal with an organocatalyst have been the most investigated in the last five years. A wide variety of organocatalysts has been involved in these reactions, including popular chiral α,α-diphenylprolinol trimethylsilyl ether, phosphoric acids, multifunctional (bi)phosphines, phosphoramides, NHC catalysts, thioureas, aminoalcohols, squaramides, amino acid derivatives, etc. Among metals used in these reactions, palladium has been the most employed, allowing a number of highly enantioselective domino reactions to be achieved. Along with palladium, many other metals have provided excellent results, including iron, copper, rhodium, silver, gold, scandium, nickel, iridium, and even alkaline earth metals such as magnesium. The field of bimetallic asymmetric relay/sequential catalysis has also encountered success in tandem reactions. However, the area of tandem reactions promoted by multiple organocatalysts has been much less developed in the last five years.

The emerging field of asymmetric multicatalyzed tandem reactions knows a fast-growing and will undoubtedly continue to be expanded in the future with the discovery of novel combinations of catalysts. The concept of combining catalysts enables unprecedented one-pot multistep reactions not possible by using each of catalysts alone. On the basis of the great number of catalysts, their combinations seem unlimited, providing tremendous opportunities to develop a completely novel chemistry. Deeper efforts to better understand the mechanisms of these multistep reactions will have to be made in the near future in order to help searching novel designed catalysts which also should have to be more environmentally benign.

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List of abbreviations

acac: acetylacetonate
Ar: aryl
Bn: benzyl
Boc: *tert*-butoxycarbonyl
BPE: 1,2-bis(2-pyridyl)ethane
Bz: benzoyl
CAPT: chiral anion phase-transfer
Cbz: benzyloxycarbonyl
cod: cyclooctadiene
Cy: cyclohexyl
dba: (*E,E*)-dibenzylideneacetone
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE: dichloroethane
de: diastereomeric excess
DIPEA: diisopropylethylamine
dme: 1,2-dimethoxyethane
DPG: 1,3-diphenylguanidine
dppe: 1,2-bis(diphénylphosphino)éthane
ee: enantiomeric excess
EWG: electron-withdrawing
Hept: heptyl
Hex: hexyl
L: ligand
MTBE: methyl *t*-butyl ether
Naph: naphthyl
MOM: methoxymethyl
MS: molecular sieves
Naph: naphthyl
NHC: N-heterocyclic carbene
Pent: pentyl
Phth: phthaloyl
pin: pinacolato
Pybox: 2,6-bis(2-oxazolyl)pyridine
r.t.: room temperature
TEMPO: 2,2,6,6-tetramethylpiperidinyloxy
Tf: trifluoromethanesulfonyl
THF: tetrahydrofuran
TMP: 2,2,6,6-tetramethylpiperidine
TMS: trimethylsilyl
Tol: tolyl
triphos: bis(diphenylphosphino-ethyl)phenylphosphine
Ts: 4-toluenesulfonyl (tosyl)