



Recent developments in enantioselective zinc-catalyzed transformations

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Recent developments in enantioselective zinc-catalyzed transformations

Hélène Pellissier

Aix-Marseille Univ, Centrale Marseille, CNRS, Marseille, France

This review collects the recent advances in the field of enantioselective zinc-catalyzed transformations, covering the literature since the beginning of 2015, illustrating the power of chiral green zinc catalysts to promote all types of reactions. A range of highly enantioselective reactions have been developed in the last six years, including cycloadditions, alkynylation/allylation reactions of carbonyl compounds and derivatives, additions of diorganozincs to carbonyl compounds and derivatives, Mannich reactions, (nitro)aldol reactions, other 1,2-nucleophilic additions to carbonyl compounds and derivatives, Michael additions, Friedel–Crafts reactions, reductions, α -functionalizations of carbonyl compounds, ring-opening reactions, epoxidations, halolactonizations, domino/tandem reactions and miscellaneous reactions.

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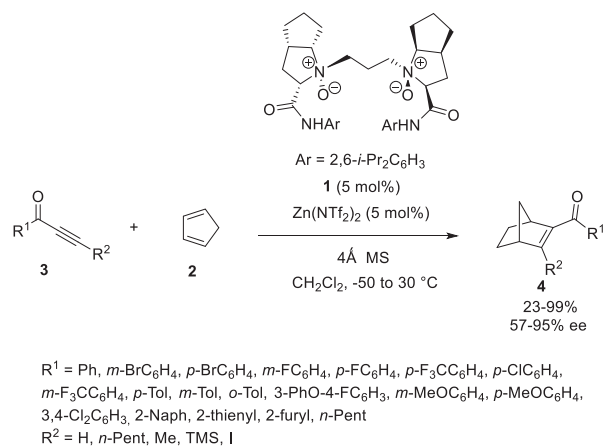
Abbreviations: Ad, adamantly; Ar, aryl; BDPP, 2,4-bis(diphenylphosphino)pentane; BINAP, 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl; BINIM, binaphthylidimine; BINOL, 1,1'-bi-2-naphthol; BIPHEP, 2,2'-bis(diphenylphosphino)-1,1'-biphenyl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bz, benzoyl; Cbz, benzyloxycarbonyl; CMHP, cumene hydroperoxide; cod, cyclooctadiene; Cy, cyclohexyl; DCE, dichloroethane; de, diastereomeric excess; Dec, decyl; DIFLUORPHOS, 5,5'-bis(diphenylphosphino)-2,2,2',2'-tetra fluoro-4,4'-bi-1,3-benzodioxole; DIMPEG, polyethyleneglycol dimethyl ether; DIPEA, diisopropylethylamine; dppe, 1,2-bis(diphenylphosphine)ethane; ee, enantiomeric excess; Hept, heptyl; Hex, hexyl; L, ligand; Mes, mesityl; MOM, methoxymethyl; MS, molecular sieves; Naph, naphthyl; NBS, *N*-bromosuccinimide; NIS, *N*-iodosuccinimide; Oct, octyl; PCPC, polycyclopentene carbonate; Pent, pentyl; PG, protecting group; Phanephos, 4,12-Bis(diphenylphosphino)-[2,2]-paracyclophane; Phth, phthalimidyl; Pin, pinacolato; Piv, pivalate; PMB, *para*-methoxybenzyl; PMHS, polymethylhydrosilane; PMP, pentamethylpiperidine; Pybox, pyridine bisoxazoline; r.t., room temperature; Salen, 1,2-bis(salicylidenamino)ethane; Segphos, 4,4'-Bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphane); TBAF, tetra-*n*-butylammonium fluoride; TBDPS, *tert*-butyldiphenylsilyl; TBHP, *tert*-butyl hydroperoxide; TBS, *tert*-butyldimethylsilyl; TEA, triethylamine; Tf, trifluoromethane sulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMS, trimethylsilyl; Tol, tolyl; Ts, 4-toluenesulfonyl (tosyl); VAPOL, 2,2'-diphenyl-[3,3'-biphenanthrene]-4,4'-diol.

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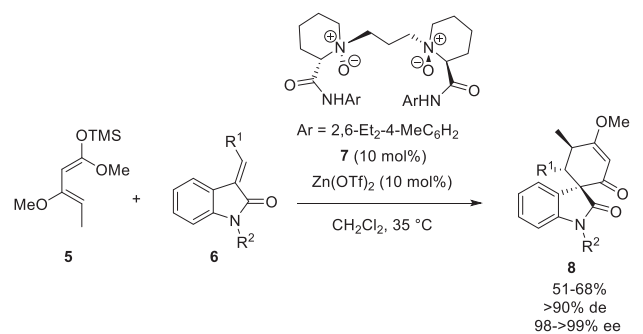
1. Introduction

Zinc is the 24th most abundant element in the Earth's crust [1], the first discovery of which goes back to 1746. As a material, zinc is used for the corrosion-resistant zinc plating of steel, and is also applied in batteries and alloys. Biologically, it is an essential element with exceptional biological importance. For example, zinc deficiency is responsible of many diseases, such as growth retardation, infection susceptibility, delayed sexual maturation, diarrhea, etc [2]. It is present as co-catalyst in many enzymes, which has inspired chemists to design artificial zinc chiral catalysts. Chemically, zinc has a completely filled electron configuration of [Ar] 3d104s2 and acts as a strong reducing agent. It tends to form bonds with a greater degree of covalency and stable complexes with N- and S-donor ligands. In synthetic organic chemistry, the main role of zinc salts is as Lewis acid catalysts. In comparison with most transition metals employed in catalysis [3], zinc complexes present the advantages to be inexpensive, abundant and less toxic, which have triggered the development of a wide range of more ecologic and economic zinc-catalyzed transformations. These green catalysts have been proven to be highly efficient to promote many

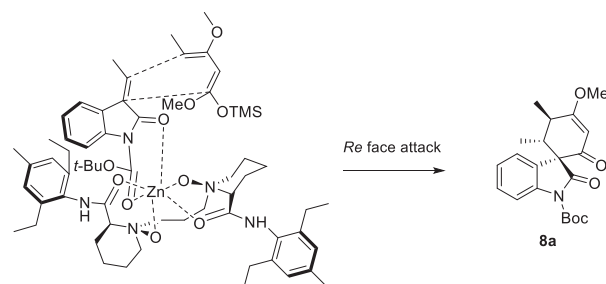
types of organic transformations spanning from basic ones, including C-C, C-O, C-N, C-S, C-P, and C-H bond forming reactions, to modern and complex one-pot methodologies, such as domino and tandem reactions. Indeed, the diversity of transformations in which zinc has been successfully applied is impressive and confirms its versatility as catalyst. This review updates the field of enantioselective zinc-catalyzed reactions published since the beginning of 2015, since this area was most recently updated by



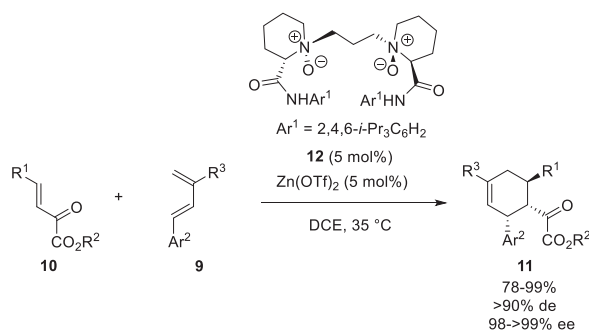
Scheme 1. Diels-Alder cycloaddition of cyclopentadiene with alkynones in the presence of a *N,N'*-dioxide ligand [17].



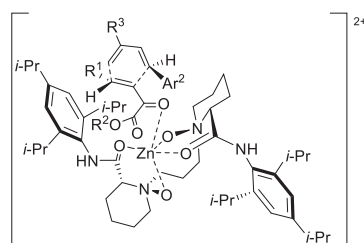
proposed transition state (with R¹ = Me, R² = Boc):



Scheme 2. Diels-Alder cycloaddition of Brassard-type diene with methyleneimides in the presence of a *N,N'*-dioxide ligand [18].

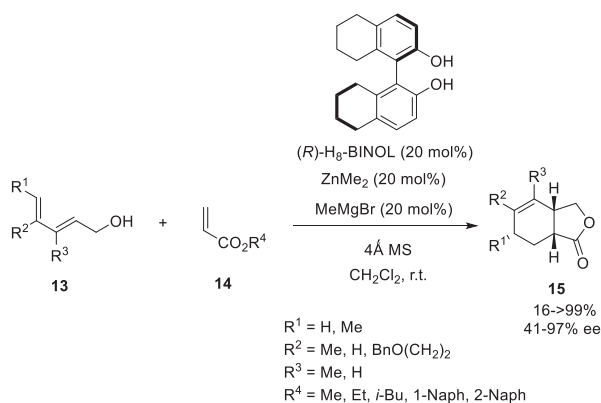


proposed transition state:



Scheme 3. Diels–Alder cycloaddition of (*E*) 1-phenyl dienes with β,γ -unsaturated α ketoesters in the presence of a *N,N'*-dioxide ligand [19].

Mlynarski this year [4]. Previously, the general field of zinc catalysis (not especially asymmetric) was reviewed by Enthaler and Wu [5]. Moreover, it must be noted that in 2015, three reports focusing on special reactions catalyzed by zinc were published, such as enantioselective aldol reactions [6], asymmetric dialkylzinc-mediated alkylation, arylation and alkenylation reactions of carbonyl compounds [7], and tandem reactions based on the use of organozinc reagents [8]. In 2017, a report on zinc-promoted Henry reactions was published, citing only five references dealing with asymmetric processes all dating back to 2015 [9]. The same year, the asymmetric alkylation of ketones with organozinc reagents was subject to a short review albeit containing none reference ≥ 2015 [10]. In 2018, a review on zinc-catalyzed Michael reactions was published with few asymmetric works and none reference ≥ 2015 [11]. Also in 2018, was reviewed the synthesis of *N*-hetero-



Scheme 4. Diels–Alder cycloaddition of 2,4-dienols with acrylates in the presence of (*R*)-H₈-BINOL ligand followed by lactonization [20].

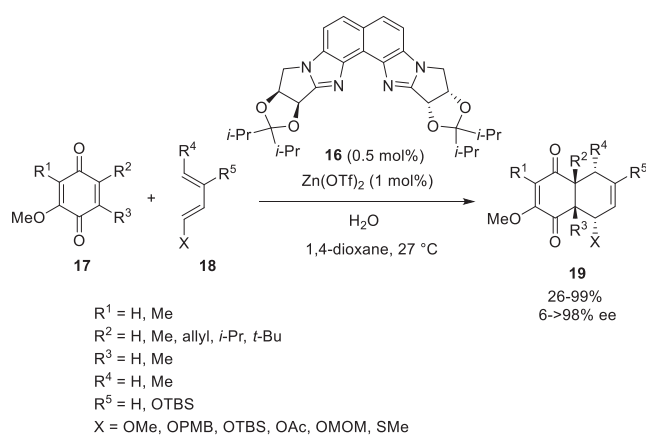
cyclic carbene-supported zinc complexes and use in racemic catalysis [12]. Later in 2019, a report on the synthesis of heterocycles via zinc catalysis was published with only one reference concerning asymmetric work and moreover dating back to 2015 [13]. In 2020, racemic zinc-catalyzed multicomponent reactions were collected in another review [14]. The present review is divided into fifteen parts, outlining successively enantioselective zinc-catalyzed cycloadditions, alkynylation/allylation reactions of carbonyl compounds and derivatives, additions of diorganozincs to carbonyl compounds and derivatives, Mannich reactions, (nitro)aldol reactions, other 1,2-nucleophilic additions to carbonyl compounds and derivatives, Michael additions, Friedel–Crafts reactions, reduction reactions, α -functionalizations of carbonyl compounds, ring-opening reactions, epoxidations, halolactonizations, domino/tandem reactions and miscellaneous reactions.

2. Cycloadditions

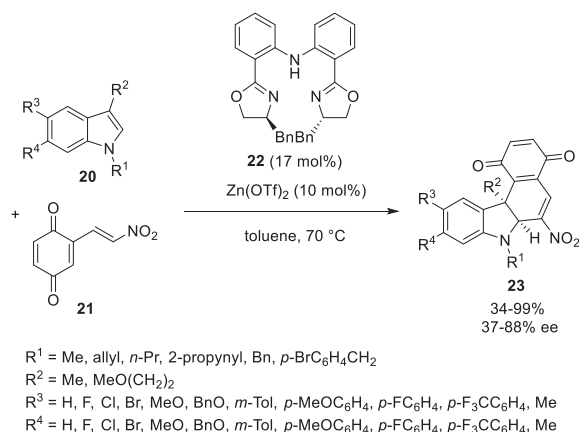
2.1. Diels–Alder cycloadditions

The first examples of enantioselective zinc-catalyzed (hetero)-Diels–Alder cycloadditions were independently reported in 1997 by the groups of Takacs [15] and Jørgensen [16] who both employed chiral bisoxazoline ligands, allowing similar enantioselectivities of 78–79% ee to be achieved. Ever since, other types of ligands have been successfully investigated in these reactions [4]. For example, chiral *N,N'*-dioxide ligand **1** was combined at 5 mol % of catalyst loading to $\text{Zn}(\text{NTf}_2)_2$ (5 mol%) to promote the enantioselective Diels–Alder cycloaddition of cyclopentadiene **2** with a variety of alkynones **3** (Scheme 1) [17]. The corresponding chiral 2-acyl substituted norbornadiene derivatives **4** were generated in dichloromethane as solvent with low to quantitative yields (23–99%) and moderate to high enantioselectivities (57–95% ee). Actually, the enantioselectivities were found of 81–95% ee for all substrates excepted for a TMS-substituted alkyne ($R^2 = \text{TMS}$) which provided the lowest enantioselectivity (57% ee).

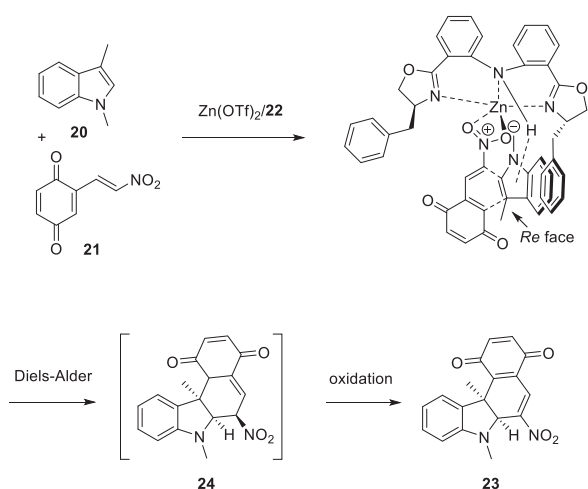
The same authors also developed asymmetric zinc-catalyzed Diels–Alder reaction of Brassard-type diene **5** with methyleneindolines **6** by using related *N,N'*-dioxide chiral ligand **7** (Scheme 2) [18]. Indeed, the chiral zinc catalyst in situ generated from 10 mol% of this ligand and the same quantity of $\text{Zn}(\text{OTf})_2$ in dichloromethane as solvent was found to promote this reaction at 35 °C, resulting in the formation of the corresponding chiral functionalized spirooxindoles **8** exhibiting three contiguous stereocenters in moderate yields (51–68%) albeit as almost single diastereo- (>90% de) and enantiomers (98–>99% ee) regardless



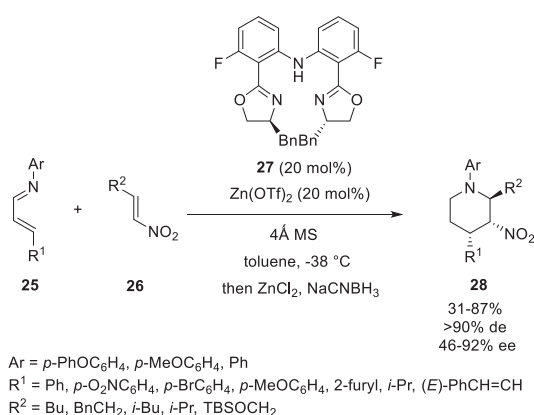
Scheme 5. Diels–Alder cycloaddition of *o*-alkoxy- and *o*-thiomethyl-*p*-benzoquinones with 1-alkoxy-1,3-butadienes in the presence of a bisamidinium ligand [21].



mechanism with $R^1 = R^2 = \text{Me, } R^3 = R^4 = \text{H}$:



Scheme 6. Inverse-electron-demand Diels-Alder cycloaddition of indoles with 2-(2-nitrovinyl)-1,4-benzoquinone in the presence of a bisoxazoline ligand followed by oxidation [22].



Scheme 7. Aza-Diels-Alder cycloaddition of 1-azadienes with nitroalkenes in the presence of a bisoxazoline ligand followed by reduction [24].

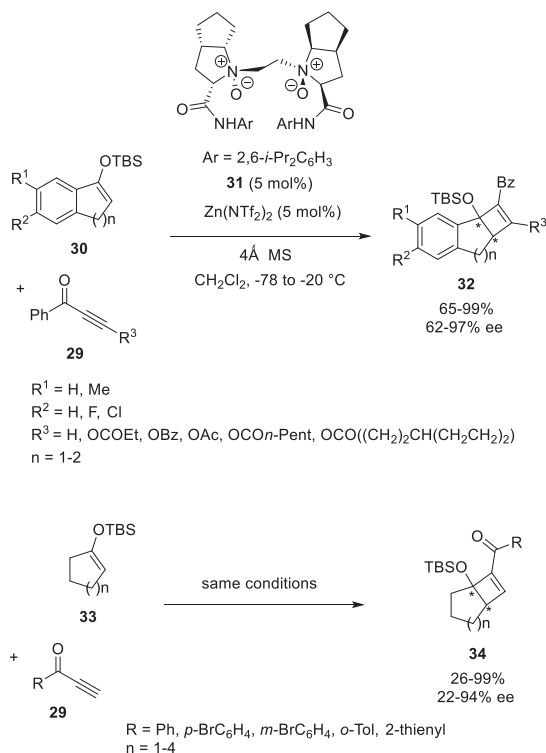
the nature of substituents beared by methyleneindolines. A possible transition state is depicted in [Scheme 2](#) in which oxygen atoms of the amide and *N*-oxide are coordinated with Zn(II) in a tetradentate manner to form a six-membered chelate ring. Meanwhile, the methyleneindolinone **6** coordinates to the Zn(II) in a bidentate fashion with its dicarbonyl groups. Then, Brassard-type diene **5**

attacks **6** from its *Re* face, since the *Si* face is shielded by the neighboring 2,6-diethyl-4-methylphenyl group of ligand **7**.

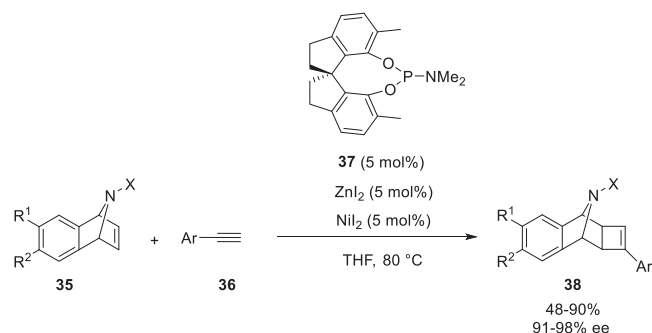
Another chiral *N,N'*-dioxide ligand was later employed by these authors to promote highly regio-, diastereo-, and enantioselective Diels-Alder cycloaddition of (*E*) 1-phenyl dienes **9** with β,γ -unsaturated α ketoesters **10** [19]. Only one diastereomer (>90% de) of the corresponding cyclohexenes **11** containing three contiguous stereocenters was obtained in all reactions when catalyzed at 35 °C by a combination of 5 mol% of ligand **12** and 5 mol% of Zn(OTf)₂ in DCE as solvent ([Scheme 3](#)). Excellent results were achieved since the cycloadducts were obtained enantiopure (98–>99% ee) in high yields (78–99%). A transition state was proposed by the authors with the four oxygens of the *N,N'*-dioxide ligand and the two oxygens of the β,γ -unsaturated α -ketoester substrate coordinated to zinc, thus forming an octahedral complex ([Scheme 3](#)). Since the *Si* face of the β,γ -unsaturated α -ketoester was shielded by the neighboring amide group of the ligand, the (*E*) 1-phenyl diene attacked from the *Re* face of the β,γ -unsaturated α -ketoester to give the final cycloadduct.

Earlier in 2015, Ishihara et al. reported the first asymmetric Diels-Alder reaction of 2,4-dienols **13** with acrylates **14** performed in the presence of an in situ generated bimetallic chiral catalyst derived from 20 mol% of (*R*)-H₈-BINOL, ZnMe₂ and MeMgBr [20]. This catalyst system allowed at room temperature in dichloromethane as solvent the formation of a series of functionalized bicyclic chiral γ -lactones **15** as single diastereomers in low to quantitative yields (16–>99%) and moderate to excellent enantioselectivities (41–97% ee), as shown in [Scheme 4](#). Actually, the Diels-Alder cycloaddition was followed by a lactonization, providing γ -lactones. It must be noted that this work could also be situated in [Section 15](#) dealing with domino/tandem reactions since it follows a domino Diels-Alder/lactonization mechanism.

In 2019, Kitamura et al. demonstrated that a chiral zinc catalyst in situ prepared from only 1 mol% of Zn(OTf)₂ and as low as 0.5 mol % of chiral bisamidine ligand **16** was able to promote an asymmet-



Scheme 8. [2 + 2] Cycloadditions of alkynones with cyclic enol silyl ethers in the presence of a *N,N'*-dioxide ligand [26].



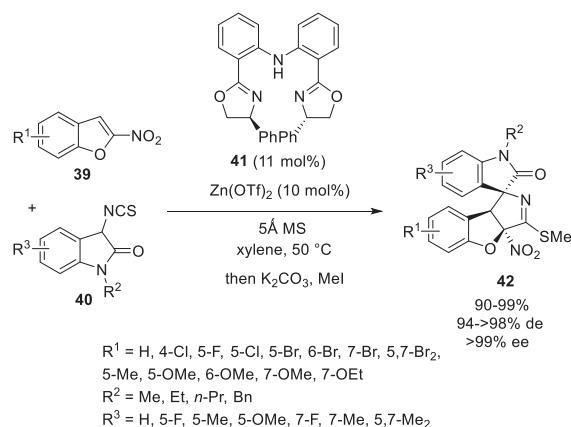
Ar = Ph, *p*-Tol, *p*-MeOC₆H₄, *m*-MeOC₆H₄, *p*-PhOC₆H₄, *p*-(HOCH₂)₂C₆H₄,
p-FC₆H₄, *p*-ClC₆H₄, *m*-ClC₆H₄, *p*-BrC₆H₄, *p*-F₃CC₆H₄
R¹ = H, Me, OMe
R² = H, Me, OMe
X = Boc, Cbz, CO₂Me

Scheme 9. [2 + 2] Cycloaddition of azabenzonorbornadienes with terminal alkynes in the presence of a phosphoramidite ligand [27].

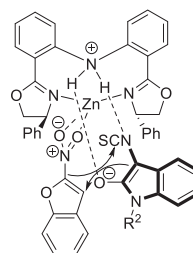
ric Diels-Alder cycloaddition between *o*-alkoxy-*p*-benzoquinones **17** and 1-alkoxy-1,3-butadienes **18** to generate highly functionalized chiral *cis*-decalins **19** [21]. As illustrated in Scheme 5, these products were synthesized at 27 °C in 1,4-dioxane as solvent with variable yields (26–99%) and enantioselectivities (6–>98% ee) as single regio- and *endo*-diastereomers. The catalyst system was also compatible with a 1-thiomethyl-1,3-butadiene (X = SMe) which gave the corresponding product in 93% yield and 84% ee. It was found that the reaction did not work in the absence of water as an additive.

In 2020, an enantioselective dearomatization inverse-electron-demand Diels-Alder cycloaddition of indoles **20** with 2-(2-nitrovinyl)-1,4-benzoquinone **21** was disclosed by Zhang et al., using a combination of 17 mol% of chiral bisoxazoline **22** with 10 mol% of Zn(OTf)₂ as catalyst system [22]. This reaction performed at 70 °C in toluene allowed the synthesis of chiral six-membered [2,3]-fused indolines **23** to be achieved as single diastereomers in moderate to quantitative yields (34–99%) and enantioselectivities (37–88% ee), as illustrated in Scheme 6. Actually, the cycloaddition underwent through the *Re* face of the 2-(2-nitrovinyl)-1,4-benzoquinone activated by the chiral zinc catalyst also *N*-chelated to the indole substrate through NH–p interaction to give Diels-Alder cycloadduct **24**. However, the latter was unstable and further underwent an oxidation to give final product **23**. It must be noted that this work could also be situated in Section 15 highlighting domino/tandem reactions since it involves a Diels-Alder/oxidation domino reaction.

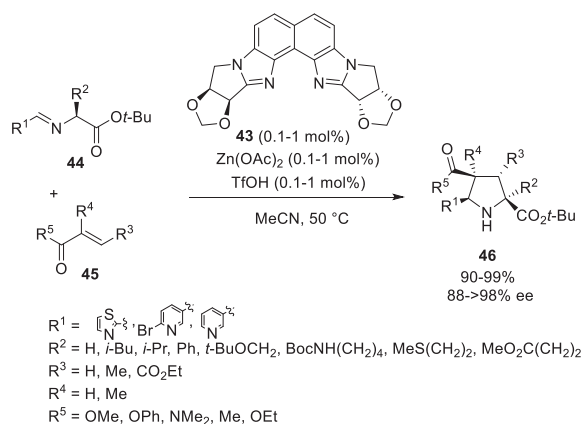
Despite the prevalence of piperidine moieties in drugs, the azaversion of the all-carbon [4 + 2] cycloaddition is still less developed [23]. To fill this gap, Rovis reported in 2015 a rare example of asymmetric synthesis of piperidines through zinc-catalyzed aza-Diels-Alder cycloaddition of 1-azadienes **25** with nitroalkenes **26** (Scheme 7) [24]. A chiral catalyst in situ generated from 20 mol% of Zn(OTf)₂ and the same quantity of chiral bisoxazoline **27** was employed in toluene at –38 °C, affording a range of chiral piperidines **28** 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 arisen from the cycloaddition, its enamine functionality was directly reduced by treatment with ZnCl₂ and NaBH₃CN in methanol to give more stable 3-nitropiperidine **28**. The lowest enantioselectivity (46% ee) was obtained in the reaction of an alkyl-substituted azadiene (R¹ = *i*-Pr). Furthermore, the reaction of a more conjugated azatriene (R¹ = (E)-PhCH = CH) required 30 mol% of catalyst to provide the corresponding product in 65% yield and 63% ee. For all the



possible transition state with R¹ = R³ = H:



Scheme 10. [3 + 2] Cycloaddition of 2 nitrobenzofurans with 3 isothiocyanato oxindoles in the presence of a bisoxazoline ligand [29].



Scheme 11. [3 + 2] Cycloaddition of chiral imino *t*-butyl esters with acrylates/acrylamides in the presence of a bisamidine ligand [30].

other differently substituted substrates, enantioselectivities ≥69% ee were obtained. This work could also be considered as a tandem aza-Diels-Alder/reduction reaction and consequently situated in Section 15.

2.2. [2+2] Cycloadditions

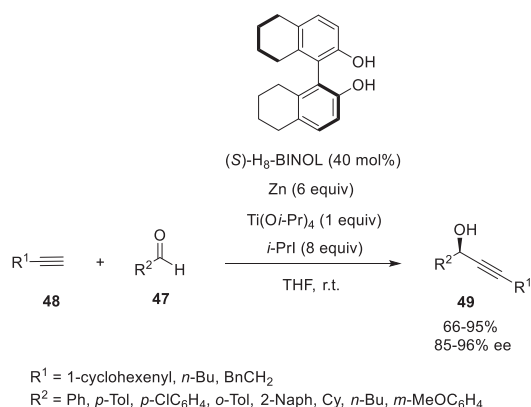
Cyclobutene moieties are found in many natural products and bioactive compounds [25]. The most direct route to these products deals with the [2 + 2] cycloaddition. However, only rare examples of asymmetric catalytic versions of this transformation have been reported so far. Among them, an enantioselective zinc-catalyzed [2 + 2] cycloaddition of alkynones **29** with cyclic enol silyl ethers **30/33** was developed in 2016 by Feng and Liu [26]. It involved a catalyst system composed of 5 mol% of chiral *N,N'*-dioxide ligand

31 and the same quantity of $\text{Zn}(\text{NTf}_2)_2$ as precatalyst. Performed in dichloromethane as solvent, the cycloaddition yielded a range of chiral fused cyclobutenes **32/34** in low to excellent yields (26–99%) and enantioselectivities (22–97% ee), as shown in [Scheme 8](#). This method was compatible with a variety of terminal alkynes **29** ($\text{R}^3 = \text{H}$) as well as cyclic enol silyl ethers **30/33**. Furthermore, internal alkynes **29** ($\text{R}^3 \neq \text{H}$) were tolerated, leading to the corresponding products **32** in good to quantitative yields (65–99%) and good enantioselectivities (71–86% ee). It must be noted that this work represented the first example of catalytic enantioselective [2 + 2] cycloaddition of internal alkynes with cyclic enol silyl ethers to give fully substituted cyclobutenes.

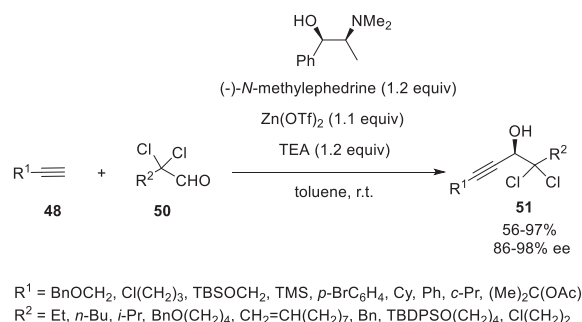
In 2018, the asymmetric [2 + 2] cycloaddition of azabenzonorbornadienes **35** with terminal alkynes **36** was investigated by Fan and Xu in the presence of a dual metal catalyst system based on nickel and zinc [27]. Indeed, promoting this reaction with 5 mol% of ZnI_2 , NiI_2 and chiral spiro phosphoramidite ligand **37** in THF at 80 °C allowed the corresponding chiral cycloadducts **38** to be synthesized in good to high yields (48–90%) and uniformly excellent enantioselectivities (91–98% ee), as presented in [Scheme 9](#). A variety of terminal alkynes and azabenzonorbornadienes exhibiting different substituents were tolerated. The exact roles of each metal in the process were not precised by the authors.

2.3. [3+2] Cycloadditions

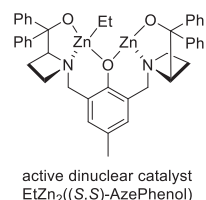
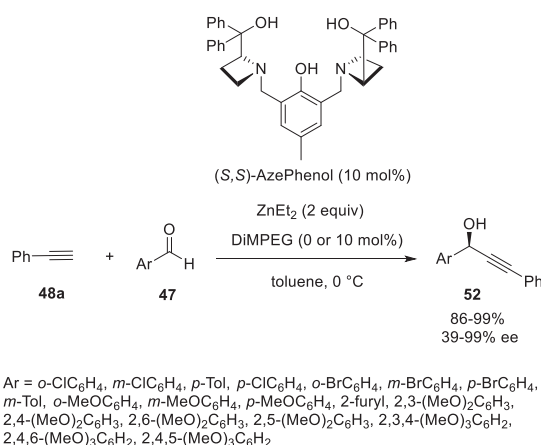
In 2002, Jørgensen et al. described the first enantioselective zinc-catalyzed [3 + 2] cycloaddition of azomethine ylides generated from glycine methyl esters with alkenes, leading in the presence of chiral bisoxazoline ligands to chiral pyrrolidines with up to 90% ee [28]. Later in 2018, Yuan and Xu reported the first enantioselective zinc-catalyzed dearomative [3 + 2] cycloaddition of 2 nitrobenzofurans **39** with 3 isothiocyanato oxindoles **40** [29]. The process, performed at 50 °C in xylene as solvent, employed a chiral catalyst in situ generated from 10 mol% of $\text{Zn}(\text{OTf})_2$ and 11 mol% of chiral bisoxazoline **41**, allowing a direct access to complex chiral spirooxindoles **42** containing a 2,3-dihydrobenzofuran motif and three contiguous stereocenters. These densely functionalized polycyclic cycloadducts were obtained in uniformly excellent yields (90–99%) as almost single stereoisomers (94–>98% de and >99% ee) in all cases of substrates studied. In a possible transition state depicted in [Scheme 10](#), the zinc atom of the chiral complex coordinated the 2 nitrobenzofuran substrate through the nitro group. At the same time, the 3 isothiocyanato oxindole substrate chelated the NH group of the ligand, acting as a Lewis base. Thus, under the bifunctional activation of the chiral zinc complex, the C3-position of the 2-nitrobenzofuran underwent nucleophilic attack at the *Re* face of the activated 3-isothiocyanato oxindole. A subse-



Scheme 12. Alkynylation of aldehydes in the presence of (S)-H₈-BINOL [35].



Scheme 13. Alkynylation of α,α -dichlorinated aldehydes in the presence of (–)-N-methylephedrine [36].

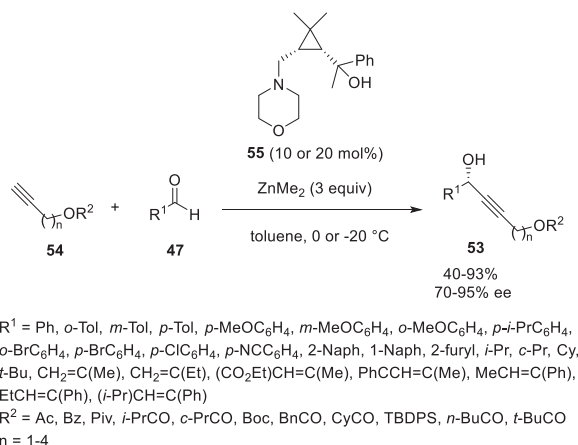


Scheme 14. Alkynylation of aromatic aldehydes in the presence of (S,S)-AzePhenol [38].

quent intramolecular annulation process from C2-position of the 2-nitrobenzofuran to the NCS group generated the final formal cycloadduct.

In 2020, Kitamura et al. employed a chiral cationic zinc acetate complex derived from as low as 0.1–1 mol% of chiral bisamidine ligand **43**, $\text{Zn}(\text{OAc})_2$ and TfOH to promote a 1,3-dipolar cycloaddition between chiral imino *t*-butyl esters **44** and acrylates **45** ($\text{R}^5 = \text{OMe}, \text{OEt}, \text{OPh}$) [30]. In the absence of an external base, the reaction led to the corresponding multi-substituted chiral prolines **46** with complete regio- and diastereoselectivities, combined with uniformly excellent yields (90–99%) and enantioselectivities (88–98% ee), as illustrated in [Scheme 11](#). The scope of the methodology could be extended to acrylamides ($\text{R}^5 = \text{NMe}_2$) and methylvinylketone ($\text{R}^3 = \text{R}^4 = \text{H}, \text{R}^5 = \text{Me}$) with comparable excellent results (93% yield, >98% ee).

It must be noted that recently, another type of cycloadditions was reported by Charette et al. [31]. It dealt with the synthesis of chiral fluorocyclopropanes via asymmetric cyclopropanation of the corresponding fluoro-substituted allylic alcohols using zinc carbenoids. Since this reaction employed a superstoichiometric amount of a chiral dioxaborolane ligand, it was decided not to detail this work.

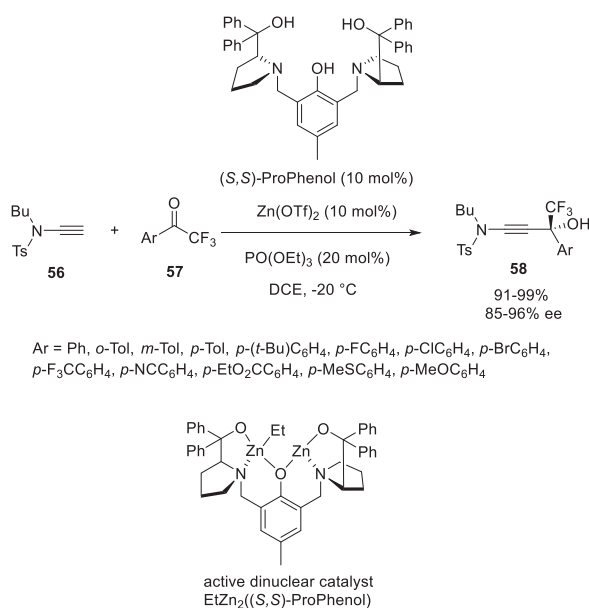


Scheme 15. Alkynylation of aldehydes in the presence of a cyclopropyl 1,4-amino alcohol ligand [39].

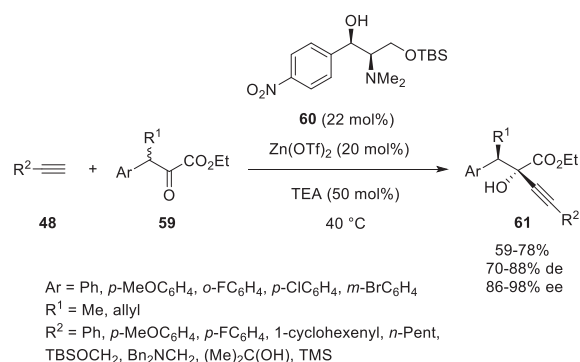
3. Alkynylation/allylation reactions of carbonyl compounds and derivatives

3.1. Alkynylation of aldehydes

The asymmetric addition of organometallic reagents to carbonyl compounds represents the most direct route to chiral alcohols [7,32]. In particular, chiral propargylic alcohols, which constitute key synthetic intermediates in the total synthesis of many natural products and drugs, can be easily prepared in situ from the reaction of acidic terminal alkynes with a zinc reagent, followed by condensation on carbonyl compounds [32c–e,33]. Since the first asymmetric addition of alkynylzinc reagents to aldehydes using chiral amino alcohol ligands derived from ephedrine reported by Niwa and Soai in 1990 [34], many chiral ligands, including 2-amino alcohol-type ligands, oxazaborolidines, BINOL derivatives, β -sulfonamide alcohols, salens, ProPhenol derivatives, and Schiff base amino alcohols, among others have been designed to catalyze



Scheme 16. Alkynylation of aromatic trifluoromethyl ketones in the presence of (S,S)-ProPhenol [41].



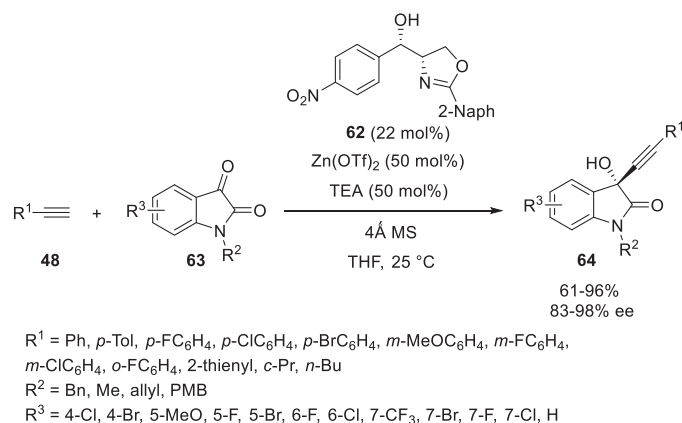
Scheme 17. Alkynylation of β -stereogenic α -ketoesters in the presence of a (-)-N-methylephedrine-derived ligand [43].

enantioselective alkynylations of carbonyl compounds. Among these catalytic systems, zinc complexes have attracted considerable attention owing to their superior catalytic efficiency. However, the asymmetric alkynylation of carbonyl compounds mediated by truly catalytic amounts of zinc still remains an underdeveloped field, with few chiral ligands disclosed to date. In 2015, (S)-H₈-BINOL was employed by Pu et al. at 40 mol% of catalyst loading in combination with Zn (6 equivalents), Ti(Oi-Pr)₄ (1 equivalent) and *i*-PrI (8 equivalents) [35]. This novel catalyst system presented the advantage to avoid the common use of pyrophoric ZnEt₂. As presented in Scheme 12, it promoted the asymmetric alkynylation of aromatic as well as aliphatic aldehydes **47** with various terminal alkynes **48** to give the corresponding chiral propargylic alcohols **49** at room temperature in THF as solvent with both high yields (66–95%) and enantioselectivities (85–96% ee).

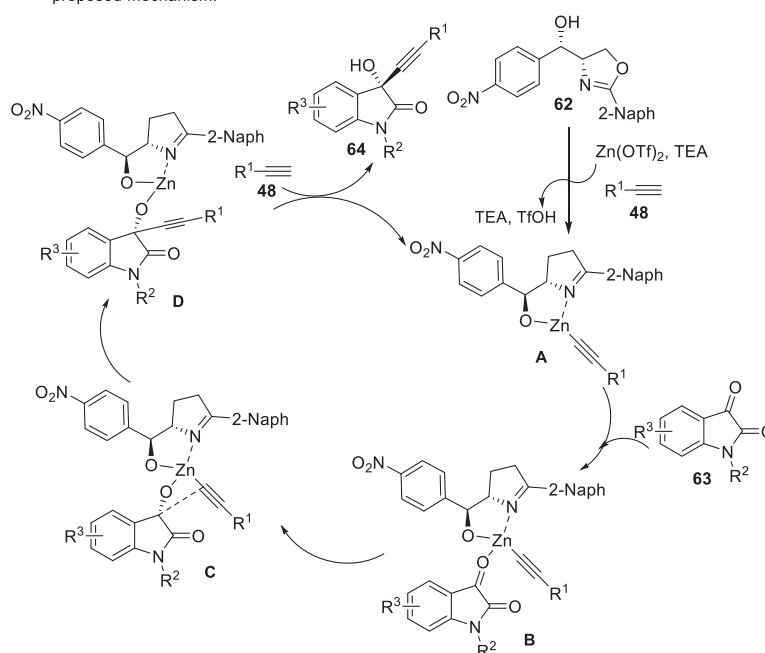
With the aim of synthesizing chlorinated natural products, such as chlorosulfolipids, Carreira et al. disclosed in 2017 an asymmetric zinc-mediated addition of terminal alkynes **48** to α,α -dichlorinated aldehydes **50** performed in the presence of a chiral 1,2-amino alcohol ligand, such as (-)-N-methylephedrine [36]. The reaction required 1.1 equivalent of Zn(OTf)₂ and 1.2 equivalent of ligand. It led in toluene at room temperature to the corresponding chiral propargylic alcohols **51** in good to quantitative yields (56–97%) and high enantioselectivities (86–98% ee), as shown in Scheme 13. A wide range of aliphatic and aromatic alkynes as well as aliphatic α,α -dichlorinated aldehydes were compatible.

The same year, Wang et al. reported the use of 10 mol% of their chiral semi-aza-crown ligand (S,S)-AzePhenol [37] combined with two equivalents of ZnEt₂ to promote the asymmetric addition of phenylacetylene **48a** to aromatic aldehydes **47** [38]. A dinuclear zinc active catalyst EtZn₂((S,S)-AzePhenol) was in situ generated in the presence of polyethyleneglycol dimethyl ether (DiMPEG) as an additive (Scheme 14), providing a range of chiral propargylic alcohols **52** to be synthesized in uniformly high yields (86–99%) and variable enantioselectivities (39–99% ee). It was found that the enantioselectivity of the reaction was dramatically influenced by the position of substituents exhibited on the phenyl ring of the aldehyde. Indeed, the highest enantioselectivities were achieved in the alkynylation of *ortho*-substituted aryl aldehydes.

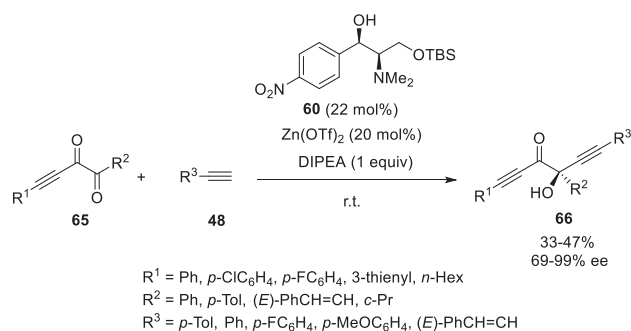
In 2020, Zong et al. developed the synthesis of a wide range of chiral hydroxyalkynol esters and ethers **53** through novel enantioselective alkynylation of aldehydes **47** with alkynyl esters and ethers **54**, respectively [39]. This simple process was catalyzed at 0 or –20 °C by a combination of three equivalents of ZnMe₂ with 10 or 20 mol% of chiral cyclopropyl 1,4-amino alcohol ligand **55** in toluene. The products were obtained in good yields (40–93%) and enantioselectivities (70–95% ee), as illustrated in Scheme 15.



proposed mechanism:



Scheme 18. Alkyne-alkylation of isatins in the presence of a hydroxyl oxazoline ligand [44].



Scheme 19. Alkyne-alkylation of alkyne 1,2-diketones in the presence of a (-)-*N*-methylephedrine-derived ligand [45].

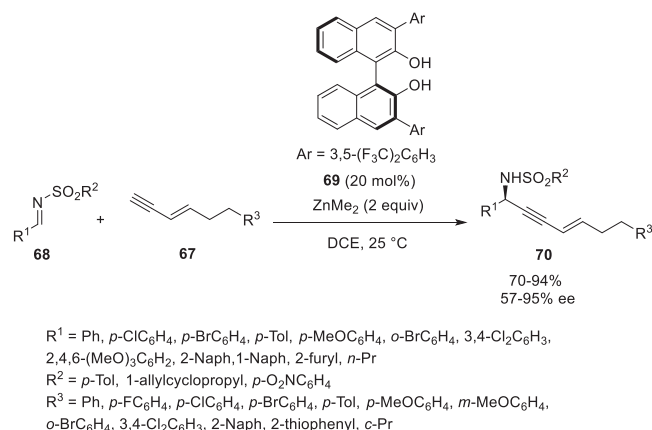
Aromatic aldehydes bearing electron-withdrawing or electron-donating substituents on the phenyl ring at *ortho*-, *meta*- or *para*-position all provided excellent enantioselectivities (85–94% ee) as well as aliphatic aldehydes (80–95% ee). The lowest

enantioselectivity (70% ee) was observed in the reaction of an heteroaromatic aldehyde ($R^1 = 2\text{-furyl}$).

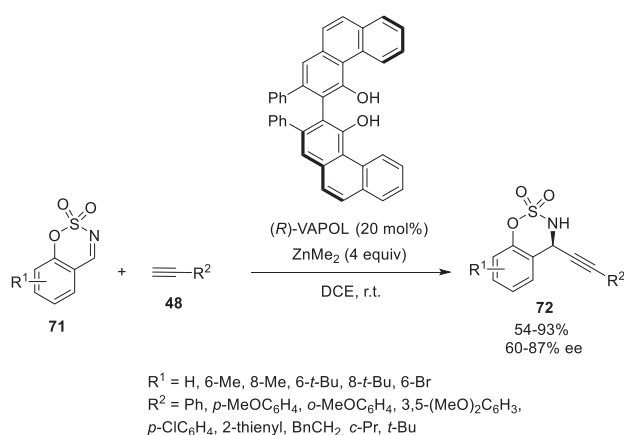
3.2. Alkyne-alkylation of ketones

The trifluoromethylated tertiary chiral alcohol moiety represents an important motif in medicinal chemistry [40]. In this context, Wolf and Cook disclosed in 2016 the first asymmetric catalytic addition of terminal ynamides **56** to trifluoromethyl ketones **57**, affording the corresponding chiral CF_3 -substituted tertiary propargylic alcohols **58** [41]. The reaction was promoted at -20°C in DCE as solvent by chiral dinuclear zinc catalyst $\text{EtZn}_2((S,S)\text{-ProPhenol})$ in situ generated from only 10 mol% of $\text{Zn}(\text{OTf})_2$ and $(S,S)\text{-ProPhenol}$ [42] as ligand (Scheme 16). The products exhibiting various substituents on the phenyl ring of the trifluoromethyl ketone were remarkably obtained in both excellent yields (91–99%) and enantioselectivities (85–96% ee).

In 2016, Johnson and Zavesky described the enantioselective addition of terminal alkynes **48** to racemic β -stereogenic α -ketoesters **59** performed under neat conditions (Scheme 17) [43]. The use of a catalyst system, composed of 20 mol% of $\text{Zn}(\text{OTf})_2$

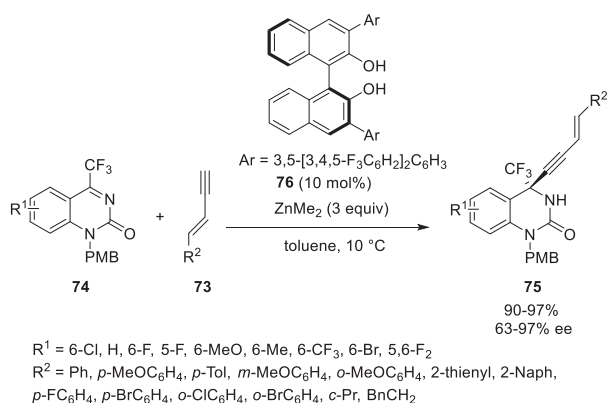


Scheme 20. Alkynylation of *N*-sulfonyl aldimines with terminal 3-en-1-ynes in the presence of a BINOL-derived ligand [47].



Scheme 21. Alkynylation of benzoxathiazine 2,2-dioxides in the presence of (*R*)-VAPOL [48].

and 22 mol% of (–)-*N*-methylephedrine-derived 1,2-amino alcohol chiral ligand **60**, allowed a range of chiral tertiary propargylic alcohols **61** containing two stereocenters to be easily synthesized in good yields (59–78%) and diastereoselectivities (70–88% de) combined with uniformly high enantioselectivities (86–98% ee). An excellent functional group tolerance was found since many aryl- and alkyl-substituted alkynes including heteroatoms



Scheme 22. Alkynylation of cyclic *N*-benzoyl trifluoromethyl ketimines in the presence of a BINOL-derived ligand [49].

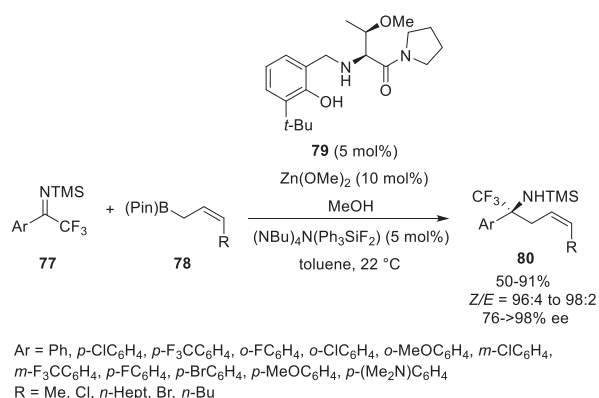
provided good results. Even the presence of a free alcohol ($R^2 = (\text{Me})_2\text{C}(\text{OH})$) was tolerated (71% yield, 74% de, 92% ee).

In 2018, Chen et al. introduced novel chloramphenicol-based chiral hydroxyl oxazoline ligands, such as **62**, to be investigated in the first $\text{Zn}(\text{OTf})_2$ -catalyzed enantioselective alkynylation of isatins **63** [44]. As depicted in Scheme 18, variously substituted isatins **63** were alkynylated with (hetero)aromatic as well as aliphatic terminal alkynes **48** to yield the corresponding chiral tertiary propargylic alcohols **64** in good to excellent yields (61–96%) and high enantioselectivities (83–98% ee). The process required 22 mol% of ligand **62** combined with 50 mol% of $\text{Zn}(\text{OTf})_2$ in THF at 25 °C. A broad substrate scope was found with excellent enantioselectivities achieved in the reaction of various *N*-alkylated and phenyl-substituted isatins, regardless of the electronic character and position of the substituent on the phenyl ring. The authors proposed the mechanism depicted in Scheme 18 in which $\text{Zn}(\text{OTf})_2$ first interacted with chiral ligand **62** and terminal alkyne **48** to give complex **A**. The latter subsequently interacted with the isatin *N*-substituents, leading to the formation of complex **B**. The terminal alkyne then migrated to the electron-deficient carbonyl carbon from the least-sterically hindered *Re* face to give complex **D** via transition structure **C**. Finally, protonation of **D** by the alkyne led to the formation of the alkynylated product **64** along with the regenerated complex **A**.

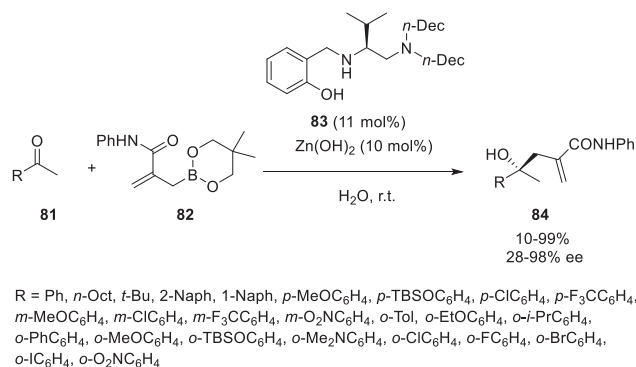
In 2020, Fang and Ding developed highly regio- and enantioselective alkynylation of alkynyl 1,2-diketones **65** under asymmetric zinc catalysis [45]. The chiral zinc catalyst was in situ generated from 20 mol% of $\text{Zn}(\text{OTf})_2$ and 20 mol% of chiral amino alcohol ligand **60** at room temperature (Scheme 19). When the reaction between variously substituted alkynyl 1,2-diketones **65** and alkynes **48** was performed in the presence of DIPEA as base, it regioselectively led to the corresponding chiral functionalized α -hydroxy ketones **66** in moderate yields (33–47%) and moderate to excellent ee values (69–99% ee). Notably, diketones bearing aliphatic substituents also reacted smoothly with moderate enantioselectivities (69–71% ee). Interestingly, the authors found that by simply changing DIPEA into TEA as base, the reaction evolved differently to selectively give chiral 3(2*H*)-furanones with excellent enantioselectivities (see section 15).

3.3. Alkynylation of imines

Chiral propargylic amines are key building blocks for the synthesis of many natural and bioactive products. They are commonly synthesized through enantioselective metal-catalyzed alkynylation of imines [32c,46]. However, most of these reactions employed single terminal alkynes. In 2015, the first catalytic



Scheme 23. Allylation of CF_3 -substituted *N*-trimethylsilyl aryl ketimines with *Z*-allyl boronates in the presence of a threonine-derived aminophenol ligand [50].

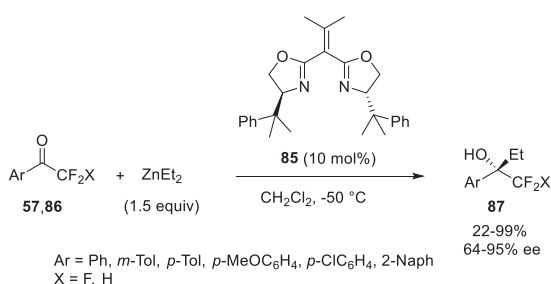


Scheme 24. Allylation of ketones with an amido-functionalized allylboronate in water and in the presence of a tertiary amine ligand [51].

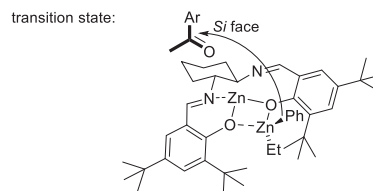
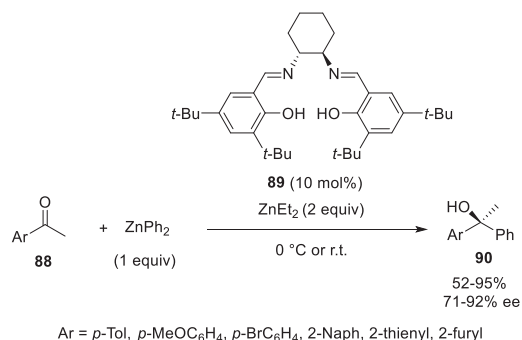
asymmetric addition of terminal 3-en-1-yne **67** to *N*-sulfonyl aldimines **68** was reported by Ma et al., using a chiral zinc catalyst [47]. The catalyst system involved 20 mol% of chiral ligand **69** derived from (*S,S*)-BINOL and two equivalents of ZnMe₂ in DCE as solvent. Performed at 25 °C, the alkynylation of a wide range of aromatic *N*-sulfonyl aldimines **68** led to chiral enyne carbinamines **70** in both high yields (78–94%) and enantioselectivities (88–95% ee), as illustrated in Scheme 20. When an aliphatic imine (R¹ = *n*-Pr) was investigated as substrate, it provided the corresponding product with both the lowest yield (70%) and enantioselectivity (57% ee).

The same year, (*R*)-VAPOL was applied as ligand by Pedro et al. to develop the first asymmetric addition of terminal alkynes to benzoxathiazine 2,2-dioxides (Scheme 21) [48]. These cyclic rigid imines constitute versatile building blocks for the synthesis of important benzo-fused cyclic sulfamidate heterocycles. Using 20 mol% of optimal ligand (*R*)-VAPOL in the presence of four equivalents of ZnMe₂ in DCE as solvent, the alkynylation of a range of benzoxathiazine 2,2-dioxides **71** with aromatic as well as aliphatic terminal alkynes **48** led at room temperature to the corresponding chiral propargylic sulfamidates **72** in both moderate to high yields (54–93%) and enantioselectivities (60–87% ee). This work represented a rare example of asymmetric alkynylation of cyclic imines.

In 2018, the first enantioselective catalytic addition of terminal 3-en-1-yne **73** to cyclic *N*-benzoyl trifluoromethyl ketimines **74** was developed by Ma and Zhang, delivering the corresponding chiral enynylated tertiary carbinamines **75** (Scheme 22) [49]. It employed a chiral zinc catalyst derived from three equivalents of ZnMe₂ and 10 mol% of chiral BINOL-derived ligand **76**. When performed at 10 °C in toluene, these densely functionalized products bearing a tertiary trifluoromethylated carbinamine center were achieved in excellent yields (90–97%) and good to high enantioselectivities (63–97% ee).



Scheme 25. Addition of ZnEt₂ to fluorinated alkyl ketones in the presence of a bisoxazoline ligand [54].

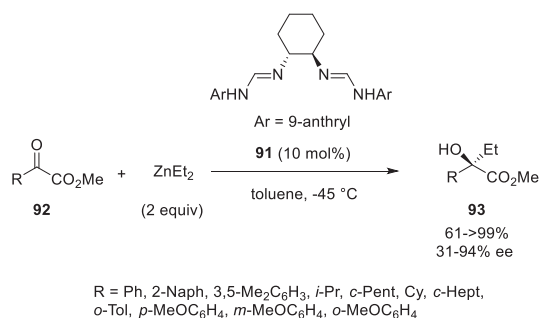


Scheme 26. Addition of ZnPh₂ to aryl ketones in the presence of a salen ligand [55].

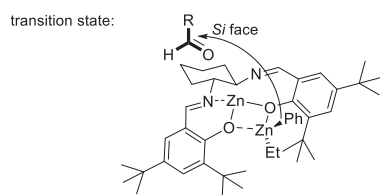
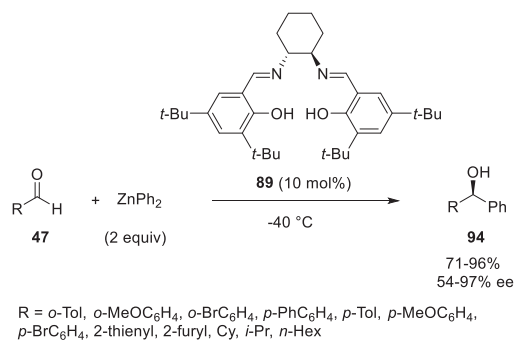
3.4. Allylations

In 2020, Hoveyda et al. reported the regio- and enantioselective allylation of CF₃-substituted *N*-trimethylsilyl aryl ketimines **77** with *Z*-allyl boronate **78** performed in the presence of 5 mol% of L-threonine-derived aminophenol ligand **79** combined to only 10 mol% of Zn(OMe)₂ [50]. As illustrated in Scheme 23, the process afforded the corresponding chiral trifluoromethyl-substituted homoallylic α-tertiary amines **80** as almost single *Z*-diastereomers (*Z/E* = 96:4 to >98:2) in moderate to high yields (50–91%) and high enantioselectivities (76–>98% ee). The catalyst system was compatible to aryl imines bearing various substituents on their phenyl ring. Moreover, the allyl boronates could exhibit an alkyl-, a chloro-, or a bromo-substituted *Z*-alkene.

Most of asymmetric allylations of carbonyl compounds and derivatives are performed in organic solvents. In 2020, Yoda et al. reported a rare example of enantioselective allylation of ketones **81** carried out in water at room temperature [51]. It employed as allylating agent water-stable amido-functionalized allylboronate **82**. The reaction was catalyzed with a combination of 10 mol% of Zn(OH)₂ and 11 mol% of chiral tertiary amine ligand **83**, resulting in the formation of the corresponding chiral homoallylic alcohols **84** in low to quantitative yields (10–99%) and enantioselectivities (28–98% ee), as presented in Scheme 24. Generally, good results were achieved in the reaction of acetophenones (56–98% ee) with higher ee values for *ortho*-substituted substrates (70–98% ee) than



Scheme 27. Addition of ZnEt₂ to α-ketoesters in the presence of a bisamidine ligand [56].



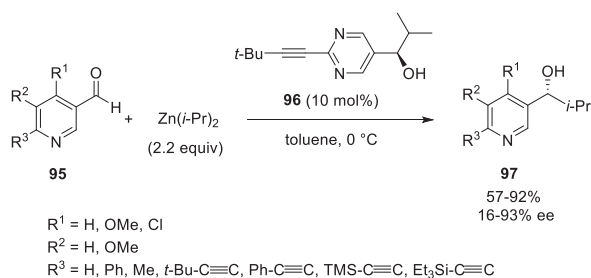
Scheme 28. Addition of ZnPh₂ to aldehydes in the presence of a salen ligand [55].

meta- (56–72% ee) or *para*-substituted ones (58–66% ee). In the case of *ortho*-substituted acetophenones, a correlation between the enantioselectivity of the reaction and the size of the *ortho*-substituent was shown. Along with aromatic ketones, alkyl methyl ketones also reacted but with generally lower yield (10% with R = *t*-Bu) and enantioselectivity (28% with R = *n*-Oct).

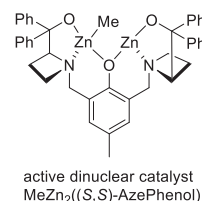
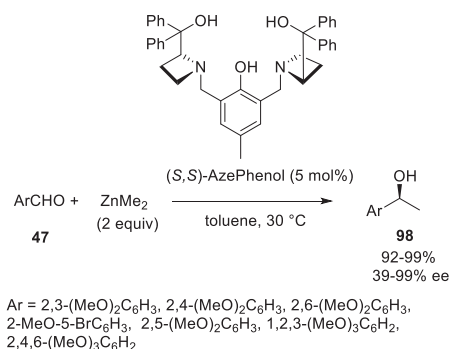
4. Additions of diorganozincs to carbonyl compounds and derivatives

4.1. Addition to ketones

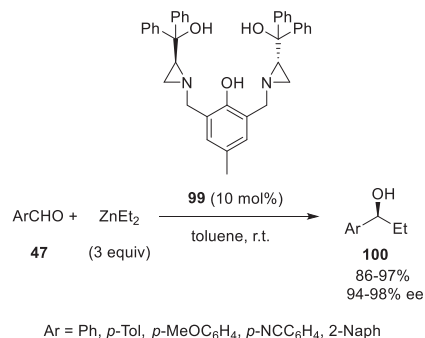
Since the first enantioselective addition of organozincs to aldehydes described in 1984 by Oguni and Omi [52], dialkylzinc reagents have been widely used for the alkylation of carbonyl compounds in direct addition as well as transmetalation reaction. In most cases, the alkylation group is transferred from zinc to a chiral Lewis acid derived from metals, such as titanium, among others. Since zinc is not directly responsible of the stereoselectivity in this type of transformations, they will not be included in the present review. So far, the direct addition of dialkylzinc reagents to carbonyl compounds and derivatives has been extensively studied using various types of chiral ligands [7,10,53]. In a recent example, chiral bisoxazoline **85** was employed by Sasaki et al. in the asymmetric nucleophilic addition of ZnEt₂ to fluorinated alkyl ketones **57**, **86** [54]. Performed in the presence of 10 mol% of ligand **85**, the reaction afforded chiral fluorine-containing tertiary alcohols



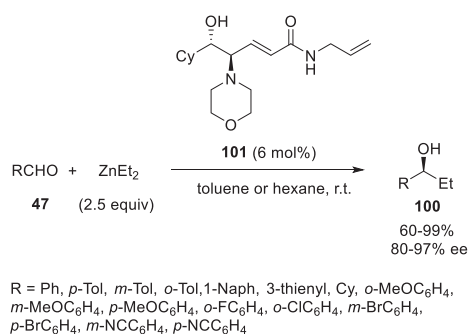
Scheme 29. Addition of Zn(*i*-Pr)₂ to azaaryl aldehydes in the presence of a (5-pyrimidyl)alkanol ligand [57].



Scheme 30. Addition of ZnMe₂ to aromatic aldehydes in the presence of (S,S)-AzePhenol [38].



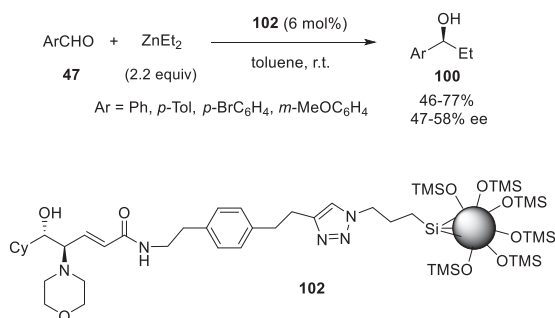
Scheme 31. Addition of ZnEt₂ to aromatic aldehydes in the presence of an aziridine alcohol ligand [58].



Scheme 32. Addition of ZnEt₂ to aldehydes in the presence of a 1,2-amino alcohol ligand [59].

87 with variable yields (22–99%) and enantioselectivities (64–95% ee), as depicted in Scheme 25.

The first enantioselective phenyl transfer of an organozinc reagent (ZnPh₂) to ketones **88** was disclosed in 2015 by Ito et al., using chiral salen ligand **89** (Scheme 26) [55]. In the presence of 10 mol% of this ligand, the addition led at 0 °C or room temperature to the corresponding chiral tertiary alcohols **90** in moderate to



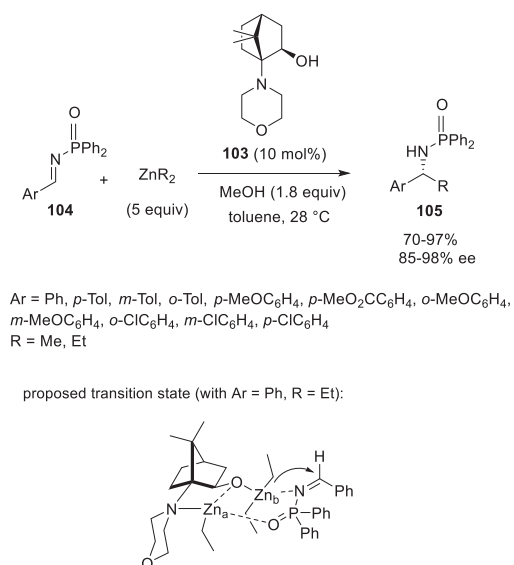
Scheme 33. Addition of ZnEt₂ to aromatic aldehydes in the presence of a supported ligand [60].

excellent yields (52–95%) and enantioselectivities (71–92% ee). The best results were achieved in the reaction of aromatic ketones while aliphatic ones provided opposite enantioselectivity and much lower ee values ($\leq 44\%$ ee). The observed stereochemistry can be explained by the transition state model depicted in Scheme 26, in which the Si face of the ketone is preferentially attacked by the zinc reagent.

In 2017, Yamanaka et al. developed a newly designed zinc catalyst derived from chiral bisamidine ligand **91** and ZnEt₂ for the enantioselective addition of ZnEt₂ to methyl α -ketoesters **92** [56]. The corresponding chiral tertiary alcohols **93** were generated by using 10 mol% of this highly coordinative ligand combined with two equivalents of ZnEt₂ in toluene at -45°C (Scheme 27). Good to quantitative yields (61–99%) associated with moderate to excellent ee values (31–94% ee) were obtained with a series of aromatic as well as aliphatic ketones.

4.2. Addition to aldehydes

In 2015, Ito et al. employed 10 mol% of chiral salen ligand **89** in an asymmetric zinc-catalyzed addition of ZnPh₂ to aldehydes **47** [55]. As illustrated in Scheme 28, the corresponding chiral secondary alcohols **94** were formed in good to high yields (71–96%)



Scheme 34. Addition of ZnEt₂/ZnMe₂ to *N*-(diphenylphosphinoyl)aldimines in the presence of a camphor-derived 1,2-amino alcohol ligand [62].

and moderate to excellent enantioselectivities (54–97% ee). Actually, aromatic aldehydes reacted with uniformly very good ee values (83–97% ee) while much lower enantioselectivities (54–76% ee) were obtained in the reaction of aliphatic aldehydes. A possible transition state is shown in Scheme 28 in which the Si face of the aldehyde is preferentially attacked by the zinc reagent.

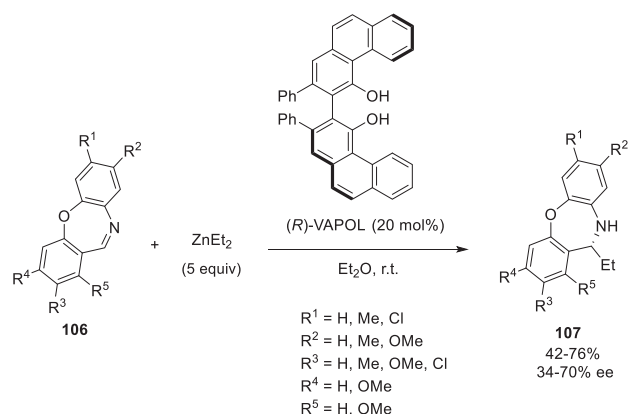
The same year, Amedjkouh et al. described the asymmetric zinc-catalyzed addition of Zn(*i*-Pr)₂ to aryl aldehydes **95** [57]. The catalyst system was composed of 10 mol% of chiral (5-pyrimidyl)alkanol ligand **96** and 2.2 equivalents of Zn(*i*-Pr)₂ in toluene. The reaction provided at 0°C a series of chiral pyridine alcohols **97** in variable enantioselectivities (16–93% ee) and good to high yields (57–92%), as depicted in Scheme 29.

In 2017, a dinuclear zinc catalyst derived from 5 mol% of (*S,S*)-AzePhenol and two equivalents of ZnMe₂ was applied by Wang et al. to promote the asymmetric addition of ZnMe₂ to aromatic aldehydes **47** (Scheme 30) [38]. Performed in toluene at 30°C , the reaction provided chiral secondary alcohols **98** in quantitative yields (92–99%) and moderate to excellent enantioselectivities (39–99% ee). The enantioselectivity of the reaction was found sensitive to both the electronic nature and position of the substituents beared on the phenyl ring of aldehydes. Generally, the best enantioselectivities were achieved in the reaction of *ortho*-substituted aryl aldehydes.

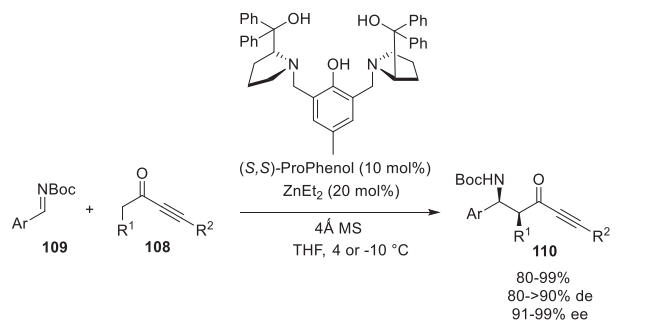
Novel chiral aziridine alcohol ligands were designed by Rachwalski et al. in 2017 to be used in the asymmetric addition of ZnEt₂ to aromatic aldehydes **47** (Scheme 31) [58]. For example, the use of 10 mol% of optimal ligand **99** combined with three equivalents of ZnEt₂ in toluene at room temperature allowed several aromatic alcohols **100** to be synthesized in remarkable enantioselectivities (94–98% ee) and excellent yields (86–97%).

In 2018, Righi et al. reported the design of a novel class of chiral amino alcohol ligands [59]. Among them, optimal ligand **101** was applied at 6 mol% of catalyst loading to the same reactions, allowing a range of aromatic as well as aliphatic secondary alcohols **100** to be formed in good to quantitative yields (60–99%) and high enantioselectivities (80–97% ee), as illustrated in Scheme 32.

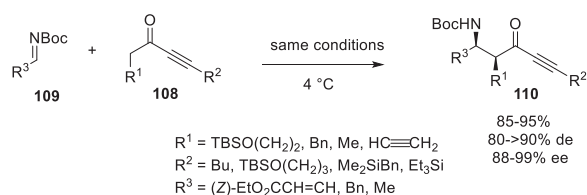
In 2020, the same authors described the synthesis of a chiral linear 1,2-amino alcohol catalyst **102** anchored on functionalized magnetite nanoparticles which was further investigated in the same reactions [60]. As illustrated in Scheme 33, ZnEt₂ was added to aromatic aldehydes **47** in toluene at room temperature by using 6 mol% of this heterogeneous catalyst, thus providing the corresponding chiral alcohols **100** in moderate yields (46–77%) and enantioselectivities (47–58% ee). The catalyst could be reused up to three times.



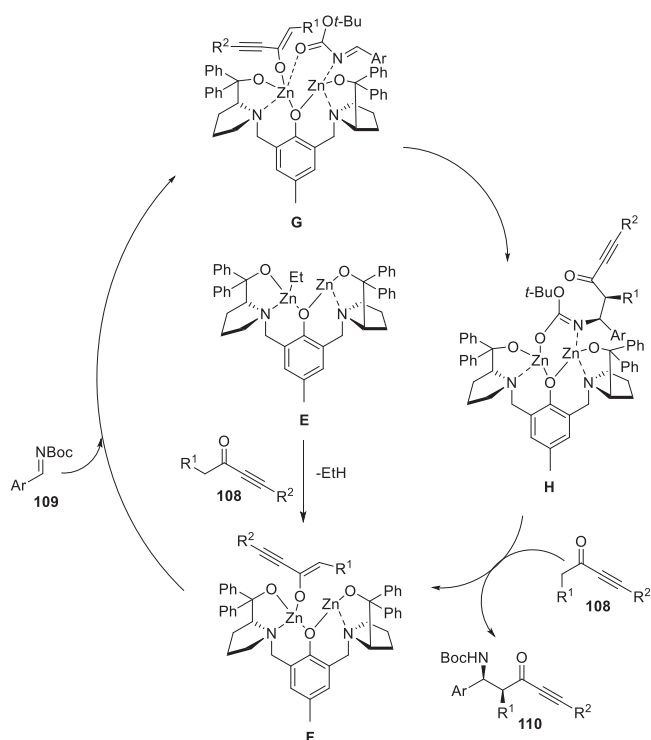
Scheme 35. Addition of ZnEt₂ to seven-membered aldimines in the presence of (*R*)-VAPOL [63].



with alkyl *N*-Boc aldimines:



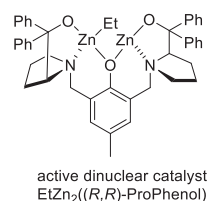
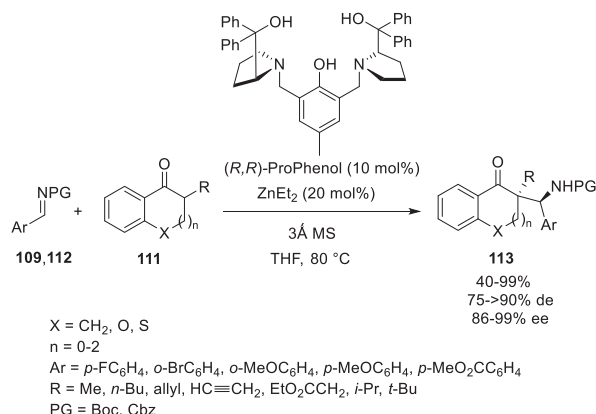
Scheme 36. Mannich reactions of ynones with *N*-Boc aldimines [64].



Scheme 37. Mechanism for Mannich reaction of ynones with *N*-Boc aldimines [64].

4.3. Addition to imines

Chiral amines are widely used as key building blocks in the synthesis of many natural and bioactive products. One of the most direct route to these compounds is based on the enantioselective addition of organozinc reagents to imines performed in the presence of a chiral ligand [61]. A drawback of this methodology is



Scheme 38. Mannich reaction of α -branched aromatic ketones with *N*-protected aryl aldimines [65].

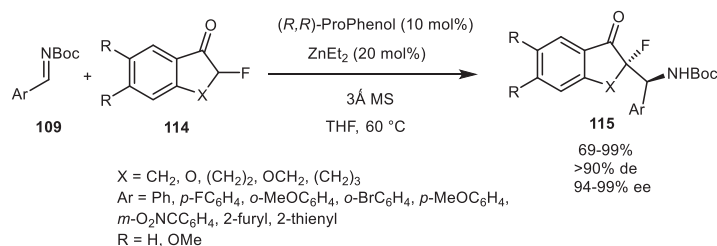
the common requirement of stoichiometric amount of chiral ligands to ensure high conversion and enantioselectivity related to the poor electrophilic character of imines. However, Uang and Huang demonstrated in 2015 that only 10 mol% of camphor-derived chiral 1,2-amino alcohol ligands, such as optimal ligand **103**, was sufficient to promote the enantioselective addition of dialkylzincs to *N*-(diphenylphosphinoyl)aldimines **104** [62]. As depicted in Scheme 34, the addition of ZnMe₂/ZnEt₂ to these aldimines performed in toluene at 28 °C afforded the corresponding chiral secondary amines **105** in good to quantitative yields (70–97%) and uniformly high enantioselectivities (85–98% ee). The obtention of these good results required the use of 1.8 equivalent of methanol as superstoichiometric additive. A transition state is proposed in Scheme 34, showing the coordination of the imine and chiral aminoalcohol ligand to two zinc atoms (Zn_a and Zn_b). Then, the transfer of one of the ethyl groups (R = Et) on Zn_b to the imine led to the addition product exhibiting a *R*-configuration.

The asymmetric addition of dialkylzincs to cyclic imines is particularly unexplored. To fill this gap, Pedro et al. investigated the enantioselective addition of ZnEt₂ to seven-membered aldimines **106** in the presence of only 20 mol% of (*R*)-VAPOL in Et₂O as solvent [63]. The reaction led at room temperature to the corresponding chiral 11-ethyl-10,11-dihydrobenzo[*b,f*][1,4]oxazepines **107** which represented attractive compounds for medicinal chemistry. As shown in Scheme 35, these products were obtained in moderate to good yields (42–76%) combined with low to moderate enantioselectivities (34–70% ee).

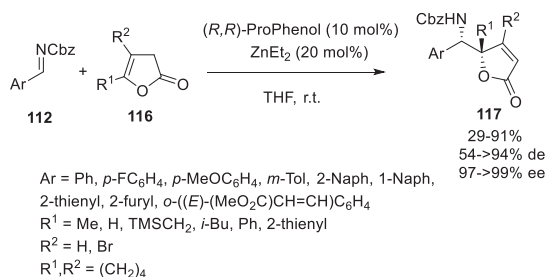
5. Mannich reactions

5.1. With ProPhenol ligand

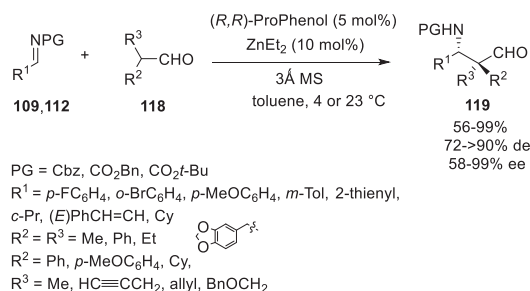
In 2015, Trost and Hung reported the first direct catalytic Mannich-type reaction between various ynones **108** and *N*-Boc aldimines **109** [64]. It involved 10 mol% of (*S,S*)-ProPhenol as ligand in combination with 20 mol% of ZnEt₂ in THF as solvent, resulting in the formation of the corresponding chiral α -substituted β -amino



Scheme 39. Mannich reaction of fluorinated aromatic ketones with *N*-Boc aryl aldimines [66].



Scheme 40. Mannich reaction of butenolides with *N*-Cbz aryl aldimines [67].

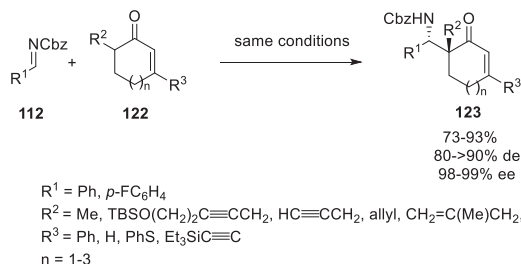
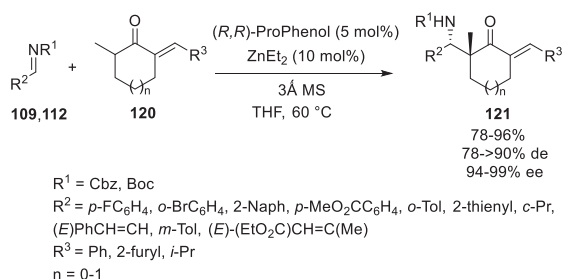


Scheme 41. Mannich reaction of α -branched aldehydes with *N*-protected aldimines [68].

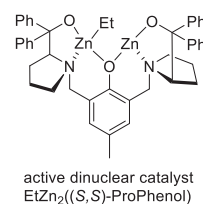
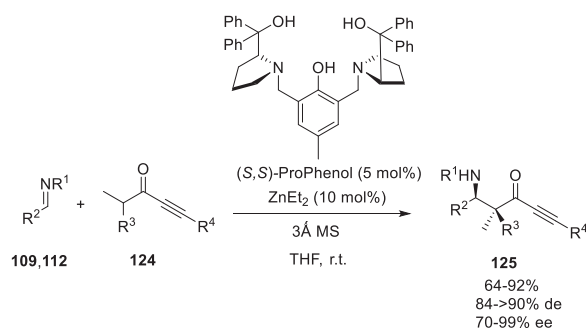
ynones **110** with excellent chemo-, diastereo-, and enantioselectivities (Scheme 36). Indeed, performed at 4 or –10 °C, the Mannich reaction of aromatic *N*-Boc aldimines **109** with various alkynones **108** afforded the corresponding products **110** in high yields (80–99%), excellent diastereoselectivities (80–>90% de) and remarkable ee values (91–99% ee). The scope of the methodology could be extended to aliphatic *N*-Boc imines **109** (R³ = alkyl) which also provided the corresponding Mannich products **110** in comparable excellent results (85–95% yield, 80–>90% de, 88–99% ee). This powerful methodology tolerated a variety of functional groups on both the two substrates, allowing a direct access to many chiral and densely functionalized α -substituted β -amino ynones.

The authors proposed a catalytic cycle depicted in Scheme 37 [64]. After the in situ generation of dinuclear active catalyst **E**, deprotonated ynone **108** chelated to **E** to give intermediate **F**. Then, *N*-Boc imine **109** coordinated to both zinc atoms to afford novel complex **G**. The enolate further attacked the electrophile to give intermediate **H**. Finally, deprotonation of ynone **108** liberated the Mannich product **110** and turnover the catalytic cycle.

In 2016, Trost et al. disclosed the first direct asymmetric Mannich reaction of α -branched ketones [65]. Using 20 mol% of ZnEt₂ and 10 mol% of (*R,R*)-ProPhenol as catalyst system, the reaction of cyclic ketones **111** with *N*-Boc/Cbz aryl aldimines **109**, **112** gave direct access to a range of chiral functionalized β -amino ketones **113** exhibiting an all-carbon quaternary stereocenter. These bicyc-



Scheme 42. Mannich reactions of α -branched cyclic enones with *N*-protected aldimines [69].



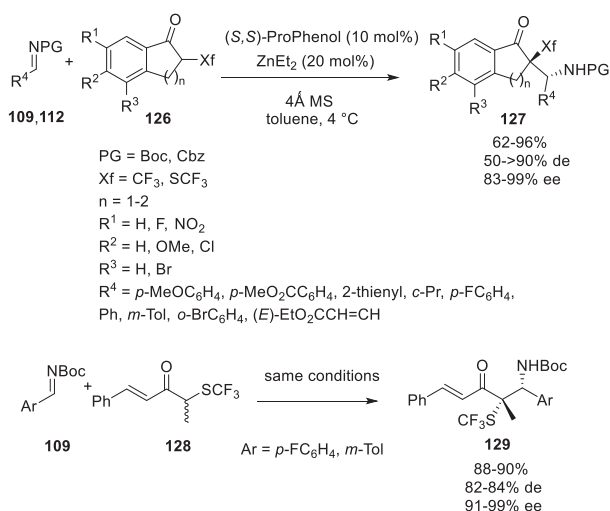
Scheme 43. Mannich reaction of α -branched ynones with *N*-protected aldimines [69].

lic products were enantio- and diastereoselectively generated with moderate to quantitative yields (40–99%), 75–>90% de and 86–99% ee (Scheme 38). The substrate scope of the methodology included different types of aromatic cyclic ketones, such as indanones, tetralones and 4-(thio)chromanones, producing the corresponding Mannich products with comparable levels of efficiency.

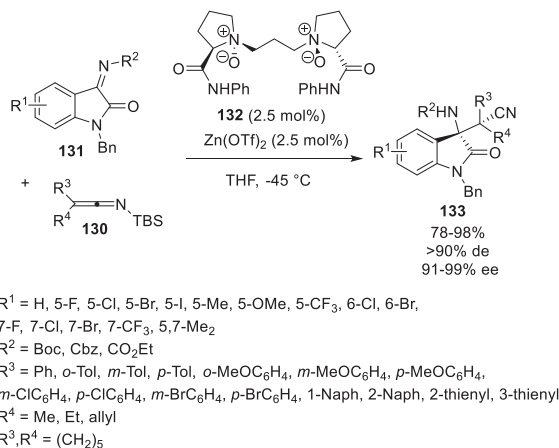
The same year, these authors employed their catalyst system to develop the first highly diastereo- and enantioselective direct Mannich reaction using fluorinated aromatic ketones as nucleophilic partners [66]. Indeed, the reaction of a range of cyclic fluorinated aromatic ketones **114** with *N*-Boc aryl aldimines **109** performed at 60 °C in THF in the presence of 10 mol% of (*R,R*)-ProPhenol as ligand and 20 mol% of ZnEt₂ as precatalyst afforded chiral β-fluoroamines **115** bearing a fluorinated tetrasubstituted carbon. These Mannich products were obtained in high yields (69–99%) as single diastereomers (>90% de) almost enantiopure (94–99% ee), as presented in Scheme 39.

In 2017, this catalyst system was also applied by the same group to perform the first enantio- and diastereoselective direct vinylogous Mannich reaction between butenolides **116** and *N*-Cbz aryl aldimines **112** (Scheme 40) [67]. A series of butenolides bearing alkyl, aryl and halogen substituents were tolerated as well as variously substituted (hetero)aryl aldimines, leading to the corresponding chiral densely functionalized Mannich products **117** in moderate to excellent yields (29–91%), moderate to excellent diastereoselectivities (54–>94% de) and remarkable enantioselectivities (97–>99% ee). In most cases of substrates, the products were obtained as single stereoisomers (>94% de and >99% ee).

This catalyst system also promoted an unprecedented Mannich reaction of a variety of branched aldehydes **118** substituted with aryl and linear alkyl groups with *N*-protected (hetero)aromatic and aliphatic aldimines **109**, **112** (Scheme 41) [68]. The reaction was carried out in toluene at 4 or 23 °C, yielding the corresponding chiral β-amino aldehydes **119** in good to excellent yields (56–99%) and enantioselectivities (58–99% ee). Challenging aldehydes substituted with two different groups ($R^2 \neq R^3$) also reacted smoothly. In the case of an aldehyde substituted with a branched alkyl group (cyclohexyl) and a linear alkyl group (methyl), the corresponding Mannich adduct was obtained with a high diastereoselectivity (>90% de) whereas an aldehyde substituted with two sterically similar linear alkyl groups (benzyl and methyl groups) led to the corresponding product with a much lower de value (72% de).

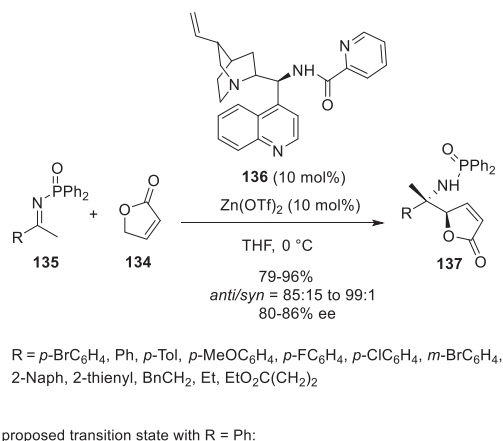


Scheme 44. Mannich reactions of α-trifluoromethyl- and α-trifluoromethylthio-substituted ketones with *N*-protected aldimines [70].



Scheme 45. Mannich reaction of silyl ketene imines with *N*-protected isatin-derived ketimines in the presence of a *N,N'*-dioxide ligand [71].

Investigating the scope of the Mannich reaction of α-branched ketones with *N*-carbamoyl imines in the presence of the same catalyst system, Trost found in 2019 that the introduction of an unsaturation adjacent to the carbonyl function of α-branched cyclic ketones dramatically improved the reactivity of the reaction [69]. When the same catalyst system was applied at 60 °C in THF as solvent to the asymmetric Mannich reaction of a range of exocyclic enones **120** with *N*-protected aldimines **109**, **112**, the corresponding chiral functionalized β-aminoketones **121** were formed in uniformly high yields (78–96%), diastereo- (78–>90% de) and enantioselectivities (94–99% ee), as shown in Scheme 42. These conditions were also compatible with various endocyclic enones **122** which reacted with *N*-Cbz aldimines **112** to afford the corresponding β-aminoketones **123** with comparable excellent results (73–93% yield, 80–>90% de, 98–99% ee). These powerful novel reactions will be undoubtedly useful to prepare important alkaloids or nitrogen-containing drugs bearing a quaternary stereocenter contiguous to an amine.



Scheme 46. Vinylogous Mannich reaction of γ-butenolide with *N*-protected ketimines in the presence of a cinchona alkaloid ligand [72].

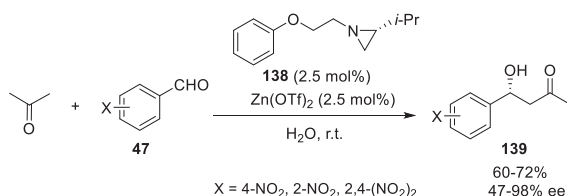
α -Branched ynones **124** were also investigated in comparable Mannich reactions with a variety of *N*-Boc and *N*-Cbz aldimines **109**, **112** [69]. In this case, enantiomeric (*S,S*)-ProPhenol was employed as ligand and the reaction was performed at room temperature. As illustrated in Scheme 43, a number of highly functionalized chiral β -amino ynones **125** were synthesized through this methodology with good to excellent yields (64–92%), high diastereoselectivities (84–>90% de) and generally very high enantioselectivities (70–99% ee).

In 2020, the same group investigated enantioselective Mannich reaction of cyclic and acyclic α -trifluoromethyl- and α -trifluoromethylthio-substituted ketones with *N*-protected imines [70]. These transformations were promoted by the same catalyst system employed at 10 mol% of catalyst loading in toluene at 4 °C. A range of cyclic α -trifluoromethyl- and α -trifluoromethylthio-substituted ketones **126** smoothly reacted with both *N*-Cbz/Boc aryl and alkyl aldimines **109**, **112** to yield the corresponding chiral β -amino ketones **127** bearing a tetrasubstituted α -CF₃ or α -SCF₃ stereogenic center in uniformly excellent enantioselectivities (83–99% ee) and in most cases excellent diastereoselectivities (50–>90% de) combined with good to quantitative yields (62–96%), as depicted in Scheme 44. The scope of the methodology could be extended to challenging acyclic α -trifluoromethylthio-substituted ketones **128**, which underwent the reaction with *N*-Boc aldimines **109** to give chiral amines **129** in excellent yields (88–90%), diastereoselectivities (82–84% de) and ee values (91–99% ee). It must be noted that this method allowed access to rare and challenging compounds with tetrasubstituted α -trifluoromethylthio β -amines.

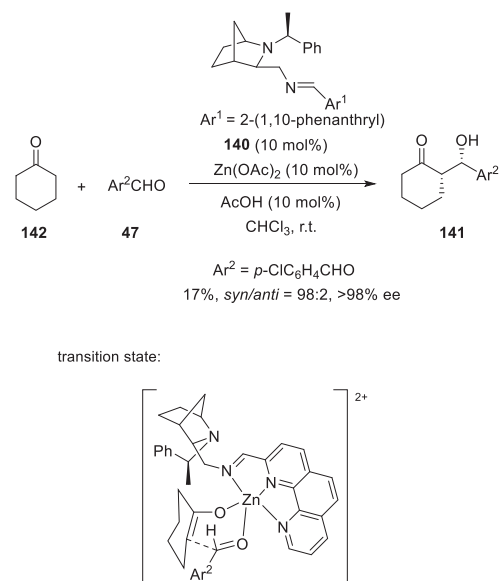
5.2. With other ligands

In 2015, Feng et al. employed a chiral *N,N'*-dioxide ligand to develop the first enantioselective Mannich reaction between silyl ketene imines **130** and *N*-protected isatin-derived ketimines **131** [71]. Only 2.5 mol% of optimal ligand **132** was combined with the same quantity of Zn(OTf)₂ to generate the corresponding chiral catalyst which allowed a range of chiral β -amino nitriles **133** bearing congested vicinal tetrasubstituted stereocenters to be synthesized at –45 °C in THF as solvent (Scheme 45). These functionalized 3-amino oxindoles were obtained as almost single diastereomers (>90% de) in both high yields (78–98%) and enantioselectivities (91–99% ee). This novel process offered a particularly broad substrate scope and functional-group tolerance.

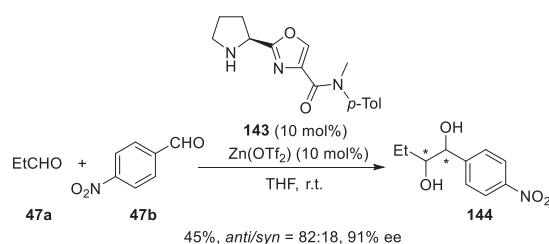
The same year, Nakamura et al. developed the first enantioselective direct vinylogous Mannich reaction of γ -butenolide **134** with various *N*-protected ketimines **135** performed in the presence of 10 mol% of a zinc chiral catalyst derived from cinchona alkaloid **136** and Zn(OTf)₂ [72]. Carried out at 0 °C in THF as solvent, the process led to the corresponding δ -amino- δ,δ -disubstituted- α,β -unsaturated carbonyl compounds **137** as major *anti*-diastereomers (*anti/syn* = 85:15 to 99:1) in high yields (79–96%) and enantioselectivities (80–86% ee), as illustrated in Scheme 46. A possible transition state for the reaction is depicted in this Scheme, showing



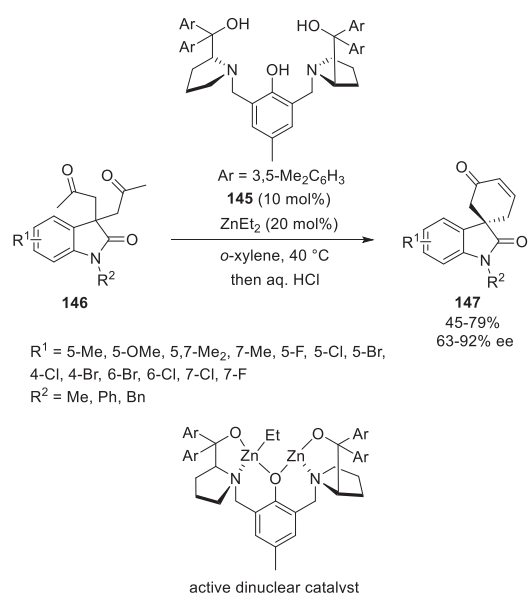
Scheme 47. Aldol reaction of acetone with nitrobenzaldehydes in water and in the presence of an aziridine-ether ligand [73].



Scheme 48. Aldol reaction of cyclohexanone with *p*-chloro-benzaldehyde in the presence of a Schiff base ligand [74].

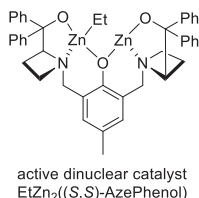
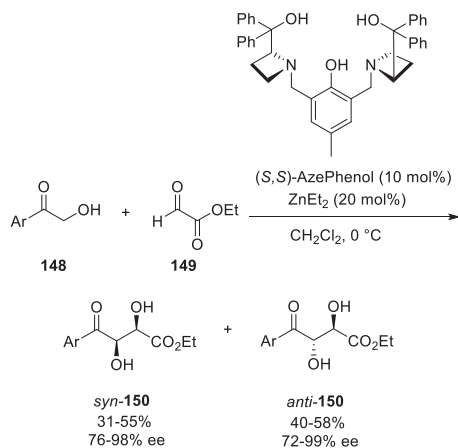


Scheme 49. Aldol reaction of propionaldehyde with *p*-nitrobenzaldehyde in the presence of an azole-carboxamide ligand [75].



Scheme 50. Intramolecular aldol reaction of oxindole-derived diketones in the presence of a ProPhenol derivative ligand [76].

that two nitrogen atoms from the picolinoyl group, two oxygen atoms from the dienolate, and a phosphoryl group coordinate to the zinc(II) cation. Furthermore, the ammonium proton on



Scheme 51. Aldol reaction of 2-hydroxyacetophenones with ethyl glyoxylate in the presence of (S,S)-AzePhenol [77].

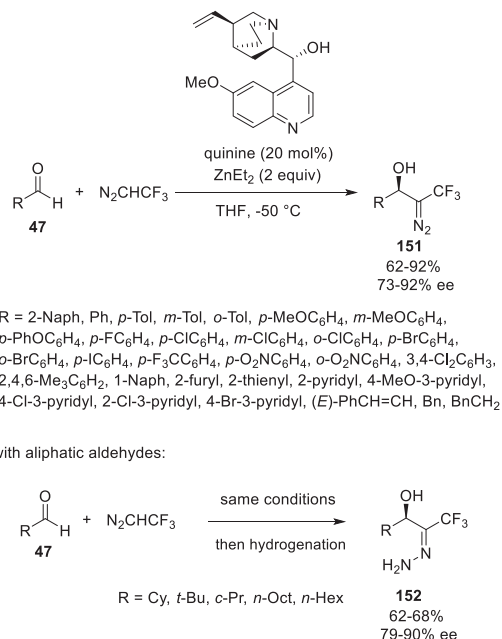
quinuclidine coordinates to the oxygen atom of the dienolate. In this structure, the *Re* face of the dienolate approaches the *Re* face of the ketimine to avoid steric repulsion of the diphenylphosphinyl group to give the final product.

6. (Nitro)aldol reactions

6.1. Aldol reactions

In 2000, Trost et al. developed the first enantioselective aldol reaction using a dinuclear zinc catalyst derived from chiral ProPhenol ligand [42]. Ever since, many types of chiral ligands have been employed in these reactions which are generally performed under mild reaction conditions [3b,5c,6]. In addition to use a non-toxic and cheap metal, these green reactions present the advantage to be sometimes performed in water. As an example, asymmetric aldol reaction of acetone with nitrobenzaldehydes **47** were developed in 2015 by Rachwalski et al. by using chiral aziridine-ether ligands in water [73]. A low catalyst loading of 2.5 mol% of optimal ligand **138** combined with the same quantity of Zn(OTf)₂ allowed the corresponding aldol products **139** to be synthesized in good yields (60–72%) and moderate to excellent enantioselectivities (47–98% ee), as shown in Scheme 47.

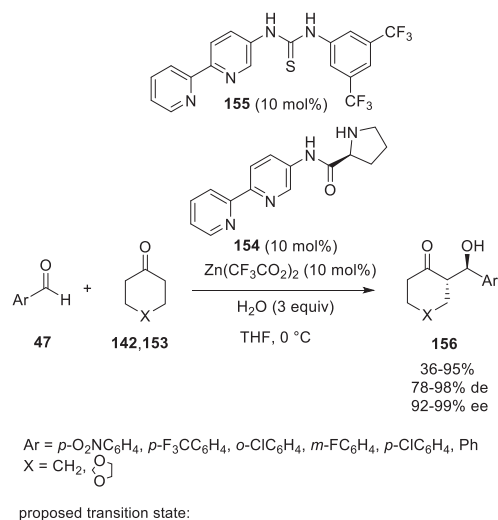
In 2016, Wojaczynska et al. designed novel chiral rigid and bicyclic ligand **140** bearing a tertiary amine and a 1,10-phenanthroline moiety appended by an imine linkage [74]. When this ligand (10 mol%) was combined to Zn(OAc)₂ (10 mol%) in chloroform as solvent and AcOH as an additive, it promoted the stereoselective formation of enantio- (>98% ee) and diastereopure (96% de) *syn*-aldol product **141** in low yield (17%) starting from the corresponding aromatic aldehyde **47** and cyclohexanone **142** (Scheme 48). A transition state is proposed in Scheme 48, in which the preferred formation of the *syn*-diastereomer is explained by



Scheme 52. Aldol reactions of aldehydes with N₂CHCF₃ in the presence of quinine [78].

the favored formation of the *Z*-enolate of cyclohexanone and position of the aromatic group of the aldehyde (Ar²) in the least sterically hindered place.

The same year, other novel multifunctional heterocyclic ligands were synthesized by Dockendorff et al. [75]. Among them, azole-carboxamide ligand **143** was found optimal when combined with



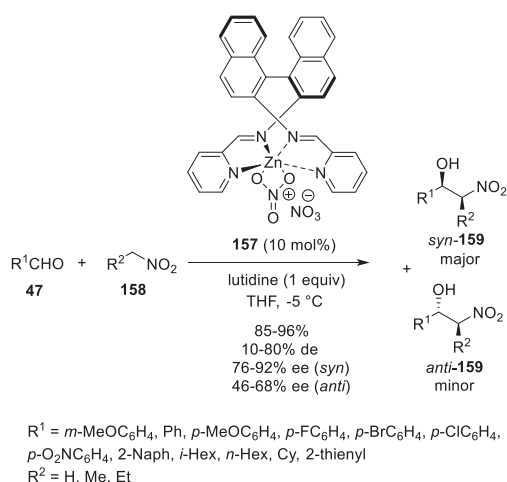
Scheme 53. Aldol reaction of cyclohexanones with benzaldehydes in the presence of bipyridine-based ligands [79].

Zn(OTf)₂ to promote enantioselective aldol condensation of propionaldehyde **47a** to *p*-nitrobenzaldehyde **47b**, delivering the corresponding chiral *anti*-diol **144** as major diastereomer (*anti*/*syn* = 82:18) in 91% ee and 45% yield (Scheme 49). However, a drawback of this novel methodology was related to the limitation of its substrate scope.

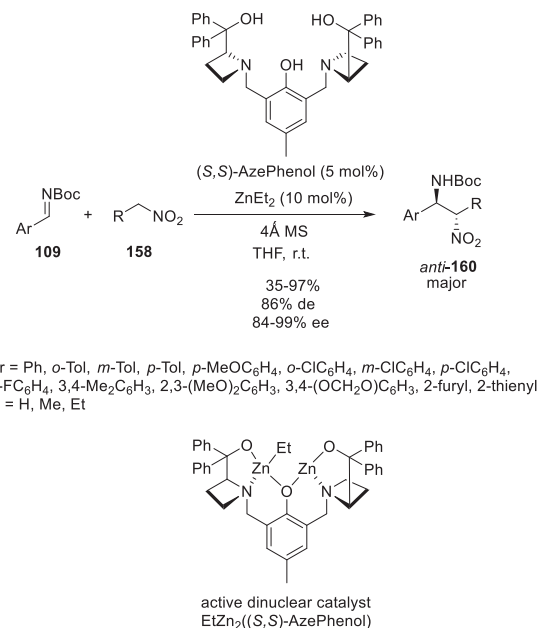
In the presence of a dinuclear zinc complex derived from ZnEt₂ (20 mol%) and 10 mol% of chiral ProPhenol derivative **145** as ligand, an enantioselective intramolecular aldol reaction of various substituted oxindole-derived diketones **146** occurred at 40 °C in *o*-xylene (Scheme 50) [76]. The corresponding cyclized products were subsequently submitted to dehydration by treatment with aqueous HCl to afford chiral spiro[cyclohexanone-oxindole] derivatives **147** in good yields (45–79%) and good to high enantioselectivities (63–92% ee).

Chiral α,β -dihydroxy esters constitute key building blocks in the synthesis of many drugs and natural products. In 2018, Wang et al. employed (S,S)-AzePhenol as ligand at 10 mol% of catalyst loading in combination with 20 mol% of ZnEt₂ in dichloromethane at 0 °C in a novel direct access to this type of products [77]. The process involved an asymmetric aldol reaction between 2-hydroxyacetophenones **148** and ethyl glyoxylate **149**, leading to mixtures of both *syn*- and *anti*- α,β -dihydroxy γ -ketoesters **150**. The presence of a range of substituents on the phenyl ring of the 2-hydroxyacetophenones was tolerated (Scheme 51). The *syn*-diastereomers were obtained in low to moderate yields (31–55%) and good to high enantioselectivities (76–98% ee) while the *anti*-products were synthesized with slightly better yields (40–58%) and comparable enantioselectivities (72–99% ee). These functionalized products can be considered as potential synthetic intermediates for the synthesis of various compounds.

In 2019, Ma and Zhang reported the first catalytic enantioselective reaction based on the use of trifluorodiazethane as an effective nucleophile to be condensed on aldehydes [78]. Indeed, an asymmetric aldol reaction of CF₃CHN₂ with a wide range of aldehydes **47** occurred in the presence of 20 mol% of quinine as ligand and two equivalents of ZnEt₂. Performed at –50 °C in THF as solvent, the reaction resulted in the formation of the corresponding chiral CF₃-containing alcohols **151** in good to high yields (62–92%) and enantioselectivities (73–92% ee), as illustrated in Scheme 52. The catalyst system was remarkably compatible with many aromatic aldehydes with electronically varied substituents at different positions of the phenyl ring and also with naphthyl and heteroaryl aldehydes. Pyridine-derived aldehydes were also tolerated with



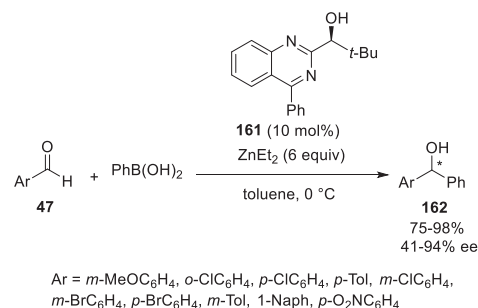
Scheme 54. Henry reaction of aldehydes with nitroalkanes in the presence of a BINIM-based Schiff base-derived catalyst [82].



Scheme 55. Aza-Henry reaction of *N*-Boc aryl aldimines with nitroalkanes in the presence of (S,S)-AzePhenol [83].

comparable enantioselectivities. Along with aromatic aldehydes, cinnamaldehyde, phenylethyl aldehyde and phenylpropyl aldehyde also reacted smoothly with comparable results. In addition, a series of simple aliphatic aldehydes **47** also underwent the reaction, leading in this case, to the corresponding CF₃-hydrazones **152** arisen from a further hydrogenation. The latter products were obtained in good yields (62–68%) and high enantioselectivities (79–90% ee).

Novel bipyridine-based ligands were synthesized by Jimeno and Sola to be combined with Zn(CF₃CO₂)₂ and further investigated in enantioselective aldol reaction of cyclohexanones **142**, **153** with benzaldehydes **47** [79]. Interestingly, the active catalyst was a bifunctional, cooperative self-assembled complex with a tetrahedral zinc complex forming the enamine of cyclohexanone **142**, **153** through the prolinamide moiety of chiral ligand **154**, whereas the thiourea group from the perpendicular achiral ligand **155** approached the aldehyde substrate through hydrogen bonding in a way that steric repulsion from the inner complex was minimized (Scheme 53). In the presence of 10 mol% of this original catalyst system and three equivalents of water in THF as solvent, a series of diversely substituted aromatic benzaldehydes **47** reacted at 0 °C with cyclohexanones **142**, **153** to give the corresponding chiral aldol products **156** with moderate to excellent yields (36–95%),

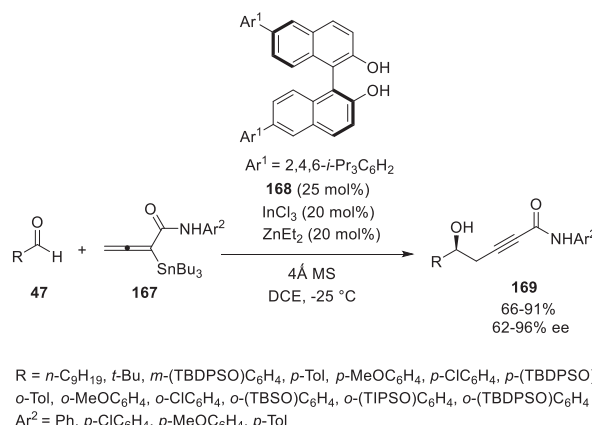


Scheme 56. Addition of PhB(OH)₂ to aromatic aldehydes in the presence of a 4-phenylquinazolinol ligand [84].

and uniformly high diastereo- (78–98% de) and enantioselectivities (92–99% ee). It was found that the presence of water as an additive was crucial to ensure the activity of the catalytic system.

6.2. Nitroaldol reactions

The nitroaldol reaction (Henry reaction) is an important C–C bond forming reaction to achieve key synthetic building blocks, such as β -nitroalcohols, from aldehydes and nitroalkanes [80]. This transformation has been the object of many investigations and a range of asymmetric versions have been developed by using both chiral metal complexes and organocatalysts. Among the works involving chiral zinc catalysts [9], is the first enantioselective zinc-catalyzed Henry reaction reported by Trost and Ye in 2002, allowing enantioselectivities of up to 93% ee to be reached by using a dinuclear zinc complex [81]. Later in 2016, Subramanian et al. investigated the use of preformed mononuclear chiral zinc catalyst **157** derived from a BINIM-based Schiff base ligand in asymmetric nitroaldol reaction of aldehydes **47** with nitroalkanes **158** (Scheme 54) [82]. Using 10 mol% of this catalyst in THF at -5°C in the presence of lutidine as stoichiometric additive, the reaction of nitromethane ($\text{R}^2 = \text{H}$) with both aromatic and aliphatic aldehydes afforded the corresponding chiral β -nitro alcohols **159** in high yields (85–96%) and enantioselectivities (74–92% ee). The scope of the process was extended to other nitroalkanes, such as nitroethane and nitropropane, which afforded the corresponding



Scheme 58. Propargylation of aldehydes with stannyl allenyl amides in the presence of a dual Zn/In catalysis and a BINOL-derived ligand [86].

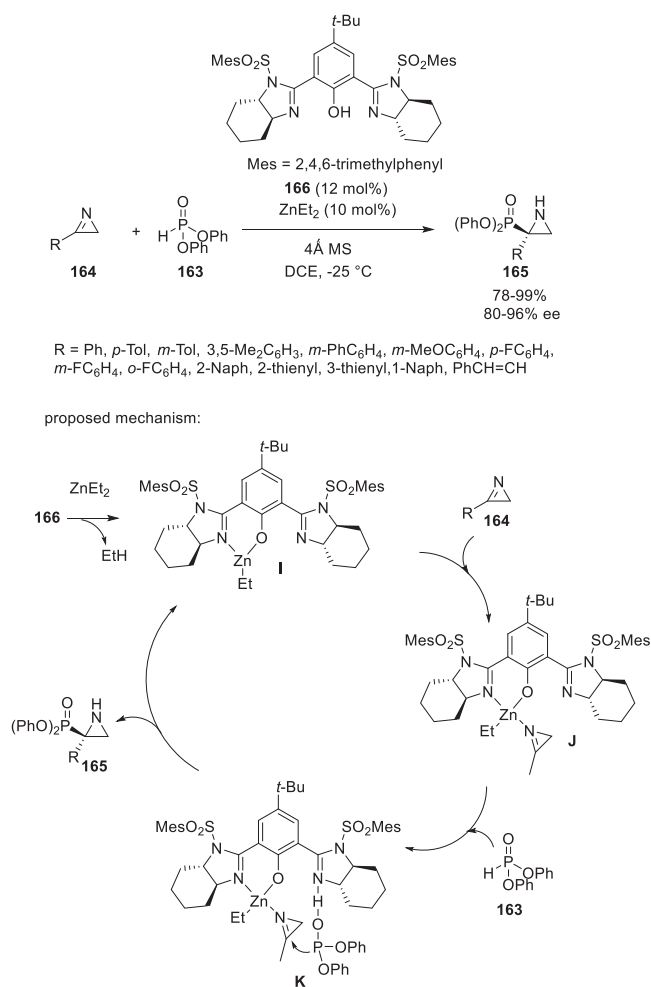
products as *syn/anti* mixtures of diastereomers with low to high diastereoselectivities in favor of the *syn*-diastereomers (10–80% de). The yields were high (83–96%) and the enantioselectivities of the *syn*- and *anti*- β -nitro alcohols of 76–92% ee and 46–68% ee, respectively. Importantly, it was found that the catalyst could be recycled and reused for up to six times without loss of efficiency.

Furthermore, the asymmetric aza-Henry reaction between imines and nitroalkanes constitutes one of the most employed methodologies to prepare chiral β -nitroamines. In 2019, Wang et al. disclosed a novel protocol for the enantioselective aza-Henry reaction of *N*-Boc aldimines and nitroalkanes performed at room temperature, which was based on the use of (*S,S*)-AzePhenol as zinc ligand [83]. As depicted in Scheme 55, a dinuclear catalyst in situ generated from 5 mol% of this ligand and 10 mol% of ZnEt₂ promoted in THF as solvent the aza-Henry reaction of a range of aromatic *N*-Boc-aldimines **109** with nitroalkanes **158** to yield the corresponding chiral β -nitroamines **160** in moderate to quantitative yields (35–97%) and uniformly excellent enantioselectivities (84–99% ee). In addition to nitromethane, nitroethane and nitropropane were also tolerated with comparable excellent results, leading to the *anti*-diastereomers with 86% de.

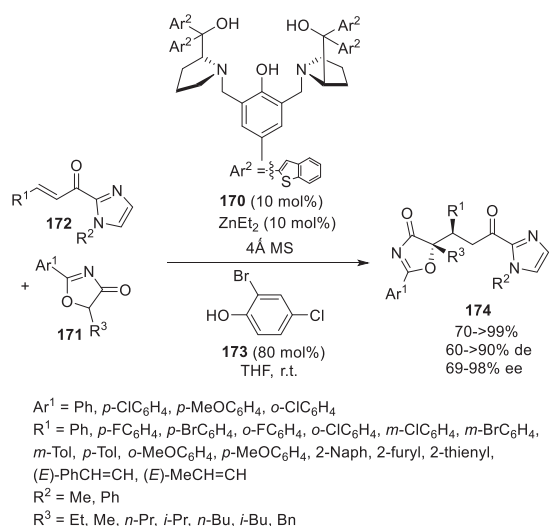
7. Other 1,2-nucleophilic additions to carbonyl compounds and derivatives

In 2016, Ulukanli et al. reported the synthesis of novel chiral 4-phenylquinazolinol ligands which were further used in several zinc-catalyzed asymmetric transformations, including enantioselective phenylboronic acid addition to aldehydes [84]. As presented in Scheme 56, the use of 10 mol% of ligand **161** in toluene at 0°C along with six equivalents of ZnEt₂ allowed the addition of PhB(OH)₂ to a series of substituted aromatic aldehydes **47** to be achieved, producing the corresponding chiral diaryl alcohols **162** with high yields (75–98%) and moderate to high enantioselectivities (41–94% ee).

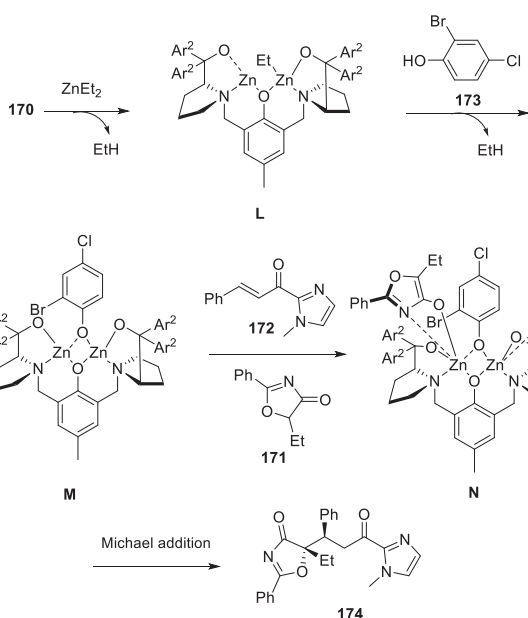
In 2017, Nakamura and Hayama reported the first example of a highly enantioselective reaction of azirines with nucleophiles [85]. It involved the asymmetric nucleophilic addition of diphenylphosphite **163** to 3-substituted 2H-azirines **164**, resulting in the formation of the corresponding chiral aziridines **165**. To promote these reactions, the authors designed novel chiral bis(imidazoline) ligands, such as **166**, which was employed at 12 mol% of catalyst loading in combination with 10 mol% of ZnEt₂ in DCE as solvent at -25°C . The corresponding chiral aziridines **165** were obtained in both uniformly high ee values (80–96% ee) and yields (78–99%), as illustrated in Scheme 57. A catalytic cycle is proposed in



Scheme 57. Addition of diphenylphosphite to 3-substituted 2H-azirines in the presence of a bis(imidazoline) ligand [85].



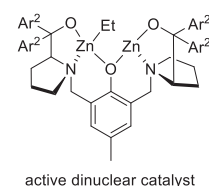
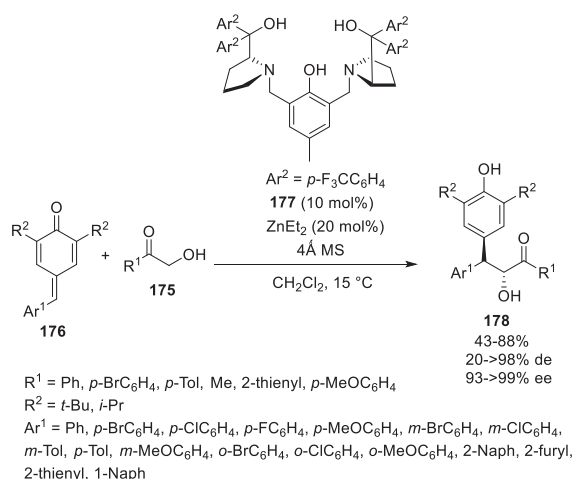
proposed mechanism with Ar¹ = R¹ = Ph, R² = Me, R³ = Et:



Scheme 59. Michael addition of 5H-oxazol-4-ones to α,β -unsaturated acyl imidazoles in the presence of a ProPhenol derivative ligand [89].

this Scheme in which ZnEt₂ reacted with the hydroxy group of the chiral ligand to form complex **I**. Then, the azirine coordinated to the zinc atom of **I** to give intermediate **J**, which further chelated and activated diphenylphosphite in complex **K**. Activated diphenylphosphite then condensed to the imine carbon atom of the azirine. Subsequently, protonation and decomplexation underwent to give the final product and regenerate **I**.

In 2019, Yoda et al. developed the first catalytic enantioselective propargylation of aldehydes with newly prepared stannyl allenyl amides to give chiral propargyl amides (Scheme 58) [86]. Indeed, a variety of aldehydes **47** were efficiently coupled with these propargylating reagents **167** under mult catalysis with 20 mol% of ZnCl₂, 20 mol% of InCl₃, and 25 mol% of chiral BINOL-derived ligand **168** to afford the corresponding amide-functionalized homopropargyl alcohols **169** in both good to high yields (66–91%) and enantioselectivities (62–96% ee). The mechanistic details of the process with the exact role of each metal were not precised by the authors.

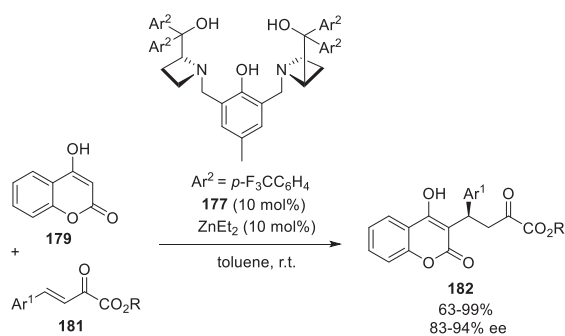


Scheme 60. 1,6-Michael addition of α -hydroxy ketones to 1,4-quinone methides in the presence of a ProPhenol derivative ligand [90].

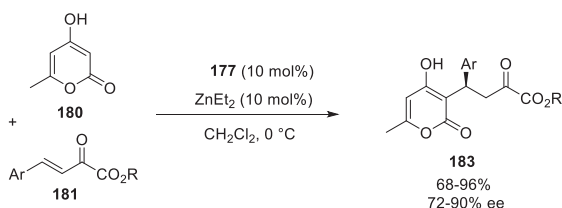
8. Michael additions

(Hetero)-Michael additions play a major role in the formation of carbon–carbon and carbon–heteroatom bonds. Many catalytic systems have been used in these reactions, including chiral organocatalysts and metal complexes. In particular, zinc catalysis in the Michael addition has achieved great importance due to the broad substrate scope, mild reaction conditions, and excellent reactivity and selectivity, along with the availability of a variety of useful chiral ligands [11]. In 2001, Shibasaki et al. reported the first highly enantioselective zinc-catalyzed Michael addition of 2-hydroxy-2'-methoxyacetophenone to α,β -unsaturated ketones [87]. Catalyzed by a BINOL-derived zinc complex, the reaction afforded the corresponding Michael products with up to 99% ee. Ever since, many types of ligands have been combined to zinc to promote such reactions [5c,88]. In an example reported in 2015 by Wang et al., novel chiral ProPhenol derivative ligand **170** was synthesized and used in the asymmetric Michael reaction of 5H-oxazol-4-ones **171** to α,β -unsaturated acyl imidazoles **172** [89]. The conjugate addition was performed in THF at room temperature in the presence of phenol **173** as an additive, leading to a wide range of chiral imidazole-modified α,β -unsaturated ketones **174** with high yields (70–>99%), moderate to generally excellent diastereoselectivities (60–>90% de) and good to high enantioselectivities (69–98% ee), as shown in Scheme 59. The authors proposed the mechanism depicted in this Scheme in which active dinuclear zinc complex **L** was generated from the chiral ligand and ZnEt₂. Then, the phenol additive coordinated to the zinc center to provide chiral intermediate **M**. Then, independent coordination of the two substrates to the two zinc atoms of complex **M** provided complex **N** which stereoselectively led to the chiral product through Michael addition.

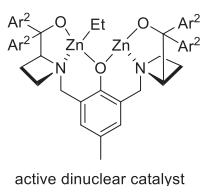
In 2018, Wang et al. described the first asymmetric 1,6-Michael addition of α -hydroxy ketones **175** to 1,4-quinone methides **176** (Scheme 60) [90]. It employed 10 mol% of (*S,S*)-ProPhenol derivative **177** as ligand and 20 mol% of ZnEt₂ in dichloromethane as solvent. Carried out at 15 °C, it resulted in the formation of chiral



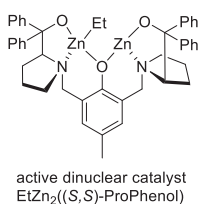
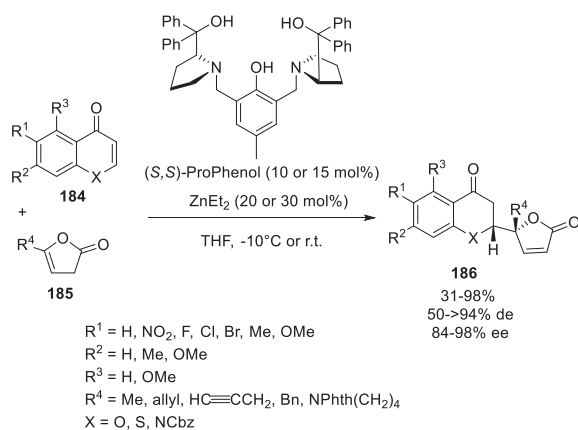
Ar¹ = Ph, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-Tol, *m*-ClC₆H₄, *m*-BrC₆H₄, *m*-Tol, *m*-MeOC₆H₄, *o*-ClC₆H₄, *o*-BrC₆H₄, 2-Naph, 2-thienyl
R = Me, Et, *i*-Pr, *t*-Bu



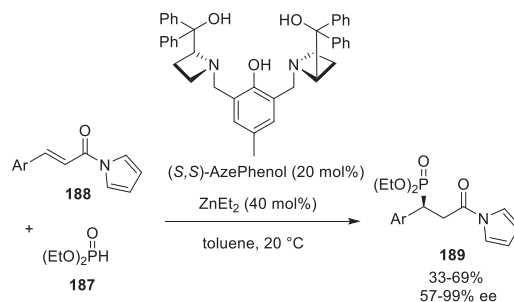
Ar = Ph, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-Tol, *m*-ClC₆H₄, *m*-BrC₆H₄, *m*-Tol, *m*-MeOC₆H₄, *o*-ClC₆H₄, *o*-BrC₆H₄, 2-Naph, 2-thienyl
R = Me, Et, *i*-Pr, *t*-Bu



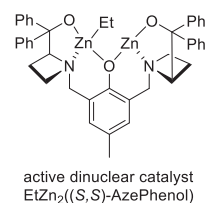
Scheme 61. Michael additions of 4-hydroxyl pyrones and 4-hydroxycoumarins to aryl-substituted α , β -unsaturated α -ketoesters in the presence of an AzePhenol derivative ligand [91].



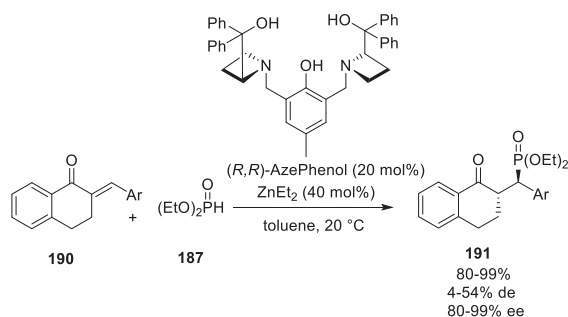
Scheme 62. Michael addition of butenolides to chromones and derivatives in the presence of (S,S)-ProPhenol [92].



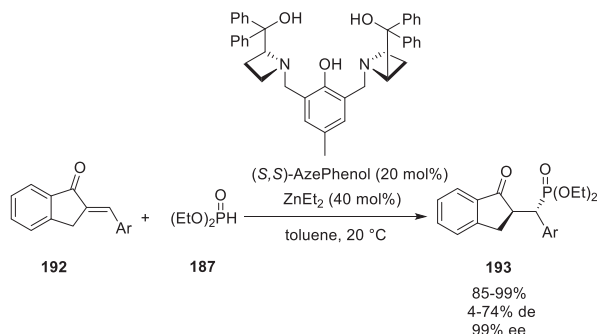
Ar = Ph, *o*-BrC₆H₄, *o*-MeOC₆H₄, *m*-MeOC₆H₄, 2-furyl, 2-Naph, 1-Naph, 2-thienyl, *p*-FC₆H₄, *p*-Tol, *p*-ClC₆H₄, *p*-FC₆H₄, *p*-BrC₆H₄, *p*-MeOC₆H₄, *p*-O₂NC₆H₄



Scheme 63. Phospha-Michael addition of diethyl phosphite to aryl-substituted *N*-acylpyrroles in the presence of (S,S)-AzePhenol [93].

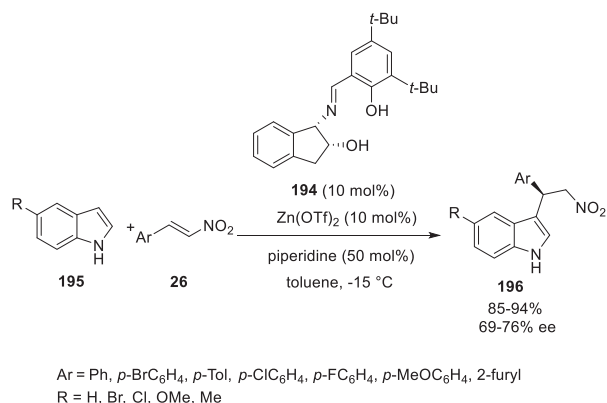


Ar = Ph, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-F₃CC₆H₄, *p*-O₂NC₆H₄, *p*-Tol, 2-furyl, 2-Naph, 1-Naph, 2-thienyl, *p*-MeOC₆H₄, *p*-(NMe₂)C₆H₄, *m*-FC₆H₄, *m*-ClC₆H₄, *m*-O₂NC₆H₄, *m*-Tol, *m*-MeOC₆H₄, *o*-BrC₆H₄, *o*-Tol, 4-Br-2-FC₆H₃, 3,4-Cl₂C₆H₃, 3,4-Me₂C₆H₃



Ar = Ph, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-Tol, 2-furyl, 2-Naph, 1-Naph, 2-thienyl, *p*-MeOC₆H₄, *m*-ClC₆H₄, *o*-MeOC₆H₄, 2,6-Me₂C₆H₃, *m*-Tol, *m*-MeOC₆H₄, *o*-Tol, 3,4-Cl₂C₆H₃, 3,4-Me₂C₆H₃, piperonyl

Scheme 64. Phospha-Michael additions of diethyl phosphonate to exocyclic α , β -unsaturated benzocyclic ketones arising from 1-tetralones and 1-indanones in the presence of (R,R)- and (S,S)-AzePhenols [94].



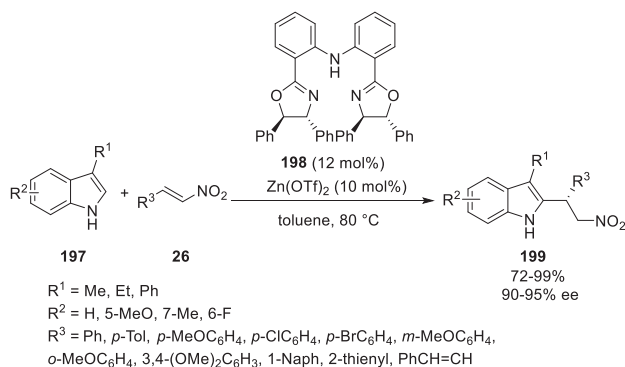
Scheme 65. Friedel-Crafts C3-alkylation of indoles with aromatic nitroalkenes in the presence of a Schiff base ligand [96].

β,β -diaryl- α -hydroxy ketones **178** in moderate to high yields (43–88%), variable diastereoselectivities (20–>98% de) and uniformly excellent enantioselectivities (93–>99% ee).

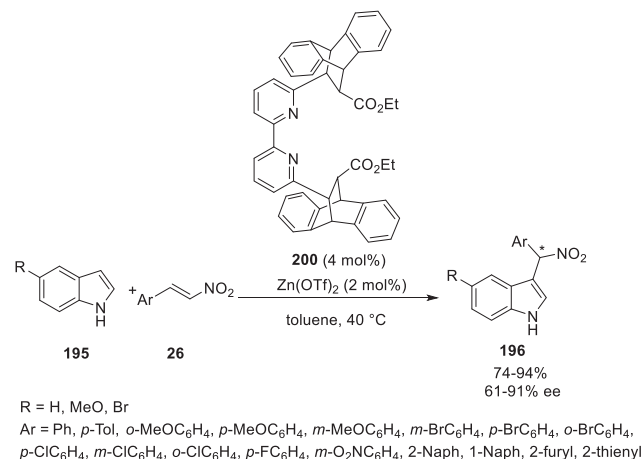
In 2019, the same authors also applied this catalyst system in asymmetric Michael additions of 4-hydroxyl pyrones **179** and 4-hydroxycoumarins **180** to aromatic β,γ -unsaturated α -ketoesters **181** [91]. In this case, the dinuclear active zinc catalyst was generated from AzePhenol derivative **177** and ZnEt₂. The reaction of 4-hydroxyl pyrones **179** with β,γ -unsaturated α -ketoesters **181** was performed at room temperature in toluene while that of 4-hydroxycoumarins **180** occurred in dichloromethane at 0 °C (Scheme 61). The corresponding chiral products **182** and **183** were respectively formed in good to quantitative yields (63–99% and 68–96%, respectively) and good to high enantioselectivities (83–94% ee and 72–90% ee, respectively). This novel simple methodology offered a direct access to various bioactive products.

The first enantioselective conjugate addition of butenolides to chromones (X = O) and derivatives was disclosed in 2019 by Trost et al. (Scheme 62) [92]. The process was catalyzed by 10 or 15 mol% of dinuclear zinc complex derived from (*S,S*)-ProPhenol and ZnEt₂ in THF at –10 °C or room temperature. Various substituted chromones but also a thiochromone (X = S) and a protected quinolone (X = NCbz) **184** reacted smoothly with differently substituted butenolides **185** to give the corresponding chiral lactones **186** in moderate to excellent yields (31–98%), diastereoselectivities (50–>94% de) combined with uniformly high enantioselectivities (84–98% ee).

Earlier in 2017, an asymmetric phospho-Michael addition of diethyl phosphite **187** to α,β -unsaturated carbonyl compounds, such as aryl-substituted α,β -unsaturated *N*-acylpyrroles **188**, cat-



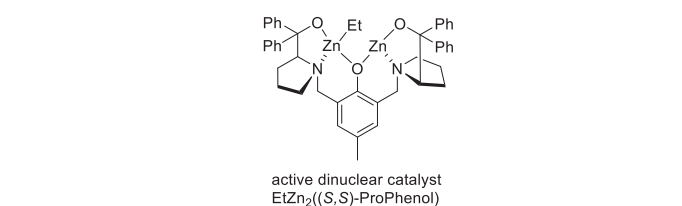
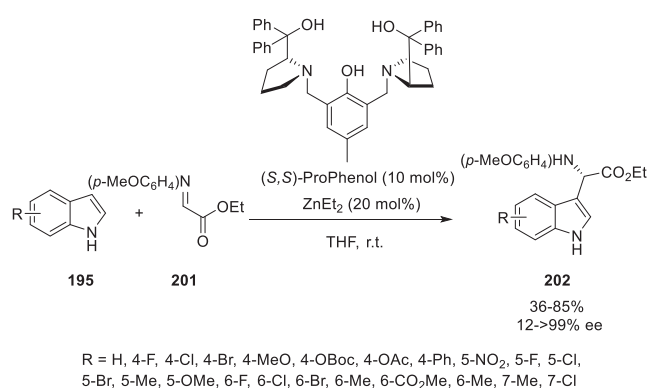
Scheme 66. Friedel-Crafts C2-alkylation of 3-substituted indoles with nitroalkenes in the presence of a bisoxazoline ligand [97].



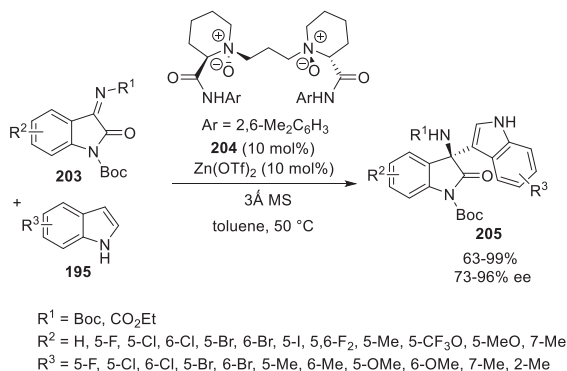
Scheme 67. Friedel-Crafts C3-alkylation of indoles with aromatic nitroalkenes in the presence of a bipyridine ligand [98].

alyzed by a dinuclear zinc catalyst in situ generated from 20 mol% of (*S,S*)-AzePhenol and 40 mol% of ZnEt₂ was developed by Wang et al. (Scheme 63) [93]. The reaction performed in toluene at 20 °C provided a wide range chiral phosphonate-containing products **189** in moderate to good yields (33–69%) and generally excellent enantioselectivities (91–99% ee). In only one case of substrate bearing a methoxy group at the *ortho*-position of the phenyl ring, the reaction provided a much lower enantioselectivity (57% ee).

The first asymmetric phospho-Michael addition of diethyl phosphonate to exocyclic α,β -unsaturated benzocyclic ketones arising from 1-tetralones and 1-indanones was reported by Wang and Hua, in 2018 (Scheme 64) [94]. Indeed, the reaction of 1-tetralone derivatives **190** with diethyl phosphonate **187**, catalyzed by a combination of 40 mol% of ZnEt₂ with 20 mol% of (*R,R*)-AzePhenol, afforded the corresponding chiral organophosphate products **191** exhibiting an 1-indanone skeleton as mixtures of diastereomers (4–54% de) with high (R¹ = Ph) yields (80–99%) and enantioselectivities (80–99% ee). On the other hand, the Michael addition of diethyl phosphonate **187** to 1-indanone



Scheme 68. Friedel-Crafts C3-alkylation of indoles with a protected ethyl glyoxylate imine in the presence of (*S,S*)-ProPhenol [99].



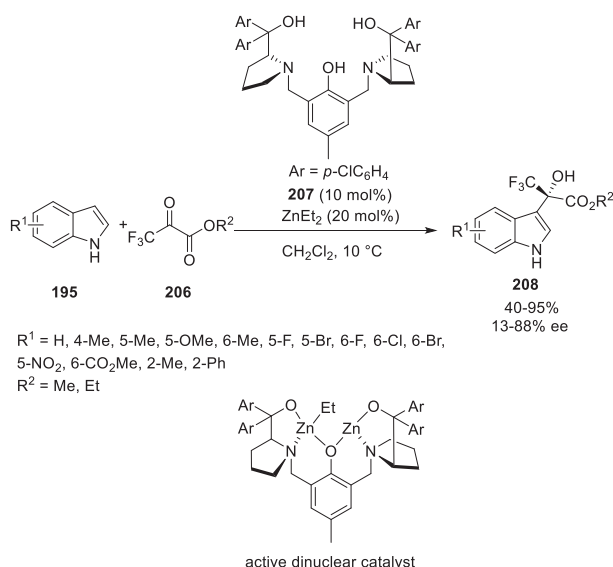
Scheme 69. Friedel-Crafts C3-alkylation of indoles with isatin-derived ketimines in the presence of a *N,N'*-dioxide ligand [100].

derivatives **192** were performed in the presence of enantiomeric ligand (*S,S*)-AzePhenol, leading to the corresponding enantiopure phosphates **193** (99% ee) in excellent yields (85–99%) albeit as diastereomeric mixtures (4–74% de).

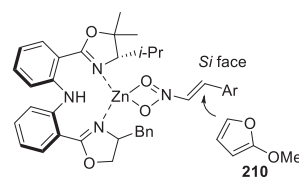
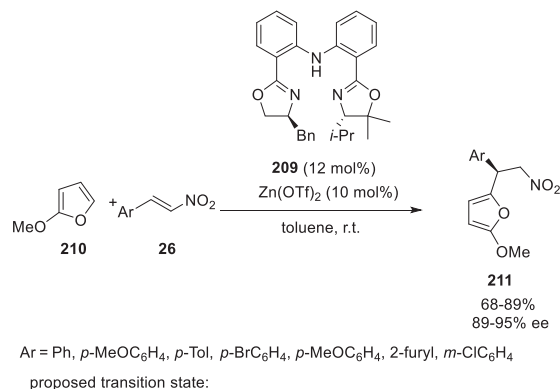
9. Friedel-Crafts reactions

The first enantioselective zinc-catalyzed Friedel-Crafts reaction was described by Zhou et al., in 2006 [95]. It involved indoles and nitrostyrene as substrates, being the two most studied partners in the asymmetric Friedel-Crafts reaction. The reaction occurred at the C3-position of indoles in the presence of a chiral bisoxazoline ligand with enantioselectivities of up to 90% ee. Ever since, other types of ligands have been successfully applied to this type of transformations. For example, chiral multidentate Schiff base ligand **194** was applied in 2015 by Bhanage et al. at 10 mol% of catalyst loading in combination of 10 mol% of $\text{Zn}(\text{OTf})_2$ in toluene at -15°C to promote the same Friedel-Crafts reaction (Scheme 65) [96]. Indeed, unprotected indoles **195** reacted with aromatic nitroalkenes **26** in the presence of piperidine as an additive to give the corresponding chiral indoles **196** in high yields (85–94%) and good enantioselectivities (69–76% ee).

Generally, Friedel-Crafts alkylations of indoles occur on the more nucleophilic C3 position of indoles. On the other hand, Friedel-Crafts

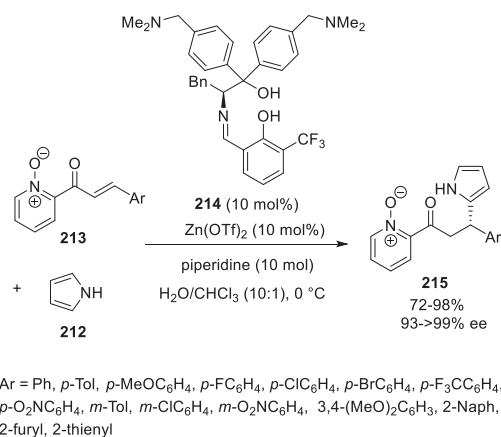


Scheme 70. Friedel-Crafts C3-alkylation of indoles with trifluoromethyl pyruvates in the presence of a ProPhenol derivative ligand [101].

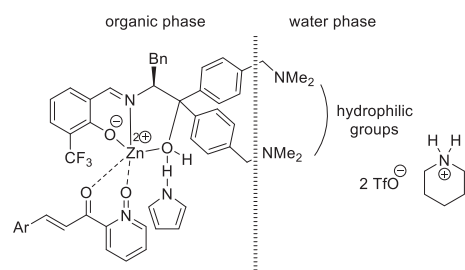


Scheme 71. Friedel-Crafts reaction of 2-methoxyfuran with aromatic nitrostyrenes in the presence of a bisoxazoline ligand [102].

del-Crafts reaction occurring at the less reactive C2 position of indoles to deliver biologically potential chiral indoles bearing C2-benzylic stereocenters remain rare. To fill this gap, Jia et al. reported in 2016 an enantioselective Friedel-Crafts C2-alkylation reaction of 3-substituted indoles **197** with nitroalkenes **26** catalyzed by a chiral zinc complex derived from bisoxazoline ligand **198** [97]. As illustrated in Scheme 66, the process furnished chiral indole derivatives **199** bearing C2-benzylic stereogenic centers in



proposed transition state:



Scheme 72. Friedel-Crafts reaction of pyrrole with 2-enoyl-pyridine *N*-oxides in the presence of a Schiff base ligand in aqueous media [103].

high yields (72–99%) and excellent enantioselectivities (90–95% ee).

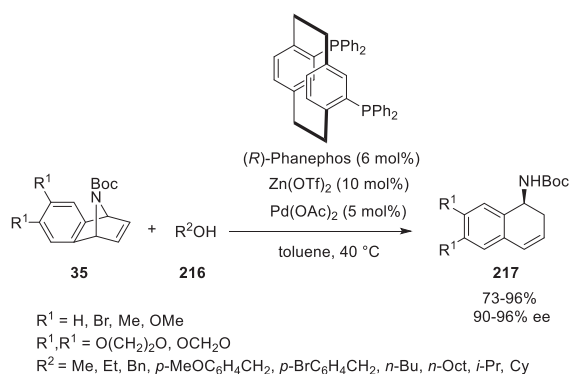
Later in 2019, Ramanathan et al. reported the first use of a chiral bipyridine ligand in asymmetric Friedel–Crafts C3-alkylation of unprotected indoles **195** with aromatic nitroalkenes **26** [98]. Indeed, the use of only 4 mol% of chiral bipyridine ligand **200** combined with 2 mol% of Zn(OTf)₂ allowed in toluene at 40 °C a range of chiral alkylated indole derivatives **196** to be synthesized in good to high yields (74–94%) and moderate to high ee values (61–91% ee), as shown in Scheme 67.

Earlier in 2016, asymmetric Friedel–Crafts reaction of unprotected indoles **195** were developed by Wang and Hua by using protected ethyl glyoxylate imine **201** as electrophile in the presence of Trost's dinuclear zinc complex derived from (*S,S*)-ProPhenol [99]. A series of 3-indolylglycine derivatives **202** were formed in low to excellent enantioselectivities (12–>99% ee) using 10 mol% of catalyst loading in THF at room temperature. As shown in Scheme 68, a wide range of substituents on the phenyl ring of indoles were compatible, providing the corresponding products **202** in moderate to high yields (36–85%).

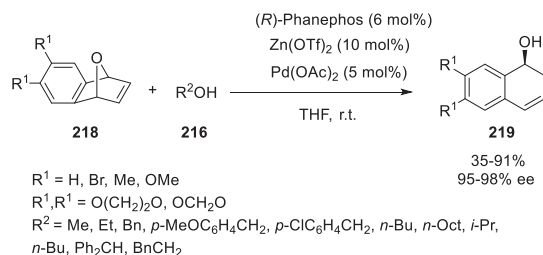
An enantioselective Friedel–Crafts reaction of unprotected indoles **195** with *N*-protected isatin-derived ketimines **203** was reported by Feng et al. in 2016 on the basis of an asymmetric catalysis with a chiral zinc complex in situ generated from 10 mol% of Zn(OTf)₂ and the same quantity of chiral *N,N'*-dioxide ligand **204** (Scheme 69) [100]. A series of chiral 3-indolyl-3-aminoxindoles **205** containing a tetrasubstituted stereocenter were obtained in good to high yields (63–99%) and enantioselectivities (73–96% ee). It must be noted that generally the enantioselectivities were found excellent (90–96% ee) excepted in the reactions of 7-methyl-substituted ketimine and 2-methyl indole which afforded the corresponding products with 74 and 73% ee, respectively.

In 2018, Wang and Yang disclosed the asymmetric Friedel–Crafts reaction of unprotected indoles **195** with trifluoromethyl pyruvates **206** (Scheme 70) [101]. Chiral ProPhenol derivative **207** was employed at 10 mol% of catalyst loading in combination with 20 mol% of ZnEt₂ in dichloromethane as solvent at 10 °C. The corresponding in situ generated chiral dinuclear complex promoted the alkylation, yielding chiral trifluoromethyl alcohol and indole-containing biological compounds **208** in moderate to excellent yields (40–95%) and variable enantioselectivities (13–88% ee).

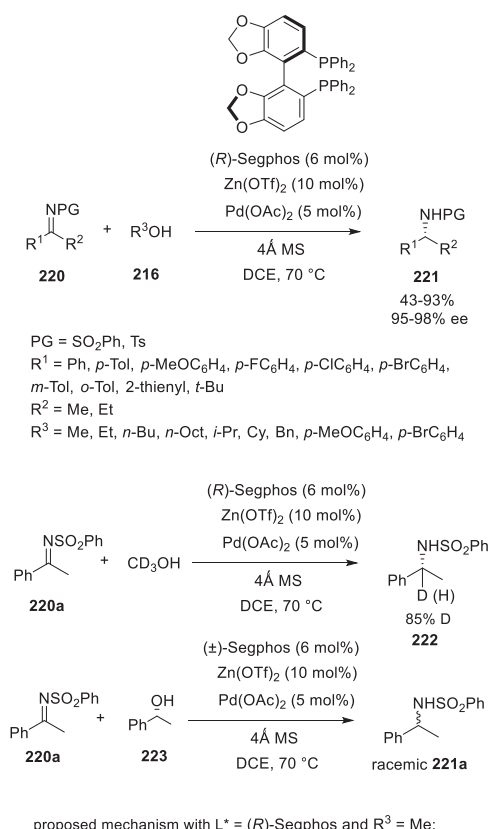
Earlier in 2015, these reactions were also investigated by Guiry et al. by using novel (*S*)-valine-derived bisoxazoline ligands, providing the alkylated products in moderate enantioselectivities (≤74% ee) [102]. However, when one of these ligands, namely **209**, was applied in the asymmetric Friedel–Crafts reaction of aromatic nitroalkenes **26** with 2-methoxyfuran **210**, the corresponding products **211** were formed in much better enantioselectivities



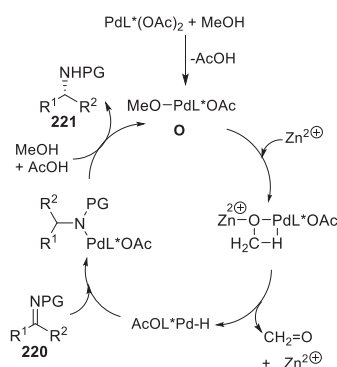
Scheme 73. Transfer hydrogenation of azabenzonorbornadienes with alcohols in the presence of a dual Zn/Pd catalyst system [104].



Scheme 74. Transfer hydrogenation of oxabenzonorbornadienes with alcohols in the presence of a dual Zn/Pd catalyst system [105].



proposed mechanism with $L^* = (R)\text{-Segphos}$ and $R^3 = \text{Me}$:



Scheme 75. Transfer hydrogenations of *N*-sulfonylimines with alcohols in the presence of a dual Zn/Pd catalyst system and (*R*)-Segphos [106].

(89–95% ee) combined with high yields (68–89%), as shown in Scheme 71. The stereoselectivity of the reaction can be explained by the transition state depicted in this Scheme in which the two oxazolinyl nitrogen atoms are coordinated to the zinc center and

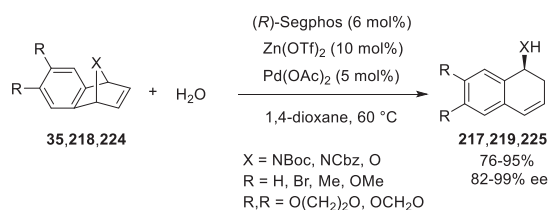
the nitro group of the nitroalkene coordinates through the two oxygen atoms to the Lewis acid center. This activates the nitroalkene to undergo a nucleophilic attack by the electron-rich arene. The attack occurs preferentially from the *Si* face due to the influence of the substituents on each of the oxazoline rings, providing chiral product **211**.

Examples of asymmetric Friedel–Crafts alkylations performed in aqueous media remain rare. In 2020, a highly enantioselective Friedel–Crafts reaction of pyrroles **212** with 2-enoyl-pyridine *N*-oxides **213** was achieved in a 10:1 mixture of water/chloroform as solvent by Wang and Yang (Scheme 72) [103]. The process was promoted by a chiral catalyst in situ generated from 10 mol % of Zn(OTf)₂ and 10 mol% of chiral multidentate Schiff base ligand **214** at 0 °C, allowing a range of chiral multifunctionalized Friedel–Crafts products **215** to be synthesized in uniformly excellent enantioselectivities (93–>99% ee) and high yields (72–98%). The authors proposed a transition state (Scheme 72) in which the two hydrophilic dimethylamino groups of the chiral ligand were dissolved in the water phase, while the 2-enoylpyridine *N*-oxide was activated through coordination to zinc in the catalyst complex, and the NH group of pyrrole served as a hydrogen bond-donating group to direct the alkylation at the *Si* face of the 2-enoylpyridine *N*-oxide, leading to chiral product **215**.

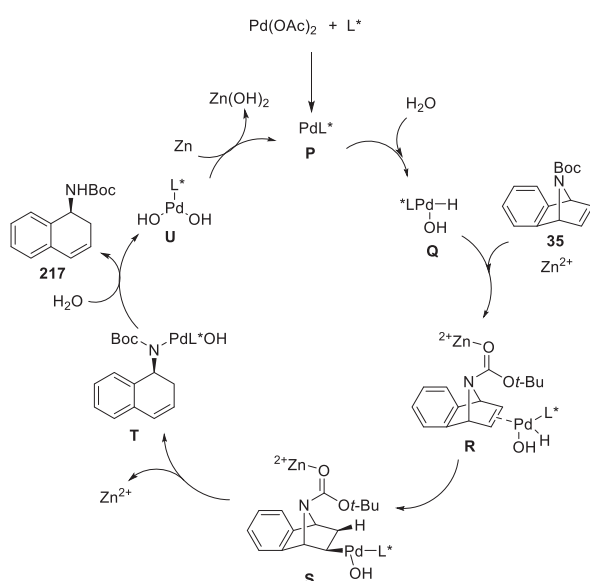
10. Reduction reactions

10.1. (Transfer) hydrogenation reactions

In 2016, a dual catalysis based on Zn/Pd was employed by Fan et al. in an enantioselective transfer hydrogenation of azaben-



proposed mechanism (with X = NBoc, R = H, L* = (R)-Segphos):



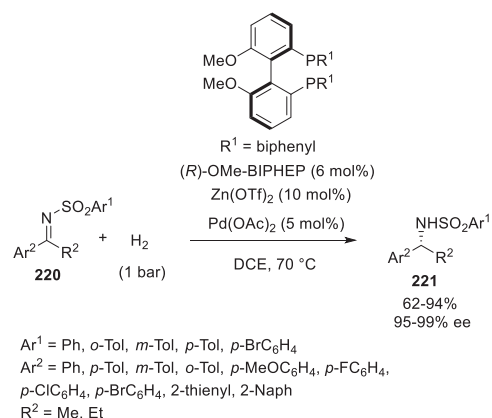
Scheme 76. Transfer hydrogenation of oxa- and azabenzonornadienes with water in the presence of (R)-Segphos [107].

zonornadienes **35** with alcohols **216** as reductants [104]. Good chemo-, regio-, and enantioselectivities were obtained when this reaction was catalyzed by a combination of 10 mol% of Zn(OTf)₂, 6 mol% of (R)-Phanephos as ligand, and 5 mol% of Pd(OAc)₂ in toluene at 40 °C (Scheme 73). A range of aliphatic alcohols were compatible, leading to chiral ring-opened amines **217** in uniformly excellent ee values (90–96% ee) and good to high yields (73–96%). The authors demonstrated that the alcohol partner was the hydrogen source. It must be noted that this work could also appear in Section 12 dealing with ring-opening reactions.

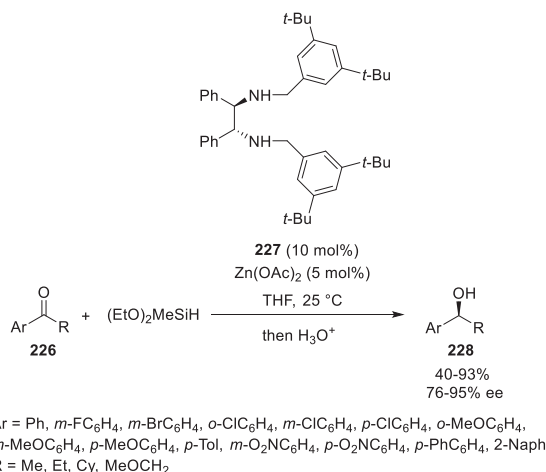
Later in 2017, the same dual Zn/Pd catalysis was applied to develop related asymmetric transfer hydrogenation of oxabenzonornadienes **218** with alcohols **216** (Scheme 74) [105]. Indeed, in the presence of the same quantities of Zn(OTf)₂, (R)-Phanephos and Pd(OAc)₂, a range of primary and secondary alcohols **216** reacted with variously substituted oxabenzonornadienes **218** to afford at room temperature in THF as solvent the corresponding almost enantiopure 1,2-dihydronaphth-1-ol products **219** (95–98% ee) in moderate to high yields (35–91%). This work could also appear in Section 12 highlighting ring-opening reactions.

A related Zn/Pd co-catalytic system was successfully employed by the same group in the asymmetric transfer hydrogenation reactions of *N*-sulfonylimines **220** with alcohols **216** (Scheme 75) [106]. Along with 10 mol% of Zn(OTf)₂ and 5 mol% of Pd(OAc)₂, was used 6 mol% of (R)-Segphos as optimal ligand. Various aliphatic and aromatic alcohols **216** reacted with a range of alkylsulfonylimines **220** in DCE at 70 °C to give the corresponding almost enantiopure amines **221** (95–98% ee) in moderate to high yields (43–93%). To get insight into the mechanism of the reaction, the authors investigated deuterium-labeling experiments. Indeed, the reaction of phenyl *N*-sulfonylimine **220a** (R¹ = Ph, R² = Me, PG = SO₂Ph) with CD₃OH (R³ = CD₃), resulted in the formation of the corresponding product **222** incorporating 85% deuterium at the benzylic position (Scheme 75). Furthermore, performing the reaction of the same phenyl *N*-sulfonylimine **220a** with enantiopure (R)-1-phenyl ethanol **223** in the presence of racemic Segphos as ligand, resulted in the formation of the corresponding racemic product **221a**. On the basis of these results, the authors assumed that the process was initiated from the [Pd–H] hydride intermediate **O** generated through dehydrogenation of the alcohol reagent rather than through metal alkoxide mechanism.

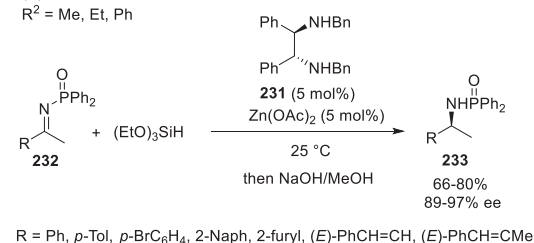
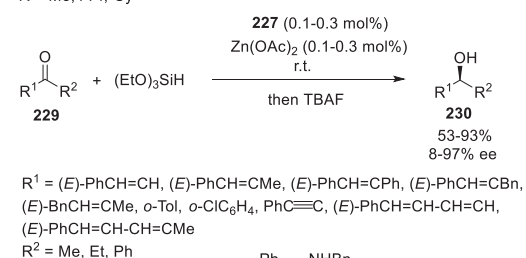
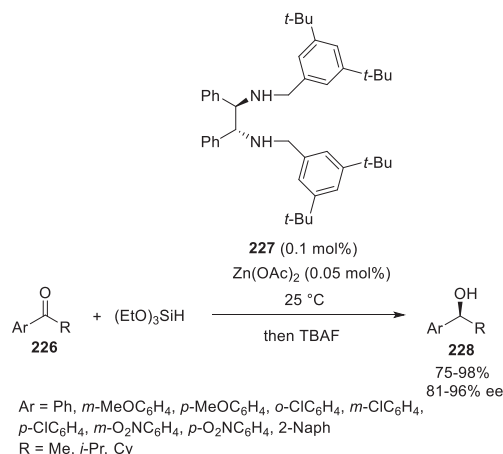
Involving the same dual catalyst system in 1,4-dioxane as solvent, these authors also accomplished asymmetric transfer hydrogenation of azabenzonornadienes **35**, **224** and oxabenzonornadienes **218** by using water as the sole hydrogen source



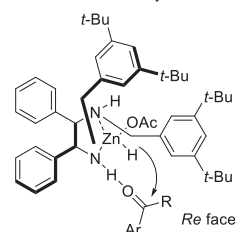
Scheme 77. Hydrogenation of *N*-sulfonylimines in the presence of (R)-OMe-BIPHEP [108].



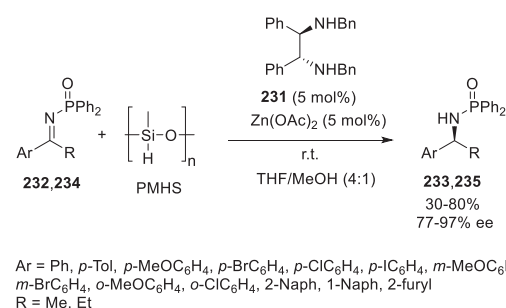
Scheme 78. Hydrosilylation of aromatic ketones in the presence of a 1,2-diamine ligand [110].



proposed transition state in the reaction of aryl ketones:



Scheme 79. Hydrosilylations of conjugated ketones and *N*-diphenylphosphinoylimines in the presence of 1,2-diamine ligands under solvent-free conditions [111].



Scheme 80. Hydrosilylation of *N*-diphenylphosphinoylimines with PMHS in the presence of a 1,2-diamine ligand [112].

[107]. As depicted in Scheme 76, a range of chiral 1,2-dihydronaphthalenes **217**, **219**, **225** were synthesized in both high yields (76–95%) and ee values (82–99% ee). Based on deuterium-labeling experiments, the mechanism depicted in Scheme 76 was proposed. It began with the coordination of (*R*)-Segphos to Pd(OAc)₂ to generate chiral palladium catalyst **P**. Then, the oxidative addition of water to complex **P** gave intermediate **Q**, which further coordinated the azabenzonorbornadiene substrate and zinc ion to provide intermediate **R**. The subsequent insertion of the alkene to the Pd–H bond led to intermediate **S**. Next, the β-elimination of nitrogen afforded ring-opened intermediate **T**, the hydration of which provided the final product. Finally, the reduction of **U** by zinc metal regenerated chiral palladium catalyst **P**. This work could also appear in Section 12 dealing with ring-opening reactions.

In 2018, Fan and Laishram described an efficient synthesis of chiral sultams **221** employing Zn(OTf)₂ and Pd(OAc)₂ as co-catalysts, evolving through asymmetric hydrogenation of a range of *N*-sulfonylimines **220** under ambient pressure of hydrogen [108]. As illustrated in Scheme 77, the reaction employed (*R*)-OMe-BIPHEP as optimal ligand, which allowed a wide range of almost enantiopure amines **221** (95–99% ee) to be prepared in good to high yields (62–94%).

10.2. Hydrosilylations of carbonyl compounds and derivatives

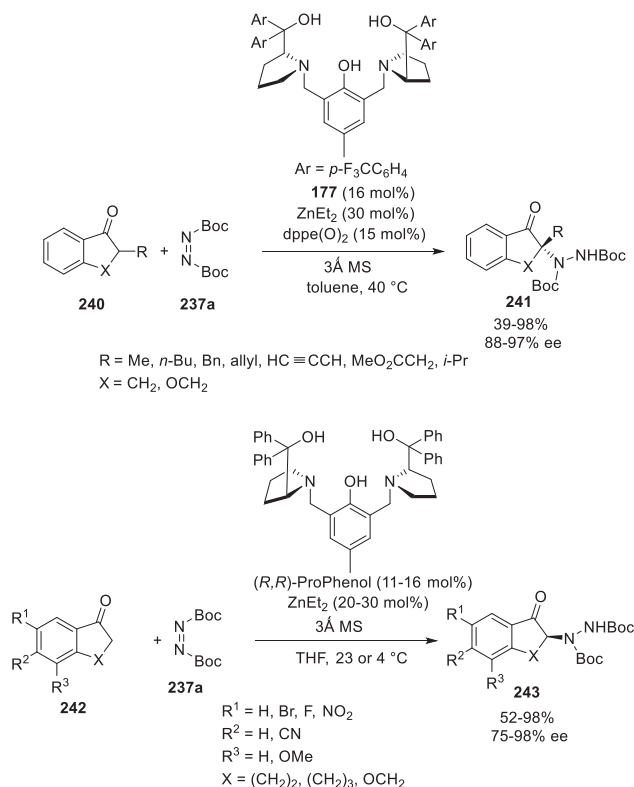
The asymmetric hydrosilylation of ketones followed by hydrolysis constitutes a direct route to chiral alcohols [109]. So far, most of chiral zinc catalysts employed in these transformations have been prepared from ZnEt₂. In contrast, hydrosilylation catalyzed by inorganic Zn salts, such as cheap Zn(OAc)₂, is still undeveloped. To fill this gap, Mlynarski et al. disclosed in 2015 the first example of highly enantioselective hydrosilylation of aromatic ketones **226** promoted by a chiral complex in situ generated from 5 mol% of Zn(OAc)₂ and 10 mol% of chiral 1,2-diamine ligand **227** (Scheme 78) [110]. The reaction carried out in THF at 25 °C led to the formation, after subsequent hydrolysis of the formed intermediate silyl ethers, to chiral alcohols **228** in good to high yields (40–93%) and high enantioselectivities (76–95% ee). The catalyst system was compatible with a broad range of aryl ketones, providing better enantioselectivities than those obtained by using previously investigated diethylzinc complexes.

With the aim of finding even greener reaction conditions for these hydrosilylations, the same authors developed in 2016 a more

convenient protocol based on the use of unprecedented very low catalyst loadings and under solvent-free conditions [111]. Indeed, the enantioselective hydrosilylation of aromatic ketones **226** could

Scheme 81. α -Amination of β -ketocarbonyl compounds with dialkyl azodicarboxylates in the presence of a phenanthroline ligand [116].

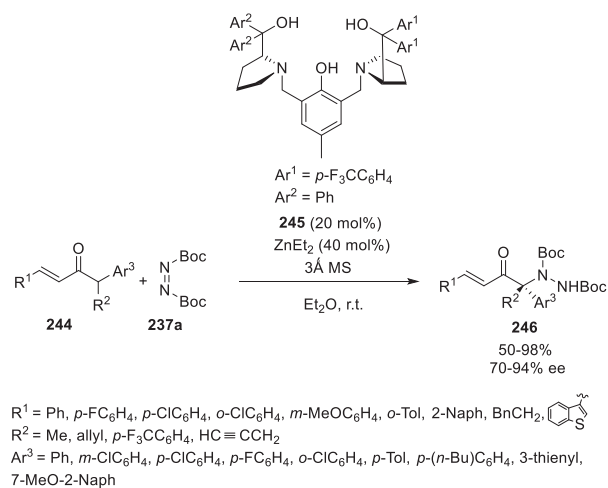
be realized in the presence of as low as 0.05 mol% of $\text{Zn}(\text{OAc})_2$ and 0.1 mol% of the same chiral 1,2-diamine ligand **227** at 25 °C under neat conditions (Scheme 79). This green and remarkable process employed $(\text{EtO})_3\text{SiH}$ as silane and provided, after subsequent silyl deprotection by treatment with TBAF, a range of aromatic chiral alcohols **228** in both uniformly high yields (75–98%) and ee values (81–96% ee). The catalyst system could also be applied to the asymmetric hydrosilylation of more challenging unsaturated ketones **229**, which afforded in the presence of 0.1–0.3 mol% of the same chiral zinc catalyst the corresponding alcohols **230** in good to high yields (53–93%) and variable enantioselectivities (8–97% ee). Moreover, in the presence of a combination of 5 mol% of related chiral 1,2-diamine ligand **231** with the same quantity of $\text{Zn}(\text{OAc})_2$ under solvent-free conditions, various conjugated *N*-



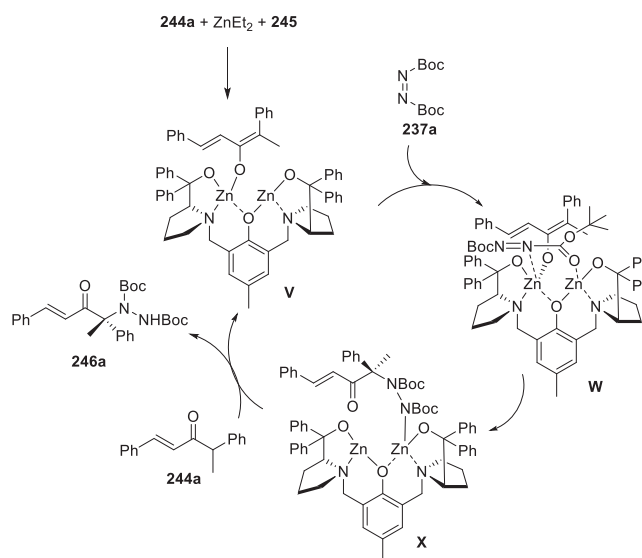
Scheme 82. α -Aminations of branched and unbranched aromatic ketones with di-*tert*-butyl azodicarboxylate in the presence of (*R,R*)-ProPhenol (derivative) ligands [117].

diphenylphosphinoylimines **232** could be reduced into the corresponding chiral amines **233** with good yields (66–80%) and uniformly high enantioselectivities (89–97% ee). A possible transition state for the hydrosilylation of aryl ketones **226** in the presence of ligand **227** is depicted in [Scheme 79](#). It involves the formation of a hydrogen bond between the amino group of the active Zn–H catalyst and the carbonyl group of the ketone. The relative orientation of the substrate is determined by steric repulsion between the bulky 3,5-di-*tert*-butylbenzene moiety of the ligand and the larger substituent adjacent to the carbonyl group of the ketone substrate. In this favored approach, zinc hydride attacks the ketone from the *Re* face, which results in the formation of chiral product **228**.

The asymmetric hydrosilylation of a range of *N*-diphenylphosphinoylimines **232**, **234** catalyzed by 5 mol% of the same catalyst system (ligand **231**) was also performed by using inexpensive polymethylhydrosilane (PMHS) as hydrosilane in a 4:1 mixture of THF and methanol as solvent [112]. At room temperature, a series of chiral (hetero)aromatic *N*-diphenylphosphinoylamines **233**, **235** were synthesized in low to



proposed mechanism ($R^1 = Ar^3 = Ph$, $R^2 = Me$):



Scheme 83. α -Amination of acyclic α -branched ketones with di-*tert*-butyl azodicarboxylate in the presence of a non- C_2 -symmetric ProPhenol derivative ligand [118].

good yields (30–80%) and high ee values (77–97% ee), as shown in Scheme 80. In addition, novel chiral C₂-symmetric bisoxazoline ligands immobilized on mesoporous silica SBA-15 were synthesized by Le Roux et al. in 2015 and further used in the asymmetric hydrosilylation of acetophenone in the presence of ZnEt₂ as precatalyst [113]. However, only moderate enantioselectivities ($\leq 50\%$ ee) were achieved in these reactions.

11. α -Functionalizations of carbonyl compounds

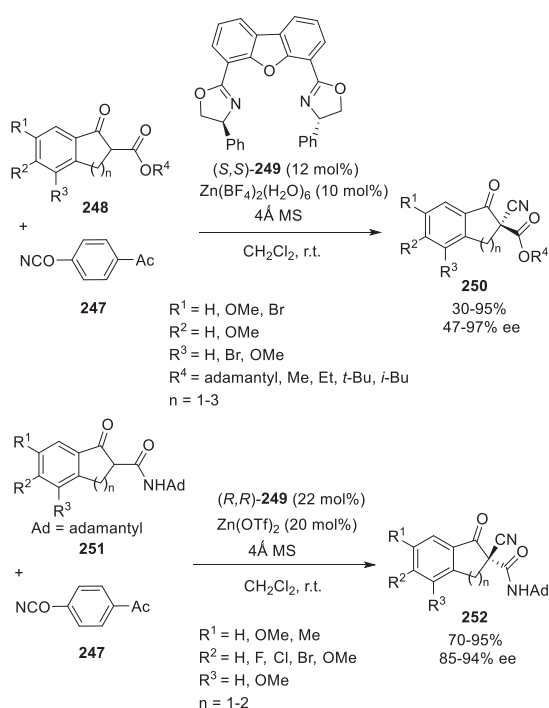
11.1. α -Aminations

Chiral α -amino acid derivatives are widely present in nature [114]. Among synthetic strategies to reach these important molecules, asymmetric electrophilic α -amination of β -ketocarbonyl compounds is one of the most direct routes [115]. Only very rare versions of these reactions using chiral zinc catalysts have been developed so far. In order to fill this gap, Naganawa and Nishiyama reported in 2015 asymmetric α -amination of β -ketocarbonyl compounds **236** using dialkyl azodicarboxylates **237** as electrophilic nitrogen sources catalyzed by a combination of 10 mol% of Zn(OTf)₂ and 11 mol% of axially chiral phenanthroline ligand **238** (Scheme 81) [116]. The reaction afforded at room temperature by using DCE as solvent the corresponding chiral α -amino- β -ketocarbonyl compounds **239** in both high yields (75–99%) and enantioselectivities (81–93% ee). With the aim of extending the scope of the reaction, the authors investigated acyclic β -ketoesters as substrates albeit without success.

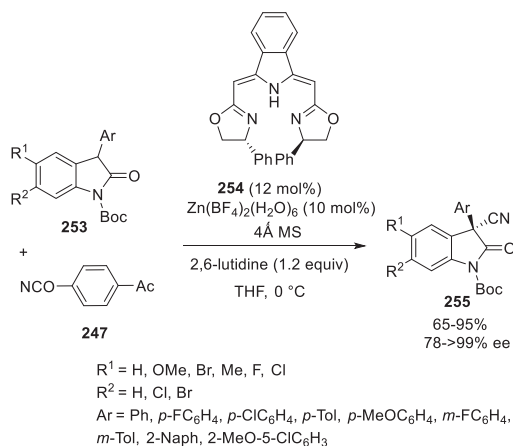
In 2018, Trost et al. reported an asymmetric amination reaction of unactivated aromatic ketones using di-*tert*-butyl azodicarboxylate **237a** as electrophilic nitrogen source [117]. As depicted in Scheme 82, a range of 2-substituted indanones **240** (X = CH₂) reacted with di-*tert*-butyl azodicarboxylate **237a** in the presence of 16 mol% of a (*S,S*)-ProPhenol derivative **177** as ligand, 30 mol% of ZnEt₂, and 15 mol% of 1,2-bis(diphenylphosphino)ethane (dppe(O)₂) as additive in toluene at 40 °C to afford the correspond-

ing chiral hydrazines **241** in moderate to quantitative yields (39–98%) and uniformly excellent enantioselectivities (88–97% ee). Especially, indanones bearing a linear alkyl chain at the 2-position provided the best results (77–98% yield, 90–97% ee) while the presence of an *i*-propyl group in this position resulted in both lower yield (39%) and ee value (88% ee). The presence of various functional groups, such as esters, alkenes and terminal alkynes, were tolerated on the alkyl chain (R). Furthermore, a six-membered aromatic ketone (X = OCH₂) was compatible, also providing good results (61% yield and 92% ee). Then, the authors employed (*R,R*)-ProPhenol as ligand in a related reaction between di-*tert*-butyl azodicarboxylate **237a** and unbranched 1-tetralones **242** (X = (CH₂)₂), eventually substituted at the 5-, 6- and 7-positions, as nucleophile partners. It yielded the corresponding chiral hydrazines **243** in both high yields (81–98%) and enantioselectivities (90–96% ee). The scope of the process was extended to 1-chromanone (X = OCH₂) and 1-benzosuberone (X = (CH₂)₃) which led to the corresponding products with moderate to high yields (52–98%) and good to high ee values (75–98% ee).

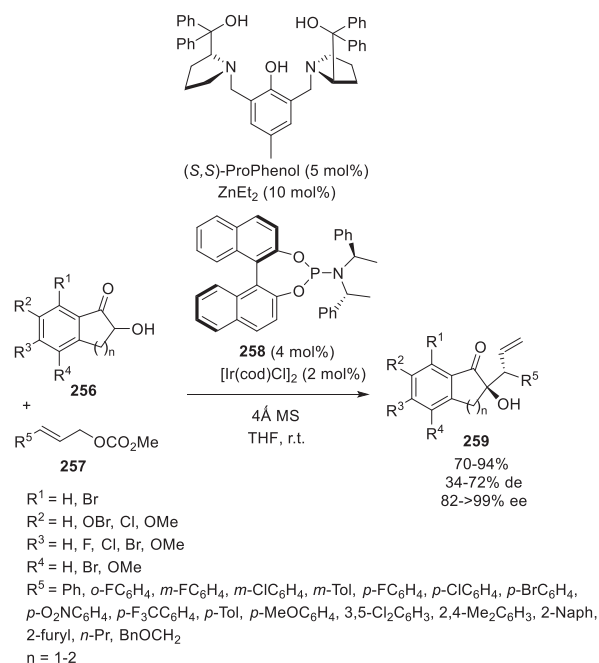
Later in 2019, the same authors disclosed the first use of challenging acyclic α -branched ketones **244** as nucleophiles in comparable electrophilic hydrazination (Scheme 83) [118]. In this case, the optimal ligand was a non-C₂-symmetric ProPhenol derivative **245** (20 mol%) associated to ZnEt₂ (40 mol%) in diethyl ether as solvent. The amination of a range of acyclic α -branched ketones **244** with di-*tert*-butyl azodicarboxylate **237a** resulted in the formation of chiral hydrazines **246** in good to quantitative yields (50–98%) and high enantioselectivities (70–94% ee). The catalyst system tolerated the presence of electron-donating and electron-withdrawing substituents on the aromatic and heteroaromatic rings of R¹. Moreover, an alkyl-substituted substrate (R¹ = BnCH₂) was also compatible, providing the corresponding product in moderate yield (50%) and good ee value (80% ee). Various substituted aromatic groups at Ar³ were also tolerated but the lowest enantioselectivity (70% ee) was obtained in the reaction of an heteroaromatic group (Ar³ = 3-thienyl). Furthermore, substitution at R² was not limited to methyl group since longer alkyl chains eventually including functional groups, such as alkenes and terminal alkynes, reacted smoothly, however, with lower yields (58–64%) than those observed with methyl substitution. The resulting hydrazines could be chemoselectively cleaved to the corresponding amines, constituting potential building blocks for medicinal synthesis. To explain the stereochemical outcome of the reaction, the authors proposed the catalytic cycle depicted in Scheme 83. After formation of the initial dinuclear zinc catalyst,



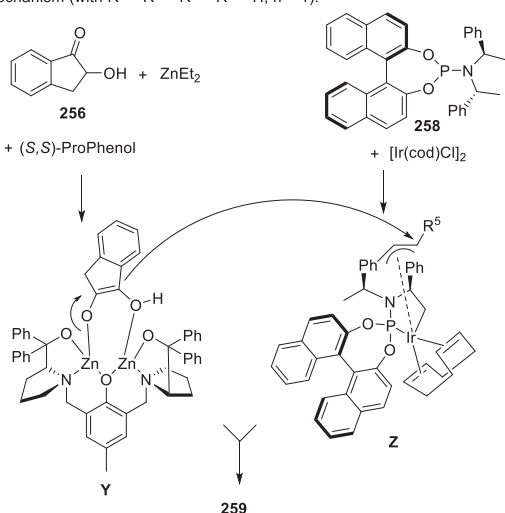
Scheme 84. α -Cyanations of β -ketoesters and β -ketoamides with *p*-acetylphenylisocyanate in the presence of a bisoxazoline ligand [119].



Scheme 85. α -Cyanation of 3-aryl-substituted oxindoles with *p*-acetylphenylisocyanate in the presence of a bisoxazoline ligand [120].



mechanism (with R¹ = R² = R³ = R⁴ = H, n = 1):

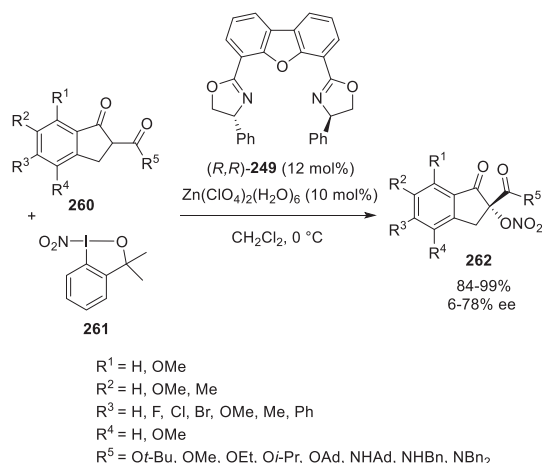


Scheme 86. α -Alkylation of unprotected α -hydroxy indanones with allyl methyl carbonates in the presence of a dual Zn/Ir catalyst system [121].

deprotonation of the ketone resulted in the formation of intermediate **V**. Then, coordination of the electrophile via two-point binding across the two zinc centers generated complex **W** in which the *E*-enolate occurred to minimize 1,3-diaxial strain between the enolate and the bulky Boc group of the di-*tert*-butyl azodicarboxylate. The resulting hydrazine complex **X** served as a base to deprotonate a new molecule of ketone, releasing the final product and closing the catalytic cycle.

11.2. Other α -functionalizations

Along with α -aminations, asymmetric α -cyanations of β -ketocarbonyl compounds have been developed in the presence of chiral zinc catalysts. For example, Chen et al. reported a novel methodology for enantioselective α -cyanation of β -ketoesters which was based for the first time on the use of *p*-acetylphenyl cyanate **247** as cationic cyano source [119]. As illustrated in Scheme 84, the reaction of the latter with a series of β -ketoesters

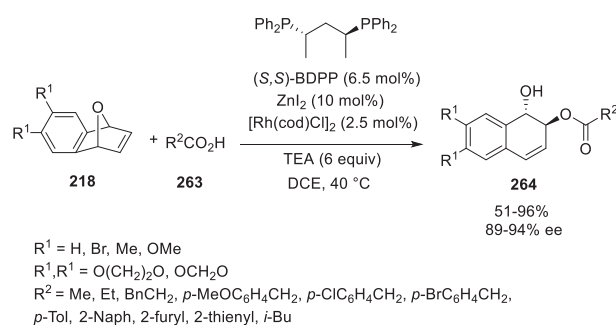


Scheme 87. α -Nitroxylation of indanone-derived β -keto esters/amides with a nitroxyating reagent in the presence of a bisoxazoline ligand [122].

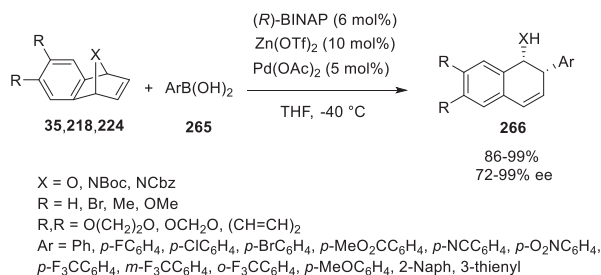
248 performed at room temperature in dichloromethane as solvent in the presence of a chiral zinc catalyst in situ generated from 10 mol% of Zn(BF₄)₂(H₂O)₆ and 12 mol% of bisoxazoline ligand (*S,S*)-249 yielded the corresponding chiral α -nitriles **250** in both moderate to high yields (30–95%) and enantioselectivities (47–97% ee). Actually, five- and six-membered β -ketoesters (n = 1–2) provided the highest ee values while the reaction of a seven-membered substrate (n = 3) occurred with only 47% ee and 30% yield. As an extension, the authors could apply enantiomeric ligand (*R,R*)-249 to the related asymmetric α -cyanation of both five- and six-membered β -ketoamides **251**, which were converted into the corresponding α -nitriles **252** with uniformly high enantioselectivities (85–94% ee) combined with good to excellent yields (70–95%).

In the same context, the first example of catalytic asymmetric cyanation of 3-aryl-substituted oxindoles **253** was disclosed by these authors using the same cyano source **247** (Scheme 85) [120]. Employing chiral pincer bisoxazoline **254** (12 mol%) in combination with Zn(BF₄)₂(H₂O)₆ as precatalyst (10 mol%) in the presence of 2,6-lutidine as a base in THF as solvent, a range of chiral 3-aryl-3-cyano oxindoles **255** were synthesized with both good to high yields (65–95%) and enantioselectivities (78–>99% ee). The poorest result (65% yield, 78% ee) was obtained in the reaction of a disubstituted aromatic group (Ar = 2-MeO-5-ClC₆H₃).

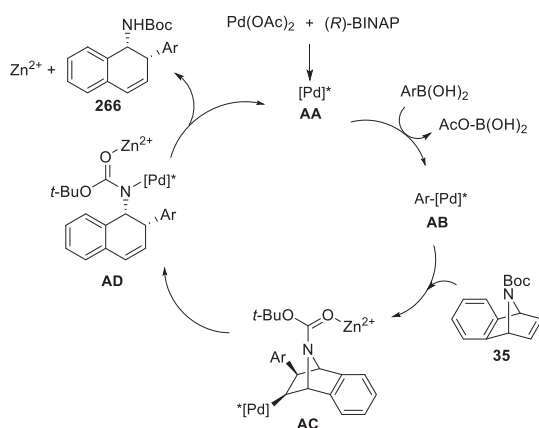
In 2017, Zhang et al. described enantioselective α alkylation of unprotected α hydroxy indanones **256** (n = 1) with allyl methyl carbonates **257** on the basis of a dual Zn/Ir catalysis (Scheme 86) [121]. Indeed, the catalyst system was composed of a chiral zinc complex derived from 10 mol% of ZnEt₂ and 5 mol% of (*S,S*)-ProPhenol as ligand and a chiral iridium catalyst in situ generated



Scheme 88. Ring-opening reaction of oxabenzonorbornadienes with carboxylic acids in the presence of a dual Zn/Rh catalyst system [123].

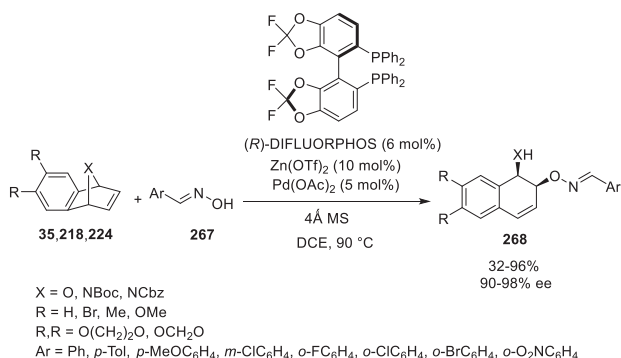


proposed mechanism (with R = H, X = NBoc):



Scheme 89. Ring-opening reaction of oxa- and azabenzonorbomadienes with aryl boronic acids in the presence of a dual Zn/Pd catalyst system [124].

from 2 mol% of $[\text{Ir}(\text{cod})\text{Cl}]_2$ and 4 mol% of chiral phosphoramidite ligand **258**. When the latter was used at room temperature in THF as solvent, a range of variously substituted chiral α hydroxy indanones **259** containing a vicinal stereocenter were synthesized with good to high yields (70–94%), low to good diastereoselectivities (34–72% de) and high enantioselectivities (82–>99% ee). Moreover, an α hydroxy tetralone ($n = 2$) was tolerated, yielding the corresponding α -allylated product in 92% yield, 34% de and 96% ee. The role of the multicatalysis is illustrated in Scheme 86. The α -hydroxy indanone coordinated to the chiral dinuclear zinc catalyst with the two O atoms of the carbonyl and the hydroxyl group, separately chelated to the two distinct zinc atoms, facilitating enolization. In the same time, the chiral iridium catalyst derived from $[\text{Ir}(\text{cod})\text{Cl}]_2$ and chiral phosphoramidite ligand **258** interacted with the allylic methyl carbonate to give allyl iridium



Scheme 90. Ring-opening reaction of oxa- and azabenzonorbomadienes with aromatic oximes in the presence of a dual Zn/Pd catalyst system [125].

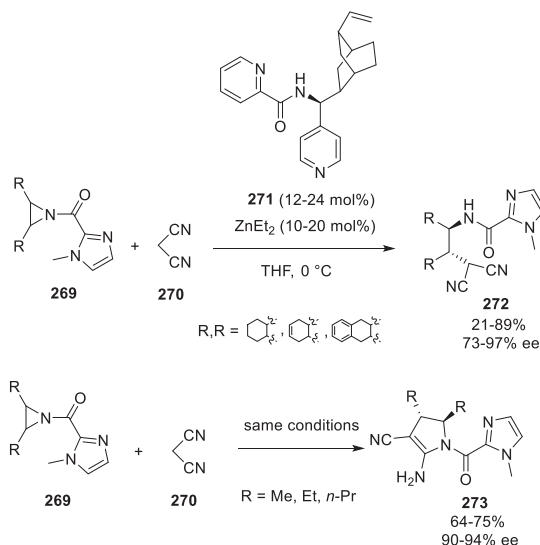
intermediate **Z** which was attacked by enolate **Y** to afford the final product.

In 2020, Deng et al. described the first example of asymmetric nitroxylation of 1,3-dicarbonyl compounds, allowing the synthesis of chiral organic nitrates [122]. As depicted in Scheme 87, the reaction of a range of indanone-derived β -keto esters **260** ($R^5 = \text{Ot-Bu, OMe, OEt, Oi-Pr, OAd}$) with nitrooxylating reagent **261** performed at 0 °C in dichloromethane as solvent and in the presence of a chiral zinc catalyst derived from 12 mol% of bisoxazoline (*R,R*)-**249** and 10 mol% of cheap $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ gave access to the corresponding α -nitrooxy β -keto esters **262** in homogeneous high yields (84–99%) and low to good enantioselectivities (6–78% ee). The best ee values (40–78% ee) were achieved in the reaction of indanone-derived *tert*-butyl β -keto esters bearing different substituents (Me, OMe, F, Cl, Br, Ph) on the phenyl ring. The stereocontrol of the reaction was found highly dependent to the presence of a *tert*-butyl on the ester group. Indeed, methyl, ethyl, isopropyl but also adamantyl esters provided much lower enantioselectivities (6–24% ee) than *tert*-butyl esters. Furthermore, the scope of the process could be extended to indanone-derived β -keto amides ($R^5 = \text{NHBn, NHAd, NBn}_2$) which afforded to the corresponding products **262** in high yields (84–91%) albeit with uniformly low enantioselectivities (6–20% ee).

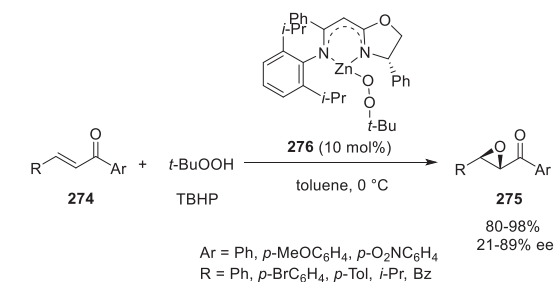
12. Ring-opening reactions

In 2017, Fan and Chen applied a Zn/Rh dual catalyst system to enantioselective ring-opening reaction of oxabenzonorbomadienes **218** with aromatic as well as aliphatic carboxylic acids **263** [123]. Carried out in DCE at 40 °C in the presence of 10 mol% of ZnI_2 , 2.5 mol% of $[\text{Rh}(\text{cod})\text{Cl}]_2$ and 6.5 mol % of chiral biposphine (*S,S*)-BDPP, the reaction resulted in the formation of chiral hydronaphthalenes **264** in uniformly excellent ee values (89–94% ee) and moderate to excellent yields (51–96%), as depicted in Scheme 88.

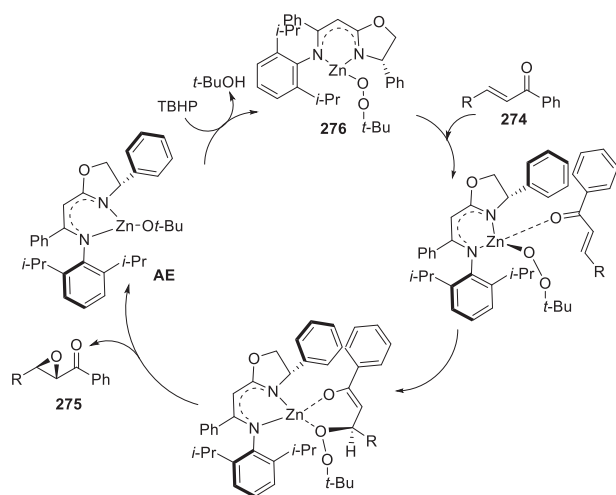
The same group also described asymmetric ring opening reactions of aza- and oxabenzonorbomadienes **35, 218, 224** with aryl boronic acids **265** by using a Zn/Pd dual catalyst system [124]. As shown in Scheme 89, a combination of 10 mol% of $\text{Zn}(\text{OTf})_2$, 6 mol% of (*R*)-BINAP and 5 mol% of $\text{Pd}(\text{OAc})_2$ was applied to promote these reactions which delivered a wide variety of chiral



Scheme 91. Ring-opening reactions of aziridines with malononitrile in the presence of a cinchona alkaloid ligand [126].



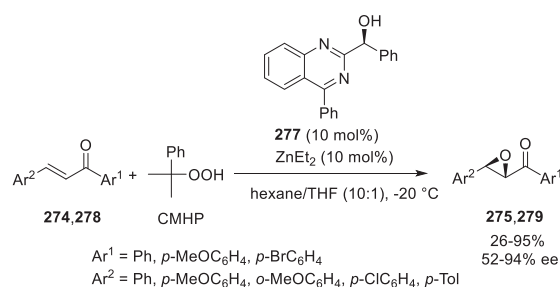
proposed mechanism (with Ar = Ph):



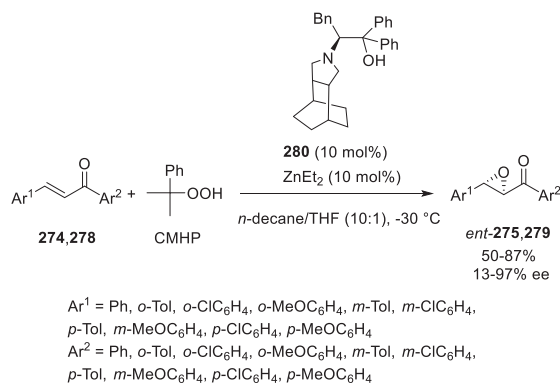
Scheme 92. Epoxidation of α,β -unsaturated ketones in the presence of a C_1 -symmetric enaminoxazoline zinc *tert*-butyl peroxide-based catalyst [129].

hydronaphthalene products **266** in homogeneous high yields (86–99%) and good to excellent enantioselectivities (72–99% ee). The mechanism depicted in [Scheme 89](#) is initiated by the coordination of Pd(OAc)₂ with (*R*)-BINAP to give the corresponding chiral palladium catalyst **AA**. Then, transmetalation of arylboronic acid generates arylpalladium intermediate **AB**. A subsequent insertion of azabenzonorbornadiene **35** into the carbon–palladium bond results in the formation of intermediate **AC**. Then, β -elimination of nitrogen opens the pyrrolidine ring and yields the ring-opened species **AD**. Finally, hydrolysis of the latter gives the final product.

In 2019, asymmetric ring-opening reactions of oxazabenzonorbornadienes **35**, **218**, **224** were also achieved by using aromatic oximes **267** as nucleophiles ([Scheme 90](#)) [125]. In this case, the employed dual Zn/Pd catalyst system contained 10 mol % of Zn(OTf)₂, 6 mol % of (*R*)-DIFLUORPHOS as ligand, and 5 mol % of Pd(OAc)₂. Performed in DCE as solvent, the process stereoselec-



Scheme 93. Epoxidation of chalcones in the presence of a 4-phenylquinazolinol ligand [84].



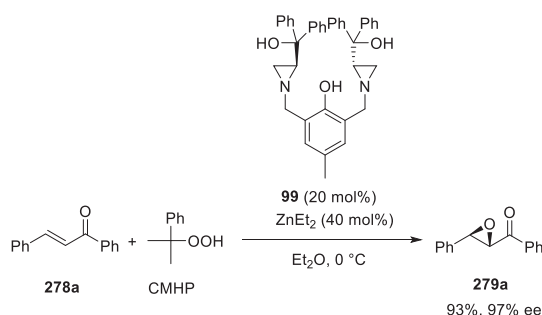
Scheme 94. Epoxidation of chalcones in the presence of a pyrrolidine alcohol ligand [130].

tively afforded at 90 °C the corresponding *cis*-products **268** in moderate to quantitative yields (32–96%) and uniformly excellent ee values (90–98% ee).

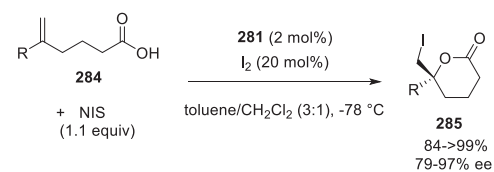
Earlier in 2017, Nakamura et al. developed the first catalytic desymmetrization of protected aziridines **269** with malononitrile **270** using 12–24 mol % of a cinchona alkaloid zinc catalyst derived from ligand **271** and ZnEt₂ [126]. As illustrated in [Scheme 91](#), the reaction of aziridines **269** having six-membered ring structures afforded by reaction with malononitrile **270** the corresponding chiral products **272** with high enantioselectivities (73–97% ee) and low to high yields (21–89%). Acyclic aziridines were also compatible substrates, leading in this case to chiral 2,3-dihydro-1H-pyrrole products **273** formed by subsequent intramolecular nucleophilic addition of amide nitrogen to the cyano group. These cyclic products were all obtained with excellent ee values (90–94% ee) combined with good yields (64–75%). These latter results could also be situated in [Section 15](#) dealing with domino and tandem reactions since they involve a domino ring-opening/cyclization reaction.

13. Epoxidations

The asymmetric epoxidation of olefins is a powerful tool to synthesize chiral epoxides, which constitute the structure of many biologically active compounds and synthetic intermediates [127]. Especially, the enantioselective epoxidation of α,β -unsaturated ketones is challenging because it offers an efficient route to many useful chiral products through further functionalization [128]. In 2016, Jurczak and Lewinski reported enantioselective epoxidation of various α,β -unsaturated ketones **274** into the corresponding chiral epoxides **275** promoted by novel zinc alkyl peroxides supported by C_1 -symmetric *N,N*-bidentate ligands [129]. Among them, chiral

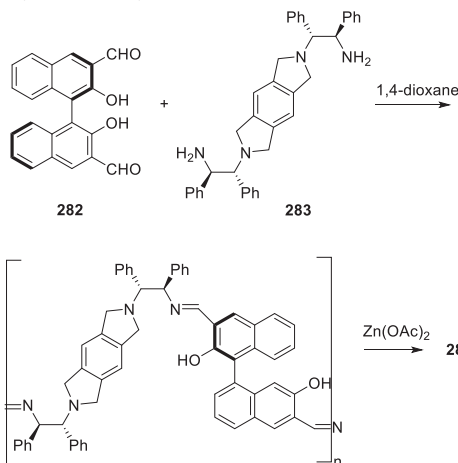


Scheme 95. Epoxidation of chalcone in the presence of an aziridine alcohol ligand [58].



R = Ph, *p*-Tol, *p*-FC₆H₄, *m*-Tol, *p*-ClC₆H₄, *p*-BrC₆H₄, Me, Cy

Synthesis of catalyst **281**:



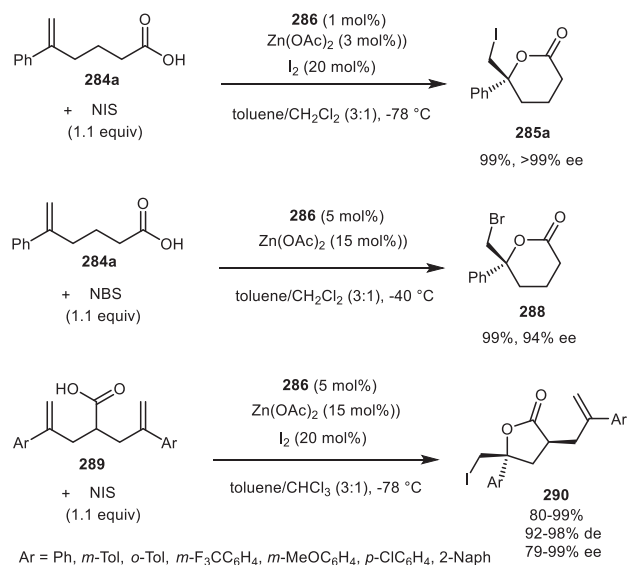
Scheme 96. Iodolactonization of 5-substituted hex-5-enoic acids in the presence of a poly-Zn₃(OAc)₄-3,3'-bis(aminoimino)binaphthoxide catalyst [131].

enaminoxazolinane zinc *tert*-peroxide **276**, in situ prepared in toluene from Zn(*t*-Bu)₂, *tert*-butyl hydroperoxide (TBHP), and the corresponding chiral *N,N*-bidentate ligand, was found to efficiently promote the epoxidation of both aliphatic and aromatic α,β -unsaturated ketones in high yields (80–98%) and generally good enantioselectivities (56–89% ee). In only one case of aliphatic substrate (R = *i*-Pr), a low ee value was observed (21% ee). In the catalytic cycle highlighted in Scheme 92, the first step consisted in the coordination of the carbonyl oxygen of the enone to zinc atom, followed by a nucleophilic attack of oxygen from the *Si* face of the activated enone, leading to the final epoxide. The cycle was completed by exchanging the O-*t*-Bu group in intermediate **AE** by a O-O-*t*-Bu group arisen from TBHP.

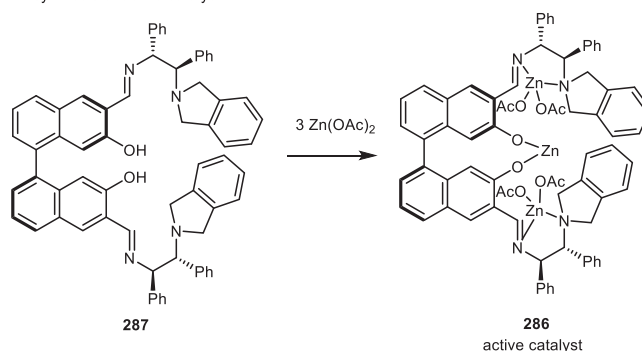
The same year, Ulukanli et al. reported the synthesis of novel 4-phenylquinazolinol ligands to be investigated in such reactions [84]. Among them, ligand **277** was found optimal to catalyze at 10 mol% of catalyst loading in a 10:1 mixture of hexane and THF as solvent the asymmetric epoxidation of chalcones **274**, **278** with cumene hydroperoxide (CMHP) as oxidant (Scheme 93). The corresponding chiral epoxides **275**, **279** were produced in low to excellent yields (26–95%) and variable enantioselectivities (52–94% ee).

In 2017, these reactions were also studied by Kilic et al. by using chiral pyrrolidine alcohol ligand **280** (Scheme 94) [130]. In the presence of 10 mol% of this ligand combined with the same quantity of ZnEt₂ in a 10:1 mixture of *n*-decane and THF as solvent, a series of variously substituted chalcones **274**, **278** were epoxidized with CMHP as oxidant at –30 °C into the corresponding chiral epoxides *ent*-**275**, **279** with good yields (50–87%) and low to excellent enantioselectivities (13–97% ee).

The same year, Rachwalski et al. reported the synthesis of novel chiral aziridine alcohol ligands which were investigated in different zinc-catalyzed asymmetric transformations, including enantioselective epoxidation of chalcone **278a** into chiral epoxides **279a** (Scheme 95) [58]. The authors selected ligand **99** as optimal to be used at 20 mol% of catalyst loading in combination with



synthesis of active catalyst:



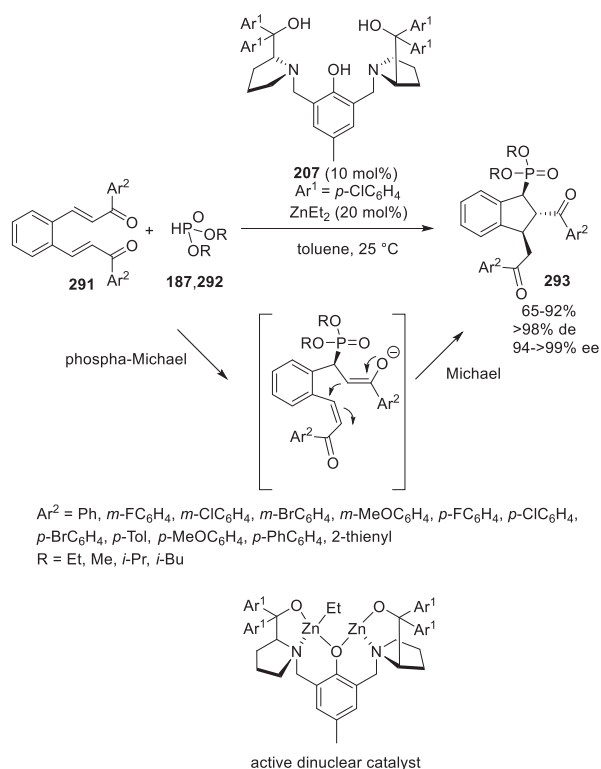
Scheme 97. Halolactonizations of 5-phenyl hex-5-enoic acid and diallyl carboxylic acids in the presence of a Zn₃(OAc)₄-3,3'-bis(aminoimino)binaphthoxide catalyst [132].

40 mol% of ZnEt₂ in the epoxidation of chalcone **278a** with CMHP as oxidant in diethyl ether as solvent. Carried out at 0 °C, the oxidation provided both excellent yield (93%) and ee value (97% ee).

14. Halolactonizations

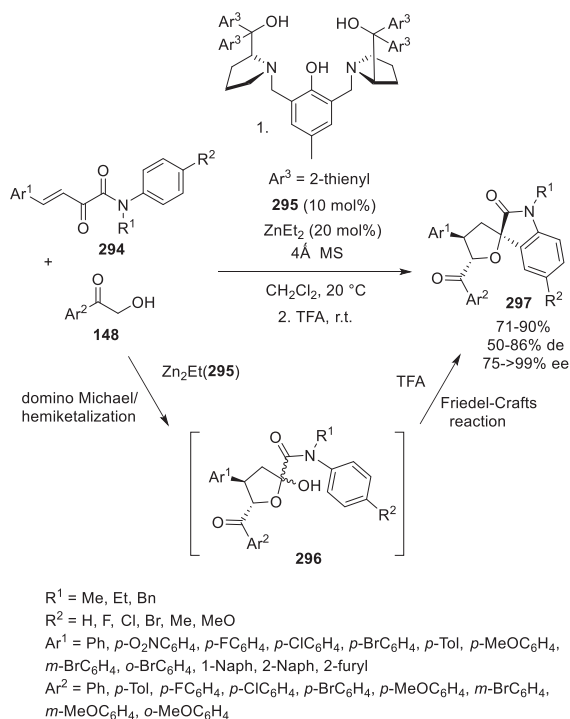
In 2015, Arai et al. described the synthesis of novel polymeric Zn₃(OAc)₄-3,3'-bis(aminoimino)binaphthoxide catalyst **281** through self-assembly of chiral 3,3'-diformylbinaphthol ligand **282**, chiral tetramine ligand **283**, and Zn(OAc)₂ (Scheme 96) [131]. This complex was found stable and efficient at only 2 mol% of catalyst loading to promote at –78 °C the asymmetric iodolactonization of a range of 5-substituted hex-5-enoic acids **284** into the corresponding chiral iodolactones **285**. 5-Arylhex-5-enoic acids bearing various electron-withdrawing or electron-donating substituents on the phenyl ring led to the corresponding iodolactones with both uniformly excellent enantioselectivities (91–97% ee) and yields (92–>99%). 5-Alkyl-substituted hex-5-enoic acids **284** (R = alkyl) also reacted smoothly with high yields (84–>99%) and ee values (79–95% ee). Importantly, this novel catalyst was recyclable and could be reused for up to five cycles.

In 2019, the same group investigated asymmetric iodo- and bromolactonizations of carboxylic acid substrates performed in the presence of Zn₃(OAc)₄-3,3'-bis(aminoimino)binaphthoxide chiral active complex **286** in situ generated from the corresponding chiral ligand **287** and Zn(OAc)₂ (Scheme 97) [132]. The



Scheme 98. Domino phospho-Michael/Michael reaction of *o*-dienones with dialkyl phosphates in the presence of a ProPhenol derivative ligand [135].

iodolactonization of 5-phenyl hex-5-enoic acid **284a** was achieved in the presence of only 1 mol% of ligand **287** in combination with 3 mol% of Zn(OAc)₂ at −78 °C with NIS and I₂ as iodine sources,



Scheme 99. Domino Michael/hemiketalization reaction of α -hydroxy aryl ketones with β,γ -unsaturated α -ketoamides followed by Friedel-Crafts reaction in the presence of a ProPhenol derivative ligand [137].

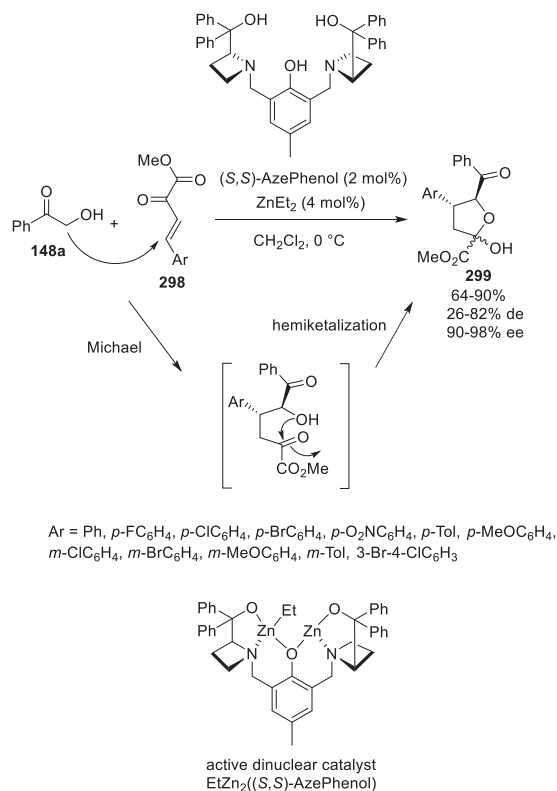
leading to enantiopure six-membered iodolactone **285a** (>99% ee) in quantitative yield (99%). The same substrate was also submitted to related bromolactonization by using NBS as bromide source, providing in the presence of 5 mol% of ligand **287** and 15 mol% of Zn(OAc)₂ at −40 °C the corresponding almost enantiopure bromolactone **288** (94% ee) in 99% yield. Furthermore, the same catalyst system was employed in the asymmetric iodolactonization of diallyl carboxylic acids **289**. The process required 5 mol% of ligand **287** and 15 mol% of Zn(OAc)₂ to produce the corresponding chiral five-membered iodolactones **290** in high yields (80–99%), diastereoselectivities (92–98% de) and enantioselectivities (79–99% ee).

15. Domino/tandem reactions

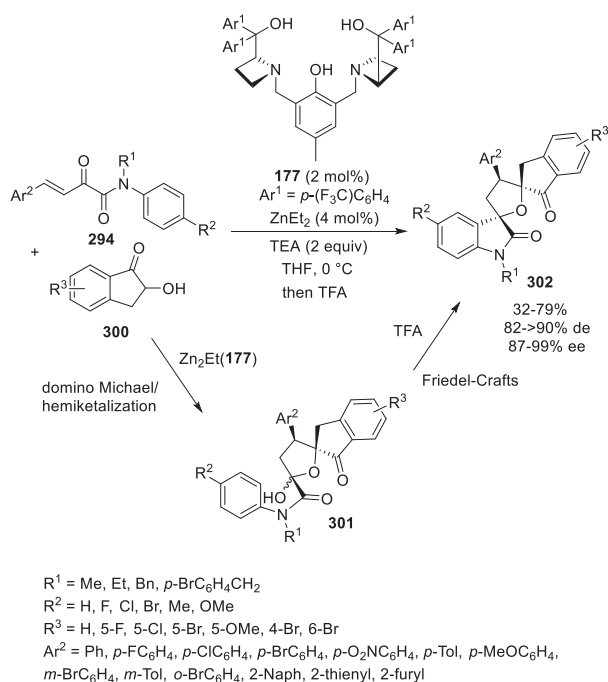
The challenging goal for rapid construction of molecular complexity has become possible through the spectacular development of asymmetric one-pot reactions, such as tandem and domino reactions, that avoid the use of costly protection/deprotection processes and purification of intermediates [133]. In most cases, these economic reactions are remarkably enantioselective, and consequently they have been intensely applied in the total synthesis of complex chiral molecules, such as bioactive and natural products [134]. This is only in the last decade that the first examples of asymmetric domino reactions catalyzed with chiral zinc complexes have been disclosed.

15.1. Michael-initiated domino reactions

In 2019, Hua and Wang reported an enantioselective domino phospho-Michael/Michael reaction of *o*-dienones **291** with dialkyl phosphates **187**, **292** based on the use of chiral ProPhenol

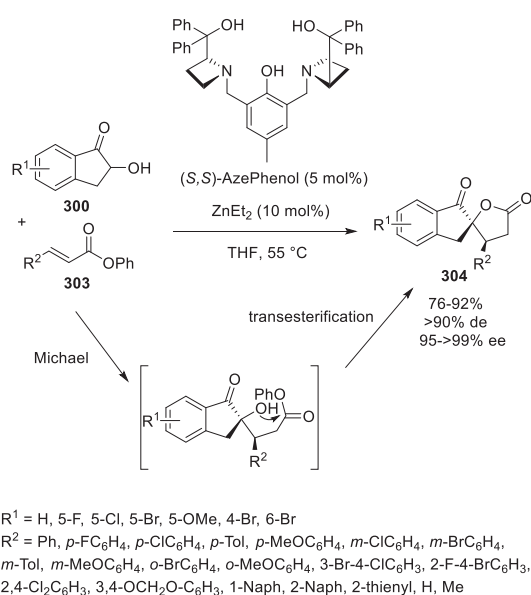


Scheme 100. Domino Michael/hemiketalization reaction of aryl-substituted β,γ -unsaturated α -ketoesters with α -hydroxyacetophenone in the presence of (*S,S*)-AzePhenol [138].

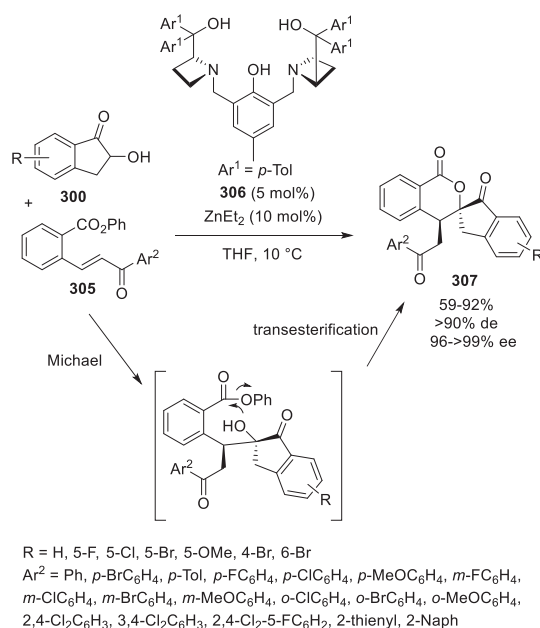


Scheme 101. Domino Michael/hemiketalization reaction of aryl-substituted β,γ -unsaturated α -ketoamides with 2-hydroxy-1-indanones followed by Friedel-Crafts reaction in the presence of an AzePhenol derivative ligand [139].

derivative **207** as ligand (10 mol%) in combination with ZnEt_2 (20 mol%) in toluene at 25 °C [135]. The sequence led to the corresponding chiral 1,2,3-trisubstituted indane derivatives **293**, bearing phosphoryl groups and three contiguous stereocenters, as almost single stereoisomers (>98% de, 94–>99% ee) in good to high yields (65–92%), as illustrated in Scheme 98. 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



Scheme 102. Domino Michael/transesterification reaction of α -hydroxy-1-indanones with phenyl α,β -unsaturated esters in the presence of (S,S)-AzePhenol [140].



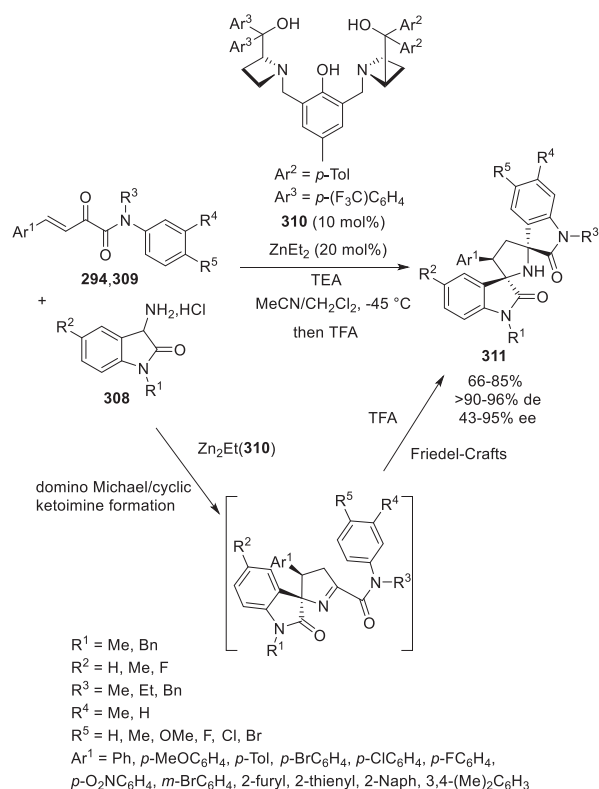
Scheme 103. Domino Michael/transesterification reaction of α -hydroxy-1-indanones with *ortho*-ester chalcones in the presence of an AzePhenol derivative ligand [141].

of the electronic nature of the substituents beared on the aryl group (Ar^2).

The synthesis of chiral tetrahydrofuran spirooxindoles is challenging related to the potent biological activities of these products [136]. In this context, the same authors developed in 2020 an enantioselective zinc-catalyzed domino Michael/hemiketalization reaction of α -hydroxy aryl ketones **148** with β,γ -unsaturated α -ketoamides **294** [137]. The reaction, performed at 20 °C in dichloromethane as solvent, was promoted by a chiral dinuclear zinc catalyst in situ generated from 20 mol% of ZnEt_2 and 10 mol% of chiral ProPhenol derivative ligand **295**. The domino products **296** were not isolated but directly submitted to Friedel-Crafts reaction performed at room temperature by adding TFA to give chiral tetrahydrofuran spirooxindoles **297** in high yields (71–90%), moderate to high diastereoselectivities (50–86% de) and good to high enantioselectivities (75–>99% ee), as shown in Scheme 99. Actually, the enantioselectivities were uniformly excellent (90–>99% ee) for differently substituted substrates excepted for *ortho*-methoxy-substituted α -hydroxy aryl ketone ($Ar^2 = o\text{-MeOC}_6\text{H}_4$), which yielded the corresponding product with a lower ee value (75% ee).

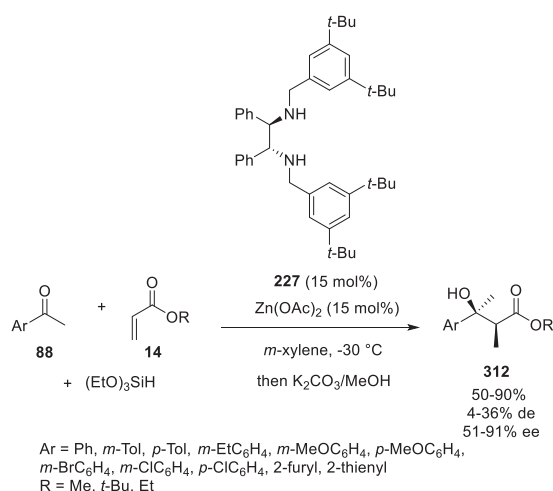
The chiral dinuclear zinc catalyst $\text{Zn}_2\text{Et}((S,S)\text{-AzePhenol})$, in situ generated from 2 mol% of (S,S)-AzePhenol and 4 mol% of ZnEt_2 , was employed in 2015 by Chang and Wang to promote an enantioselective domino Michael/hemiketalization reaction (Scheme 100) [138]. It involved aryl-substituted β,γ -unsaturated α -ketoesters **298** and α -hydroxyacetophenone **148a** as substrates in dichloromethane as solvent, leading at 0 °C to the corresponding chiral 2,2,4,5-tetrasubstituted tetrahydrofurans **299** 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 β,γ -unsaturated α -ketoesters bearing substituents at the *meta*-position of the phenyl ring.

In 2019, the same authors developed a novel route to chiral bispirotetrahydrofuran oxindoles based on an enantioselective cascade Michael/hemiketalization/Friedel-Crafts reaction of β,γ -unsaturated α -ketoamides **294** with 2-hydroxy-1-indanones **300**



Scheme 104. Domino Michael/cyclic ketoimine formation reaction of 3-amino oxindole hydrochlorides with β,γ -unsaturated α -keto amides followed by Friedel-Crafts reaction in the presence of a C₁-symmetric AzePhenol derivative ligand [142].

(Scheme 101) [139]. The sequence was initiated by an asymmetric domino Michael/hemiketalization catalyzed by a chiral dinuclear zinc complex in situ generated from 4 mol% of ZnEt_2 and 2 mol% of chiral AzePhenol derivative ligand **177**. The reaction, performed in THF at 0 °C, provided unstable hemiketal domino products **301** which were not isolated but directly submitted to a Friedel-Crafts reaction by treatment with TFA. This led to chiral bispiro[3,2'-tetrahydrofuran-5',2''indanone] oxindoles **302** exhibiting three contiguous stereocenters in variable yields (32–79%), and high diastereo- (82–>90% de) and enantioselectivities (87–99% ee).



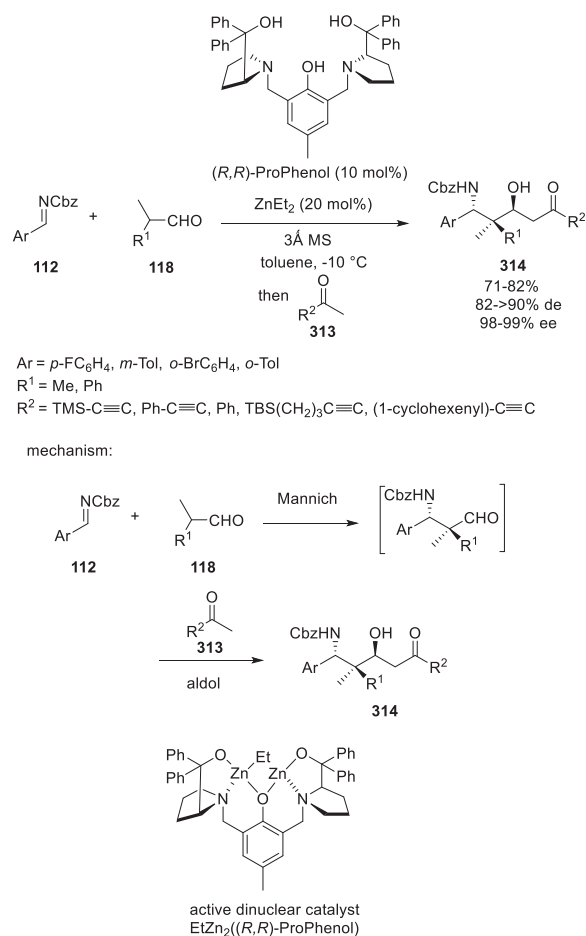
Scheme 105. Three-component domino reductive Michael/aldol reaction of acrylates, aromatic ketones and $(\text{EtO})_3\text{SiH}$ in the presence of a diamine ligand [143].

The scope of the process was wide since a range of electron-donating and electron-withdrawing substituents were tolerated on the phenyl ring of each substrates.

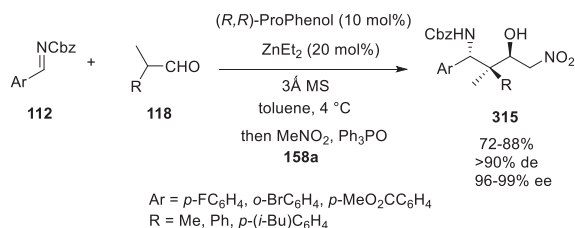
In the same year, these authors also employed dinuclear zinc complex in situ generated from 5 mol% of (*S,S*)-AzePhenol as ligand and 10 mol% of ZnEt_2 to catalyze an enantioselective domino Michael/transesterification reaction between α -hydroxy-1-indanones **300** and phenyl α,β -unsaturated esters **303** (Scheme 102) [140]. Indeed, variously substituted chiral spiro[1-indanone-5,2'- γ -butyrolactones] **304** were synthesized at 55 °C in THF as solvent as almost single stereoisomers (>90% de, 95–>99% ee) in high yields (76–92%).

In 2020, a related enantioselective zinc-catalyzed domino Michael/transesterification reaction of α -hydroxy indanones **300** with *ortho*-ester chalcones **305** was disclosed by the same group (Scheme 103) [141]. In this case, chiral AzePhenol derivative **306** was used at 5 mol% of catalyst loading as optimal ligand in combination with 10 mol% of ZnEt_2 to generate the active dinuclear catalyst. The latter allowed at 10 °C in THF as solvent a range of chiral spiro[indanone-2,3'-isochromane-1-one] derivatives **307** to be obtained as almost single stereoisomers (>90% de, 96–>99% ee) in good yields (59–92%). It was found that the electronic nature and position of substituents on the phenyl ring of either α -hydroxy indanones or *ortho*-ester chalcones had little impact on the stereoselectivity of the reaction.

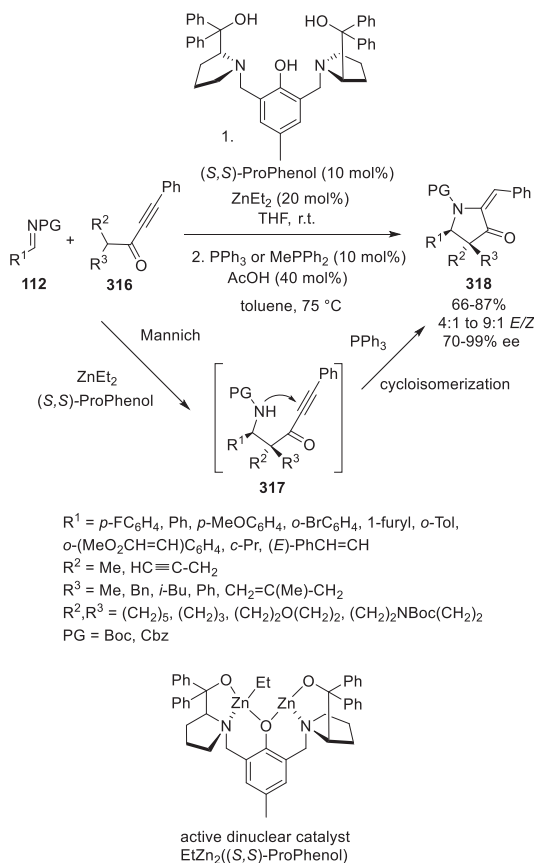
Earlier in 2019, the same group also developed a new asymmetric domino Michael/cyclic ketoimine formation reaction of



Scheme 106. Tandem Mannich/aldol reaction of branched aldehydes, aromatic aldimines and ketones in the presence of (*R,R*)-ProPhenol [68].

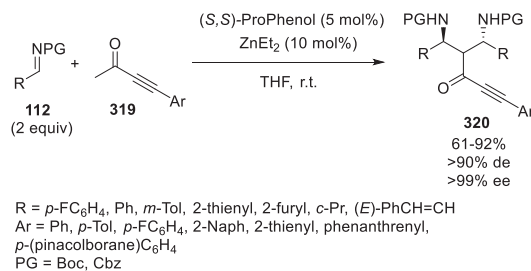


Scheme 107. Tandem Mannich/Henry reaction of branched aldehydes, aromatic aldimines and nitromethane in the presence of (*R,R*)-ProPhenol [68].



Scheme 108. Tandem Mannich/cycloisomerization reaction of aldimines with alkynones in the presence of (*S,S*)-ProPhenol [144].

3-amino oxindole hydrochlorides **308** with aryl-substituted β,γ -unsaturated α -ketoamides **294**, **309** followed by a Friedel–Crafts reaction performed in a single vessel [142]. This cascade process occurred at $-45\text{ }^{\circ}\text{C}$ in a mixture of acetonitrile and dichloromethane as solvent, leading to chiral pyrrolidinyl dispirooxindoles **311**. Among chiral ligands investigated in this process, C_2 -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_1 -symmetric ligand **310**, with electronically and sterically divergent units (Scheme 104). The use of a combination of 10 mol% of this ligand with 20 mol% of ZnEt_2 allowed pyrrolidinyl dispirooxindoles **311** exhibiting two quaternary stereocenters to be obtained as single diastereomers (>90 – 96% de) in high yields (66–85%) and moderate to high enantioselectivities (43–95% ee). The presence of various substituents at the phenyl ring of aryl-substituted β,γ -unsaturated α -ketoamides **294**, **309** was tolerated. Generally, substrates with electron-donating groups at the *para* position of the



Scheme 109. Pseudo-three-membered domino double Mannich reaction of ynones with aldimines in the presence of (*S,S*)-ProPhenol [145].

phenyl ring (Ar^1) provided higher enantioselectivities than those with electron-withdrawing groups. The catalytic system was also compatible with heteroaromatic-substituted β,γ -unsaturated α -ketoamides and γ -naphthyl-substituted substrates.

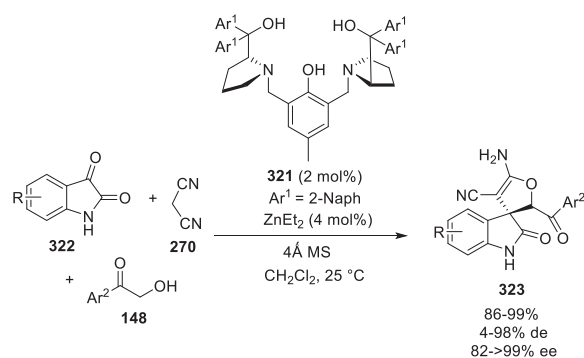
In 2020, Mlynarski et al. described the first enantioselective three-component domino reductive Michael/aldol reaction of acrylates **14**, (hetero)aromatic ketones **88** and $(\text{EtO})_3\text{SiH}$ using $\text{Zn}(\text{OAc})_2$ as cheap precatalyst [143]. Optimal diamine ligand **227** was employed at 15 mol% of catalyst loading in *m*-xylene as solvent to promote the reaction at $-30\text{ }^{\circ}\text{C}$. As shown in Scheme 105, a series of chiral β -hydroxy esters **312** were synthesized in moderate to high yields (50–90%) and enantioselectivities (51–91% ee) in combination with generally low diastereoselectivities (4–36% de).

15.2. Mannich-initiated domino/tandem reactions

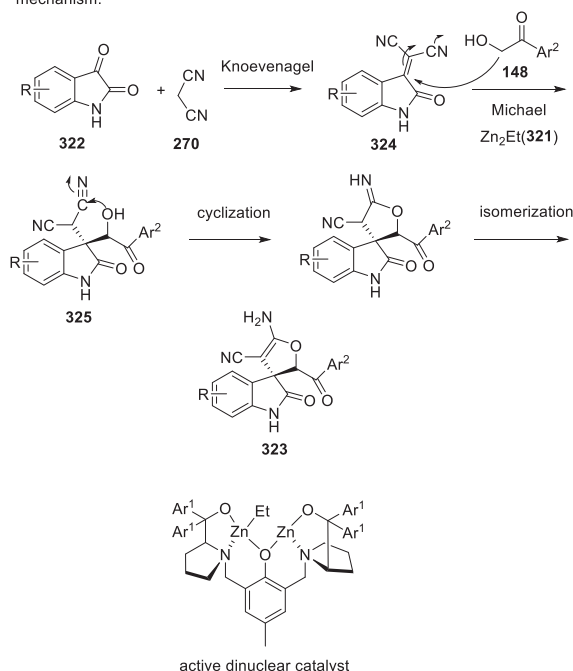
In 2018, Trost et al. described an enantioselective tandem Mannich/aldol reaction between branched aldehydes **118**, aromatic aldimines **112** and ketones **313** catalyzed by a combination of 10 mol% of (*R,R*)-ProPhenol and 20 mol% of ZnEt_2 in toluene at $-10\text{ }^{\circ}\text{C}$ (Scheme 106) [68]. This one-pot three-component process required the separated addition of ketone **313** into the reaction vessel upon completion of the asymmetric Mannich process. It delivered the corresponding enantiopure 1,3-amino alcohols **314** (98–99% ee) exhibiting three contiguous stereocenters in high yields (71–82%) and diastereoselectivities (82– $>90\%$ de).

In addition, the same catalyst system was applied to develop related enantioselective tandem three-component Mannich/Henry reaction between aromatic aldimines **112**, branched aldehydes **118** and nitromethane **158a** as added nucleophilic third partner, affording the corresponding chiral 1,3-amino alcohols **315** as almost single stereoisomers ($>90\%$ de, 96–99% ee) in high yields (72–88%), as presented in Scheme 107 [68].

Later in 2019, an enantioselective zinc-catalyzed tandem Mannich/cycloisomerization reaction of aldimines **112** with alkynones **316** was described by the same group [144]. A combination of 20 mol% of ZnEt_2 and 10 mol% of (*S,S*)-ProPhenol was used as catalyst system in THF at room temperature. The Mannich reaction led to intermediate β -amino ynone **317**, which was subsequently cycloisomerized at $75\text{ }^{\circ}\text{C}$ in the presence of 10 mol% of PPh_3 and 40 mol% of AcOH in toluene as solvent, to afford pyrrolidones **318** in good yields (66–87%) and enantioselectivities (70–99% ee) combined with a good *E/Z* stereoselectivity (up to 9:1) as shown in Scheme 108. Aromatic aldimines with 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 an heteroaromatic aldimine ($\text{R}^1 = 1\text{-furyl}$). Moreover, a vinyl aldimine ($\text{R}^1 = (\text{E})\text{-PhCH=CH}$) was cyclized in 68% yield and 87% ee whereas the reaction of *c*-propyl aldimine ($\text{R}^1 = c\text{-Pr}$) required the use of a more nucleophilic additive, such as MePPh_2 instead of PPh_3 , to



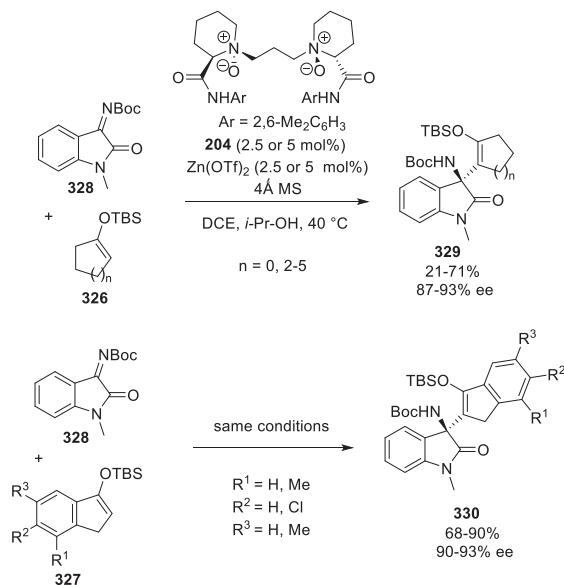
mechanism:



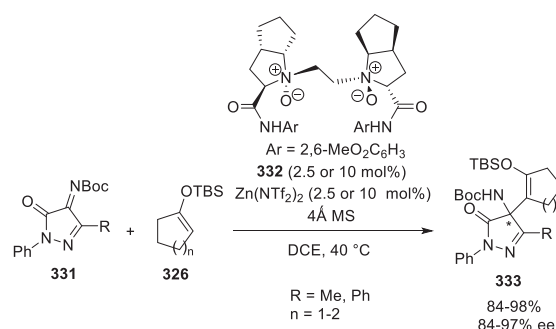
Scheme 110. Three-component domino Knoevenagel/Michael/cyclization/isomerization reaction of isatins, malononitrile and α -hydroxy acetophenones in the presence of a ProPhenol derivative ligand [146].

perform the cycloisomerization, leading to the corresponding pyrrolidone in 79% yield and 92% ee. Interestingly, heterocyclic chiral spirocycles, such as a tetrahydropyran ($\text{R}^2, \text{R}^3 = (\text{CH}_2)_2\text{O}$) and a *N*-Boc piperidine ($\text{R}^2, \text{R}^3 = (\text{CH}_2)_2\text{NBoc}(\text{CH}_2)_2$), could be synthesized with good yields (86 and 66%, respectively) and high enantioselectivities (92 and 82% ee, respectively).

In 2020, a combination of 5 mol% of (*S,S*)-ProPhenol with 10 mol% of ZnEt_2 was used by Trost and Gnanamani at room temperature in THF as solvent to promote an asymmetric pseudo-three-component reaction between ynones **319** and two equivalents of aldimines **112** (Scheme 109) [145]. This domino double Mannich reaction produced enantio- and almost diastereopure 1,3-diamines **320** (>90% de, >99% ee) in good to high yields (61–92%). Along with (hetero)aromatic aldimines, cyclopropyl imine ($\text{R} = \text{c-Pr}$) also underwent the reaction with comparable excellent results (78% yield, >90% de and >99% ee). Furthermore, a variety of (hetero)aromatic ynones were tolerated.



Scheme 111. Domino α -alkenyl addition/proton shift reactions of silyl enol ethers with isatin-derived ketimines in the presence of a *N,N'*-dioxide ligand [147].

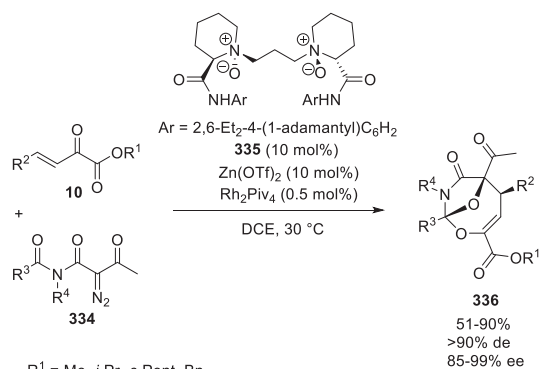


Scheme 112. Domino α -alkenyl addition/proton shift reaction of silyl enol ethers with pyrazolinone-derived ketimines in the presence of a *N,N'*-dioxide ligand [147].

15.3. Other domino reactions

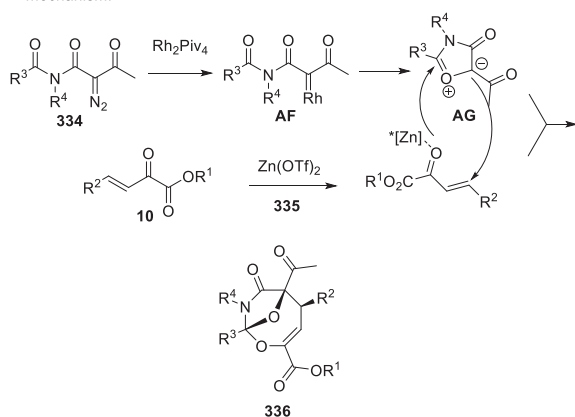
A three-component reaction was disclosed in 2019 by Wang et al. based on the use of ProPhenol derivative ligand **321** (Scheme 110) [146]. Only 2 mol% of this semi-aza-crown ligand was combined with 4 mol% of ZnEt_2 in this domino Knoevenagel/Michael/cyclization/isomerization reaction between isatins **322**, malononitrile **270** and α -hydroxy acetophenones **148**. Carried out at 25 °C in dichloromethane as solvent, the process resulted in the formation of chiral 3,3'-dihydrofuran spirooxindoles **323** in high yields (86–99%) and enantioselectivities (82–>99% ee) 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 110, the Knoevenagel reaction of isatin **322** with malononitrile **270** afforded intermediate **324**, which was further submitted to asymmetric zinc-catalyzed Michael addition of α -hydroxy acetophenone **148** to give intermediate **325**. The latter was then submitted to cyclization followed by isomerization to afford the final product.

In 2019, chiral *N,N'*-dioxide ligands were applied by Feng et al. to develop the first enantioselective domino α -alkenyl addition/proton shift reaction of silyl enol ethers with cyclic ketimines [147]. As depicted in Scheme 111, silyl enol ethers **326** and **327**

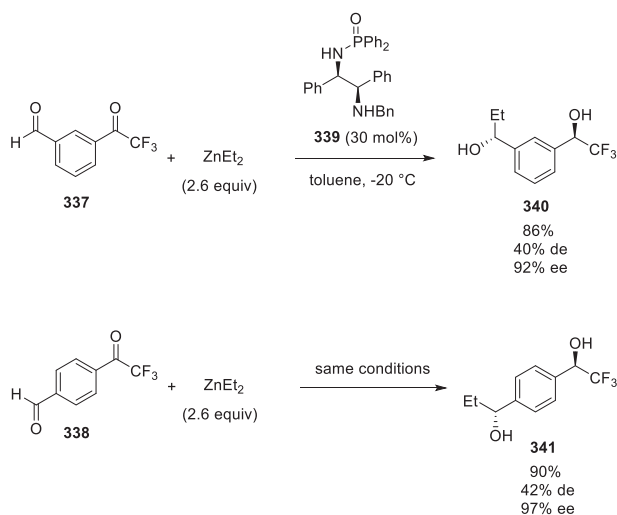


R¹ = Me, *i*-Pr, *c*-Pent, Bn
 R² = Ph, *p*-Tol, *o*-MeOC₆H₄, *m*-MeOC₆H₄, *p*-MeOC₆H₄, *p*-PhC₆H₄,
p-HOOC₆H₄, *p*-FC₆H₄, *m*-ClC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, 2-Naph, 2-thienyl,
 3-furyl, (*E*)-PhCH=CH
 R³ = Ph, *i*-Pr, *p*-ClC₆H₄, *p*-MeOC₆H₄, Me
 R⁴ = Me, Bn

mechanism:

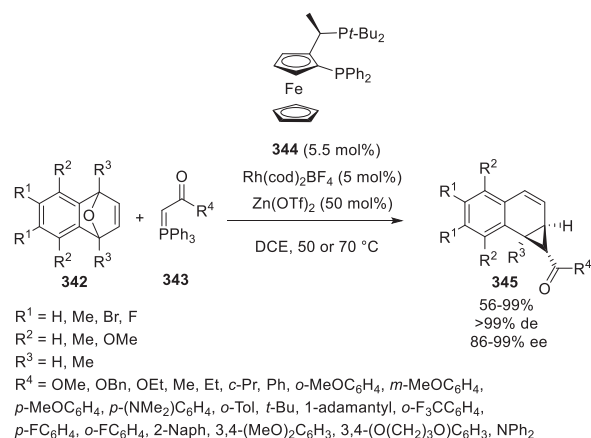


Scheme 113. Domino carbonylimide formation/[4 + 3] cycloaddition reaction of β, γ-unsaturated α-ketoesters with diazoimides in the presence of a *N,N'*-dioxide ligand [148].

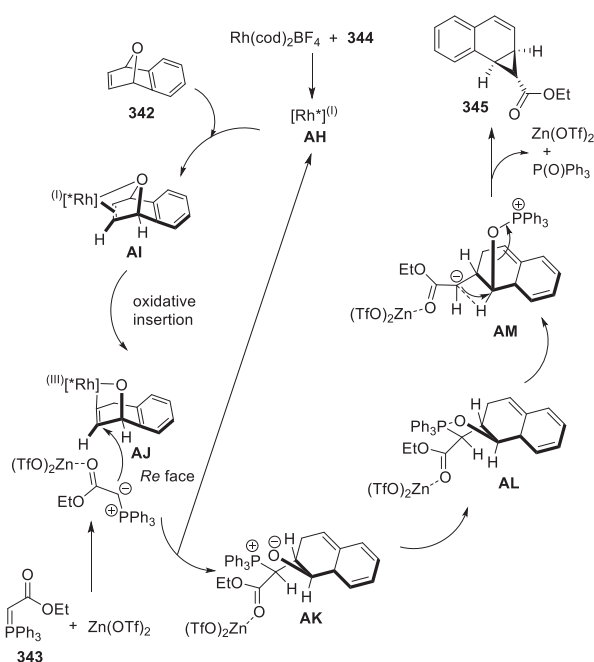


Scheme 114. Domino transfer reduction/ethylation reactions of aryl α-trifluoromethylketones with ZnEt₂ in the presence of a 1,2-amino phosphoramidate ligand [149].

reacted with isatin-derived ketimine **328** in the presence of 2.5–5 mol% of a chiral zinc catalyst in situ generated from Zn(OTf)₂ and chiral *N,N'*-dioxide ligand **204** at 40 °C to give the correspond-



mechanism with R¹ = R² = R³ = H, R⁴ = OEt:

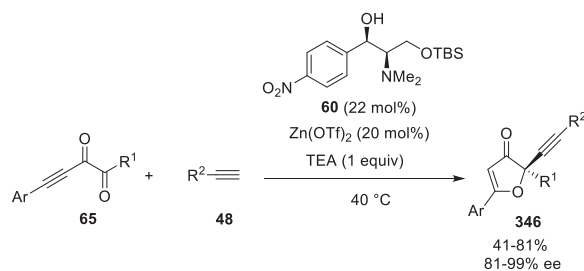


Scheme 115. Domino ring-opening/cyclopropanation reaction of oxabenzonorbornadienes with phosphorus ylides in the presence of a biphosphine ligand [150].

ing β-amino silyl enol ethers **329** and **330**, respectively, in high enantioselectivities (87–93% ee) and variable yields (21–90%).

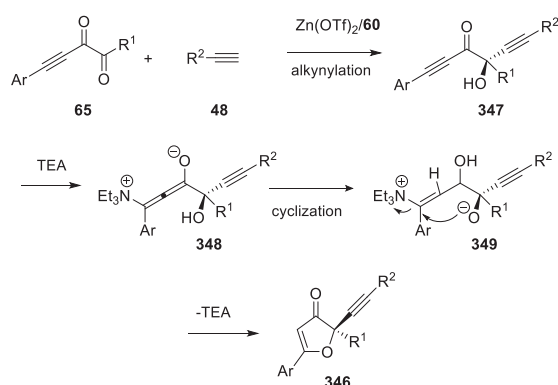
These authors extended the scope of this novel process to pyrazolinone-derived ketimines **331** which reacted with silyl enol ethers **326** (Scheme 112) [147]. In this case, the catalyst system was composed of a related *N,N'*-dioxide ligand **332** and Zn(NTf₂)₂, allowing the formation of chiral β-amino silyl enol ethers **333** with both high yields (84–98%) and enantioselectivities (84–97% ee).

In 2019, a dual bimetallic relay catalysis was employed by Feng and Lin in an enantioselective domino reaction of β,γ-unsaturated α-ketoesters **10** with diazoimides **334** (Scheme 113) [148]. The catalyst system included an achiral rhodium complex, such as Rh₂Piv₄, and a chiral zinc catalyst in situ generated from Zn(OTf)₂ and chiral *N,N'*-dioxide ligand **204**. The rhodium catalyst allowed the generation of a carbonyl ylide intermediate from the diazoimide substrate which subsequently reacted through asymmetric [4 + 3] cycloaddition with the β,γ-unsaturated α-ketoester



Ar = Ph, *p*-ClC₆H₄, *p*-EtC₆H₄, 3-thienyl
 R¹ = Ph, *p*-ClC₆H₄, 1-Naph, 2-thienyl, (*E*)-PhCH=CH, *p*-MeOC₆H₄, *p*-Tol
 R² = *p*-Tol, Ph, *p*-FC₆H₄, (*E*)-PhCH=CH, *p*-EtOC₆H₄, 3-thienyl, *p*-MeOC₆H₄,
p-EtC₆H₄, *m*-ClC₆H₄, *o*-FC₆H₄

mechanism:

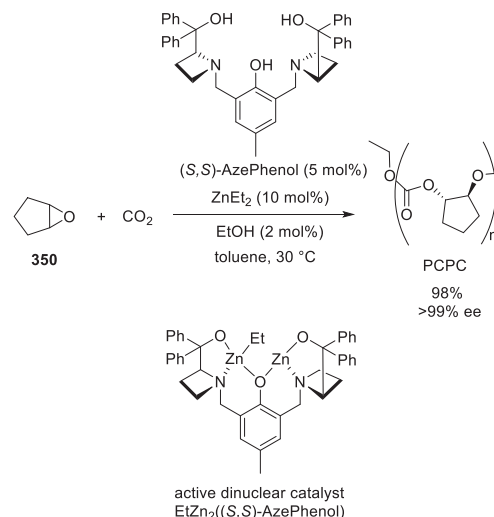


Scheme 116. Domino alkynylation/cyclization reaction of alkynyl 1,2-diketones with alkynes in the presence of a 1,2-amino alcohol ligand [45].

catalyzed by the chiral zinc complex. This domino carbonyl imide formation/[4 + 3] cycloaddition reaction provided chiral oxabridged oxazocines **336** as almost single *exo*-diastereomers (>90% de) in good to high yields (51–90%) and high enantioselectivities (85–99% ee). Various (hetero)aryl-substituted β,γ -unsaturated α -ketoesters **10**, bearing either electron-withdrawing or electron-donating substituents at different positions of the phenyl group, were tolerated. Heteroaromatic-substituted substrates were also compatible as well as various alkyl ester groups (R¹). Furthermore, variously (*N*)-substituted diazoimides reacted smoothly. The process evolved through the formation of rhodium carbene species **AF** from the reaction between diazoimide **334** and Rh_2Piv_4 . Then, an intramolecular carbonyl attack on the rhodium carbene occurred to generate 1,3-dipole **AG**. The latter reacted with the β,γ -unsaturated α -ketoester substrate activated by the chiral zinc catalyst through a [4+3] cycloaddition to provide the final domino product.

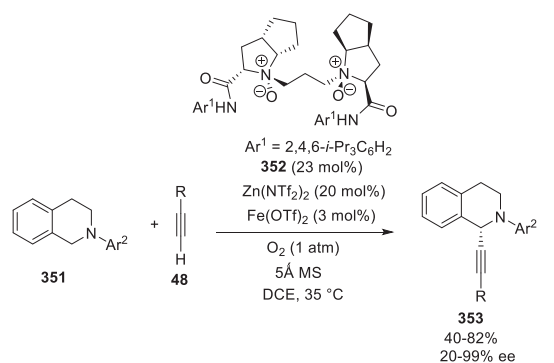
Earlier in 2015, Song et al. described enantioselective zinc-catalyzed domino transfer reduction/ethylation reaction of aryl α -trifluoromethylketones **337**, **338** with ZnEt_2 performed in the presence of 30 mol% of chiral 1,2-amino phosphoramidate ligand **339** [149]. The process included the asymmetric β -H transfer reduction of the aryl α -trifluoro ketones and the enantioselective addition of ZnEt_2 to the aromatic aldehyde moieties (Scheme 114). It produced in toluene at –20 °C almost enantiopure fluorinated diols **340**, **341** (92–97% ee) in high yields (86–90%) albeit with low diastereoselectivities (40–42% de).

In 2019, Shao et al. developed the first enantioselective domino ring-opening/cyclopropanation reaction of oxabenzonorbornadienes **342** with phosphorus ylides **343** (Scheme 115) [150]. The process involved a dual bimetallic rhodium/zinc catalysis with 5 mol% of $\text{Rh}(\text{cod})_2\text{BF}_4$, 50 mol% of $\text{Zn}(\text{OTf})_2$ and 5.5 mol% of chiral biphenyl phosphine ligand **344**. It formed chiral benzonorcaradienes **345** as sin-



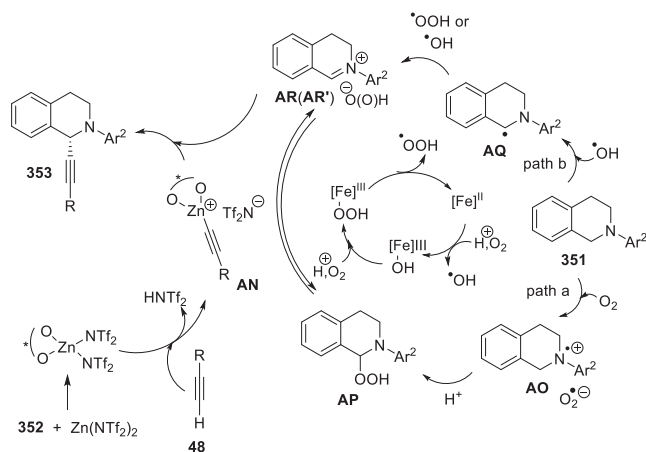
Scheme 117. Copolymerization of cyclopentene oxide with CO_2 in the presence of (*S,S*)-AzePhenol [152].

gle diastereomers in good to high yields (56–99%) and high enantioselectivities (86–99% ee). A possible mechanism is depicted



R = Ph, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-Tol, *p*-EtC₆H₄, *p*-PrC₆H₄, *p*-BuC₆H₄,
p-PentC₆H₄, *p*-MeOC₆H₄, *p*-MeO₂CC₆H₄, *p*-NCC₆H₄, *o*-FC₆H₄, *o*-ClC₆H₄,
m-FC₆H₄, *m*-ClC₆H₄, *m*-Tol, *m*-MeOC₆H₄, *m*-O₂NC₆H₄, 3,5-F₂C₆H₃, 1-Naph,
 2-thienyl, BnCH₂, *c*-Pr, *n*-Dec
 Ar² = *p*-MeOC₆H₄, *p*-Tol, *p*-EtC₆H₄, *p*-PhC₆H₄, 3,5-Me₂C₆H₃, 3-Cl-4-MeC₆H₃,
 2,4-(MeO)₂C₆H₃,

proposed mechanism:



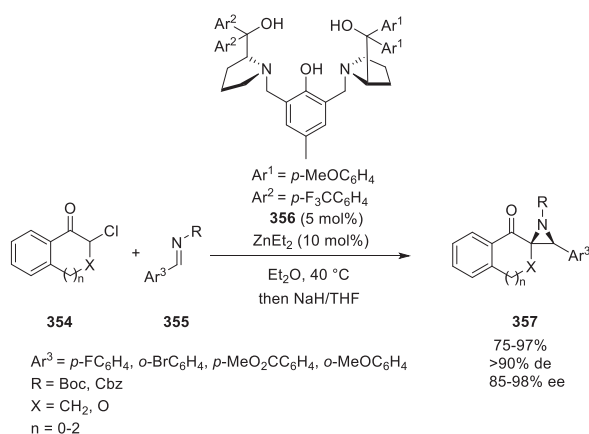
Scheme 118. Cross-dehydrogenative coupling of tetrahydroisoquinolines with terminal alkynes in the presence of a *N,N'*-dioxide ligand [153].

in [Scheme 115](#), beginning with the formation of chiral rhodium catalyst **AH** which coordinated the oxabenzonorbornadiene from the *exo* face to give intermediate **AI**. Then, oxidative insertion with retention into a bridgehead C–H bond provided complex **AJ**. Subsequently, phosphorus ylide **343** activated by Zn(OTf)₂ attacked **AJ** from the *Re* face to give intermediate **AK** and regenerated rhodium catalyst. Then, **AK** was submitted to ring-closing to give intermediate **AL**. The latter underwent ring-opening to produce the intermediate **AM** through cleavage of the C–P bond. Finally, intermediate **AM** underwent an intramolecular S_N2 reaction to deliver the product with elimination of O = PPh₃. In this mechanism, Zn(OTf)₂ played the role of Lewis acid cocatalyst, by activating the phosphorus ylide and bridging oxygen, facilitating the asymmetric ring-opening.

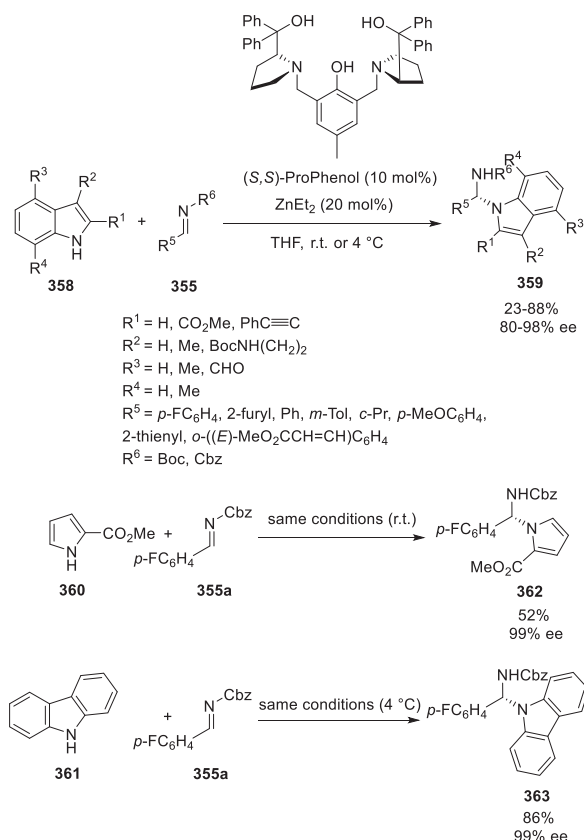
In 2020, Fang and Ding developed highly regio- and enantioselective domino alkylation/cyclization reaction of alkynyl 1,2-diketones **65** with alkynes **48** under asymmetric zinc catalysis [45]. The zinc catalyst was in situ generated from 20 mol% of Zn(OTf)₂ and 20 mol% of chiral amino alcohol ligand **60** at room temperature ([Scheme 116](#)). Whereas in the presence of DIPEA as base, the reaction evolved through a simple alkylation (see [Scheme 19](#), section 3.2), when performed with TEA as base at 40 °C, the alkylation was followed by cyclization. As depicted in [Scheme 116](#), alkynyl 1,2-diketones **65** reacted with alkynes **48** in the presence of TEA through a domino alkylation/cyclization reaction to give the corresponding chiral biologically important 3(2*H*)-furanones **346** in moderate to good yields (41–81%) and high enantioselectivities (81–99% ee). A mechanism is proposed in [Scheme 116](#), involving the nucleophilic addition of TEA to the alkyne unit of the intermediate alkylation product **347** to give allenic intermediate **348**. Then, the latter underwent a proton transfer to provide intermediate **349** which cyclized into the final 3(2*H*)-furanone **346**.

16. Miscellaneous reactions

Chiral polycarbonates constitute starting materials for the synthesis of new materials because of their well-defined chemical structures and special physical properties [151]. Previous studies on the asymmetric copolymerization of cyclopentene oxide **350** with CO₂ have been catalyzed by chiral zinc catalysts, providing chiral poly(cyclopentene carbonate) with moderate enantioselectivities. To improve these results, Chang and Wang reinvestigated this reaction by using a chiral dinuclear catalyst derived from 10 mol% of ZnEt₂ and 5 mol% of (*S,S*)-AzePhenol as ligand [152]. The process employed ethanol as an additive and toluene as a sol-



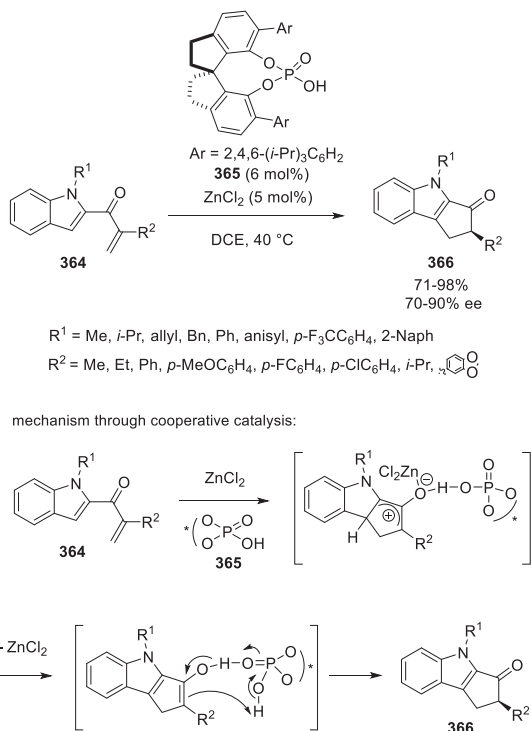
Scheme 119. Aza-Darzens reaction of chlorinated aromatic ketones with *N*-protected aldimines in the presence of a C₁-symmetric ProPhenol derivative ligand [154].



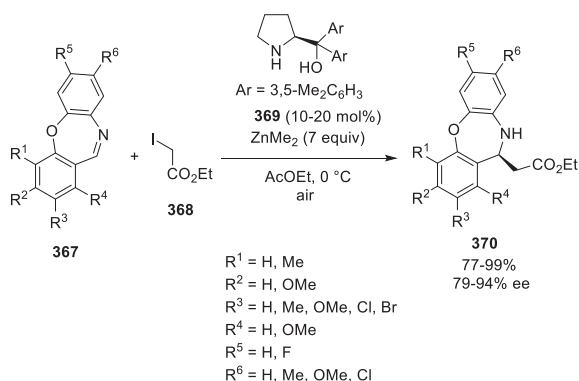
Scheme 120. *N*-Alkylations of indoles, methyl pyrrole-2-carboxylate and carbazole with *N*-protected aldimines in the presence of (*S,S*)-ProPhenol [155].

vent. Performed at 30 °C, it led to enantiopure completely alternating copolymer poly(cyclopentene carbonate) (PCPC) (>99% ee) in quantitative yield (98%), as illustrated in [Scheme 117](#).

With the aim of synthesizing biologically active tetrahydroisoquinoline derivatives, Feng and Liu developed in 2017 the first enantioselective aerobic cross-dehydrogenative coupling between tetrahydroisoquinolines **351** and terminal alkynes **48** under mild reaction conditions ([Scheme 118](#)) [153]. The process, which employed O₂ as the sole oxidant, was based on a bimetallic cooperative catalysis involving 20 mol% of Zn(NTf₂)₂, 3 mol% of Fe(OTf)₂, and 23 mol% of chiral *N,N'*-dioxide ligand **352**. The reaction occurred in DCE at 35 °C to afford a wide range of chiral α -alkynyl substituted tetrahydroisoquinolines **353** in good yields (40–82%) and in most cases high enantioselectivities (20–99% ee). Many substituted ethynylbenzenes underwent the reaction with good yields (40–82%) and uniformly high enantioselectivities (85–99% ee) regardless of the electronic nature or position of the substituents on the phenyl group. On the other hand, the reaction of alkyl-substituted terminal alkynes gave lower enantioselectivities (20–61% ee). A mechanism is proposed in [Scheme 118](#) in which the in situ generated chiral *N,N'*-dioxide-Zn(II) complex reacts with terminal alkyne **48** to form zinc acetylide intermediate **AN**. Concomitantly, without additional Fe(II) catalyst (path a), auto-oxidation of the tetrahydroisoquinoline results in the formation of **AO** containing the amine radical cation of tetrahydroisoquinoline^{•+} and superoxide radical anion O₂^{•−}. A further H-abstraction provides hydroperoxide tetrahydroisoquinoline-OOH **AP** which is in equilibrium with iminium species **AR'**. In the presence of aerobic iron catalyst, Fe(III) species are generated along with HO[•] radical. The latter abstracts a H atom from the tetrahydroisoquinoline to



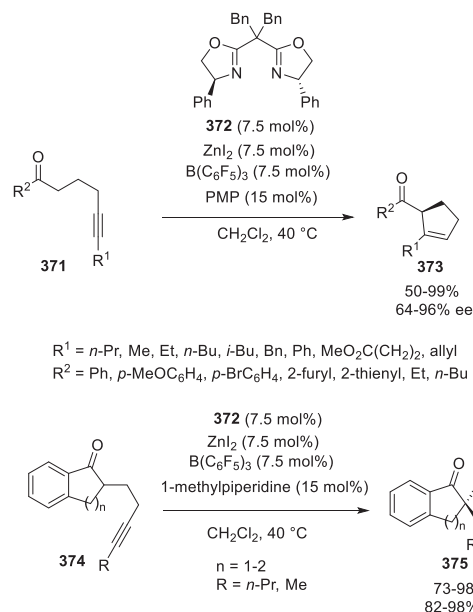
Scheme 121. Nazarov reaction of indoles in the presence of a cooperative dual Zn/phosphoric acid catalysis [157].



Scheme 122. Aza-Reformatsky reaction of seven-membered cyclic imines with ethyl iodoacetate in the presence of a diaryl prolinol ligand [158].

give radical **AQ** (path b). On the other hand, Fe(III) species convert into Fe(III)OOH species, which undergoes homolysis of Fe–O bond to generate HOO· radical, which benefits to the formation of iminium species **AR**. Enantioselective alkynylation controlled by the chiral *N,N'*-dioxide-Zn(II) complex finally yields the cross-coupling product and the regenerated catalyst.

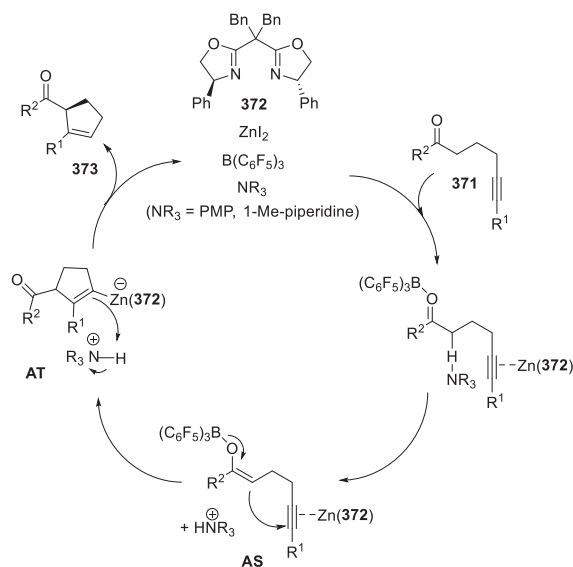
To date, the only reported catalytic enantioselective aza-Darzens reaction is restricted to chloroacetylacetone, which affords aziridines possessing a single stereogenic center. With the aim of developing a new access to chiral complex trisubstituted aziridines, Trost et al. disclosed in 2017 enantioselective aza-Darzens reactions of chlorinated aromatic ketones **354** with aromatic aldimines **355** [154]. The reaction was catalyzed at 40 °C by a combination of 10 mol% of ZnEt₂ and 5 mol% of ProPhenol derivative ligand **356** in diethyl ether as solvent, leading after subsequent treatment with NaH in THF to the corresponding chiral aziridines **357** as almost single diastereomers (>90% de) in high yields



Scheme 123. Conia-ene-type cyclizations of alkynyl ketones in the presence of a multicatalyst system [159].

(75–97%) and enantioselectivities (85–98% ee), as presented in Scheme 119.

The same authors also developed the first asymmetric *N*-alkylation of indoles **358** with *N*-protected aldimines **355** promoted by a dinuclear zinc catalyst derived from (*S,S*)-ProPhenol (10 mol%) and ZnEt₂ (20 mol%) [155]. This reaction was performed at room temperature or 4 °C in THF as solvent, leading to the corresponding chiral *N*-alkylated indoles **359** in low to high yields (23–88%) and high enantioselectivities (80–98% ee), as illustrated in Scheme 120. In addition to be compatible to a wide range of indoles, the catalyst system was applicable to other nitrogen-containing heterocycles, such as pyrrole derivative **360** and carbazole **361**. Indeed, the reaction of methyl pyrrole-2-carboxylate **360** with imine **355a** led to the corresponding enantiopure (99% ee) *N*-alkylated pyrrole **362** in 52% yield and that of carbazole

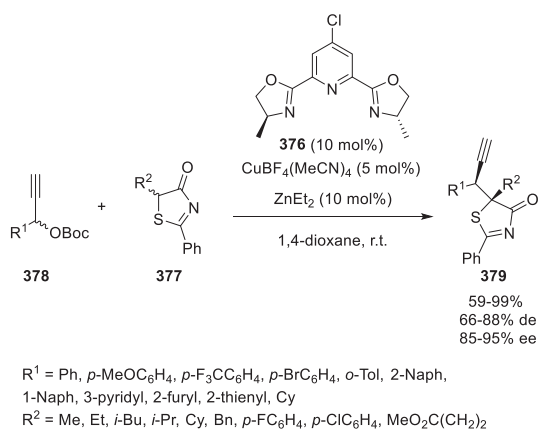


Scheme 124. Mechanism for Conia-ene-type cyclization of alkynyl ketones in the presence of a multicatalyst system [159].

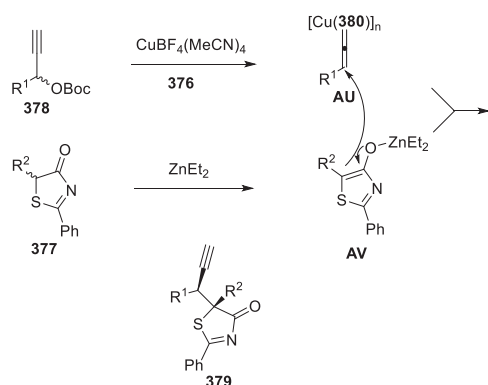
361 with the same imine provided enantiopure amine **363** in 86% yield.

The combination of metal catalysis with asymmetric organocatalysis attracts increasing attention in the synthetic community [156]. In 2017, this powerful methodology was applied by Zhou and Zhu to promote asymmetric Nazarov cyclizations of indole enones **364** [157]. Indeed, a combination of 5 mol% of ZnCl_2 with 6 mol% of chiral phosphoric acid **365** was found to cooperatively catalyze these reactions in DCE at 40 °C to give the corresponding chiral cyclopenta[b]indoles **366** in high yields (71–98%) and good to high enantioselectivities (70–90% ee), as presented in Scheme 121. The cooperative catalysis with ZnCl_2 as Lewis acid and chiral phosphoric acid **365** as Brønsted acid is illustrated in this Scheme. This work represents a very rare example of cooperative catalysis involving a chiral organocatalyst and zinc.

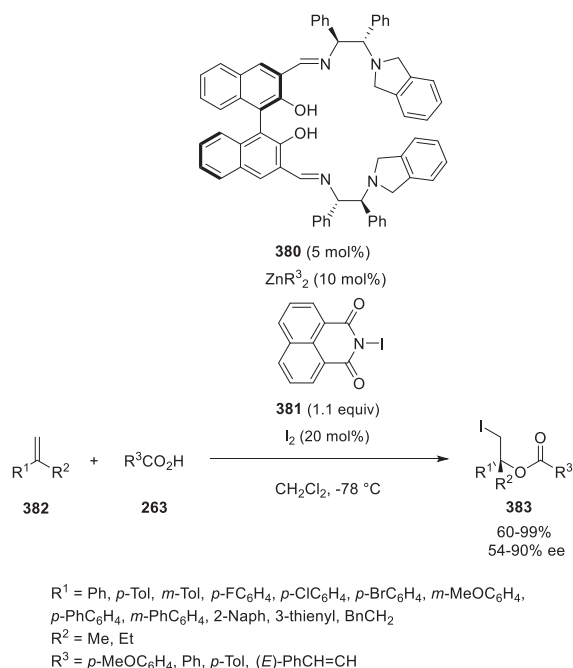
Many biologically interesting products are constructed on a dibenzo[b,f][1,4]oxazepine skeleton and, consequently, the synthesis of such complex structures attracts great attention from chemists. In 2017, Pedro and Vila described a novel asymmetric access to this type of products based on an enantioselective zinc-catalyzed aza-Reformatsky reaction of seven-membered cyclic imines dibenzo[b,f][1,4]oxazepines **367** with ethyl iodoacetate **368** [158]. The process was carried out at 0 °C under air atmosphere in ethyl acetate as solvent, using seven equivalents of ZnMe_2 as precatalyst and 10–20 mol% of chiral diaryl prolinol **369** as ligand. It allowed the formation of the corresponding chiral β -amino esters **370** with both high yields (77–99%) and enantioselectivities (79–94% ee), as illustrated in Scheme 122. It must be highlighted that this work represented the first enantioselective aza-Reformatsky reaction of seven-membered cyclic imines.



possible mechanism:



Scheme 125. Propargylic substitution of 5H-thiazol-4-ones with propargyl carbonates in the presence of a dual Zn/Cu catalyst system [160].



Scheme 126. Iodoesterification of alkenes in the presence of a BINOL-derived ligand [161].

In 2019, Wasa et al. developed enantioselective Conia-ene-type cyclizations of alkynyl ketones **371** on the basis of a three-component catalyst system composed of a zinc catalyst derived from chiral bisoxazoline **372**, $\text{B}(\text{C}_6\text{F}_5)_3$, and an *N*-alkylamine, such as 1,2,2,6,6-pentamethylpiperidine (PMP), as shown in Scheme 123 [159]. Indeed, through the cooperative action of $\text{B}(\text{C}_6\text{F}_5)_3$ and amine, ketones **371** with poorly acidic $\alpha\text{-C-H}$ bonds could be converted in situ into the corresponding enolates. Subsequent asymmetric zinc-catalyzed cyclization led to the formation of chiral cyclopentenones **373** with good to quantitative yields (50–99%) and moderate to excellent ee values (64–96% ee). In most cases of substrates, the enantioselectivity of the reaction was $\geq 90\%$ ee. The catalyst system was compatible with both aromatic and aliphatic ketones, providing comparable results. In addition, indanone and tetralone derivatives **374** also underwent the reaction but required a less hindered Brønsted base, such as 1-methylpiperidine instead of PMP. The corresponding chiral spiro cyclopentenones **375** were obtained with good to high yields (73–98%) and ee values (82–98% ee).

A mechanism shown in Scheme 124 explains the role of this multicatalyst system, composed of strong Lewis acid $\text{B}(\text{C}_6\text{F}_5)_3$, Brønsted base NR_3 , and chiral zinc Lewis acid derived from ZnI_2 and bisoxazoline **372**, in the stereoselectivity of these reactions [159]. First, base NR_3 could deprotonate $\text{B}(\text{C}_6\text{F}_5)_3$ -activated ketone **371**, generating enolate in **AS** along with ammonium ion $^+\text{H-NR}_3$. Simultaneously, the chiral zinc catalyst activated the alkyne unit in **AS**. Then, a stereoselective 5-*endo-dig* cyclization of the enolate with the alkyne group occurred, leading to cyclic intermediate **AT**. Subsequent protonation with the ammonium ion resulted in the formation of final chiral cyclopentenyl product **373**.

In 2018, Zhang and Niu investigated a dual metal catalytic system based on zinc and copper in the asymmetric propargylic substitution reaction of 5H-thiazol-4-ones [160]. Indeed, the combined use of 5 mol% of $\text{CuBF}_4(\text{MeCN})_4$, 10 mol% of ZnEt_2 and 10 mol% of chiral Pybox ligand **376** promoted the asymmetric propargylic substitution of aryl- and alkyl-substituted 5H-thiazol-4-ones **377** with various propargyl carbonates **378** in 1,4-dioxane

as solvent, leading at room temperature to the corresponding chiral highly functionalized terminal-alkyne-containing products **379** in good to high yields (59–99%) and diastereoselectivities (66–88% de) associated to uniformly high enantioselectivities (85–95% ee), as presented in Scheme 125. In this process, the chiral copper catalyst was supposed to form chiral allenic intermediate **AU** with propargyl carbonate **378** while ZnEt₂ activated the 5H-thiazol-4-one nucleophile into enolate **AV**.

While asymmetric intramolecular halocyclizations have been well studied (Section 14), intermolecular versions using alkenes and carboxylic acids are still limited due to the difficulty of controlling the intermolecular reaction. In 2020, Arai et al. described the first example of asymmetric iodoesterification of simple non-functionalized alkenes, which was catalyzed by a chiral zinc complex derived from (*R*)-BINOL-derived bis(aminoimino) ligand **380** (5 mol%) [161]. As shown in Scheme 126, the process employed *N*-iodonaphthalenimide **381** as iodide agent combined with I₂. The iodoesterification of a series of simple alkenes **382** with different carboxylic acids **263** performed in dichloromethane at –78 °C led to the corresponding chiral iodoesters **383** in good to quantitative yields (60–99%) and moderate to high enantioselectivities (54–90% ee).

17. Conclusions

As an inexpensive, abundant and less toxic metal, zinc has gained a significant importance in green catalysis. While underestimated for a long time, zinc catalysts are more and more applied to promote all types of economic and ecologic transformations. Especially, a spectacular development of highly enantioselective zinc-catalyzed transformations has emerged. This review highlights the recent advances in asymmetric synthesis promoted by chiral zinc catalysts reported since the beginning of 2015, demonstrating that zinc has become capable of replacing other transition metals. The diversity of the chiral zinc complexes employed reflects that of the asymmetric reactions successfully developed, including cycloadditions, alkynylation and allylation reactions of carbonyl compounds and derivatives, additions of diorganozincs to carbonyl compounds and derivatives, Mannich reactions, (nitro)aldol reactions, other 1,2-nucleophilic additions to carbonyl compounds and derivatives, Michael additions, Friedel-Crafts reactions, reductions, α -functionalizations of carbonyl compounds, ring-opening reactions, epoxidations, halolactonizations, domino and tandem reactions among other reactions. In these generally highly enantioselective processes, a wide variety of chiral ligands have been chelated to zinc, such as semi-aza-crown ligands, e.g. chiral ProPhenol and AzePhenol respectively introduced by Trost and Wang, but also bisoxazolines, *N,N'*-dioxides, biphosphines, amino alcohols, BINOL derivatives, diamines, Schiff bases, cinchona alkaloids, bisamidines, and salen ligands among others. Moreover, dual metal catalysis, combining a chiral zinc catalyst with another metal, such as nickel, indium, palladium, iridium, rhodium, palladium, iron or copper, has generated excellent results in many types of enantioselective transformations, spanning from [2 + 2] cycloadditions, propargylations of aldehydes, transfer hydrogenations, α -allylations of indanones, ring-opening reactions, cross-dehydrogenative couplings, propargylic substitutions, etc to more complex domino reactions. The low price of zinc makes zinc catalysis suiting the growing demand for more environmentally benign 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 and that this original field is growing very rapidly. Even if remarkable results have been described, challenges remain such as the use of zinc in more multicatalyzed processes especially that based on the combi-

nation of zinc with organocatalysts. Moreover, more applications in the total synthesis of important biologically active and natural products are needed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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