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# Asymmetric Zinc Catalysis in Green One-Pot Processes

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**Abstract:** This review collects for the first time enantioselective one-pot processes promoted by green chiral zinc catalysts. It illustrates how much these cheap, non-toxic and environmentally benign catalysts allow unprecedented asymmetric domino and tandem reactions of many types to be achieved, allowing direct access to a wide variety of very complex chiral molecules.

**Keywords:** Asymmetric one-pot reactions; asymmetric domino reactions; asymmetric tandem reactions; asymmetric zinc catalysis; metal catalysis; chirality.

## 1. INTRODUCTION

With the aim of conciliating efficient sustainable chemical production with safeguarding human health as well as environment, organic chemists have taken a decisive step in the last decades towards green catalytic synthesis. In this context, the development of novel, nontoxic and effective catalytic systems capable of driving value-added chemical transformations in environmentally benign conditions has become an urgent challenge [1-3]. As a cheap, abundant [4] and less toxic metal in comparison with many transition metals employed in catalysis [5], zinc has gained significant importance in green catalysis. While underdeveloped for a long time, zinc catalysts are more and more applied as Lewis acid complexes to promote all types of more economical and ecological transformations spanning from simple reactions [6] to more sophisticated domino and tandem processes, allowing very complex molecules to be synthesized in a single vessel without costly isolation and purification of intermediates [7]. Among these one-pot reactions are powerful domino processes occurring under strictly the same reaction conditions [8] and combining these simple methodologies with asymmetric zinc catalysis perfectly suit the growing demand for more efficient and environmentally benign synthesis. This interest has resulted in a spectacular development of highly enantioselective zinc-catalyzed one-pot processes in the last decade that this review intends to collect for the first time. Zinc is an essential element for life with high biological importance [9, 10], since it is present as a co-catalyst in more than 300 enzymes and 1000 transcription factors [11], which has inspired chemists to design artificial zinc chiral catalysts. Actually, zinc is the second most abundant trace metal in humans after iron and it is the only metal which appears in all enzyme classes [12]. In proteins, zinc is coordinated to the amino acid side chains of aspartic acid, glutamic acid, cysteine and histidine [13]. Zinc becomes toxic above an overdose of around 50 mg in-

gested. The consequence of excessive absorption of zinc is the suppression of copper and iron absorption. The free zinc ion in solution is highly toxic to bacteria, plants, invertebrates and vertebrate fishes [14-16].

On the other hand, zinc constitutes an essential trace metal with very low toxicity in humans with a daily dose of 12-15 mg [17, 18]. In the area of asymmetric catalytic applications of zinc, a wide diversity of chiral zinc complexes have been developed and employed to promote many reactions, reflecting that of the processes disclosed. A range of chiral ligands, including semi-aza-crown ligands, bis(oxazoline)s, bis(imidazoline)s, *N,N'*-dioxides, 1,1'-bi-2-naphthol (BINOL) derivatives, diamines, amino alcohols, cinchona alkaloids, among others, have been already chelated to zinc. It must be noted that the field of asymmetric zinc-catalyzed reactions of all types was most recently updated by Mlynarski in 2015 including only three references concerning asymmetric domino processes [19]. Moreover, the more general field of zinc catalysis (not especially asymmetric) was reviewed by Enthaler and Wu the same year [20]. Also in 2015 Lee and Bouffard reported the field of tandem reactions based on the use of organozinc reagents, albeit with no reference dealing with asymmetric zinc-catalyzed tandem reactions [21]. In 2019, a review on the synthesis of heterocycles via zinc catalysis was published by Beller and Anilkumar, including no reference concerning asymmetric work [22]. In 2020, Anilkumar reviewed zinc-catalyzed multicomponent reactions but with only one asymmetric work [23]. Even if the general field of asymmetric metal-catalyzed domino reactions has been the subject of precedent reviews covering the literature up to 2018 [5p,w-x], it must be noted that the largest share of activity in enantioselective zinc-catalyzed one-pot reactions dated after 2018. This demonstrates that this special and original field has blossomed in very recent years to become an area in its own right, deserving a special review. The present review is divided into six parts according to the type of chiral ligands employed to promote the reactions, highlighting successively semi-aza-crown ligands, bis(oxazoline)s and bis(imidazoline)s, *N,N'*-dioxides, BINOL derivatives, 1,2-diamines, and other

ligands. The low price of zinc makes zinc catalysis suiting the growing demand for greener processes and offers the real opportunity to replace other toxic and expensive metals in the near future. This review demonstrates that zinc brings a novel potential for green catalysis when combined with complex asymmetric one-pot processes and that this original area is growing very rapidly.

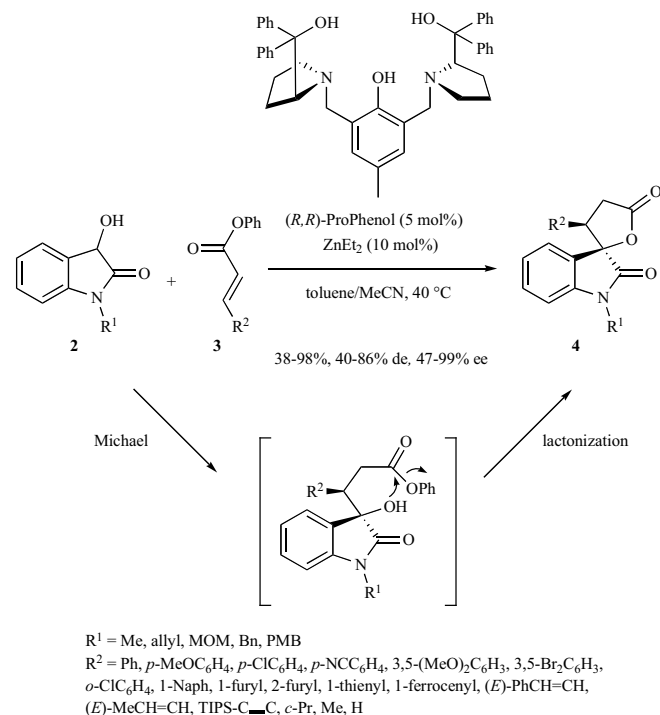
## 2. REACTIONS USING SEMI-AZA-CROWN LIGANDS

### 2.1. ProPhenol Ligand and Derivatives

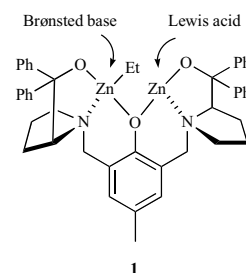
ProPhenol is a semi-aza-crown ligand [24], which was firstly developed in 2000 by Trost and Ito and applied to promote asymmetric zinc-catalyzed aldol reactions [25]. The authors showed that this ligand generated, in the presence of diethyl zinc, a dinuclear bifunctional zinc catalyst **1** (Scheme 1), possessing both a Brønsted base site and a Lewis acid site embedded within a chiral pocket formed by the ProPhenol ligand. In the aldol reaction, one zinc atom bound to the enolate form of the ketone substrate while the second zinc atom chelated the aldehyde/ketone substrate. The aldol condensation in the chiral pocket formed by the semi-crown ligand was achieved with enantioselectivities of up to 99% ee and high yields. Later, Trost's ligand was successfully applied to many types of other enantioselective zinc-catalyzed reactions [26], including Henry reaction [27], Mannich reactions [28], Michael additions [29], alkynylations of carbonyl compounds [30], Friedel–Crafts reactions [31], among others. In 2012, Trost and Hirano also demonstrated the use of this ligand to catalyze more complex asymmetric reactions, such as enantioselective domino Michael/lactonization reaction between 3-hydroxyoxindoles **2** and  $\alpha,\beta$ -unsaturated esters **3** [32]. This process, performed in the presence of 5 mol% of (*R,R*)-ProPhenol as ligand and 10 mol% of ZnEt<sub>2</sub> in a mixture of toluene and acetonitrile as solvent, afforded at 40 °C the corresponding chiral spirocyclic oxindoles **4** in moderate to excellent yields (38–98%), diastereoselectivities (40–86% de) and enantioselectivities (47–99% ee), as illustrated in Scheme 1. A range of variously substituted phenyl groups (R<sup>2</sup>) were tolerated on the  $\alpha,\beta$ -unsaturated esters, providing spirocyclic  $\delta$ -lactones **4** in uniformly excellent enantioselectivities (92–99% ee), good to high yields (65–89%) albeit combined with variable diastereoselectivities (52–86% de) dependent on the electronic properties of the substituents on the phenyl ring. Excellent results (72–98% yield, 58–72% de, 95–98% ee) were also obtained in the reaction of esters bearing heteroaromatic substituents. On the other hand, alkyl-substituted esters (R<sup>2</sup> = Me, *c*-Pr) provided lower enantioselectivities (54–75% ee) and yields (38–67%) combined with moderate diastereoselectivities (40–62% de). A ferrocenyl-substituted ester (R<sup>2</sup> = 1-ferrocenyl) also underwent the domino process with 55% yield, 84% de and 96% ee while the reaction of an yneanoate (R<sup>2</sup> = TIPS-C $\equiv$ C) was performed with 84% yield, 84% de and 76% ee. It was found that  $\beta,\gamma,\delta$ -unsaturated esters (R<sup>2</sup> = (*E*)-PhCH=CH, (*E*)-MeCH=CH) also yielded the conjugated products exclusively in excellent enantioselectivities (97–98% ee), high yields (82–83%) and moderate to good diastereoselectivities (42–74% de). The lowest enantioselectivity (47% ee) was obtained in the reaction of phenyl acrylate (R<sup>2</sup> = H), which gave the corresponding product with 67% yield. Moreover, different nitrogen protecting groups (R<sup>1</sup>) on the 3-hydroxyoxindoles were tolerated, including methyl, allyl, methoxymethyl, benzyl and *p*-methoxybenzyl.

To explain these results, the authors proposed the catalytic cycle depicted in Scheme 2. In a first time, 3-hydroxyoxindole **2** was deprotonated by an ethylzinc species to give intermediate **A**. Then,  $\alpha,\beta$ -unsaturated ester **3** coordinated to the less hindered zinc atom

to form intermediate **B**, which tautomerized into intermediate **C**. The latter subsequently underwent intramolecular transesterification to release the final spirocyclic oxindole **4** and regenerate the zinc phenoxide species **D** that could deprotonate another equivalent of 3-hydroxyoxindole.



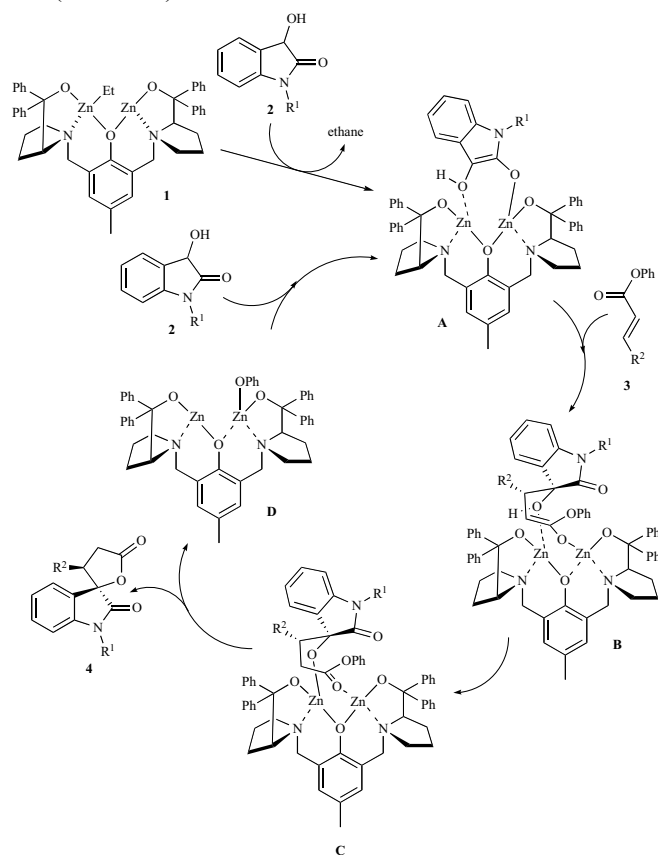
structure of the *in situ* generated active dinuclear catalyst:



**Scheme 1.** Domino Michael/lactonization reaction of 3-hydroxyoxindoles with  $\alpha,\beta$ -unsaturated esters.

In 2013, Marek *et al.* reported asymmetric alkynylation of acyl silanes **5** with alkyne **6** promoted by 2.4 equivalents of ZnEt<sub>2</sub> and 5 mol% of (*S,S*)-ProPhenol in toluene at 5 to 15 °C, leading in a one-pot operation to propargylic alcohols **7** after subsequent addition of an electrophile (EX) followed by oxidation [33]. Actually, the first step of the sequence consisted of a tandem alkynylation/Brook rearrangement/ene–allene cyclization of acyl silanes **5** with alkyne **6**, providing intermediate **G**. As depicted in Scheme 3, the zinc-promoted asymmetric alkynylation led to chiral zinc intermediate **E**, which then underwent a Brook rearrangement to give allenyl zinc intermediate **F**. Then, the latter was submitted to zinc-promoted ene–allene cyclization, leading to cyclic zinc intermediate **G**. The addition of an electrophile (EX) trapped **G** into functionalized product **8** which was subsequently oxidized in the presence of aqueous hydrogen peroxide H<sub>2</sub>O<sub>2</sub> with concomitant desilylation into final acyclic product **7**. This tandem alkynylation/Brook rearrangement/ene–allene cyclization/electrophile addition/oxida-

tion sequence performed in one-single vessel allowed a range of chiral propargylic alcohols **7** to be synthesized as single diastereomers (>96% de) in good yields (56-83%) and high enantioselectivities (76-90% ee).

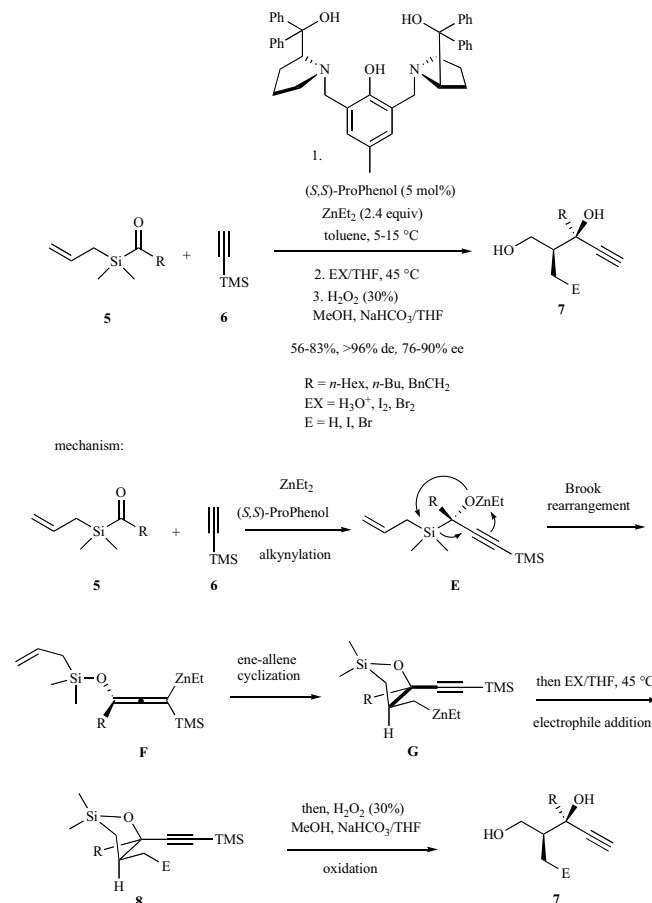


**Scheme 2.** Catalytic cycle for domino Michael/lactonization reaction of 3-hydroxyoxindoles with  $\alpha,\beta$ -unsaturated esters.

In 2014, Chang *et al.* reported the use of (*S,S*)-ProPhenol in an enantioselective zinc-catalyzed domino Michael/hemiketalization reaction of cyclic 1,3-diketones **9** with aryl-substituted  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters **10** [34]. The sequence was performed at 10 °C in tetrahydrofuran (THF) as a solvent in the presence of 10 mol% of  $\text{ZnEt}_2$  and 5 mol% of (*S,S*)-ProPhenol. It yielded the corresponding chiral chromenes **11** in both uniformly high yields (85-96%) and enantioselectivities (76-94% ee), as shown in Scheme 4. The yields were found lower when the steric hindrance of the ester group ( $\text{R}^1$ ) increased. Different substituents on the phenyl ring of the aryl-substituted  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoester were tolerated in both *meta* and *para* positions, providing high yields and enantioselectivities, whereas *ortho*-substituted aryl substrates afforded very low yields ( $\leq 7\%$ ) because of steric reasons. To explain the stereoselectivity of the reaction, a transition state is proposed in Scheme 4, in which the cyclic 1,3-diketone activated by the Brønsted basic zinc nucleus formed the corresponding zinc enolate. Meanwhile, the  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoester was activated by the other Lewis acidic zinc nucleus through bidentate coordination of the 1,2-dicarbonyl moiety. In these conditions, the zinc enolate attacked from the *Re* face of the coordinated Michael acceptor.

In 2018, Trost *et al.* described an enantioselective tandem Mannich/aldol reaction of branched aldehydes **12** with *N*-benzyloxycarbonyl (Cbz)-protected aromatic aldimines **13** and ketones **14** catalyzed by a combination of 10 mol% of (*R,R*)-ProPhenol ligand and 20 mol% of  $\text{ZnEt}_2$  in toluene at -10 °C [35].

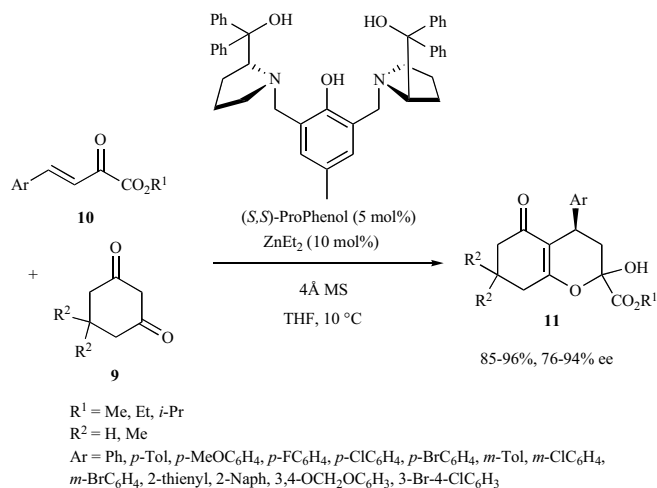
This one-pot reaction required the separated addition of ketones **14** into the reaction vessel upon completion of the asymmetric Mannich process (Scheme 5). It delivered the corresponding chiral 1,3-aminoalcohols **15** exhibiting three contiguous stereocenters in good yields (71-82%), combined with both high diastereo- (82->90% de) and enantioselectivities (98-99% ee). The same catalyst system could be applied to related enantioselective tandem Mannich/Henry reaction of *N*-Cbz protected aromatic aldimines **13**, branched aldehydes **12** and nitromethane **16** as added nucleophilic third partner, affording the corresponding chiral 1,3-aminoalcohols **17** as single diastereomers (>90% de) in excellent enantioselectivities (96-99% ee) and high yields (72-88%), as presented in Scheme 5.



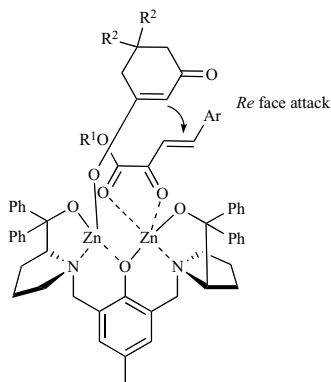
**Scheme 3.** Tandem alkylation/Brook rearrangement/ene-allene cyclization reaction followed by electrophile addition and oxidation.

Later in 2019, the same authors developed an enantioselective zinc-catalyzed tandem Mannich/cycloisomerization reaction of *N*-protected aldimines **13,18** with alkynes **19** performed in the presence of 10 mol% of (*S,S*)-ProPhenol and 20 mol% of  $\text{ZnEt}_2$  in THF at room temperature [36]. The Mannich reaction led to intermediate  $\beta$ -amino ynone **20**, which was subsequently cycloisomerized at 75 °C in toluene as a solvent to afford pyrrolidones **21** after the addition of 10 mol% of  $\text{PPh}_3$  and 40 mol% of acetic acid (AcOH). The chiral products were obtained with a good *E/Z* selectivity (up to 9:1) with good to high yields (66-87%) and enantioselectivities (70-99% ee), as shown in Scheme 6. *N*-Cbz-protected aldimines provided comparable results as *N*-*tert*-butoxycarbonyl (Boc) derivatives in terms of yields and enantioselectivities. A range of aromatic aldimines exhibiting neutral or electron-rich substituents on the phenyl ring gave uniformly excellent enantioselectivities (83-99% ee) while the lowest enantioselectivity (70% ee) was obtained in the

reaction of a heteroaromatic aldimine ( $R^1 = 1\text{-furyl}$ ). Moreover, a vinyl aldimine ( $R^1 = (E)\text{-PhCH=CH}$ ) was cyclized with 68% yield and 87% ee. In contrast, the reaction of *c*-propyl aldimine ( $R^1 = c\text{-Pr}$ ) required the use of a more nucleophilic catalyst, such as methyldiphenylphosphine ( $\text{MePPh}_2$ ) instead of triphenylphosphine ( $\text{PPh}_3$ ), to promote the cycloisomerization, leading to the corresponding pyrrolidone in 79% yield and 92% ee. Interestingly, heterocyclic chiral spirocycles, such as a tetrahydropyran ( $R^2, R^3 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ ) and an *N*-Boc piperidine ( $R^2, R^3 = (\text{CH}_2)_2\text{NBoc}(\text{CH}_2)_2$ ), could be synthesized with good yields (86 and 66%, respectively) and high enantioselectivities (92 and 82% ee, respectively).

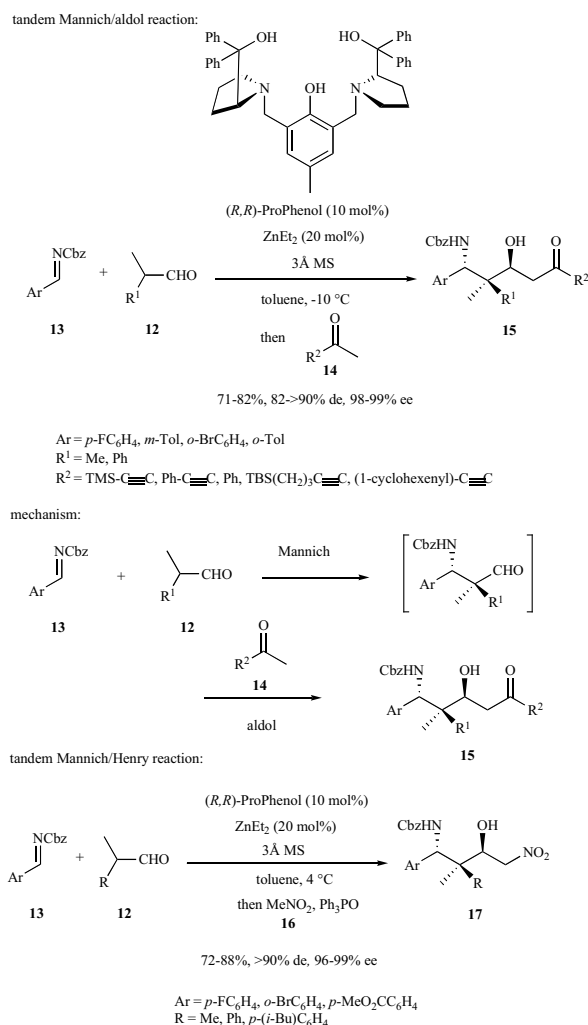


transition state:

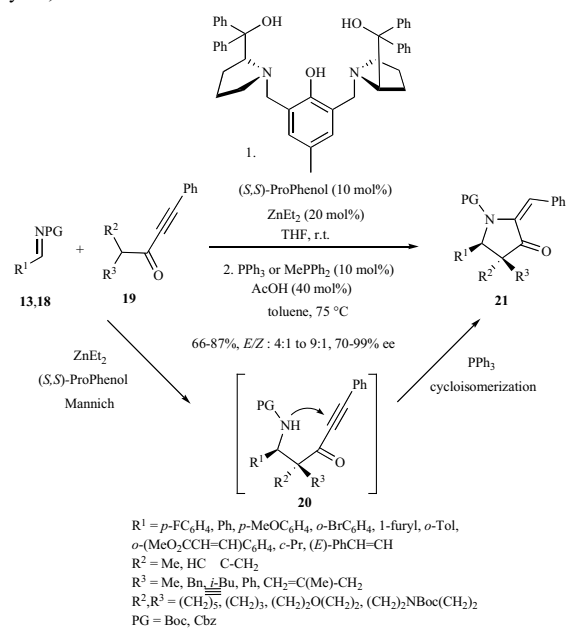


**Scheme 4.** Domino Michael/hemiketalization reaction of cyclic 1,3-diketones with aryl-substituted  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters.

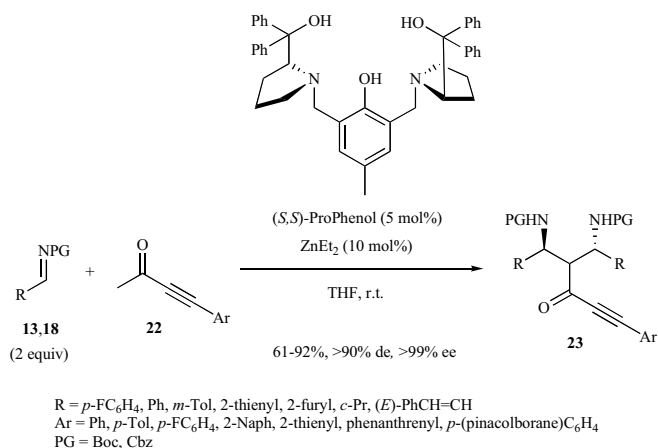
In 2020, a combination of 5 mol% of (*S,S*)-ProPhenol with 10 mol% of  $\text{ZnEt}_2$  was used at room temperature in THF as a solvent to promote an asymmetric pseudo-three-component process between two equivalents of *N*-protected aldimines **13,18** and ynone **22** [37]. This remarkable reaction evolved through a domino double Mannich reaction, yielding enantiopure 1,3-diamines **23** (>99% ee) in good to excellent yields (61-92%). Moreover, in all cases of substrates, the domino products were obtained as almost single diastereomers (>90% de), as shown in Scheme 7. In addition to a range of (hetero)aromatic aldimines which all delivered the enantiopure domino products, nonaromatic aldimines, such as cyclopropyl imine ( $R = c\text{-Pr}$ ), underwent the double Mannich reaction with 78% yield and remarkable enantio- and diastereoselectivities (>90% de, >99% ee). Various (hetero)aromatic ynone were compatible to the catalyst system.



**Scheme 5.** Tandem Mannich/aldol reaction of branched aldehydes, aromatic aldimines and ketones and tandem Mannich/Henry reaction of branched aldehydes, aromatic aldimines and nitromethane.

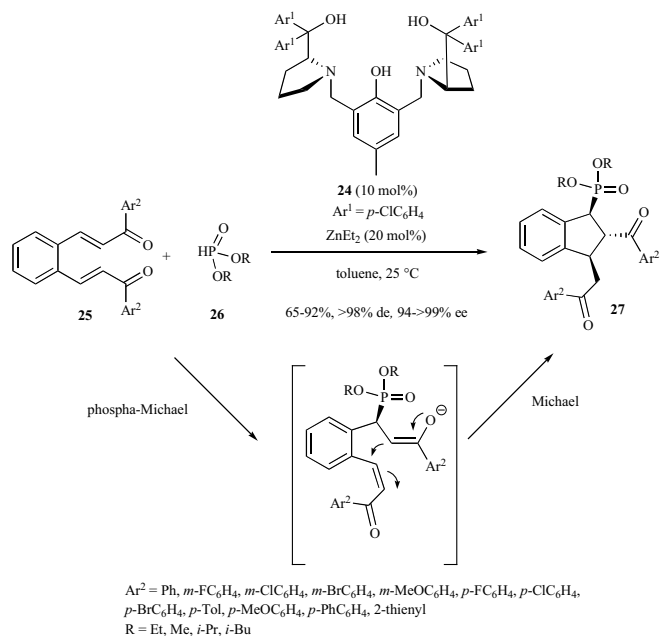


**Scheme 6.** Tandem Mannich/cycloisomerization reaction of aldimines with alkyynes.



**Scheme 7.** Pseudo-three-membered domino double Mannich reaction of ynones with aldimines.

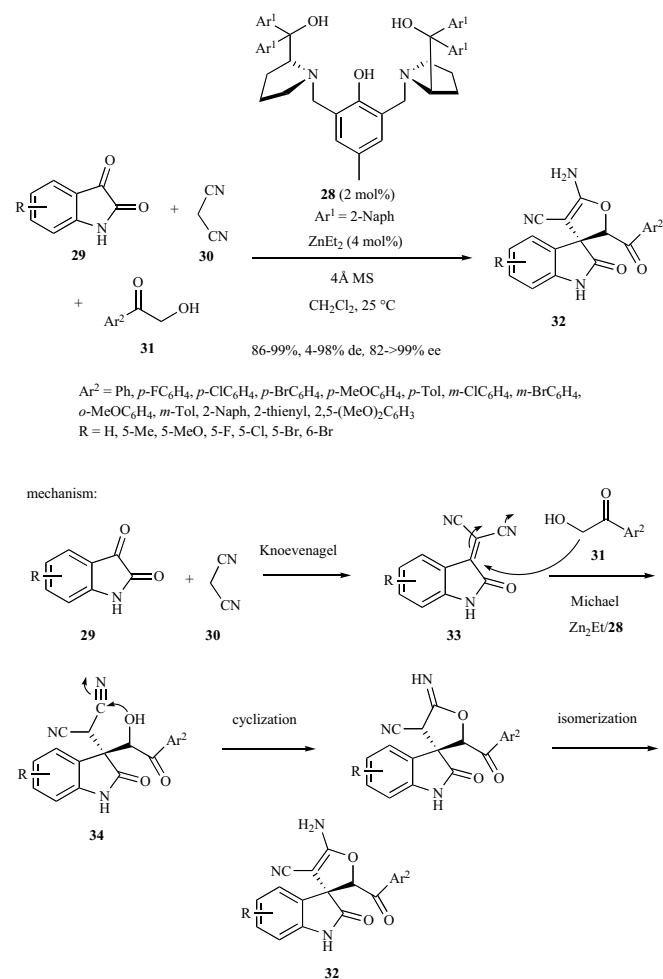
Earlier in 2019, ProPhenol derivative ligand **24** (10 mol%) was combined to  $\text{ZnEt}_2$  (20 mol%) to promote in toluene at 25 °C an enantioselective domino phospho-Michael/Michael reaction between *o*-dienones **25** and dialkyl phosphates **26** [38]. The reaction afforded the corresponding chiral biologically interesting 1,2,3-trisubstituted indane derivatives **27**, bearing phosphoryl groups and three contiguous stereocenters, as single diastereomers (>98% de) in good to high yields (65-92%) and uniformly excellent enantioselectivities (94->99% ee), as illustrated in Scheme 8. Various dialkyl phosphates were compatible with the catalytic system, providing homogeneously excellent results (96-99% ee). Furthermore, comparable excellent yields and enantioselectivities were achieved in the reaction of a series of aryl substituted *o*-dienones, regardless of the electronic nature of the substituents present in the aryl group ( $\text{Ar}^2$ ). This work constituted a rare example of enantioselective double Michael domino reactions catalyzed by metals.



**Scheme 8.** Domino phospho-Michael/Michael reaction of *o*-dienones with dialkyl phosphates.

Another ProPhenol-type ligand, such as **28**, was employed in 2019 by Wang *et al.* to catalyze at only 2 mol% of catalyst loading combined with 4 mol% of  $\text{ZnEt}_2$  an enantioselective three-component domino reaction of isatins **29**, malononitrile **30** and  $\alpha$ -

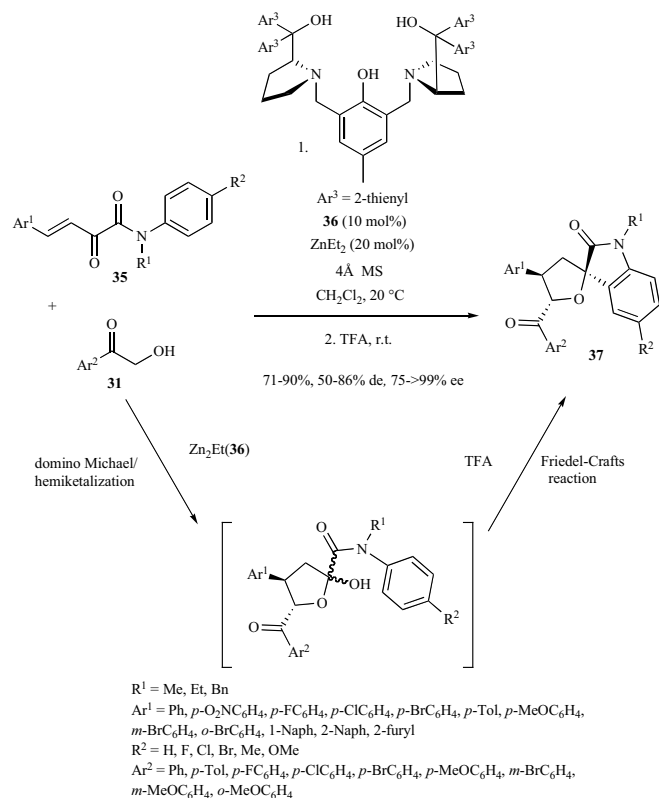
hydroxy acetophenones **31** [39]. This process, performed at 25 °C in dichloromethane as a solvent, evolved through a domino Knoevenagel/Michael/cyclization reaction to yield the corresponding chiral 3,3'-dihydrofuran spirooxindoles **32** in both uniformly high yields (86-99%) and enantioselectivities (82->99% ee) combined with variable diastereoselectivities (4-98% de). Generally, the reaction of isatins bearing electron-rich substituents provided slightly higher enantioselectivities than those exhibiting electron-deficient groups. As depicted in Scheme 9, the sequence began with the Knoevenagel condensation of malononitrile **30** to isatin **29** to give product **33**. In the presence of the chiral dinuclear zinc catalyst *in situ* generated from  $\text{ZnEt}_2$  and ligand **28**,  $\alpha$ -hydroxy acetophenone **31** was deprotonated into a zinc enolate which underwent asymmetric Michael addition to intermediate **33**, leading to intermediate **34**. The latter was then submitted to cyclization followed by isomerization to afford the final 3,3'-dihydrofuran spirooxindole.



**Scheme 9.** Three-component domino Knoevenagel/Michael/cyclization reaction of isatins, malononitrile and  $\alpha$ -hydroxy acetophenones.

Among spirooxindoles, chiral tetrahydrofuran spirooxindoles are especially attractive related to their potent biological activities [40]. In this context, a novel route to these products was developed in 2020 by Hua and Wang on the basis of an enantioselective zinc-catalyzed domino Michael/hemiketalization reaction followed by Friedel-Crafts reaction [41]. This sequence involved  $\alpha$ -hydroxy aryl ketones **31** and  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoamides **35** as substrates. The domino reaction, performed at 20 °C in dichloromethane as solvent, was promoted by a chiral dinuclear zinc catalyst *in situ*

generated from 20 mol% of  $\text{ZnEt}_2$  and 10 mol% of chiral ProPhenol-derived ligand **36**. The domino products were not isolated but directly submitted to Friedel–Crafts reaction performed at room temperature by adding trifluoroacetic acid (TFA). The one-pot sequence afforded a wide range of chiral tetrahydrofuran spirooxindoles **37** in high yields (71–90%), moderate to high diastereoselectivities (50–86% de) and high to excellent enantioselectivities (75–>99% ee), as illustrated in Scheme 10. Actually, the enantioselectivities were uniformly excellent (90–>99% ee) for differently substituted substrates excepted for *ortho*-methoxy-substituted  $\alpha$ -hydroxy aryl ketone ( $\text{Ar}^2 = o\text{-MeOC}_6\text{H}_4$ ), which provided the corresponding product with the lowest ee value (75% ee).

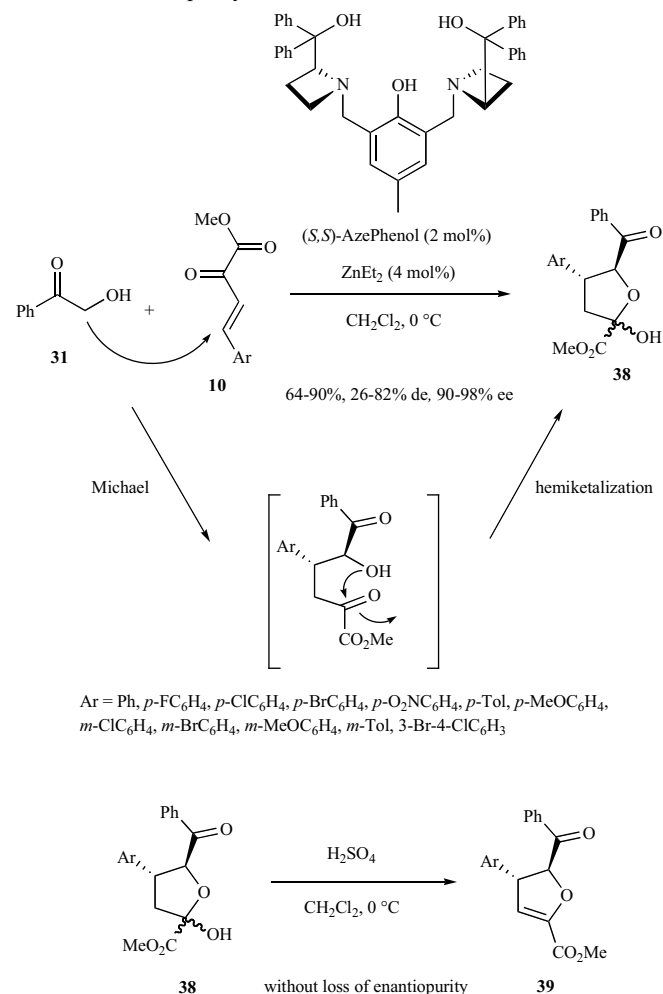


**Scheme 10.** Domino Michael/hemiketalization reaction of  $\alpha$ -hydroxy aryl ketones with  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoamides followed by Friedel–Crafts reaction.

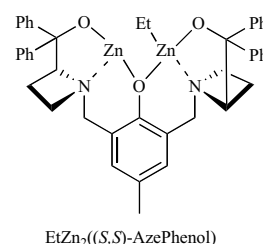
## 2.2. AzePhenol Ligand and Derivatives

In 2014, Chang and Wang reported the synthesis of a novel chiral semi-aza-crown ligand, namely AzePhenol, exhibiting a more rigid azetidone ring compared with that of pyrrolidine present in ProPhenol ligand [42]. The corresponding chiral dinuclear zinc catalyst  $\text{Zn}_2\text{Et}((S,S)\text{-AzePhenol})$ , *in situ* generated from 2 mol% of this ligand and 4 mol% of  $\text{ZnEt}_2$ , was employed in 2015 by the same authors to promote an enantioselective domino Michael/hemiketalization reaction (Scheme 11) [43]. It involved aryl-substituted  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters **10** and  $\alpha$ -hydroxyacetophenone **31** as substrates in dichloromethane as a solvent, leading at 0 °C to the corresponding chiral 2,2,4,5-tetrasubstituted tetrahydrofurans **38** in good yields (64–90%), uniformly excellent enantioselectivities (90–98% ee) and low to good diastereoselectivities (26–82% de). The lowest diastereoselectivities (26–40% de) were obtained in the reaction of  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters with substituents on the phenyl ring at the *meta*-position. Interestingly, products **38** could be converted under acidic conditions into the

corresponding chiral 2,3,5-trisubstituted 2,3-dihydrofurans **39** without loss of enantiopurity.



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



**Scheme 11.** Domino Michael/hemiketalization reaction of aryl-substituted  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters with  $\alpha$ -hydroxyacetophenone.

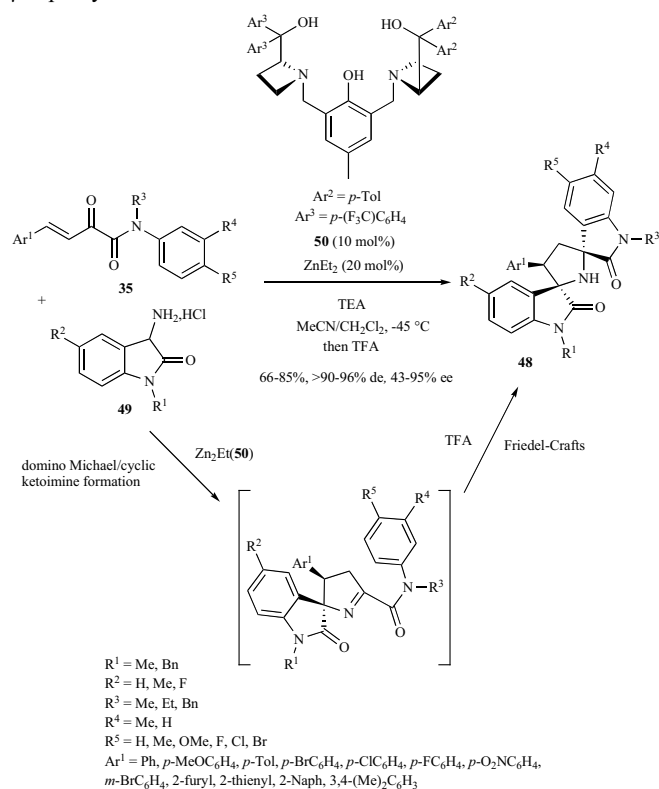
In 2019, the same authors developed a novel route to chiral bispirotetrahydrofuran oxindoles based on an enantioselective cascade Michael/hemiketalization/Friedel–Crafts reaction of  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoamides **35** with 2-hydroxy-1-indanones **40** (Scheme 12) [44]. The sequence began with an asymmetric domino Michael/hemiketalization catalyzed by a chiral dinuclear zinc complex  $\text{Zn}_2\text{Et}(\mathbf{41})$  derived from 4 mol% of  $\text{ZnEt}_2$  and 2 mol% of chiral AzePhenol-type ligand **41**. The reaction, performed in THF at 0 °C, afforded the unstable hemiketal domino product **42** which was not isolated but directly submitted to TFA which promoted the final





### 2.3. C<sub>1</sub>-Symmetric Aza-Crown Ligands

In 2019, Wang and Hua developed new access to chiral pyrrolidinyl dispirooxindoles **48** which constitute potent biologically active products [47]. The methodology was based on a novel asymmetric domino Michael/cyclic ketoimine formation reaction followed by a Friedel–Crafts reaction performed in a single vessel. The sequential reaction occurred at -45 °C between 3-amino oxindole hydrochlorides **49** and aryl-substituted  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoamides **35** in a mixture of acetonitrile and dichloromethane as solvent. Among chiral ligands investigated in this process, C<sub>2</sub>-symmetric (*S,S*)-ProPhenol and AzePhenol derivatives all provided low enantioselectivities ( $\leq 33\%$  ee). In this context, the authors developed nonsymmetrical ligands, such as C<sub>1</sub>-symmetric ligand **50**, with electronically and sterically divergent units. The use of a combination of 10 mol% of this ligand with 20 mol% of ZnEt<sub>2</sub> allowed a range of pyrrolidinyl dispirooxindoles **48** exhibiting two quaternary stereocenters as single diastereomers (>90-96% de) to be synthesized in high yields (66-85%) and moderate to high enantioselectivities (43-95% ee), as illustrated in Scheme 15. The presence of various substituents at the phenyl ring of aryl-substituted  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoamides **35** was tolerated. Generally, substrates with electron-donating groups at the *para* position of the phenyl ring (Ar<sup>1</sup>) provided higher enantioselectivities than those with electron-withdrawing groups. The catalytic system was also compatible with heteroaromatic-substituted  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoamides and  $\gamma$ -naphthyl-substituted substrates.

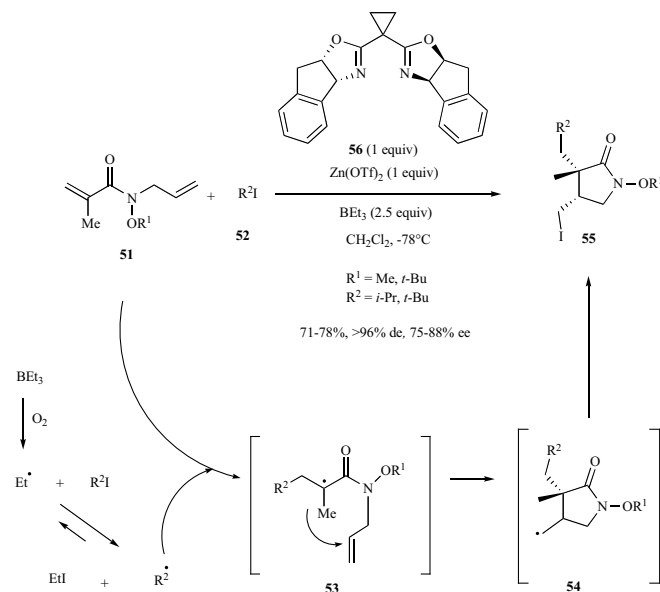


**Scheme 15.** Domino Michael/ cyclic ketoimine formation reaction of 3-amino oxindole hydrochlorides with  $\beta,\gamma$ -unsaturated  $\alpha$ -keto amides followed by Friedel–Crafts reaction.

### 3. REACTIONS USING BIS(OXAZOLINE) AND BIS(IMIDAZOLINE) LIGANDS

Chiral bis(oxazolines) [48] have been successfully employed as zinc ligands in various types of asymmetric reactions, including Michael additions [3e], and hydrosilylations of ketones [49], among

others. In 2006, this type of ligands was investigated by Takemoto et al. in an enantioselective zinc-catalyzed domino radical addition/cyclization reaction between hydroxamate esters **51** and alkyl iodides **52** [50]. The reaction evolved through the addition of a radical generated from the alkyl iodide followed by cyclization of the thus formed radical intermediate **53** into five-membered intermediate **54**. Then, the latter led to final lactam **55** through iodide atom-transfer (Scheme 16). Several chiral lactams **55** were synthesized by this methodology as almost single diastereomers (>96% de) with good yields (71-78%) and good enantioselectivities (75-88% ee). It must be noted that this novel domino reaction presented the disadvantage to require a stoichiometric quantity of catalyst derived from zinc trifluoromethanesulfonate (Zn(OTf)<sub>2</sub>) and bis(oxazoline) **56**.

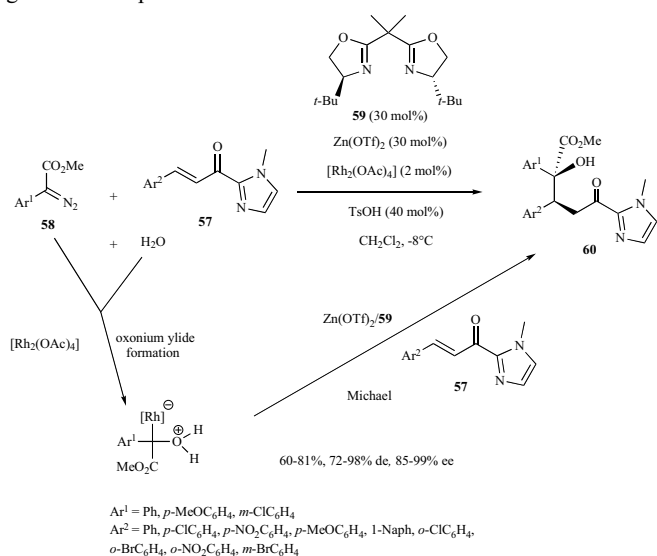


**Scheme 16.** Domino radical addition/cyclization reaction of hydroxamate esters with alkyl iodides.

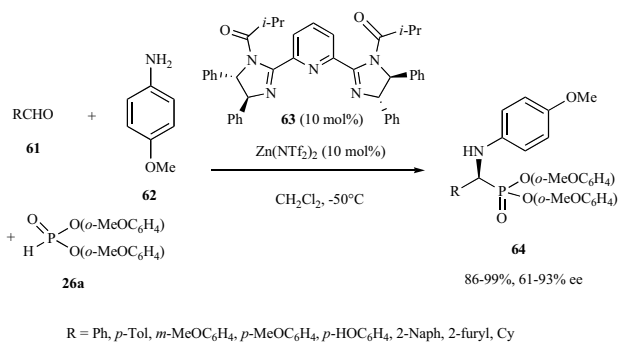
Multicatalysis attracts more attention from chemists [51]. As an example, Hu et al. developed in 2010 an enantioselective three-component domino oxonium ylide formation/Michael reaction of  $\alpha,\beta$ -unsaturated 2-acyl imidazoles **57**, diazo compounds **58** and water [52]. As shown in Scheme 17, the process was multicatalyzed by a combination of a chiral zinc complex, *in situ* generated from 30 mol% of Zn(OTf)<sub>2</sub> and the same quantity of chiral bis(oxazoline) ligand **59**, and 2 mol% of dirhodium tetraacetate ([Rh<sub>2</sub>(OAc)<sub>4</sub>) in dichloromethane as solvent. This cooperative catalysis allowed at -8 °C to synthesize a range of chiral  $\gamma$ -hydroxyketones **60** bearing two contiguous stereogenic centers, including one quaternary. These products were obtained in good yields (60-81%) and diastereoselectivities (72-98% de) combined with high enantioselectivities (85-99% ee). The rhodium catalyst was supposed to promote the formation of an oxonium ylide from the diazoacetate reagent and water, which was further trapped by the  $\alpha,\beta$ -unsaturated 2-acyl imidazole activated by the zinc catalyst through a Michael reaction to give the final domino product. It was found that electronic variations on the aromatic substituents of both the imidazoles and the diazoacetates were tolerated.

In 2011, Shibata et al. developed an enantioselective three-component Kabachnik–Fields reaction of aldehydes **61**, *p*-aminophenol **62** and diarylphosphite **26a** catalyzed by a chiral zinc complex derived from 10 mol% of bis(imidazoline) ligand **63** and

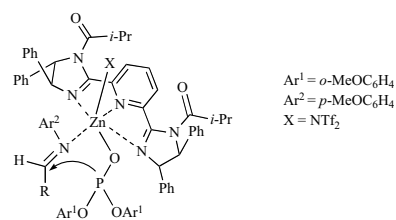
the same quantity of zinc di[bis(trifluoromethylsulfonyl)imide] ( $\text{Zn}(\text{NTf}_2)_2$ ) [53]. Performed at  $-50^\circ\text{C}$  in dichloromethane as solvent, the one-pot process afforded a range of chiral  $\alpha$ -aminophosphonates **64** in excellent yields (86-99%) and good to high enantioselectivities (61-93% ee), as presented in Scheme 18. Actually, the reaction of (hetero)aromatic aldehydes all provided high enantioselectivities (82-93% ee), while the lowest enantioselectivity (61% ee) was obtained in the reaction of an aliphatic aldehyde ( $\text{R} = \text{Cy}$ ). In a possible transition state depicted in Scheme 18, the imine *in situ* generated from aldehyde **61** and *p*-aminophenol **62** coordinated to the chiral zinc catalyst in equatorial position by avoiding the steric repulsion from the bis(imidazoline) ligand. The coordination of the oxygen atom in phosphite to zinc and deprotonation of phosphite afforded the corresponding phosphonate, which attacked the imine avoiding steric repulsion with phenyl groups to give the final product.



**Scheme 17.** Three-component domino oxonium ylide formation/Michael reaction of  $\alpha,\beta$ -unsaturated 2-acyl imidazoles, diazo compounds and water.

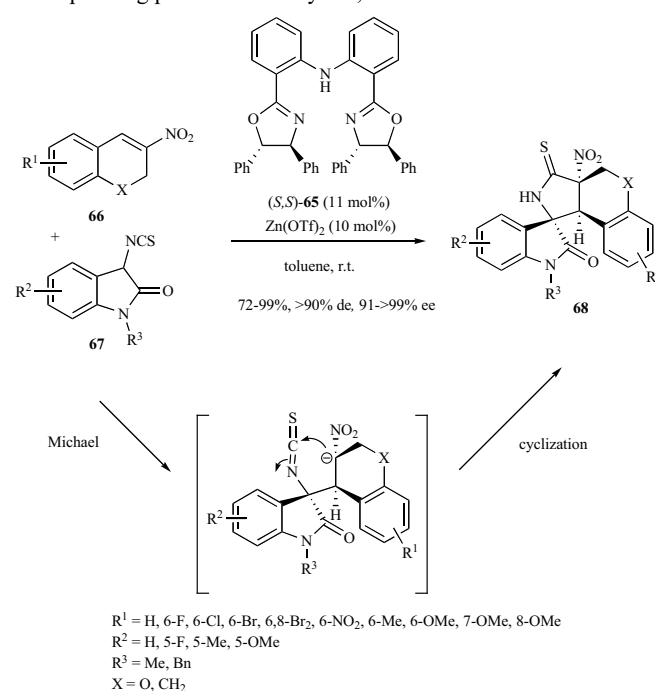


proposed transition state:



**Scheme 18.** Three-component Kabachnik-Fields reaction of aldehydes, *p*-aminophenol and a diarylphosphite.

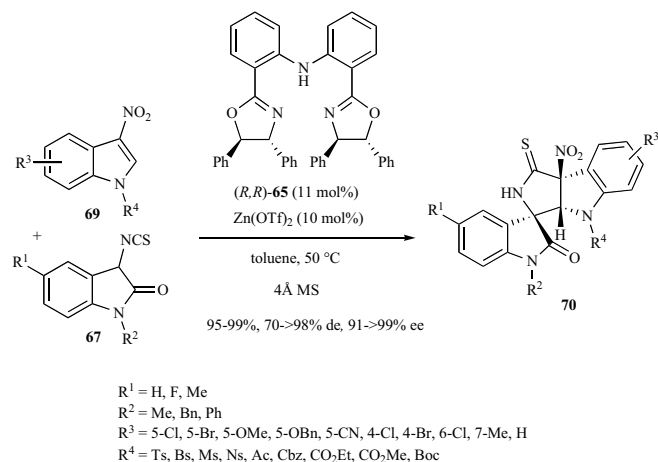
Using chiral bis(oxazoline) ligand (*S,S*)-**65** bearing a free NH group, a novel enantioselective zinc-catalyzed domino Michael/cyclization reaction of 3-nitro-2*H*-chromenes **66** ( $\text{X} = \text{O}$ ) with 3-isothiocyanatooxindoles **67** was developed by Chen and Xiao in 2014 [54]. Indeed, a combination of 11 mol% of ligand (*S,S*)-**65** with 10 mol% of  $\text{Zn}(\text{OTf})_2$  promoted this domino process at room temperature in toluene as solvent, which led to complex and densely functionalized chiral spirooxindoles **68** as single diastereomers (>90% de) in good to quantitative yields (72-99%) and uniformly excellent enantioselectivities (91->99% ee), as shown in Scheme 19. The catalyst system was compatible with the presence of both electron-withdrawing and electron-donating substituents ( $\text{R}^1$ ) at different positions on the aromatic ring of 3-nitro-2*H*-chromenes, providing comparable excellent results. Moreover, variously (*N*)-substituted 3-isothiocyanatooxindoles all provided comparable high levels of stereoselectivities. Furthermore, when the oxygen atom of 3-nitro-2*H*-chromene was replaced by a methylene group ( $\text{X} = \text{CH}_2$ ), the reaction also proceeded, affording the corresponding product in 95% yield, >90% de and >99% ee.



**Scheme 19.** Domino Michael/cyclization reaction of 3-nitro-2*H*-chromenes ( $\text{X} = \text{O}$ ) with 3-isothiocyanatooxindoles.

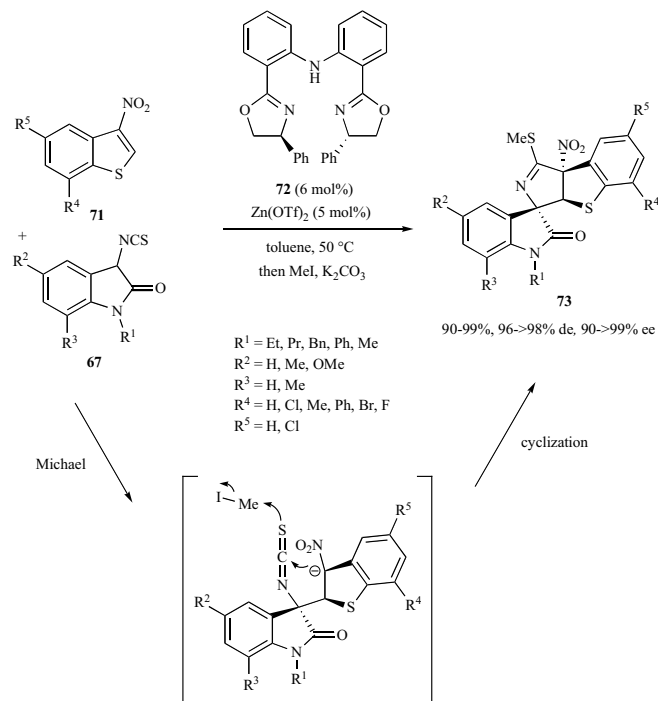
In 2015, Xu and Yuan reported a related enantioselective domino Michael/cyclization reaction by using the (*R,R*)-enantiomer of the same ligand **65** [55]. As shown in Scheme 20, the reaction occurred between 3-isothiocyanatooxindoles **67** and 3-nitroindoles **69** in the presence of 11 mol% of ligand (*R,R*)-**65** and 10 mol% of  $\text{Zn}(\text{OTf})_2$  in toluene at  $50^\circ\text{C}$ , affording the corresponding chiral polycyclic spirooxindoles **70** in quantitative yields (95-99%), uniformly impressive enantioselectivities (91->99% ee) and generally excellent diastereoselectivities (70->98% de). In most cases of substrates, they were obtained as single diastereomers especially for *N*-methyl protected 3-isothiocyanatooxindoles. Indeed, the lowest diastereo- (70% de) and enantioselectivities (91% ee) were observed in the reaction of *N*-phenyl protected 3-isothiocyanatooxindole ( $\text{R}^2 = \text{Ph}$ ). Furthermore, the catalytic system was compatible with a range of 3-nitroindoles with no influence of both the electronic nature and the substitution pattern of the substituents ( $\text{R}^3$ ) on the

phenyl ring. Moreover, substrates bearing different *N*-substituents ( $R^4$ ) provided comparable excellent results.



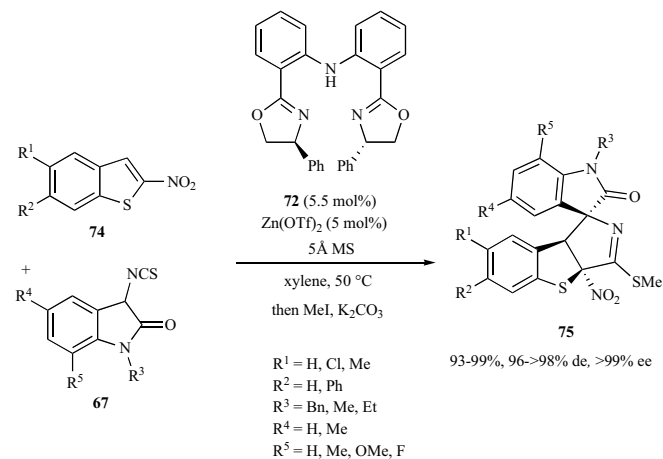
**Scheme 20.** Domino Michael/cyclization reaction of 3-nitroindoles with 3-isothiocyanatooxindoles.

In 2018, the same authors developed enantioselective domino Michael/cyclization reaction of 3-isothiocyanatooxindoles **67** with 3-nitrobenzothiophenes **71** [56]. The reaction was promoted at 50 °C in toluene by a chiral zinc catalyst *in situ* generated from 5 mol% of  $\text{Zn}(\text{OTf})_2$  and 6 mol% of chiral bis(oxazoline) ligand **72**. It afforded the corresponding chiral polycyclic spirooxindoles **73** containing a 2,3-dihydrobenzothiophene motif with excellent yields (90–99%), diastereoselectivities (96–>98% de) and enantioselectivities (90–>99% ee), as presented in Scheme 21. Different electron-donating and electron-withdrawing substituents on the phenyl ring of either the 3-isothiocyanatooxindole substrate or the 3-nitrobenzothiophene were tolerated, providing similar exceptional results whatever their position. Moreover, different alkyl groups on the N1-position of the 3-isothiocyanatooxindole were compatible.



**Scheme 21.** Domino Michael/cyclization reaction of 3-nitrobenzothiophenes with 3-isothiocyanatooxindoles.

The same catalyst system was also applied by these authors to the related enantioselective domino Michael/cyclization reaction of 2-nitrobenzothiophenes **74** with 3-isothiocyanatooxindoles **67** [57]. Again, the results were impressive since the reaction performed in xylene at 50 °C resulted in the formation of the corresponding complex polycyclic spirooxindoles **75** as almost single diastereomer (96–>98% de) and enantiomers (>99% ee) in uniformly excellent yields (93–99%), as illustrated in Scheme 22. The presence of various groups on the aromatic rings was tolerated as well as that of different alkyl *N*-substituents. It must be noted that this work represented the first asymmetric formal dearomative [3+2] cycloaddition of 2-nitroindoles with 3-isothiocyanatooxindoles.

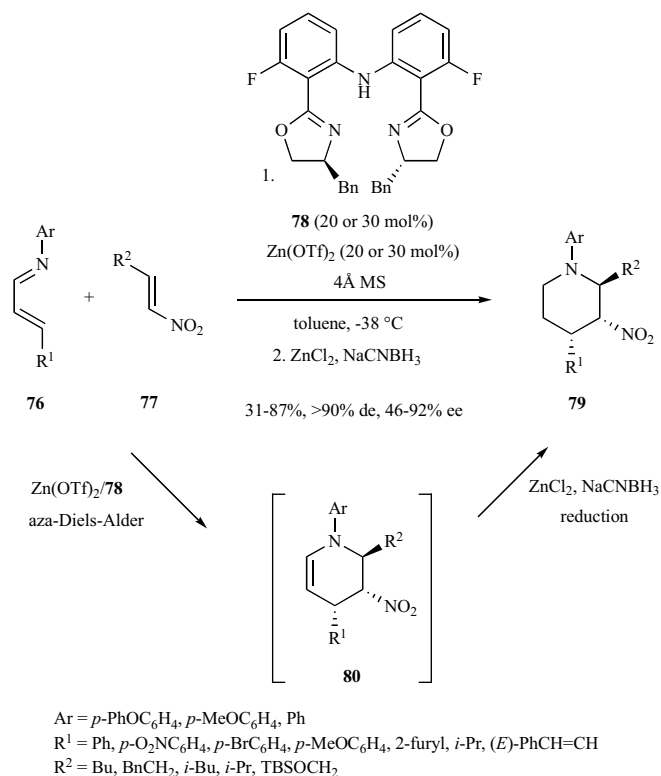


**Scheme 22.** Domino Michael/cyclization reaction of 2-nitrobenzothiophenes with 3-isothiocyanatooxindoles.

Despite the prevalence of piperidine moieties in drugs, the azaversion of the all-carbon [4+2] cycloaddition is less developed [58]. In this context, Rovis reported in 2015 a rare example of asymmetric synthesis of piperidines which was based on an enantioselective tandem aza-Diels–Alder/reduction reaction of 1-azadienes **76** with nitroalkenes **77** (Scheme 23) [59]. The chiral catalyst was *in situ* generated from 20 mol% of  $\text{Zn}(\text{OTf})_2$  and the same quantity of chiral bis(oxazoline) **78** in toluene at -38 °C, affording a range of chiral piperidines **79** in variable yields (31–87%) and enantioselectivities (46–92% ee) as single regio- and diastereomers (>90% de). Actually, due to the instability of the tetrahydropyridine **80** arisen from the cycloaddition, its enamine functionality was further reduced by treatment with  $\text{ZnCl}_2$  and sodium cyanoborohydride ( $\text{NaBH}_3\text{CN}$ ) in methanol to give a more stable 3-nitropiperidine **79**. The lowest enantioselectivity (46% ee) was obtained in the reaction of an alkyl-substituted azadiene ( $R^1 = i\text{-Pr}$ ). Furthermore, the reaction of a more conjugated azatriene ( $R^1 = (E)\text{-PhCH=CH}$ ) required 30 mol% of catalyst to provide the corresponding product in 65% yield and 63% ee. For all the other differently substituted substrates, enantioselectivities  $\geq 69\%$  ee were obtained.

In 2020, Zhang *et al.* disclosed an enantioselective domino inverse-electron-demand Diels–Alder/oxidation reaction between indoles **81** and 2-(2-nitrovinyl)-1,4-benzoquinone **82** [60]. It was promoted by a combination of 17 mol% of chiral bis(oxazoline) **78** combined with 10 mol% of  $\text{Zn}(\text{OTf})_2$  at 70 °C in toluene as solvent, providing the formation of chiral six-membered [2,3]-fused indolines **83** as single diastereomers in moderate to quantitative yields (34–99%) and enantioselectivities (37–88% ee), as presented in Scheme 24. The cycloaddition underwent through the *Re* face of the 2-(2-nitrovinyl)-1,4-benzoquinone activated by the chiral zinc catalyst which was also *N*-chelated to the indole substrate through NH–

p interaction to give Diels–Alder cycloadduct **84**. The latter was unstable and subsequently underwent oxidation to give the final product **83**.



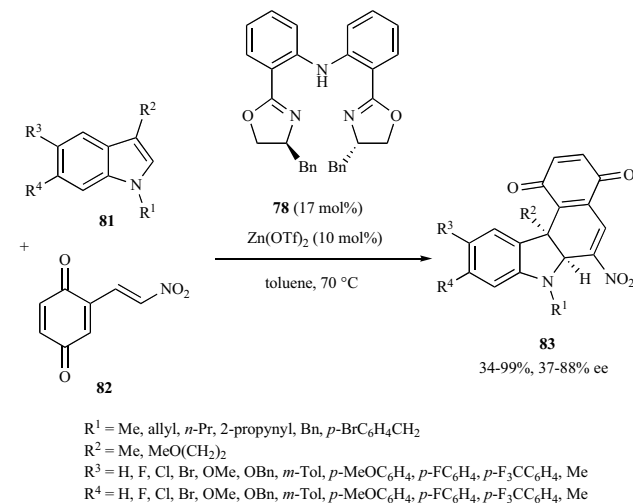
**Scheme 23.** Tandem aza-Diels–Alder/reduction reaction of 1-azadienes with nitroalkenes.

#### 4. REACTIONS USING *N,N'*-DIOXIDE LIGANDS

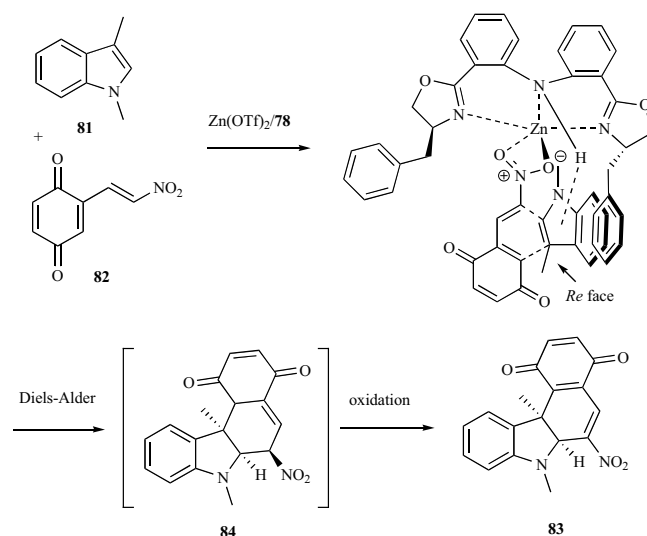
Chiral *N,N'*-dioxide ligands developed by Feng *et al.* have been widely employed as ligands in asymmetric catalysis so far [61]. In 2011, these authors employed a combination of 20 mol% of *N,N'*-dioxide ligand **85** with 10 mol% of precatalyst zinc perchlorate hexahydrate (Zn(ClO<sub>4</sub>)<sub>2</sub>(H<sub>2</sub>O)<sub>6</sub>) to promote in dichloromethane as solvent an enantioselective three-component reaction between salicylaldehydes **86**, malononitrile **30** and indoles **87** [62]. As presented in Scheme 25, the reaction performed at 35 °C led to a range of chiral 2-amino-4H-chromenes **88** in good to high yields (37–89%) and high enantioselectivities (80–90% ee). The one-pot process evolved through a domino Knoevenagel/Pinner/Friedel–Crafts reaction. First, a Knoevenagel/Pinner sequence between salicylaldehyde **86** and malononitrile **30** provided an iminochromene intermediate **89** which subsequently underwent in the presence of indole **87** and the chiral zinc catalyst a Friedel–Crafts reaction to afford the final product. It was found that indoles containing electron-withdrawing groups on the aromatic ring gave higher enantioselectivities than those exhibiting electron-donating groups. The lowest yield (37%) was observed in the reaction of 4-methoxy-substituted salicylaldehyde. Related to the biologic importance of many natural chromenes, this novel simple route to this type of products is attractive.

In 2019, the first catalytic enantioselective domino  $\alpha$ -alkenyl addition/proton shift reactions of silyl enol ethers with cyclic ketimines, such as isatin- and pyrazolinone-derived ketimines, was developed by the same authors in the presence of other *N,N'*-dioxide ligands [63]. As depicted in Scheme 26, silyl enol ethers **90** and **91** reacted with isatin-derived ketimine **92** in the presence of

2.5–5 mol% of a chiral zinc catalyst *in situ* generated from Zn(OTf)<sub>2</sub> and chiral *N,N'*-dioxide ligand **93** at 40 °C to give the corresponding  $\beta$ -amino silyl enol ethers **94** and **95**, respectively, in excellent enantioselectivities (87–93% ee) and variable yields (21–90%). With the aim of extending the scope of this novel process, the authors investigated the reaction of pyrazolinone-derived ketimines **96** with silyl enol ethers **90**. In this case, the best results were achieved by using a closely related *N,N'*-dioxide ligand **97** in combination with Zn(NTf<sub>2</sub>)<sub>2</sub>. Under these conditions, a series of other chiral  $\beta$ -amino silyl enol ethers **98** were synthesized with both high yields (84–98%) and enantioselectivities (84–97% ee).

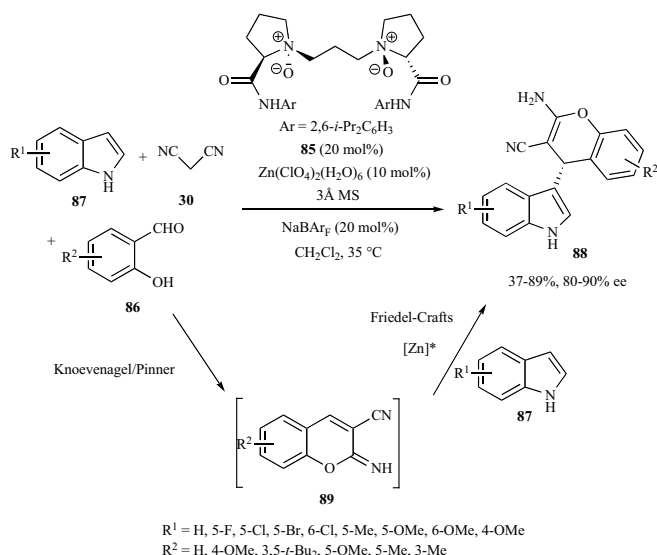


mechanism with R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = R<sup>4</sup> = H:

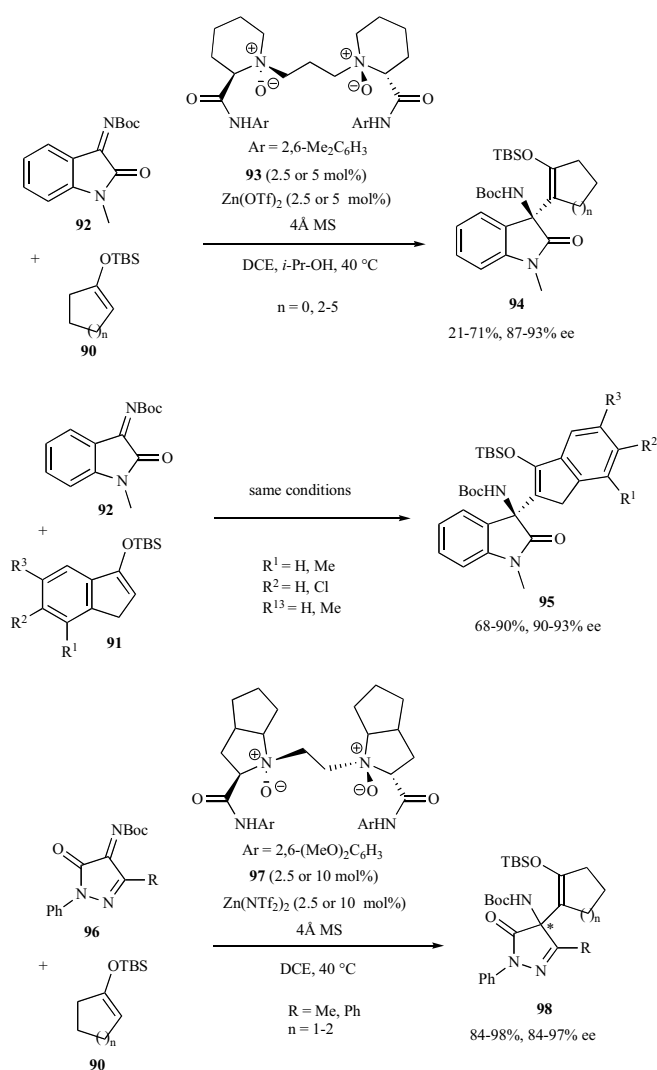


**Scheme 24.** Domino inverse-electron-demand Diels–Alder/oxidation reaction of indoles with 2-(2-nitrovinyl)-1,4-benzoquinone.

In the same year, these authors also reported an enantioselective domino reaction of  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters **10** with diazoimides **99** promoted at 30 °C in 1,2-dichloroethane (DCE) as solvent through bimetallic relay catalysis using an achiral rhodium complex, such as dirhodium tetrapivalate (Rh<sub>2</sub>Piv<sub>4</sub>) (0.5 mol%), and a chiral zinc catalyst *in situ* generated from 10 mol% of Zn(OTf)<sub>2</sub> and 10 mol% of chiral *N,N'*-dioxide ligand **100** [64]. The rhodium catalyst allowed to generate a carbonyl ylide intermediate from the diazoimide which subsequently reacted through asymmetric [4+3]

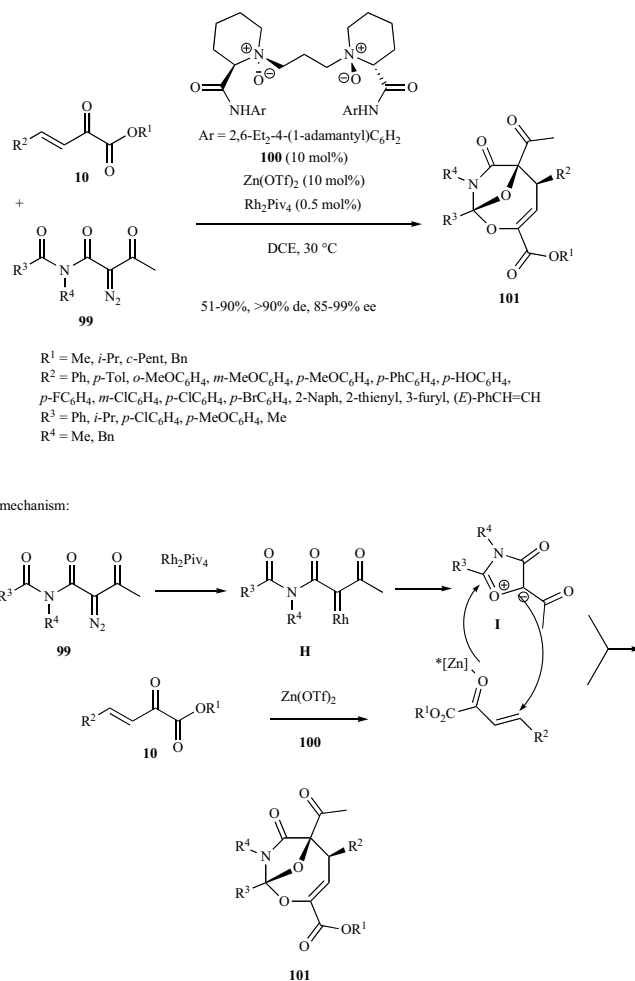


**Scheme 25.** Three-component domino Knoevenagel/Pinner/Friedel-Crafts reaction of salicylaldehydes, malononitrile and indoles.



**Scheme 26.** Domino  $\alpha$ -alkenyl addition/proton shift reactions of silyl enol ethers with isatin- and pyrazolinone-derived ketimines.

cycloaddition with the  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoester catalyzed by the chiral zinc complex. As illustrated in Scheme 27, this domino carbonyl imide formation/[4+3] cycloaddition reaction resulted in the formation of a range of chiral oxa-bridged oxazocines **101** as almost single *exo*-diastereomers (>90% de) in good to high yields (51-90%) and uniformly high enantioselectivities (85-99% ee). The catalyst system was compatible with various (hetero)aryl-substituted  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters **10**, bearing either electron-withdrawing or electron-donating substituents at different positions of the phenyl group. Heteroaromatic-substituted substrates were also compatible, as well as various alkyl ester groups ( $R^1$ ). Furthermore, variously (*N*)-substituted diazoimides reacted smoothly. The mechanism proposed in Scheme 27 shows the formation of rhodium carbene species **H** from diazoimide **99** and  $\text{Rh}_2\text{Piv}_4$ . Then, an intramolecular carbonyl attack on the rhodium carbene occurred to form intermediate **I**. The latter reacted with the  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoester **10** activated by the chiral zinc catalyst through a [4+3]-cycloaddition to provide the final product.

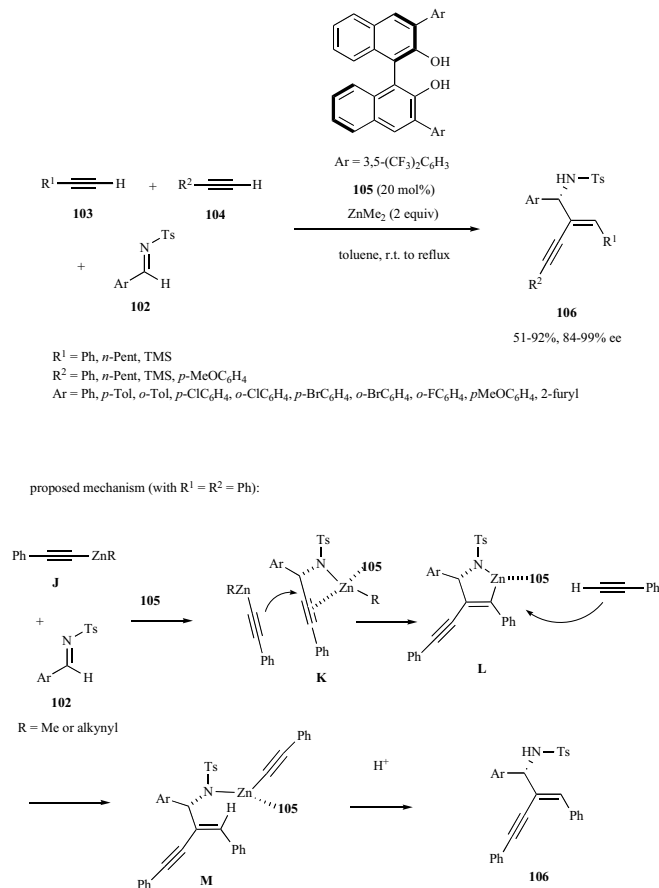


**Scheme 27.** Domino carbonylimide formation/[4+3] cycloaddition reaction of  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters with diazoimides.

## 5. REACTIONS USING BINOL-DERIVED LIGANDS

In 2009, Xu et al. reported an asymmetric zinc-promoted three-component reaction occurring between *N*-tosylaldimines **102** and two different terminal alkynes **103** and **104** [65]. The process was mediated by two equivalents of dimethyl zinc combined with 20 mol% of BINOL-derived ligand **105** in toluene at room temperature to reflux. It resulted in the formation of chiral propargylic amines

**106** in moderate to high yields (51-92%) and uniformly high enantioselectivities (84-99% ee), as shown in Scheme 28. The mechanism involved the formation of alkynylzinc **J** which added to *N*-tosylaldimine **102** to give  $\pi$ -complex intermediate **K**. Then, the latter underwent an attack by another alkynylzinc to form cyclic intermediate **L**. The carbon-zinc bond in **L** could be subsequently cleaved by an excess of alkyne to give intermediate **M**. Then, the acidic hydrolysis of **M** led to the final product.



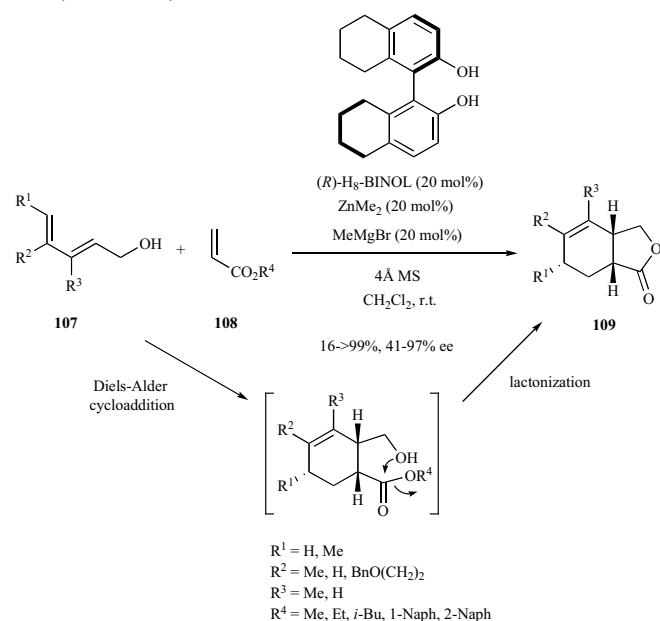
**Scheme 28.** Three-component reaction of *N*-tosylaldimines with two different terminal alkynes.

In 2015, Ishihara et al. reported the first asymmetric domino Diels–Alder/lactonization reaction of 2,4-dienols **107** with acrylates **108** performed in the presence of a catalyst system composed of 20 mol% of (*R*)-H<sub>8</sub>-BINOL, 20 mol% of ZnMe<sub>2</sub> and 20 mol% of methyl magnesium bromide [66]. This bimetallic catalyst allowed at room temperature in dichloromethane as a solvent the formation of chiral bicyclic  $\gamma$ -lactones **109** as single diastereomers in low to quantitative yields (16->99%) and moderate to excellent enantioselectivities (41-97% ee), as shown in Scheme 29.

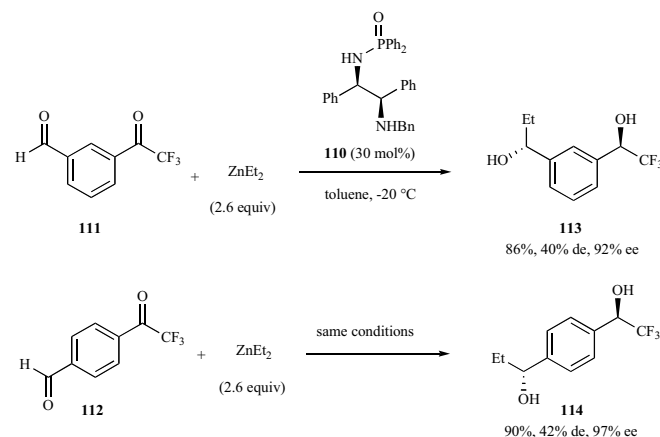
## 6. REACTIONS USING 1,2-DIAMINE LIGANDS

In 2015, Song et al. demonstrated that chiral 1,2-amino phosphoramidate ligand **110** was efficient in both the asymmetric  $\beta$ -H transfer reduction of aryl  $\alpha$ -trifluoromethylketones **111,112** and enantioselective addition of ZnEt<sub>2</sub> of aromatic aldehydes performed in one-pot under the same reaction conditions [67]. As shown in Scheme 30, the corresponding chiral fluorinated diols **113,114** were obtained from the domino transfer reduction/ethylation reaction performed in toluene at -20 °C in the presence of 30 mol% of

ligand **110** in high yields (86-90%) with excellent enantioselectivities (92-97% ee) albeit combined with moderate diastereoselectivities (40-42% de).



**Scheme 29.** Domino Diels–Alder/lactonization reaction of 2,4-dienols with acrylates.



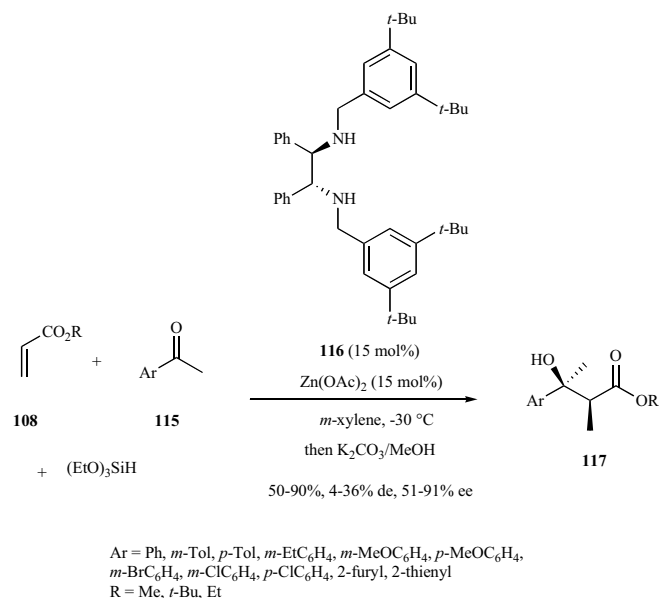
**Scheme 30.** Domino transfer reduction/ethylation reactions of aryl  $\alpha$ -trifluoromethylketones with ZnEt<sub>2</sub>.

In 2020, a novel asymmetric synthesis of  $\beta$ -hydroxy esters was disclosed by Mlynarski et al. through the first enantioselective three-component domino reductive Michael/aldol reaction of acrylates **108**, (hetero)aromatic ketones **115** and triethoxysilane ((EtO)<sub>3</sub>SiH) using zinc acetate as cheap precatalyst [68]. Among chiral ligands based on (*R,R*)-diphenylethylenediamine, diamine **116** was selected as optimal ligand to promote this reaction at 15 mol% of catalyst loading in *m*-xylene as a solvent. As illustrated in Scheme 31, a series of chiral  $\beta$ -hydroxy esters **117** were generated at -30 °C with moderate to high yields (50-90%) and enantioselectivities (51-91% ee). However, the diastereoselectivity of the reaction was found low (4-36% de) and substrate-dependent.

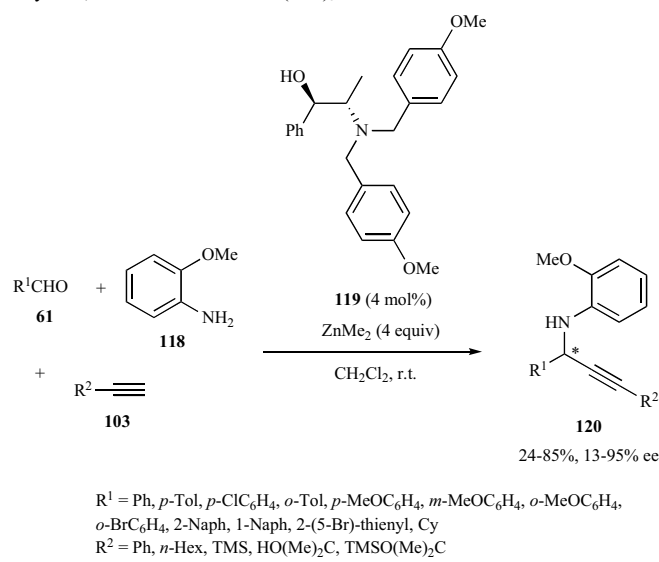
## 7. REACTIONS USING OTHER LIGANDS

In 2007, Bolm et al. disclosed an asymmetric synthesis of *N*-aryl propargylic amines based on an enantioselective three-component reaction of aldehydes **61**, terminal alkynes **103** and *o*-methoxyaniline **118** (Scheme 32) [69]. This reaction was mediated

at room temperature in dichloromethane as solvent by four equivalents of  $\text{ZnMe}_2$  in the presence of 4 mol% of chiral  $\beta$ -amino alcohol ligand **119** derived from norephedrine. It evolved by forming an imine from aldehyde **61** and *o*-methoxyaniline **118**, which was then submitted to alkylation to give the corresponding domino imine formation/alkynylation product **120** in both variable yields (24-85%) and enantioselectivities (13-97% ee). Homogeneously good to high enantioselectivities (68-97% ee) were obtained in the reaction of phenylacetylene, whereas much lower enantioselectivities (13-53% ee) were observed with other alkynes. Moreover, a range of aromatic, heteroaromatic and also aliphatic aldehydes provided, by reaction with *o*-anisidine and phenylacetylene, moderate to high enantioselectivities (68-97% ee).



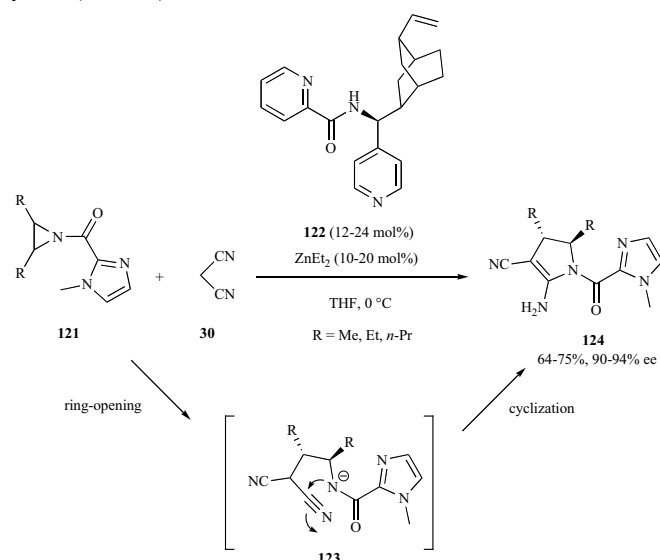
**Scheme 31.** Three-component domino reductive Michael/aldol reaction of acrylates, aromatic ketones and  $(\text{EtO})_3\text{SiH}$ .



**Scheme 32.** Three-component domino imine formation/alkynylation reaction of aldehydes, terminal alkynes and *o*-methoxyaniline.

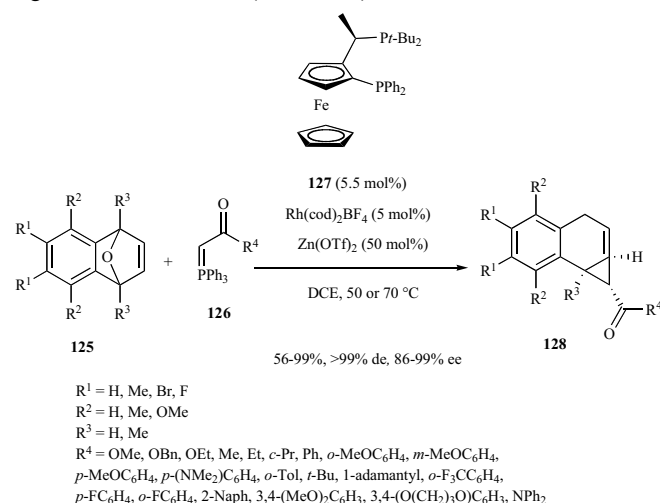
In 2017, Nakamura et al. investigated for the first time the ring-opening reaction of protected aziridines **121** with malononitrile **30** using 12-24 mol% of a cinchona alkaloid zinc catalyst derived from ligand **122** and  $\text{ZnEt}_2$  (10-20 mol%) [70]. As illustrated in Scheme

**33**, acyclic aziridines **121** reacted with malononitrile **30** to give the corresponding ring-opened products **123** which subsequently underwent an intramolecular nucleophilic addition of the amide nitrogen to the cyano group to provide chiral 2,3-dihydro-1H-pyrrole products **124** in excellent enantioselectivities (90-94% ee) and good yields (64-75%).



**Scheme 33.** Domino ring-opening/cyclization reaction of aziridines with malononitrile.

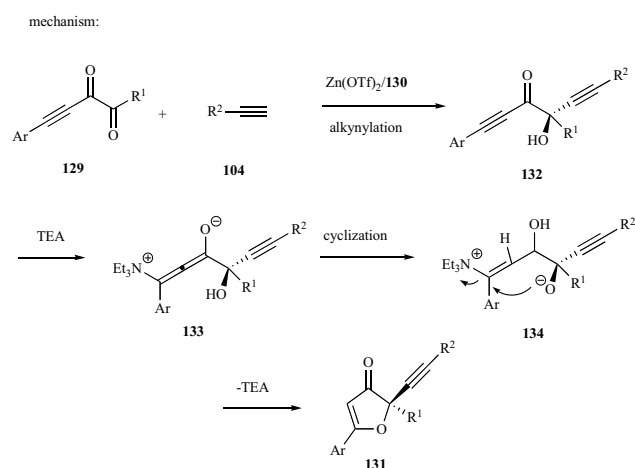
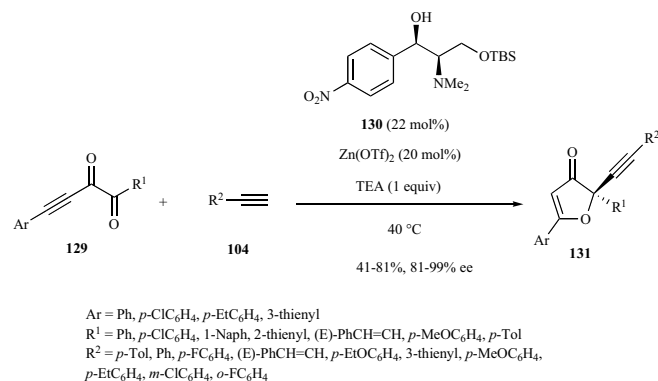
In 2019, a bimetallic rhodium/zinc catalysis was employed by Shao et al. to promote the first enantioselective domino ring-opening/cyclopropanation reaction of oxabenzonorbornadienes **125** with phosphorus ylides **126** [71]. The dual catalysis involved a combination of 5 mol% of bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate ( $\text{Rh}(\text{cod})_2\text{BF}_4$ ), 50 mol% of  $\text{Zn}(\text{OTf})_2$  and 5.5 mol% of chiral biphenyl ligand **127**. The reaction allowed a range of chiral benzenorcaradienes **128** to be synthesized as single diastereomers (>99% de) in good to quantitative yields (56-99%) and high enantioselectivities (86-99% ee), as illustrated in Scheme **34**.



**Scheme 34.** Domino ring-opening/cyclopropanation reaction of oxabenzonorbornadienes with phosphorus ylides.

In 2020, Fang and Ding developed an enantioselective domino alkylation/cyclization reaction of alkynyl 1,2-diketones **129** with alkynes **104** catalyzed by a combination of 20 mol% of  $\text{Zn}(\text{OTf})_2$  and 20 mol% of chiral amino alcohol ligand **130** at room tempera-

ture (Scheme 35) [72]. The reaction was performed at 40 °C in the presence of triethylamine (TEA) as the base, resulting in the formation of biologically important chiral 3(2*H*)-furanones **131** in moderate to good yields (41-81%) and uniformly high enantioselectivities (81-99% ee). It evolved through the mechanism depicted in Scheme 35, involving the nucleophilic addition of TEA to the alkyne unit of the alkylation product **132** to give allenic intermediate **133**. Then, the latter underwent a proton transfer to provide intermediate **134**, which cyclized into the final domino product **131**.



**Scheme 35.** Domino alkylation/cyclization reaction of alkyne 1,2-diketones with alkynes.

## CONCLUSION

As an abundant, inexpensive and less toxic metal, zinc has gained significant importance in green catalysis. While underdeveloped for a long time, zinc catalysts are more and more applied to promote economic and ecologic transformations. Especially, a spectacular development of highly enantioselective zinc-catalyzed one-pot reactions has emerged. This review highlights for the first time the developments in enantioselective domino and tandem reactions promoted by chiral zinc catalysts derived from various types of ligands, such as semi-aza-crown ligands, bis(oxazoline)s, bis(imidazoline)s, *N,N'*-dioxides, BINOL derivatives, 1,2-diamines, amino alcohols, among others. It shows that zinc catalysis suits the growing demand for greener processes and offers the real opportunity to replace other toxic and expensive metals in the near future. It demonstrates that zinc brings a novel potential for green catalysis, especially when combined with efficient sophisticated asymmetric one-pot processes and that this original area is growing very rapidly. Indeed, this field is in full bloom, allowing one-pot access to many types of complex functionalized chiral molecules from simple

starting materials by using environmentally benign catalysts, and will undoubtedly continue to be expanded in the future with the discovery of novel catalysts. Even if remarkable results have been described, challenges remain, such as the application of these processes in the total synthesis of important biologically active and natural products, as well as the involvement of zinc in even more complicated multicatalyzed processes.

## LIST OF ABBREVIATIONS

Ar	= Aryl
BArF	= Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINOL	= 1,1'-bi-2-naphthol
Bn	= Benzyl
Boc	= <i>tert</i> -butoxycarbonyl
Bs	= <i>p</i> -bromobenzenesulfonyl (brosyl)
Cbz	= Benzyloxycarbonyl
cod	= Cyclooctadiene
Cy	= Cyclohexyl
DCE	= 1,2-dichloroethane
de	= Diastereomeric excess
ee	= Enantiomeric excess
Hex	= Hexyl
Ms	= Mesityl
MOM	= Methoxymethyl
MS	= Molecular sieves
Naph	= Naphthyl
Ns	= Nosyl (4-nitrobenzene sulfonyl)
Pent	= Pentyl
PG	= Protecting group
Piv	= Pivalate
PMB	= <i>para</i> -methoxybenzyl
r.t.	= Room temperature
TBS	= <i>tert</i> -butyldimethylsilyl
TEA	= Triethylamine
Tf	= Trifluoromethane sulfonyl
TFA	= Trifluoroacetic acid
THF	= Tetrahydrofuran
TIPS	= Triisopropylsilyl
TMS	= Trimethylsilyl
Tol	= Toly
Ts	= 4-toluenesulfonyl (tosyl)



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