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Enantioselective Zirconium-Catalyzed Transformations

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Abstract: Cheaper and less-toxic metals of Group 4 compared with common metals used in catalysis are more and more applied in catalysis, resulting in the development of many types of novel greener transformations. Among these metals, zirconium presents the advantage to be abundant, non-toxic, and exhibit a remarkably diversified chemical reactivity. Since the first asymmetric zirconium-catalyzed reaction disclosed by Nugent in 1992, a wide variety of chiral zirconium catalysts have been proven to be capable of promoting many types of highly enantioselective transformations, spanning from standard reactions, such as Friedel–Crafts reactions, cycloadditions, aldol reactions, Mannich reactions, epoxidations, nucleophilic additions to carbonyl compounds and derivatives, cyanations, ring-opening reactions, hydroxylations, hydroformylations, carboaluminations among others, to more modern and complex domino and tandem processes. The aim of this review is to collect the major progress achieved in the field of enantioselective transformations of all types promoted by chiral zirconium catalysts, covering the literature since the beginning of 2003 and illustrating the power of these non-toxic catalysts to provide high enantioselectivity in almost all kinds of asymmetric organic reactions. It is divided into ten parts, focussing consecutively with enantioselective Friedel–Crafts reactions, cycloadditions, aldol reactions, Mannich reactions, epoxidations, additions of alkylzinc reagents to imines, cyanations, ring-opening reactions, hydroxylations, and domino/tandem reactions. The diversity of these transformations well reflects that of the products synthesized. For example, chiral indole and pyrrole derivatives were prepared from Friedel–Crafts reactions; pyranones, pyridones and pyrazolidines from cycloadditions; β -hydroxy α -diazo carbonyl compounds, β -hydroxy (thio)esters and β -hydroxy- α -amino acid derivatives from aldol reactions; β -amino (thio)esters from Mannich reactions; functionalized epoxides from epoxidations; amines from additions of alkylzinc reagents to imines; amino nitriles from cyanations; 1,2-diamines and β -vinyloxy alcohols from ring-opening processes; 2-hydroxy 1-indanones from hydroxylations; various amines, 1,3-*anti*-diol monoesters, β -amino esters, α,β -dihydroxy acid derivatives, α -amino ketones, indoles, cyclopentanes and aryl α -aminophosphonates from domino/tandem reactions. Furthermore, the utility of these novel methodologies was demonstrated in the total synthesis of numerous important bioactive products, such as (+)-prelactone C, (+)-9-deoxygoniopypyrone, (+)-coniine, vancomycin, (+)-fusarisetin A, mycolipenic acid, onchidin, indoxacarb, tachykinin receptor antagonists, cerebroprotecting agent MS-153, and *L-erythro*-sphingosine.

The advances achieved in the last three decades demonstrate that the non-toxicity, abundance, and efficiency of zirconium make its application in catalysis suiting the growing demand for more environmentally benign processes, offering the real opportunity to replace other toxic and expensive metals in the near future.

Keywords: Zirconium; asymmetric catalysis; transition metals; enantioselectivity; enantioselective transformations; chirality

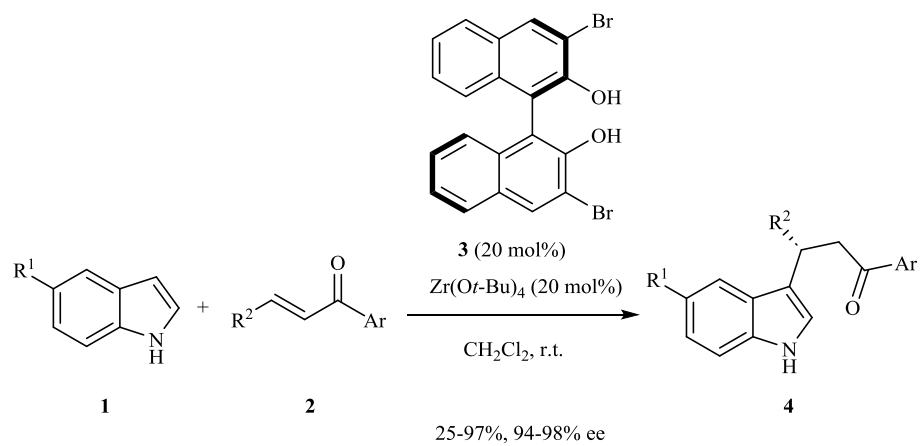
1. INTRODUCTION

Cheaper and less-toxic metals of Group 4 compared with common metals used in catalysis [1] are more and more applied in catalysis, resulting in the development of many types of novel greener transformations [2]. Among these metals, zirconium presents the advantage to exhibit a diverse chemical reactivity. Since the discovery of the hydrozirconation of alkenes by Schwartz and Hart in 1974 [3], zirconium catalysts have attracted increasingly the attention of chemists [4]. For example, the zirconium-catalyzed alkyne

carboalumination was disclosed by Negishi et al. in 1978 [5]. Later in the 1990's, zirconium catalysts were applied to promote oxidations of alcohols [6], Diels–Alder reactions [7] or polymerizations [8]. This is only in 1992 that the first asymmetric zirconium-catalyzed transformation was described by Nugent [9]. This work involved a zirconium catalyst derived from a chiral BINOL ligand which allowed the ring-opening reaction of *meso*-epoxides with azides with up to 93% ee. Later in 1995, high enantioselectivities of 95% ee were disclosed by Negishi et al. in the carboalumination of alkenes (ZACA reaction) catalyzed by zirconium [10]. Since then, many types of zirconium catalysts have been demonstrated to be capable of promoting a broad diversity of highly enantioselective methodologies, spanning from standard reactions, such as Friedel–Crafts reactions, cycloadditions, aldol reactions, Mannich reactions, epoxidations, nucleophilic additions to carbonyl compounds and derivatives, cyanations, ring-opening reactions, hydroxylations, hydroformylations, carboaluminations among others, to more modern and elaborated domino and tandem processes. The aim of this review is to collect the developments in enantioselective zirconium-catalyzed transformations published since the beginning of 2003, since the most recent report in this field was published in 2002 by Hoveyda in a book chapter [11], and previously in 2001 by Shibasaki et al. [12]. Ten parts compose the review, focussing consecutively with enantioselective Friedel–Crafts reactions, cycloadditions, aldol reactions, Mannich reactions, epoxidations, additions of alkylzinc reagents to imines, cyanations, ring-opening reactions, hydroxylations, and domino/tandem reactions. It must be noted that enantioselective zirconium-catalyzed hydroaminations and carboaluminations of alkenes are not included because these special fields have been recently reviewed [13].

2. ENANTIOSELECTIVE ZIRCONIUM-CATALYZED FRIEDEL–CRAFTS REACTIONS

Asymmetric versions of the Friedel–Crafts reaction allow the synthesis of useful chiral alkylated arenes to be achieved [14]. Especially, numerous biologically active and natural products have been synthesized through enantioselective Friedel–Crafts reactions of indoles. For example in 2007, Pedro et al. described an asymmetric Friedel–Crafts reaction of indoles **1** with β -substituted α,β -unsaturated ketones **2** (Scheme 1) [15]. The reaction was catalyzed at room temperature by 20 mol% of a combination of $Zr(Ot\text{-}Bu)_4$ and chiral BINOL-derived ligand **3** in dichloromethane as solvent, which afforded a variety of chiral 3-alkylated indoles **4** with 25-97% yields and 94-98% ee. Later in 2012, the scope of this methodology was extended to other substituted indoles with comparable results [16]. A mechanism is proposed in Scheme 1 showing the formation of dimeric active catalyst **A** from the reaction between $Zr(Ot\text{-}Bu)_4$ and two equivalents of the chiral ligand. Then, active catalyst **A** reacted with the enone to form complex **B**, which further coordinated the indole to generate intermediate **C**. Subsequently, intermediate **C** underwent a conjugate addition of the indole to the enone, thus producing intermediate **D**. The latter underwent a H-shift to provide chiral enolate intermediate **E**, which finally afforded the expected Friedel–Crafts product together with the regeneration of catalyst **A**.

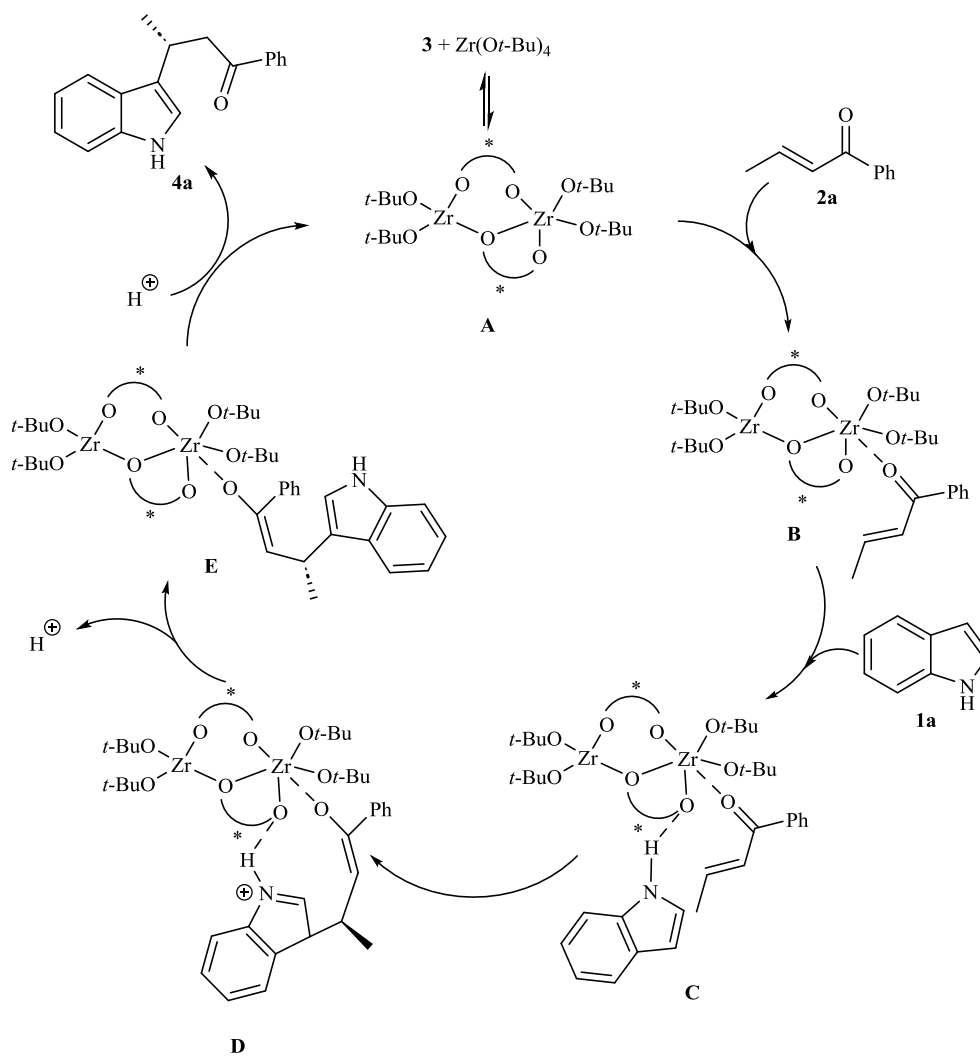


$\text{R}^1 = \text{H, Me, OMe, Cl}$

$\text{R}^2 = \text{Me, Et, Pr, Ph}$

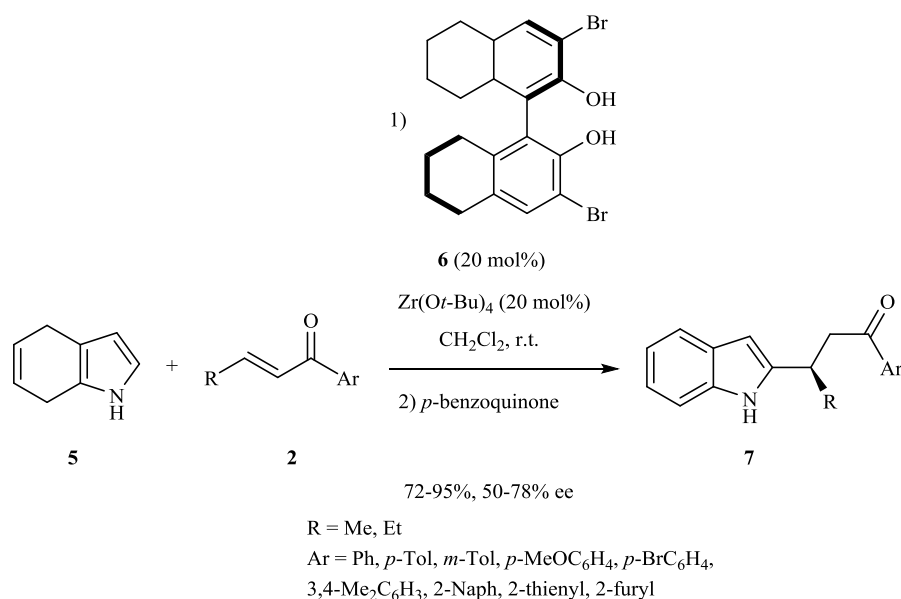
$\text{Ar} = \text{Ph, } p\text{-Tol, } m\text{-Tol, } o\text{-MeOC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, 2\text{-Naph, } 2\text{-thienyl}$

proposed mechanism (with $\text{Ar} = \text{Ph, R}^1 = \text{H, R}^2 = \text{Me}$):

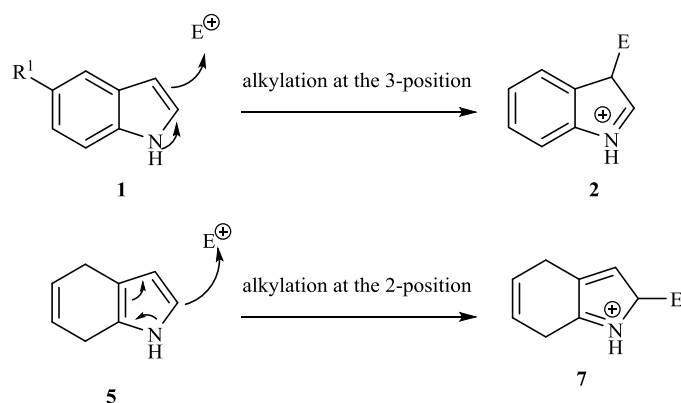


Scheme 1. Friedel–Crafts reaction of indoles with β -substituted α,β -unsaturated ketones.

In 2007, these authors disclosed the first asymmetric Friedel–Crafts alkylation taking place at the 2-position of an indole derivative in the presence of the same electrophiles [17]. As illustrated in Scheme 2, the reaction of 4,7-dihydroindole **5** with β -substituted α,β -unsaturated ketones **2** involved the presence of 20 mol% of $Zr(Ot-Bu)_4$ and the same quantity of chiral ligand **6** derived from BINOL as catalyst system. After further oxidation with *p*-benzoquinone, chiral indoles **7** alkylated at the 2-position were obtained with 72-95% yields and 50-78% ee. The distinct regioselectivity observed in the alkylation of indoles **1** (Scheme 1) and dihydroindoles **5** (Scheme 2) is comparable to that between indoles and pyrroles. Indeed, indoles are known to undergo electrophilic substitution preferentially at the 3-position whereas pyrrole reacts at the 2-position. This positional selectivity is explained by the stability of the Wheland intermediates for electrophilic substitution. The intermediate cations from β - for indoles and α - for pyrroles are the more stabilized. The two mechanistic pathways depicted in Scheme 2 illustrate the different regioselectivity.

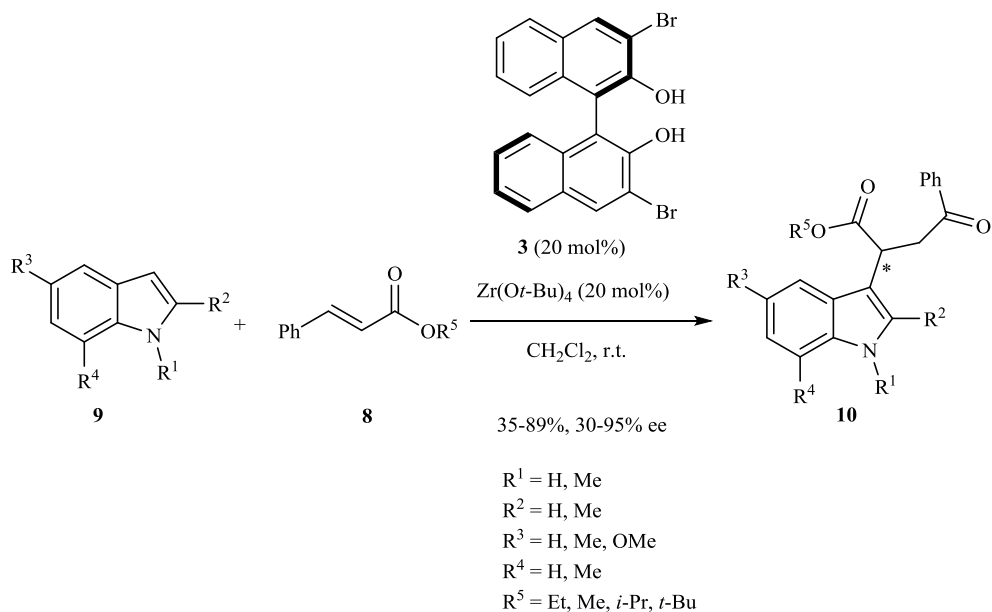


Distinct regioselectivity at the 3-/2-position of indoles **1**/dihydroindoles **5** (with E = electrophile):



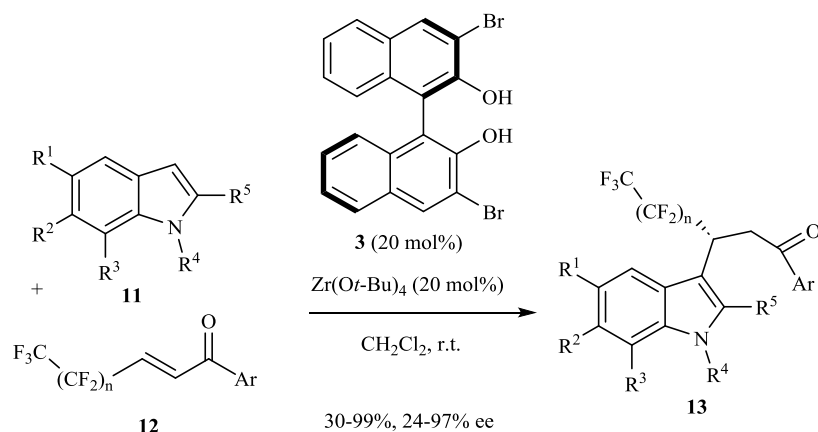
Scheme 2. Friedel–Crafts reaction at the 2-position of 4,7-dihydroindole with β -substituted α,β -unsaturated ketones.

In 2009, the scope of the methodology described in Scheme 1 could be extended to other electrophiles, such as (*E*)-4-oxo-4-phenylbutenoates **8** [18]. Indeed, the Friedel–Crafts reaction of these substrates with indoles **9** afforded chiral functionalized indoles **10** with 35-89% yields and 30-95% ee, as presented in Scheme 3.



Scheme 3. Friedel–Crafts reaction of indoles with (*E*)-4-oxo-4-phenylbutenoates.

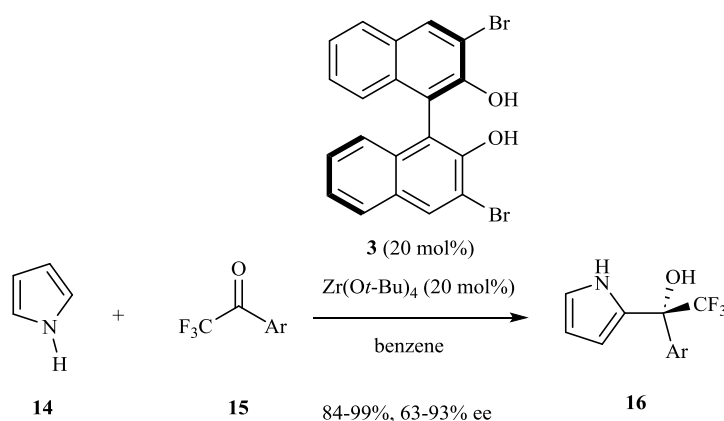
The biological properties of molecules are sometimes influenced by the presence of a trifluoromethyl group in their skeletons. In this context, the same catalyst was later employed in the asymmetric Friedel–Crafts reaction of indole derivatives **11** with β -perfluoroalkyl-substituted α,β -unsaturated ketones **12** (Scheme 4) [19]. The reaction occurred smoothly to deliver variously substituted chiral fluoroalkylated indoles **13** with 30-99% yields and 24-97% ee.



$\text{R}^1 = \text{H, Me, OMe, Br}$
 $\text{R}^2 = \text{H, Me}$
 $\text{R}^3 = \text{H, Me}$
 $\text{R}^4 = \text{H, Me}$
 $\text{R}^5 = \text{H, Me}$
 $\text{Ar} = \text{Ph, } p\text{-Tol, } o\text{-Tol, } p\text{-MeOC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4,$
 $p\text{-O}_2\text{NC}_6\text{H}_4, 2\text{-Naph, } 2\text{-thienyl}$
 $n = 0\text{-}1$

Scheme 4. Friedel–Crafts reaction of indoles with β -perfluoroalkyl-substituted α,β -unsaturated ketones.

Along with indole derivatives as nucleophilic partners, the same authors also disclosed in 2009 the first zirconium-catalyzed Friedel–Crafts reaction of unprotected pyrrole **14** with trifluoroacetophenones **15** [20]. As shown in Scheme 5, the same catalyst was employed in benzene as solvent, allowing chiral pyrroles **16** bearing a trifluoromethyl-substituted tertiary alcohol to be produced with 63–93% ee and 84–99% yields. Studying the substrate scope of the process, the authors found that the reaction of an aliphatic trifluoromethyl ketone (Et instead of Ar) with pyrrole **14** led to the corresponding product with only 21% ee while combined with 92% yield.

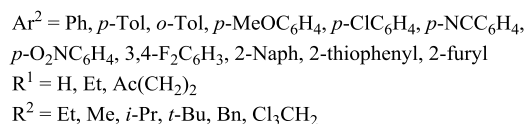
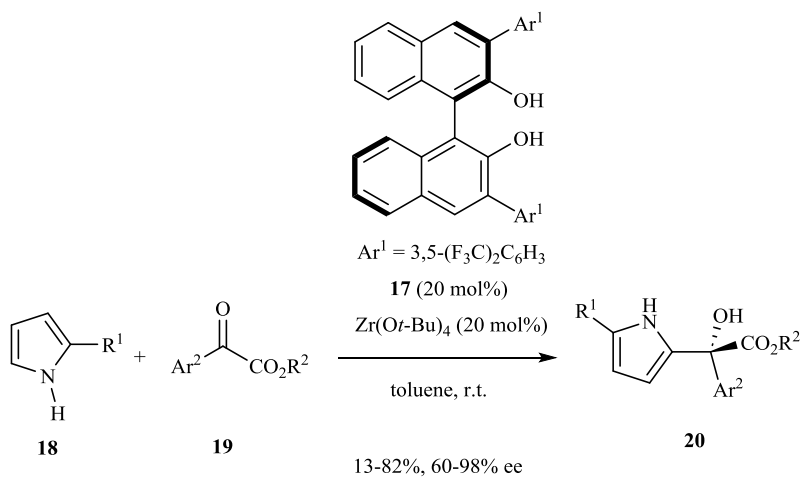


$\text{Ar} = \text{Ph, } p\text{-Tol, } p\text{-MeOC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-EtC}_6\text{H}_4,$
 $p\text{-MeSC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, m\text{-FC}_6\text{H}_4,$
 $m\text{-MeOC}_6\text{H}_4, m\text{-Tol, } 3,4\text{-F}_2\text{C}_6\text{H}_3, 3,4\text{-Cl}_2\text{C}_6\text{H}_3$

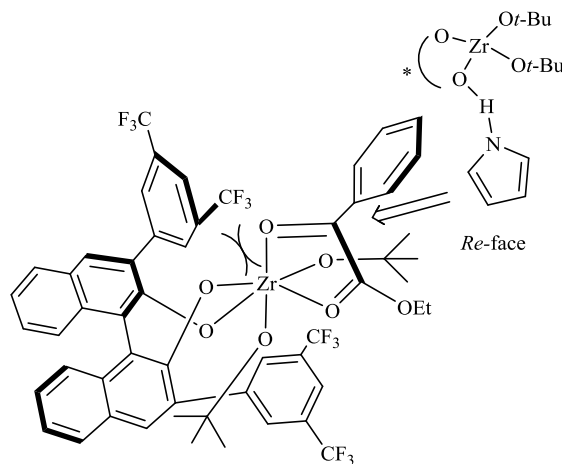
Scheme 5. Friedel–Crafts reaction of pyrrole with trifluoroacetophenones.

In 2011, chiral BINOL-derived ligand **17** was employed at 20 mol% of catalyst loading with 20 mol% of $\text{Zr(O}t\text{-Bu)}_4$ to promote the first enantioselective Friedel–Crafts reaction of pyrroles **18** with α -ketoesters **19** (Scheme 6) [21]. The reaction afforded at room temperature in toluene chiral tertiary alcohols **20** with 13–82%

yields and 60-98% ee. The stereoselectivity of the process can be explained by the octahedral transition state depicted in Scheme 6 in which the zirconium center was chelated to the two oxygen atoms of the ligand and to the α -ketoester with its ketone carbonyl group situated in one of the apical positions. In this context, the pyrrole attacked preferentially from the *Re*-face of the ketone moiety since the *Si*-face was hampered by one of the naphthyl moieties of the ligand, which finally delivered the product.



proposed transition state (with $\text{Ar}^2 = \text{Ph}, \text{R}^1 = \text{H}, \text{R}^2 = \text{Et}$):

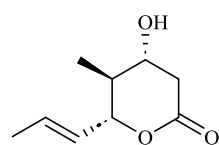
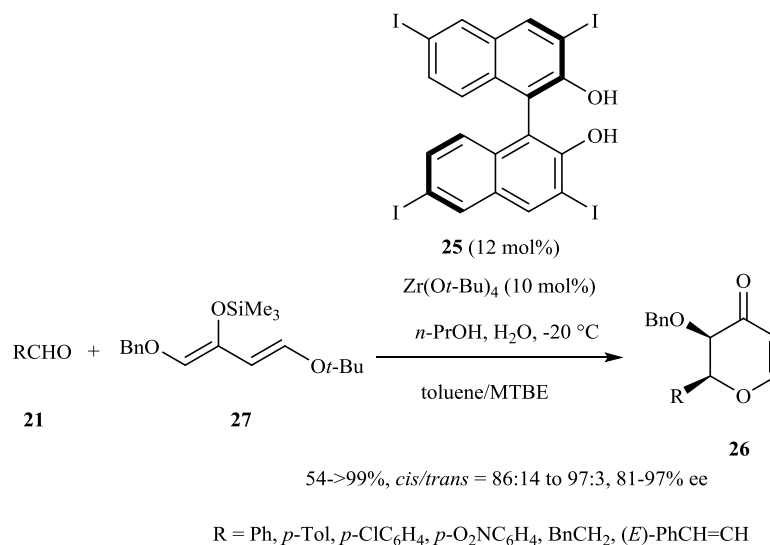
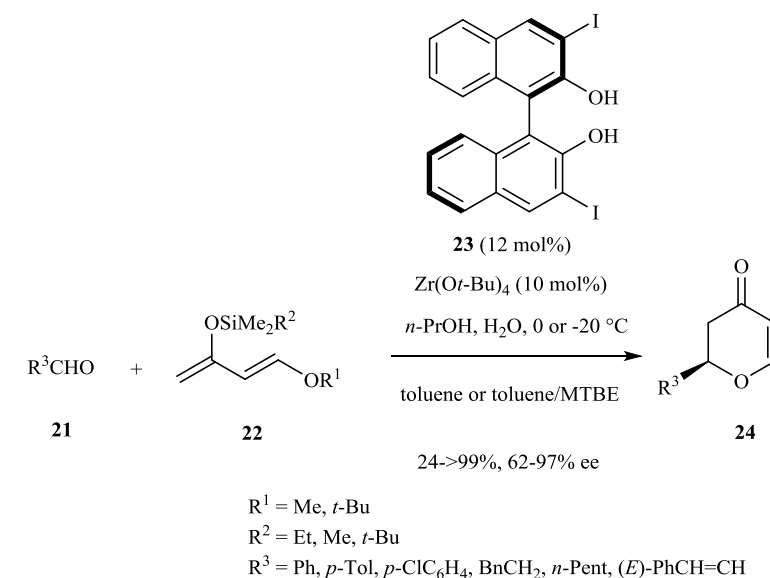


Scheme 6. Friedel–Crafts reaction of pyrroles with α -ketoesters.

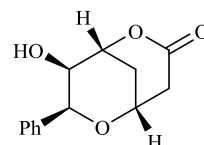
3. ENANTIOSELECTIVE ZIRCONIUM-CATALYZED CYCLOADDITIONS

Chiral six-membered heterocycles can be directly synthesized from asymmetric hetero-Diels–Alder cycloadditions [22]. A range of chiral metal complexes, including zirconium catalysts, have been applied to promote these reactions between aldehydes and activated dienes [23]. In 1998, Kobayashi et al. described the first enantioselective zirconium-catalyzed aza-Diels–Alder reaction of aldimines with Danishefsky’s diene to give chiral piperidine derivatives with up to 93% ee [24]. In an example reported later in 2003, the same authors investigated enantioselective hetero-Diels–Alder cycloaddition of Danishefsky’s dienes **22** with aldehydes **21** catalyzed by a combination of 10 mol% of $\text{Zr(O}t\text{-Bu)}_4$ and 12 mol% of BINOL-derived chiral ligand **23** (Scheme

7) [25]. The reaction proceeded smoothly at 0 or -20 °C in the presence of *n*-propanol and water as additives to afford chiral pyranone derivatives **24** in 24->99% yields and 62-97% ee. Moreover, closely related chiral BINOL-derivative **25** was found optimal ligand to prepare chiral 2,3-*cis*-pyranones **26** from the oxa-Diels–Alder cycloaddition of the corresponding aldehydes **21** with 4-benzyloxy Danishefsky's diene **27**. These cycloadducts were synthesized in 54->99% yields with both good to high *cis*-diastereoselectivities (*cis/trans* = 86:14 to 97:3) and enantioselectivities (81-97% ee). The utility of this novel methodology was demonstrated in the synthesis of important natural bioactive pyranones (+)-prelactone C and (+)-9-deoxygoniopyrone.



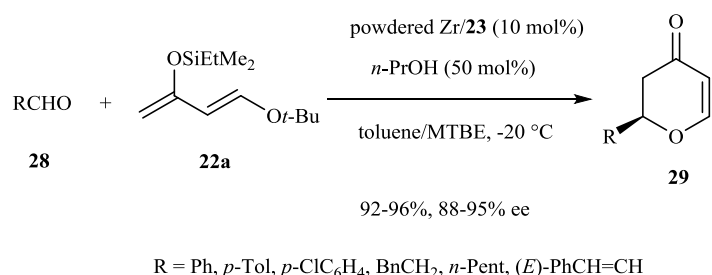
(+)-prelactone C



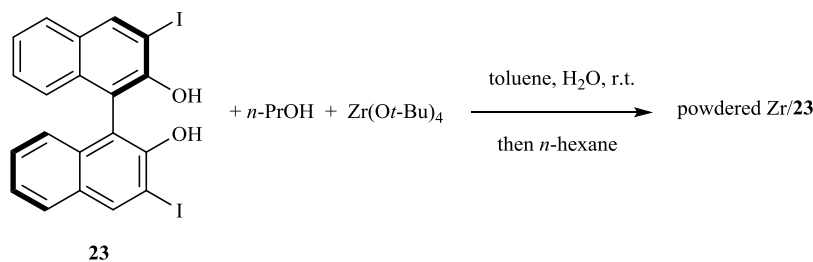
(+)-9-deoxygoniopyrone

Scheme 7. Oxa-Diels–Alder cycloadditions of aldehydes with Danishefsky's dienes.

Lewis acid catalysts are generally sensitive to air and moisture and, consequently, they cannot be stored for long periods. With the aim of developing an isolable and storable chiral zirconium catalyst to be employed in comparable cycloadditions, Kobayashi et al. described in 2007 a new storable powdered chiral zirconium catalyst (powdered Zr/**23**) readily synthesized from stirring at room temperature $Zr(Ot\text{-}Bu)_4$, chiral BINOL-derived ligand **23**, and *n*-propanol in toluene, followed by addition of dry *n*-hexane which underwent precipitation of the solid catalyst [26]. This catalyst was employed to induce the enantioselective oxa-Diels–Alder cycloaddition of Danishefsky’s diene **22a** with aromatic or aliphatic aldehydes **28** to deliver the corresponding chiral pyranones **29** with 92-96% yields and 88-95% ee, as illustrated in Scheme 8. It must be noted that this catalyst could be stored several months without loss of activity.

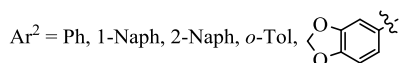
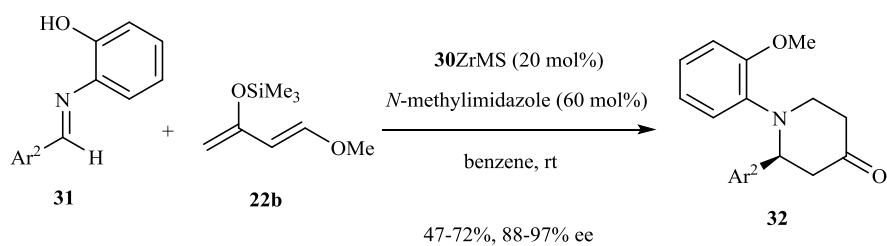


preparation of powdered Zr/**23**:

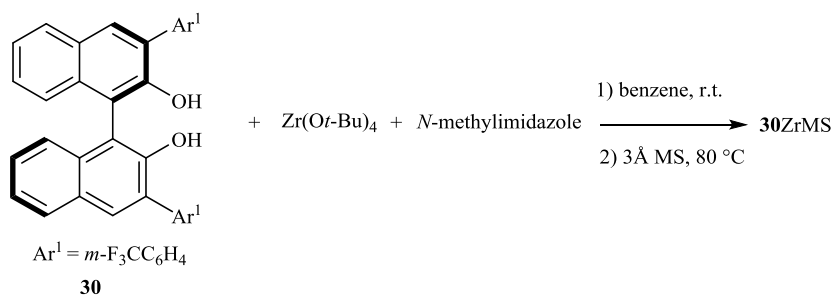


Scheme 8. Oxa-Diels–Alder cycloaddition of aldehydes with Danishefsky’s diene in the presence of powdered Zr/**23**.

Earlier in 2004, the same authors developed other stable chiral zirconium Lewis acids which could be stored for long periods in air at room temperature in the presence of molecular sieves without loss of activity [27]. Among these recoverable preformed catalysts, complex **30**ZrMS was generated from the reaction at room temperature between $Zr(Ot\text{-}Bu)_4$, chiral BINOL-derived ligand **30**, and *N*-methylimidazole in benzene, followed by addition of molecular sieves and then heating at 80 °C. Using 20 mol% of this catalyst in the presence of *N*-methylimidazole as an additive in benzene allowed the enantioselective aza-Diels–Alder cycloaddition between aromatic imines **31** and Danishefsky’s diene **22b** to be achieved at room temperature (Scheme 9). The process led to chiral 2,3-dihydro-4-pyridones **32** in 47-72% yields and 88-97% ee.

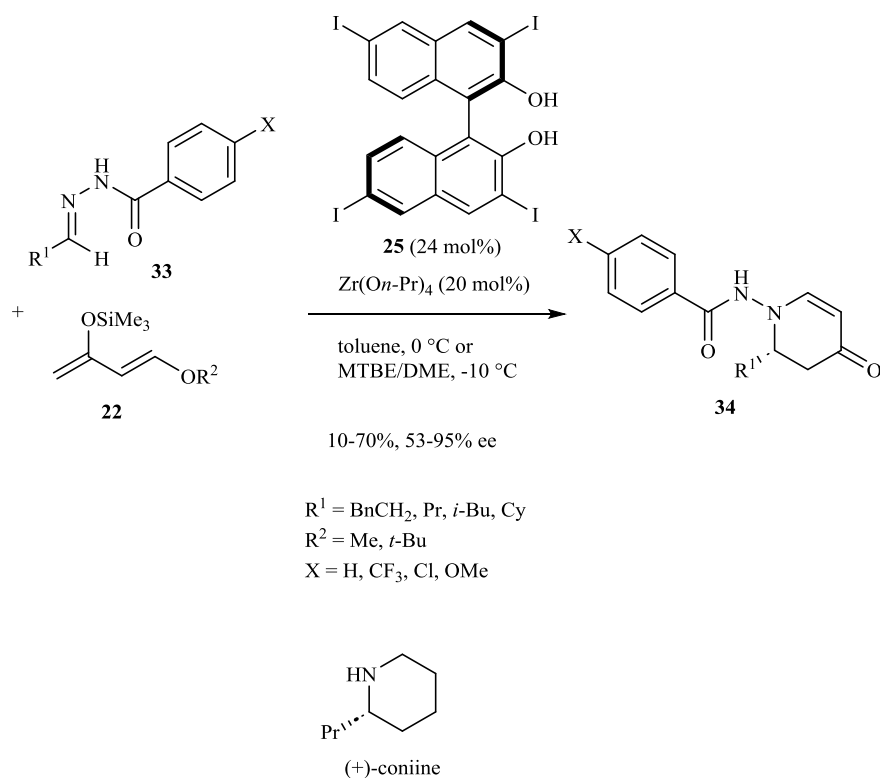


preparation of catalyst **30ZrMS**:



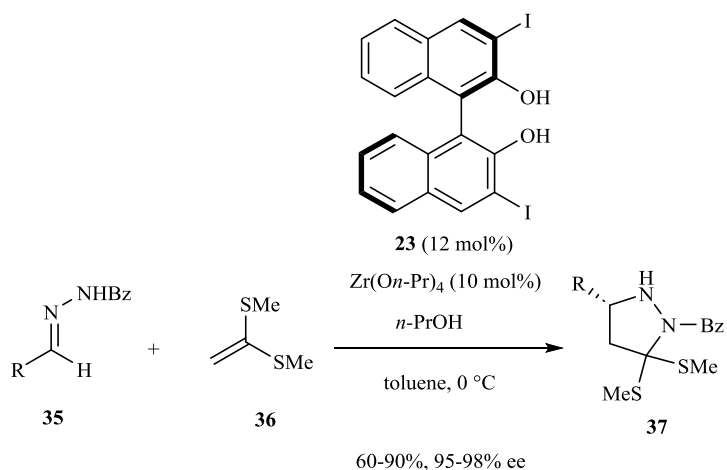
Scheme 9. Aza-Diels–Alder cycloaddition of aromatic imines with Danishefsky’s diene in the presence of **30ZrMS**.

The precedent methodology suffered from a limited substrate scope, since it was not applicable to aliphatic imines. To fill this gap, the same authors developed in 2005 enantioselective aza-Diels–Alder cycloadditions of aliphatic acylhydrazones **33** with Danishefsky’s dienes **22** [28]. As illustrated in Scheme 10, a chiral zirconium complex in situ prepared from 20 mol% of $\text{Zr(}On\text{-Pr)}_4$ and 24 mol% of chiral BINOL-derived ligand **25** was found to be effective at 0 °C in toluene to produce a series of chiral 2,3-dihydro-4-pyridones **34** with 53-95% ee and 10-70% yields. This methodology was applied to develop a formal synthesis of natural product (+)-coniine.

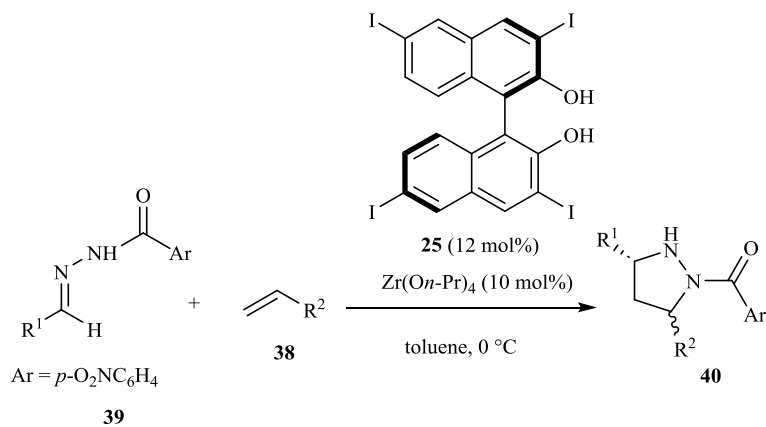


Scheme 10. Aza Diels–Alder cycloaddition of aliphatic acylhydrazones with Danishefsky’s dienes.

Chiral five-membered heterocycles can be directly synthesized through asymmetric [3+2] cycloadditions of olefins with 1,3-dipoles [29]. In 2004, Kobayashi et al. investigated the enantioselective 1,3-dipolar cycloaddition of acylhydrazones with alkenes promoted by chiral zirconium catalysts derived from BINOL-derived chiral ligands [30]. For example, a combination of 10 mol% of $\text{Zr}(\text{On-Pr})_4$ with 12 mol% of chiral ligand **23** was found capable of promoting at 0 °C in toluene in the presence of propanol as an additive the enantioselective [3+2] cycloaddition of benzoylhydrazones **35** with ketene dimethyl dithioacetal **36**. This led to chiral pyrazolidines **37** in 60-90% yields and 95-98% ee (Scheme 11). In addition, other types of olefins, such as vinyl (thio)ethers **38**, were compatible to the [3+2] cycloaddition with acylhydrazones **39**, thus producing chiral pyrazolidines **40** as mixtures of two diastereomers. These products were obtained with 4-62% de and 38-95% yields when the reaction was catalyzed at 0 °C in toluene by a catalyst derived from 10 mol% of $\text{Zr}(\text{On-Pr})_4$ and 12 mol% of related chiral ligand **25**. The major and minor diastereomers were obtained with 84-99% ee and 92-99% ee, respectively. The authors demonstrated that the cycloadditions proceeded via concerted pathways depicted in Scheme 11. The methodology allowed the synthesis of cerebroprotecting agent MS-153 to be achieved.



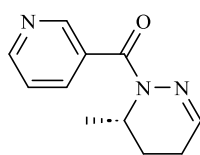
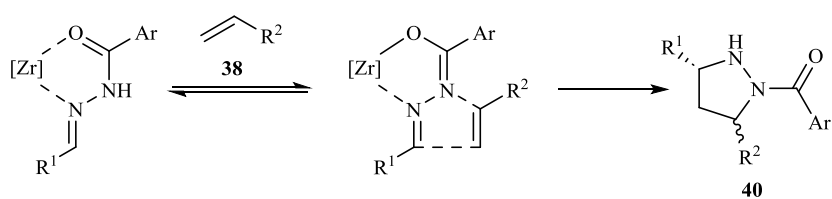
R = BnCH₂, *i*-Bu, Cy, Bu, Pr, Bn, TBSO(CH₂)₂



R¹ = BnCH₂, *i*-Bu, Cy, *n*-Bu, Bn

R² = OEt, OPr, *O**t*-Bu, SEt

concerted pathway:

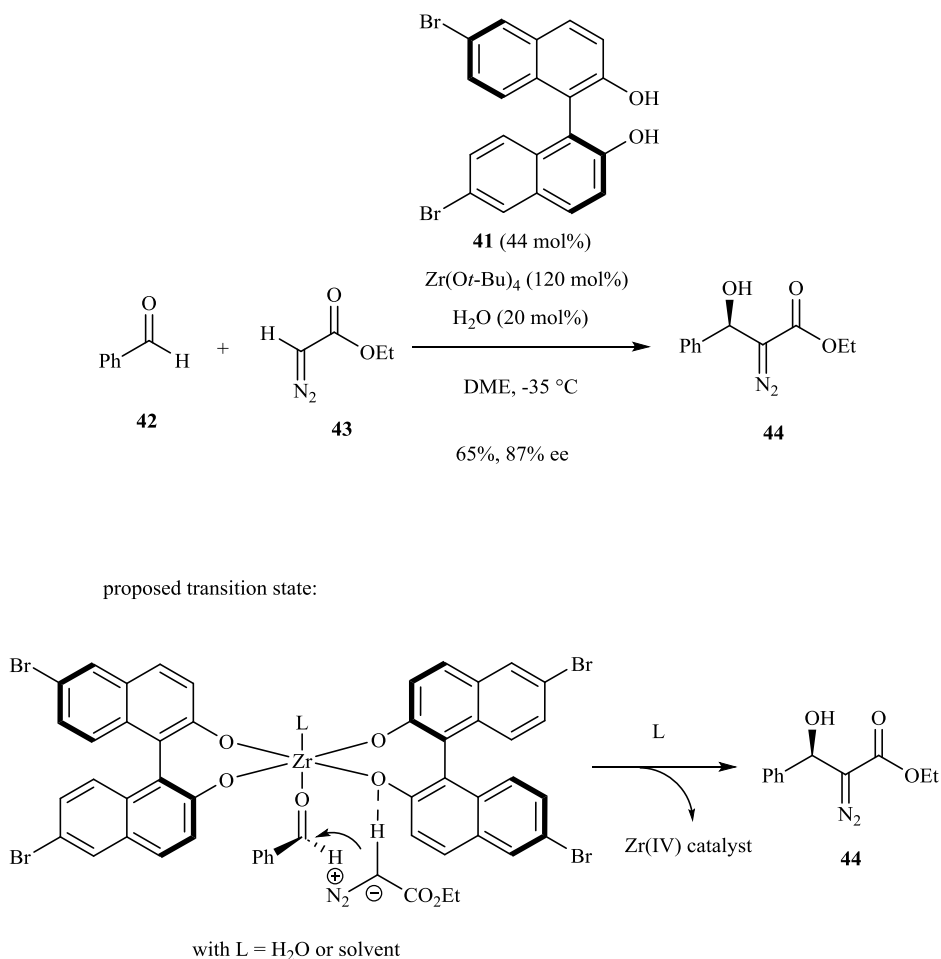


ent-MS-153

Scheme 11. [3+2] Cycloadditions of hydrazones with olefins.

4. ENANTIOSELECTIVE ZIRCONIUM-CATALYZED ALDOL REACTIONS

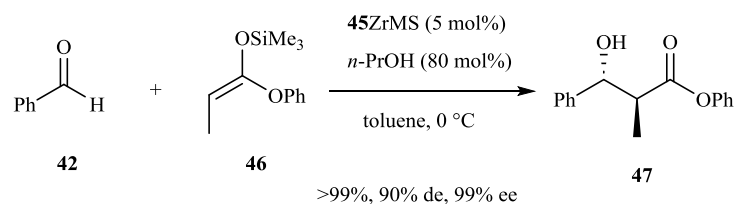
Chiral β -hydroxy carbonyl compounds, constituting key intermediates in synthesis, can be easily synthesized from direct catalytic asymmetric aldol reaction. In particular, a wide variety of catalysts have been employed in aldol reactions of aldehydes [31]. In 2003, Wang and Yao reported for the first time the application of ethyl diazoacetate as nucleophile in a catalytic asymmetric aldol-type reaction with aldehydes by using a chiral zirconium catalyst [32]. As illustrated in Scheme 12, the latter was formed from the reaction between 20 mol% of $Zr(Ot\text{-}Bu)_4$ and 44 mol% of chiral BINOL-derived ligand **41** in DME as solvent. The reaction provided better results when performed in the presence of water as an additive at $-35\text{ }^\circ\text{C}$. The highest enantioselectivity (87% ee) was achieved in the reaction occurring between benzaldehyde **42** and ethyl diazoacetate **43**, leading to the corresponding chiral β -hydroxy α -diazo carbonyl compound **44** with 65% yield. Other aromatic but also aliphatic aldehydes were tolerated by using closely related chiral ligands but lower ee values were obtained (53–79% ee) in all cases. The stereoselectivity of the reaction can be explained by the transition state depicted in Scheme 12 in which the zirconium center was chelated by two equivalents of chiral ligand and carbonyl group of the aldehyde substrate. Then, one ligand brought the ethyl diazoacetate substrate close to the aldehyde through hydrogen bonding to allow the nucleophilic attack to occur.



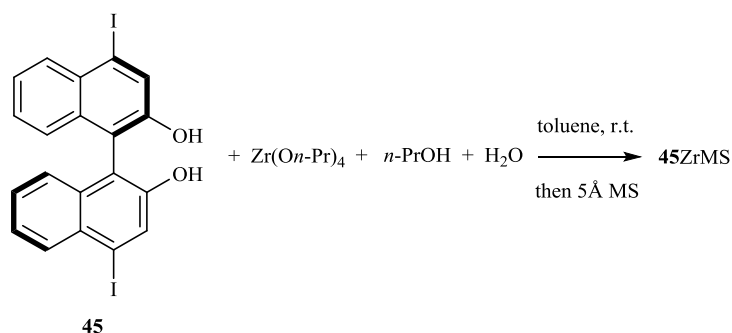
Scheme 12. Aldol-type reaction of benzaldehyde with ethyl diazoacetate.

In the same year, Kobayashi et al. developed asymmetric Mukaiyama aldol reactions between aldehydes and ketene silyl acetals promoted by a novel stable chiral oligomeric zirconium catalyst **45**ZrMS combined with molecular sieves powder, which could be stored for several months at room temperature [33]. The preparation of the latter consisted in mixing at room temperature $Zr(On\text{-}Pr)_4$, chiral BINOL-derived ligand **45**, *N*-methylimidazole, propanol, and water in toluene, followed by incorporation of molecular sieves. When this

catalyst was used at 5 mol% of catalyst loading at 0 °C in toluene in the presence of propanol as an additive to promote the aldol reaction between benzaldehyde **42** and ketene silyl acetal **46**, it led to the corresponding enantiopure (99% ee) aldol product **47** with 90% de and quantitative yield (Scheme 13).

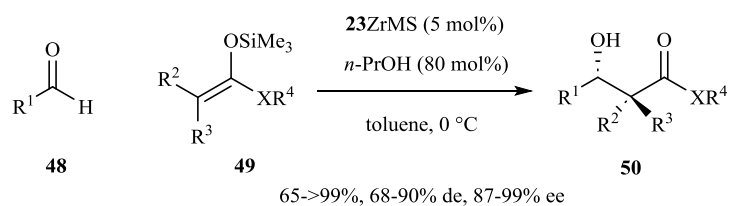


preparation of catalyst **45**ZrMS:



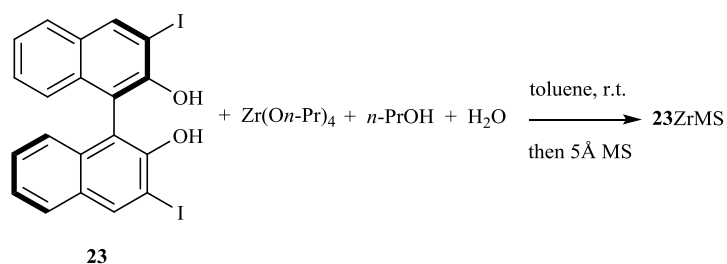
Scheme 13. Mukaiyama aldol reaction of benzaldehyde with a ketene silyl acetal in the presence of **45**ZrMS.

In 2004, these authors investigated a related chiral catalyst in order to extend the scope of these Mukaiyama aldol reactions between other aldehydes **48** and ketene silyl acetals **49** (Scheme 14) [27]. It was found that other substrates smoothly underwent the reaction when 5 mol% of catalyst **23**ZrMS was employed in association with 80 mol% of propanol as additive. Both aromatic and aliphatic aldehydes were tolerated, providing the corresponding aldol products **50** with 65->99% yields, 68-90% de, and 87-99% ee. The best results (80-99% yields, $\geq 84\%$ de and 92-99% ee) were achieved in the reaction of aromatic aldehydes while aliphatic ones ($R^1 = BnCH_2$, (*E*)-PhCH=CH) led to the desired products with generally decreased yields (65% for $R^1 = BnCH_2$), diastereoselectivities (68-70% de), and enantioselectivities (87% ee for $R^1 = BnCH_2$).



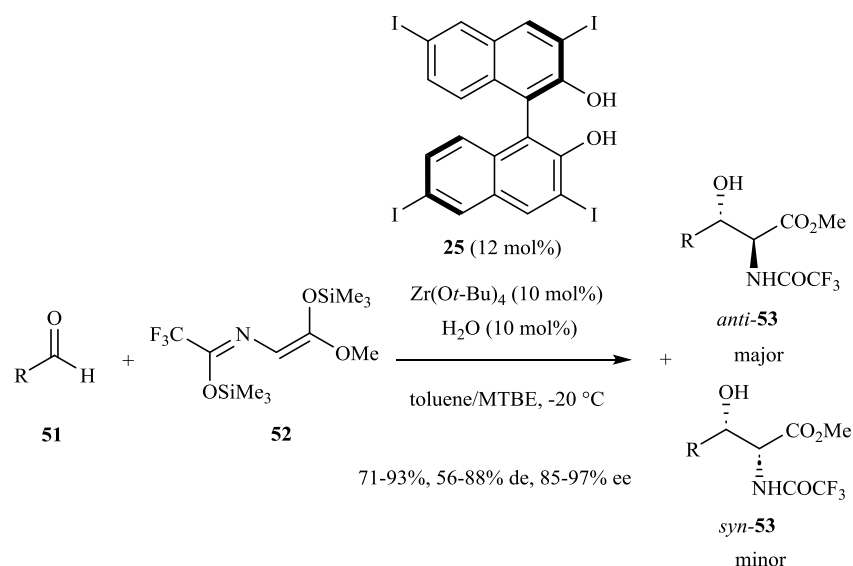
$R^1 = \text{Ph, } p\text{-MeOC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, (E)\text{-PhCH=CH, BnCH}_2$
 $R^2 = \text{H, Me}$
 $R^3 = \text{H, Me}$
 $\text{XR}^4 = \text{OMe, OPh, SEt}$

preparation of catalyst *ent*-**23**ZrMS:

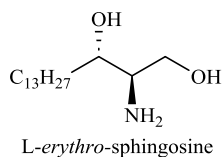


Scheme 14. Mukaiyama aldol reaction of aldehydes with ketene silyl acetals in the presence of **23**ZrMS.

β -Hydroxy- α -amino acids constitute important components of many bioactive and natural products. A privileged route to these molecules is the aldol reaction of aldehydes with glycine derivatives. In 2004, Kobayashi et al. developed a rare asymmetric version of this methodology based on the involvement of a chiral zirconium catalyst (Scheme 15) [34]. Indeed, aldehydes **51** reacted at $-20\text{ }^\circ\text{C}$ with glycine-derived silicon enolate **52** in the presence of a chiral complex derived from 10 mol% of $\text{Zr}(\text{O}t\text{-Bu})_4$ and 12 mol% of chiral BINOL-derived ligand **25** by using water (10 mol%) as an additive and a solvent composed of toluene and MTBE. The Mukaiyama aldol process resulted in the formation of chiral β -hydroxy- α -amino acid derivatives **53** as mixtures of *anti*- and *syn*-diastereomers with 71-93% yields and 56-88% de. Moreover, the major *anti*-diastereomers were achieved with uniformly high ee values (85-97% ee). The methodology was applied to develop an asymmetric synthesis of a cell membrane component L-*erythro*-sphingosine.

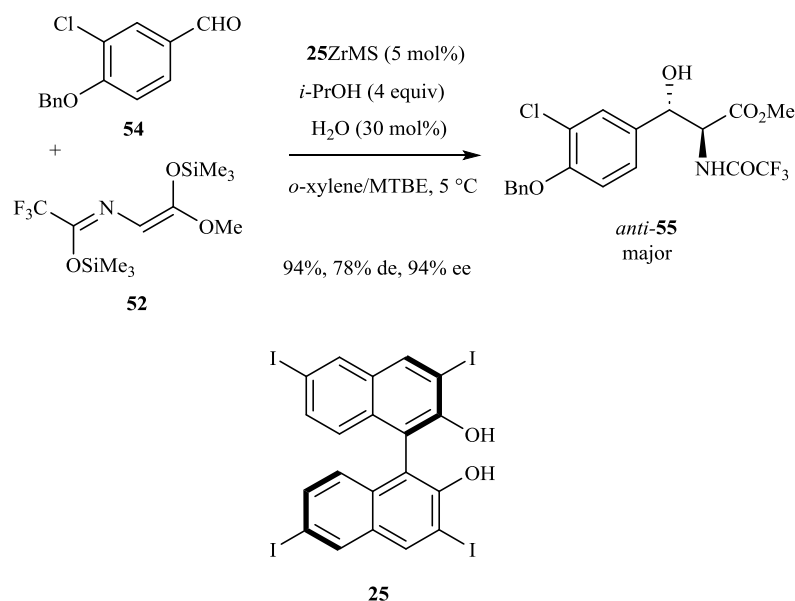


R = Ph, *p*-Tol, *m*-MeOC₆H₄, *p*-ClC₆H₄, *m*-Tol, *m*-ClC₆H₄,
3,5-(MeO)₂C₆H₃, 2-Naph, 2-furyl, Bn(CH₂)₂C≡C, TBDPSOCH₂C≡C



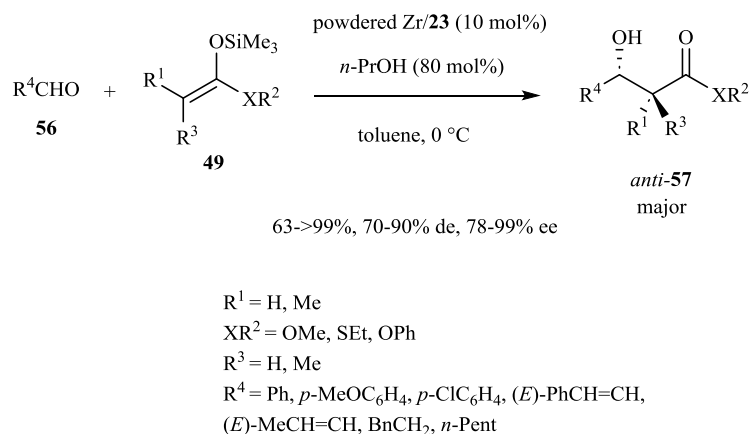
Scheme 15. Mukaiyama aldol reaction of aldehydes with a glycine-derived silicon enolate.

Later in 2006, the same group disclosed the preparation of a key building block for the synthesis of antibacterial vancomycin on the basis of a related methodology (Scheme 16) [35]. It dealt with the enantioselective Mukaiyama aldol reaction of aromatic aldehyde **54** with glycine-derived silicon enolate **52** performed at 5 °C in the presence of 5 mol% of a stable chiral zirconium molecular sieves combined catalyst **25**ZrMS. This catalyst was prepared by mixing Zr(*O-n*-Pr)₄, chiral BINOL-derived ligand **25**, and molecular sieves (5 Å MS) in toluene. The aldol condensation required the presence of four equivalents of isopropanol and 30 mol% of water as additives in a mixture of *o*-xylene and MTBE as solvent to afford expected chiral key building block **55** for the synthesis of vancomycin which was obtained as major *anti*-diastereomer with 78% de, 94% yield, and 94% ee.



Scheme 16. Mukaiyama aldol reaction of an aromatic aldehyde with a glycine-derived silicon enolate in the presence of **25ZrMS**.

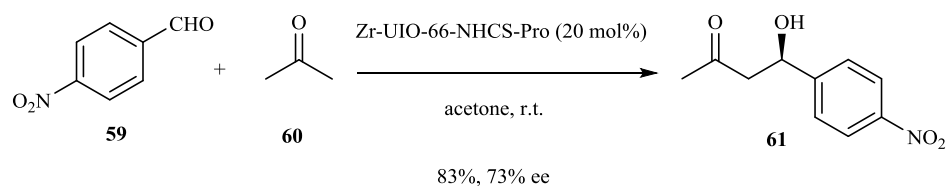
The novel stable powdered chiral zirconium catalyst (powdered **Zr/23**), readily prepared by mixing in toluene at room temperature $\text{Zr}(\text{O}t\text{-Bu})_4$, chiral BINOL-derived ligand **23**, *n*-propanol, and water followed by addition of dry *n*-hexane (Scheme 8), was developed and used by Kobayashi et al. to promote enantioselective Mukaiyama aldol reaction between aldehydes **56** and ketene silyl acetals **49** (Scheme 17) [26]. The reaction was carried out at 0 °C in toluene in the presence of 10 mol% of catalyst and *n*-propanol as an additive to give chiral *anti*-aldol products **57** with 63->99% yields, 70-90% de, and 78-99% ee. It must be noted that the reaction of aromatic aldehydes provided homogeneously high de values ($\geq 82\%$ de) while lower diastereoselectivities (70-78% de) were observed in that of aliphatic aldehydes.



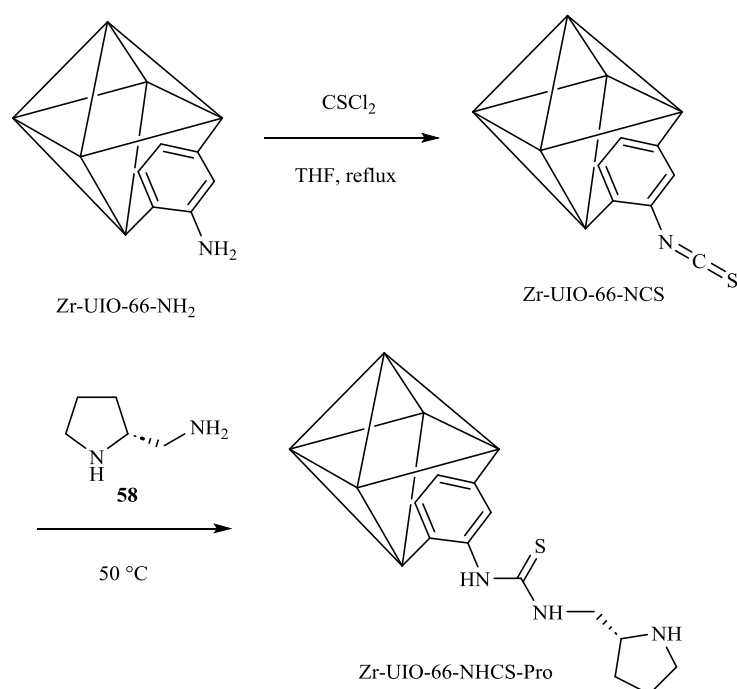
Scheme 17. Mukaiyama aldol reaction of aldehydes with ketene silyl acetals in the presence of powdered **Zr/23**.

Due to their high stability, metal-organic frameworks (MOFs) based on zirconium are much used [36]. In 2022, Liu and Meng reported the synthesis of novel zirconium-based MOFs, namely **Zr-UiO-66-NHCS-Pro**, through grafting proline-derived chiral moieties inside MOF cavities [37]. As shown in Scheme 18, **Zr-UiO-66-NH₂** reacted with sulfur phosgene to give the corresponding isothiocyanate **Zr-UiO-66-NCS**, which was subsequently submitted to proline-derived chiral amine **58** to generate final active catalyst **Zr-UiO-66-NHCS-**

Pro. The latter was further investigated as promotor in the asymmetric aldol reaction between acetone **60** and 4-nitrobenzaldehyde **59** (Scheme 18). In the presence of 20 mol% of this catalyst at room temperature in acetone as solvent, aldol product **61** was synthesized with 83% yield and 73% ee.



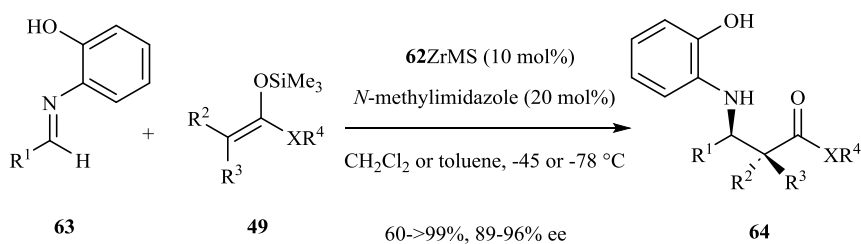
preparation of Zr-UIO-66-NHCS-Pro:



Scheme 18. Aldol reaction of 4-nitrobenzaldehyde with acetone in the presence of Zr-UIO-66-NHCS-Pro.

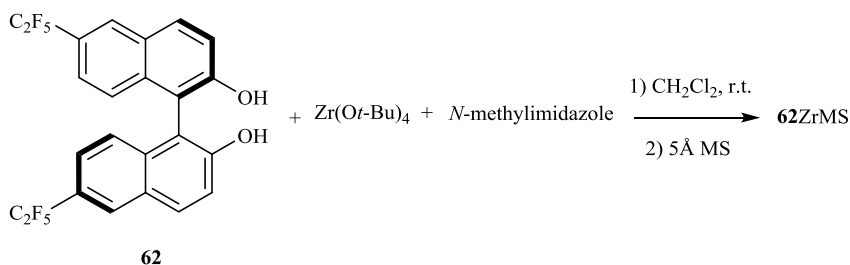
5. ENANTIOSELECTIVE ZIRCONIUM-CATALYZED TWO-COMPONENT MANNICH REACTIONS

In 1997, Kobayashi et al. reported the first enantioselective Mannich-type reaction of aldimines derived from 2-aminophenol with trimethylsilyl enolates catalyzed by a chiral zirconium complex [38]. This catalyst was in situ produced in the presence of $\text{Zr}(\text{O}t\text{-Bu})_4$ and a chiral BINOL-derived ligand, allowing enantioselectivities of up to 98% ee to be achieved. Ever since, modifications of this methodology have been made to improve the catalytic activity of chiral zirconium catalysts. Among them, the synthesis of stabilized zirconium catalyst **62**ZrMS from $\text{Zr}(\text{O}t\text{-Bu})_4$, chiral BINOL-derived ligand **62**, *N*-methylimidazole, and molecular sieves was reported by the same authors, in 2004 [27]. Strong electron-withdrawing C_2F_5 groups in ligand **62** increased the Lewis acidity of the zirconium, dramatically enhancing the reactivity. Using 10 mol% of this catalyst in the presence of *N*-methylimidazole as an additive in dichloromethane or toluene as solvent, the Mannich-type reaction of aldimines **63** derived from 2-aminophenol with trimethylsilyl enolates **49** afforded chiral Mannich products **64** with 60->99% yields and 89-96% ee, as shown in Scheme 19.



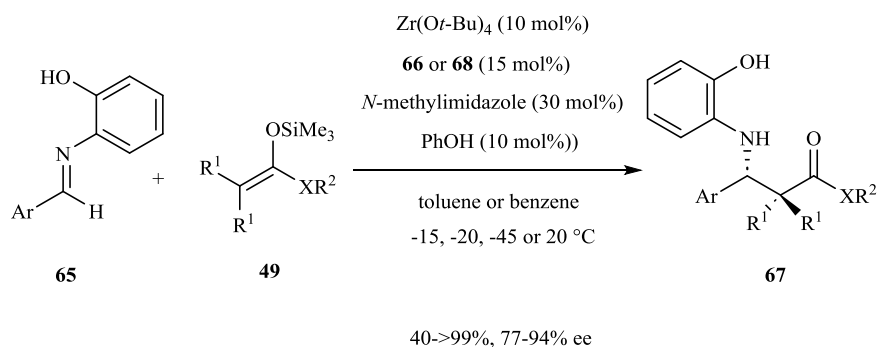
$\text{R}^1 = \text{Ph, 1-Naph, 2-furyl, } p\text{-ClC}_6\text{H}_4, i\text{-Bu}$
 $\text{R}^2 = \text{H, Me, OBn}$
 $\text{R}^3 = \text{H, Me, OTBS}$
 $\text{XR}^4 = \text{OMe, SEt, Oi-Pr, OPh}$

preparation of catalyst **62ZrMS**:

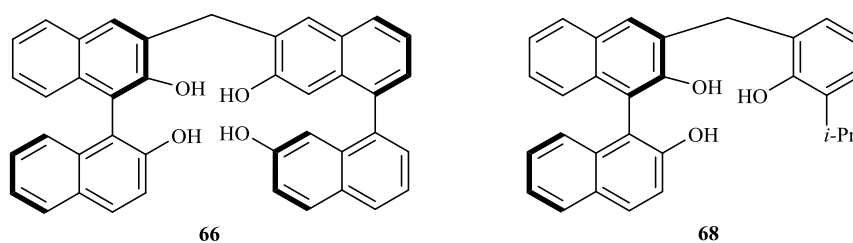


Scheme 19. Mannich-type reaction of aldimines with trimethylsilyl enolates in the presence of **62ZrMS**.

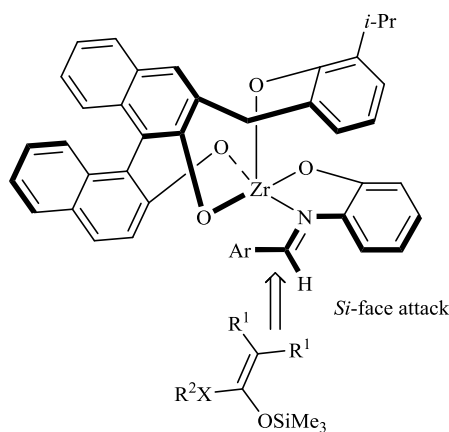
In 2005, the same authors designed a novel type of tetradentate BINOL-derived ligands to be employed in comparable reactions [39]. As shown in Scheme 20, the enantioselective zirconium-catalyzed Mannich-type reaction of aromatic aldimines **65** derived from 2-aminophenol with trimethylsilyl enolates **49** was performed in the presence of 10 mol% of $\text{Zr(O}t\text{-Bu)}_4$, 15 mol% of optimal tetradentate ligand **66**, and 30 mol% of *N*-methylimidazole in toluene at 0 or -45 °C, leading to chiral amines **67** in 40-98% yields and 77-94% ee. In addition, novel tridentate BINOL-derived ligand **68** was investigated in the same processes, providing comparable yields (55->99%) and ee values (86-94% ee). In this case, the reaction was carried out at -15 , -20 , -40 or 20 °C in toluene or benzene as solvent with 10 mol% of phenol as an additive in some cases of substrates. The reaction evolved through the transition state (with ligand **68**) depicted in Scheme 20 in which the silicon enolate attacked the aldimine through the *Si*-face.



Ar = Ph, *p*-ClC₆H₄, *m*-ClC₆H₄, *p*-MeOC₆H₄, *o*-Tol,
p-F₃CC₆H₄, 1-Naph, 2-Naph, 2-furyl, 3-furyl, 3-thienyl
 R¹ = Me, H
 XR² = OMe, OEt, SEt

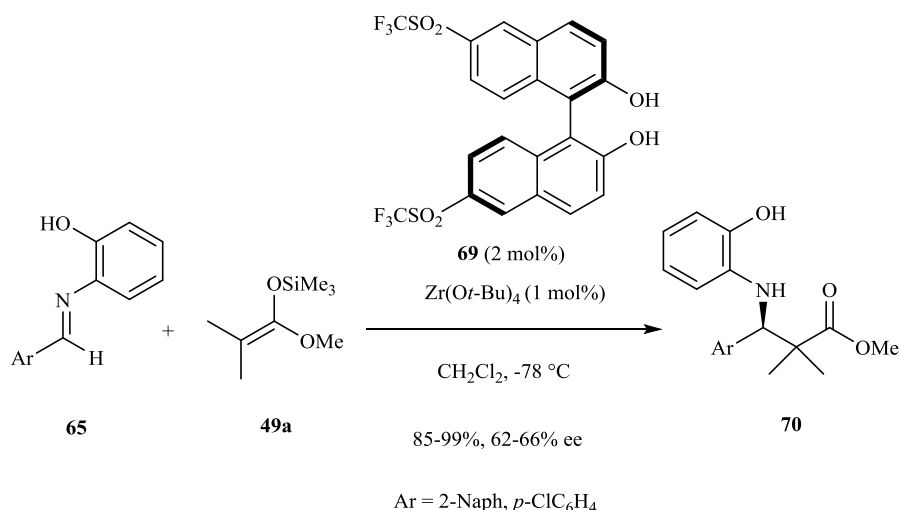


proposed transition state with ligand **68**:



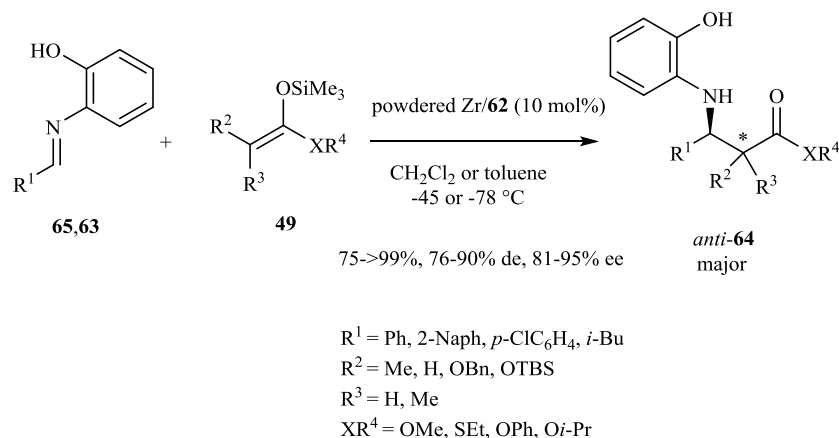
Scheme 20. Mannich-type reaction of aromatic aldimines with trimethylsilyl enolates in the presence of tetra- and tridentate BINOL-derived ligands.

In 2006, Le Roux et al. developed the synthesis of novel BINOL-derived chiral ligand **69** [40]. The latter was applied as catalyst system in combination with $\text{Zr}(\text{O}t\text{-Bu})_4$ in asymmetric Mannich-type reactions of aromatic imines **65** with trimethylsilyl enolate **49a** derived from methyl isobutyrate in dichloromethane as solvent. A high reactivity was observed since the reaction required only 2 mol% of catalyst loading at -78 °C to produce chiral Mannich-type products **70** in 85-99% yields albeit combined with moderate enantioselectivities (62-66% ee), as presented in Scheme 21.

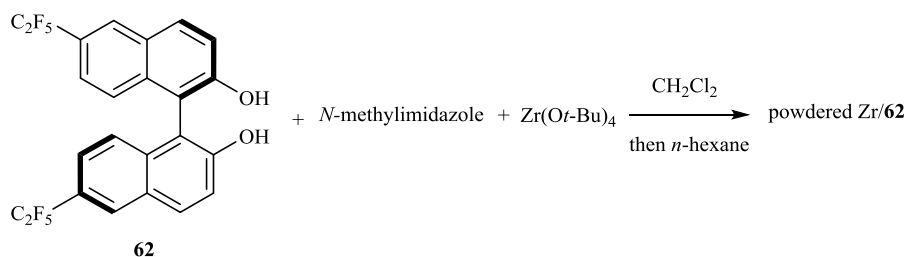


Scheme 21. Mannich-type reaction of aromatic aldimines with a trimethylsilyl enolate in the presence of ligand **69**.

In the same year, Kobayashi and Saruhashi employed 10 mol% of powdered reusable zirconium catalyst (powdered Zr/**62**), prepared from Zr(*O**t*-Bu)₄, BINOL-derived ligand **62**, and *N*-methylimidazole, in enantioselective Mannich-type reaction of aldimines **63,65** with trimethylsilyl enolates **49** [41]. The process was performed in most cases at -45 °C in dichloromethane as solvent, thus providing chiral products **64** as major or almost single *anti*-diastereomers (76-90% de) with 75->99% yields and 81-95% ee, as shown in Scheme 22. The catalyst could be recovered and reused up to three times.



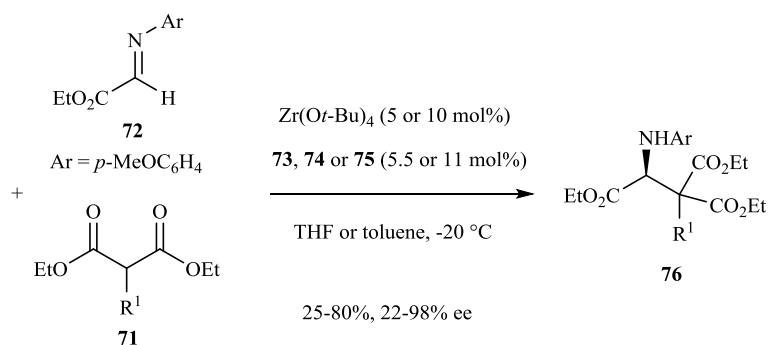
preparation of powdered Zr/**62**:



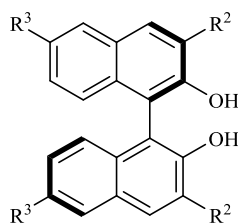
Scheme 22. Mannich-type reaction of aldimines with trimethylsilyl enolates in the presence of powdered Zr/**62**.

In another context, enantioselective direct Mannich-type reactions between iminoesters **72** and malonates **71** were developed in 2010 by Kobayashi et al. under catalysis with chiral zirconium catalysts derived from BINOL-based ligands **73, 74** and **75** (Scheme 23) [42]. The reaction was promoted at -20 °C in THF or toluene

as solvent by 5 or 10 mol% of $\text{Zr}(\text{O}t\text{-Bu})_4$ combined with 5.5 or 11 mol% of ligand **73**, **74** or **75**, thus leading to chiral α -amino acid derivatives **76** with 25-80% yields and 22-98% ee. In general, the reaction of alkyl-substituted malonates provided high ee values (87-98% ee) while phenyl- and chloro-substituted substrates ($\text{R}^1 = \text{Ph, Cl}$) reacted with dramatically lower enantioselectivities (10-22% ee). A mechanism is proposed in Scheme 23 in which the malonate chelated to the chiral catalyst through a bidentate fashion to give intermediate **F**. Then, the iminoester substrate coordinated to the zirconium atom in **F**. Subsequently, the metal enolate attacked the imine group of the iminoester substrate to deliver the final α -amino ester.



$\text{R}^1 = \text{Et, Pr, Bu, allyl, Bn, } i\text{-Pr, Ph, Cl}$

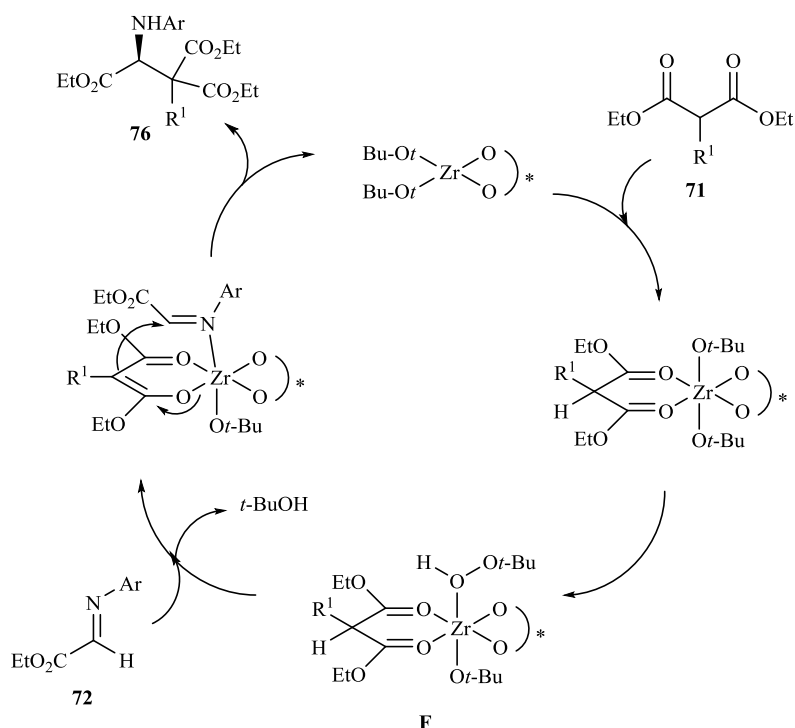


73: $\text{R}^2 = \text{Me, R}^3 = \text{H}$

74: $\text{R}^2 = \text{Br, R}^3 = \text{I}$

75: $\text{R}^2 = \text{Br, R}^3 = \text{H}$

proposed mechanism:

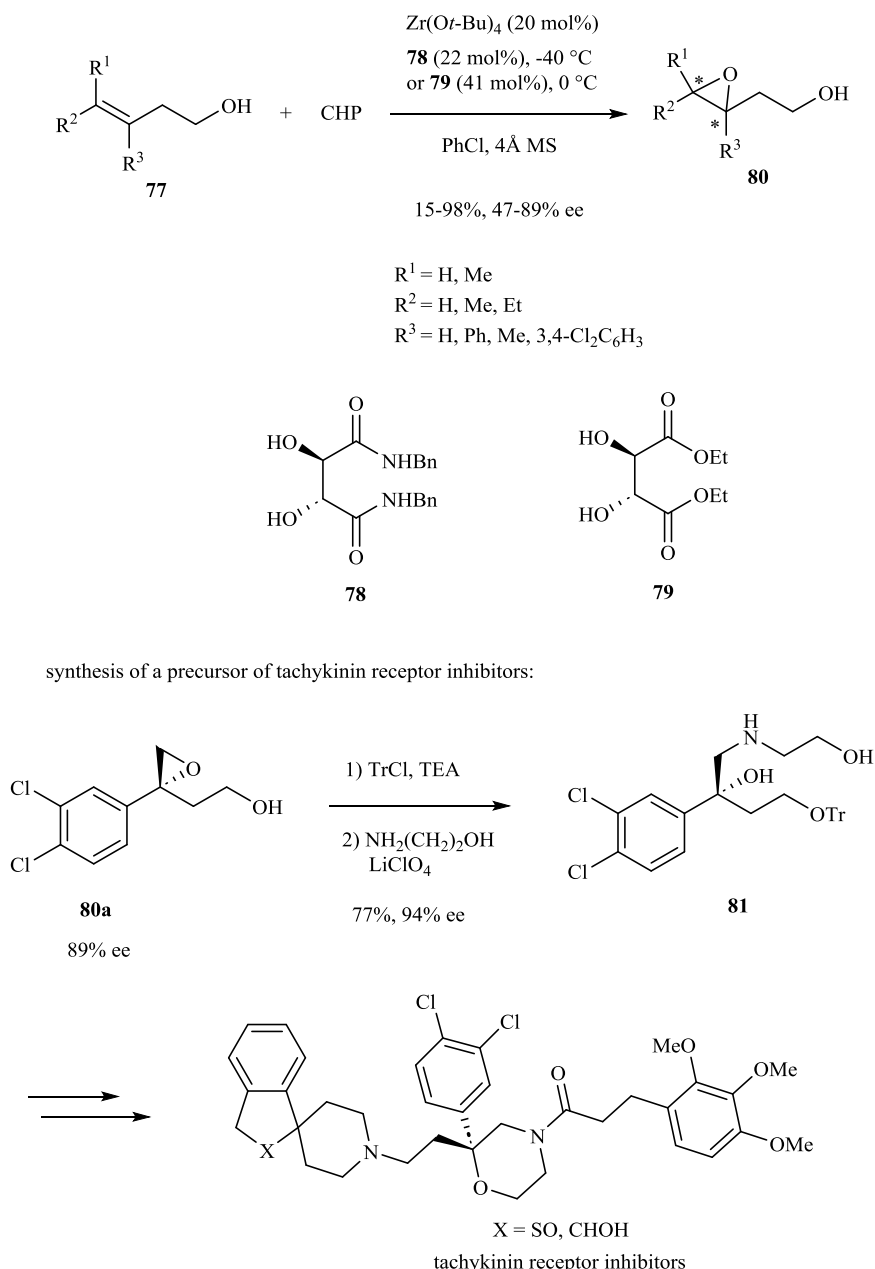


Scheme 23. Direct Mannich-type reaction of malonates with iminoesters.

6. ENANTIOSELECTIVE ZIRCONIUM-CATALYZED EPOXIDATIONS

Among methodologies to prepare chiral epoxides [43], asymmetric metal-catalyzed epoxidations of alkenes, initiated by Sharpless and Katsuki [44], have been intensively developed [45]. In 1987, Katsuki and co-workers

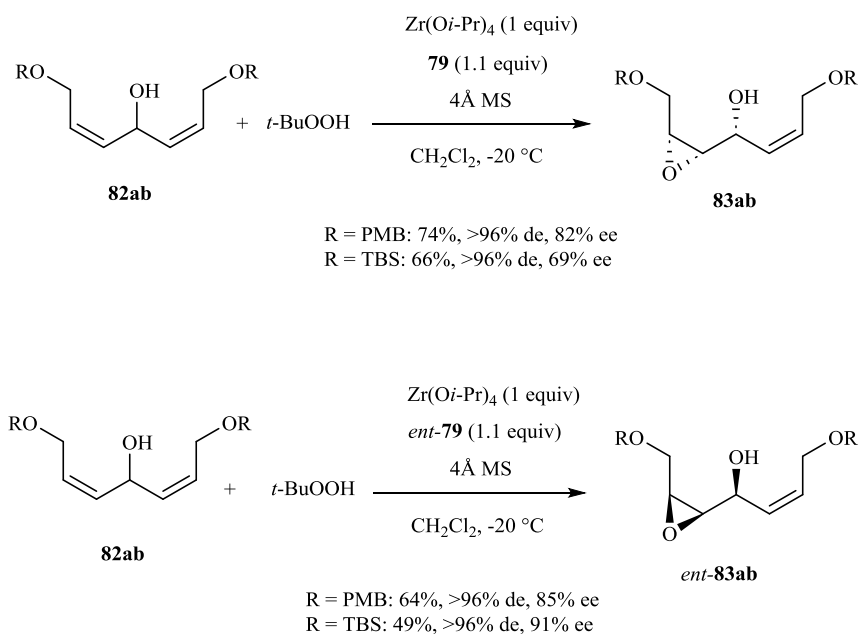
disclosed the first asymmetric zirconium-catalyzed epoxidation of a *cis*-configured homoallylic alcohol which was catalyzed by a combination of $Zr(O*n*-Pr)_4$ and a chiral ligand derived from tartramides [46]. This afforded the desired product with 77% ee and 25% yield [47]. In 2003, a general methodology for the asymmetric epoxidation of homoallylic alcohols **77** was described by Onaka et al. [48]. The catalyst consisted in an association of 20 mol% of $Zr(O*t*-Bu)_4$ and 22 mol% of dibenzyl L-tartramide **78** or 41 mol% of diisopropyl L-tartrate **79**. Carried out at -40 or 0 °C in chlorobenzene as solvent in the presence of cumene hydroperoxide (CHP) as the oxidant, the reaction produced a series of chiral epoxides **80** with 15-98% yields and 47-89% ee. The use of tartramide ligand **78** allowed generally better yields (55-98%) than that of tartrate ligand **79** (15-93%) while combined with comparable enantioselectivities (47-87% ee with **79**, 49-89% with **78**). The methodology was applied to the development of a synthesis of key intermediate **81** in the synthesis of tachykinin receptor antagonists (Scheme 24).



Scheme 24. Epoxidation of homoallylic alcohols in the presence of tartrate/tartramide ligands.

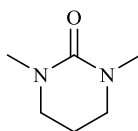
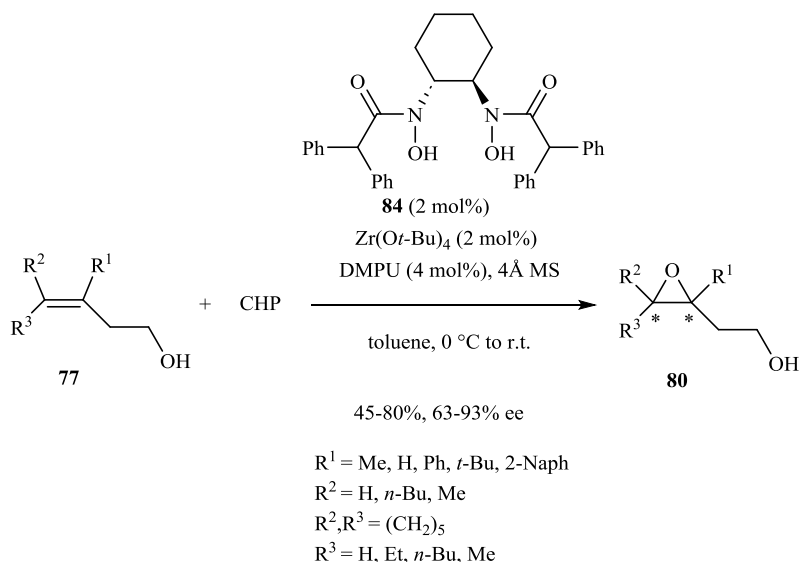
In 2008, Brückner et al. involved chiral zirconium catalysts to promote the first asymmetric epoxidation of *cis/cis*-divinylcarbinols with *t*-butylhydroperoxide as oxidant [49]. Remarkably, the process evolved through *syn*-selective monoepoxidation of *cis/cis*-divinylcarbinols **82ab** to afford chiral epoxides **83ab** when the reaction was mediated at -20 °C in dichloromethane as solvent by a combination of 1 equivalent of $Zr(O*i*-Pr)_4$ combined

with 1.1 equivalent of ligand **79**. These products were obtained as single diastereomers (>96% de) in 69-82% ee and 66-74%, as presented in Scheme 25. The authors found that the involvement of enantiomeric ligand *ent*-**79** under the same conditions allowed the synthesis of enantiomeric products *ent*-**83ab** to be achieved as single diastereomers (>96% de) in 49-64% yields and 85-91% ee.



Scheme 25. Epoxidations of *cis/cis*-divinylcarbinols in the presence of tartrate ligands.

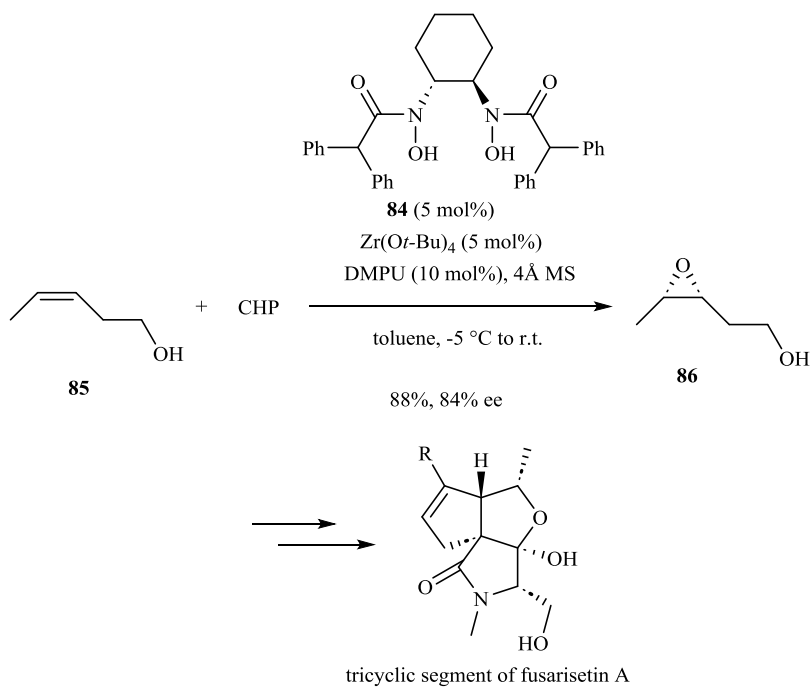
In 2010, Yamamoto and Li developed enantioselective zirconium-catalyzed epoxidation of homoallylic alcohols **77** by using chiral bishydroxamic acid ligands [50]. The reaction was catalyzed in toluene at 0 °C to room temperature by only 2 mol% of $\text{Zr(O}t\text{-Bu)}_4$ combined with 2 mol% of optimal ligand **84**. When DMPU was used as an additive, a range of chiral epoxides **80** were produced in 45-80% yields and 63-93% ee, as illustrated in Scheme 26. A metal screening showed that even better results were obtained by using an hafnium(IV) complex of the same ligand.



DMPU

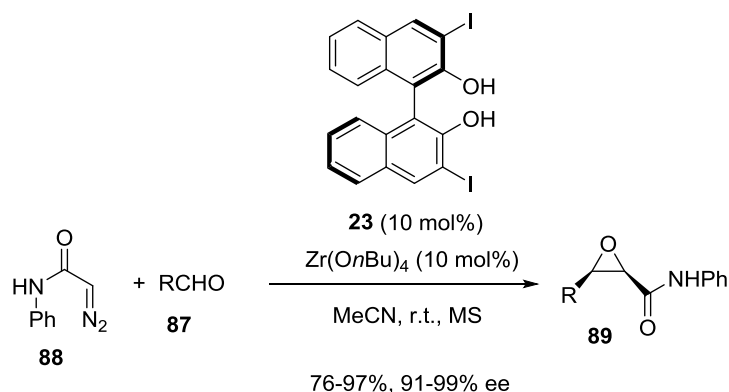
Scheme 26. Epoxidation of homoallylic alcohols in the presence of a bishydroxamic acid ligand.

Related conditions were applied in 2016 by Iwabuchi et al. to develop the synthesis of the chiral tricyclic moiety of natural product fusarisetin A (Scheme 27) [51]. Indeed, the key step of the synthesis was based on the asymmetric zirconium-catalyzed epoxidation of (*Z*)-homoallylic alcohol **85** with cumene hydroperoxide (CHP) as oxidant promoted at $-5\text{ }^\circ\text{C}$ to room temperature in toluene by 5 mol% of a combination of $\text{Zr}(\text{O}t\text{-Bu})_4$ and ligand **84**. This led to chiral epoxide **86** in 88% yield and 84% ee, which was further converted into the expected tricyclic segment of anticancer agent (+)-fusarisetin A [52].



Scheme 27. Synthesis of the tricyclic moiety of fusarisetin A through epoxidation of an homoallylic alcohol.

Another methodology to achieve chiral epoxides is the asymmetric Darzens reaction. In 2010, Gong et al. developed a practical enantioselective Darzens reaction promoted by a stable chiral zirconium catalyst to synthesize *cis*-glycidic amides [53]. As shown in Scheme 28, the latter was preformed by mixing 10 mol% of $Zr(On-Bu)_4$ and the same quantity of chiral BINOL-derived ligand **23**. Under these conditions, a wide variety of (hetero)aromatic as well as aliphatic aldehydes **87** reacted smoothly at room temperature with *N*-phenyl-diazoacetamide **88** in acetonitrile to give exclusively *cis*-glycidic amides **89** in 76-97% yields and 91-99% ee.

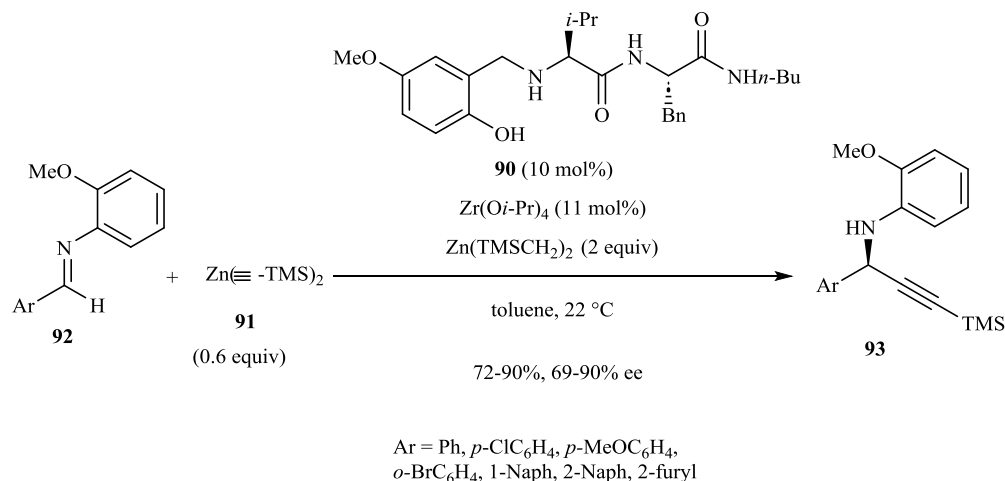


R = Ph, *p*-O₂NC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-NCC₆H₄, *m*-NCC₆H₄,
m-HOC₆H₄, *o*-O₂NC₆H₄, *m*-BrC₆H₄, *m*-ClC₆H₄, *m*-MeOC₆H₄,
p-Tol, 1-Naph, 2-Naph, 2-pyridinyl, *o*-FC₆H₄, *o*-ClC₆H₄, *o*-BrC₆H₄,
Et, Pr, BnCH₂, Cy, BnOCH₂

Scheme 28. Darzens reaction of aldehydes with *N*-phenyl-diazoacetamide.

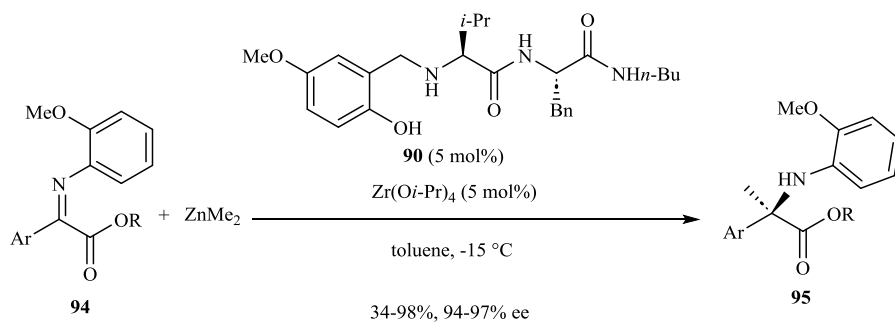
7. ENANTIOSELECTIVE ZIRCONIUM-CATALYZED ADDITIONS OF ALKYLZINC REAGENTS TO IMINES

In 2005, Snapper and Hoveyda investigated enantioselective zirconium-catalyzed additions of alkynylzinc reagents to a variety of *o*-anisidyl imines [54]. The catalyst was in situ formed at 22 °C in toluene from 11 mol% of $Zr(Oi-Pr)_4$ and 10 mol% of chiral peptidic ligand **90** (Scheme 29). When the direct addition of dialkynylzinc reagent **91** to aromatic aldimines **92** was investigated, it afforded expected chiral amines **93** albeit with a low conversion (5-10%). However, in the presence of two equivalents of $Zn(TMSCH_2)_2$, the enantioselective addition of alkynylzinc reagents to various *o*-anisidyl imines **92** afforded desired chiral aromatic amines **93** with 72-90% yields and 69-90% ee.

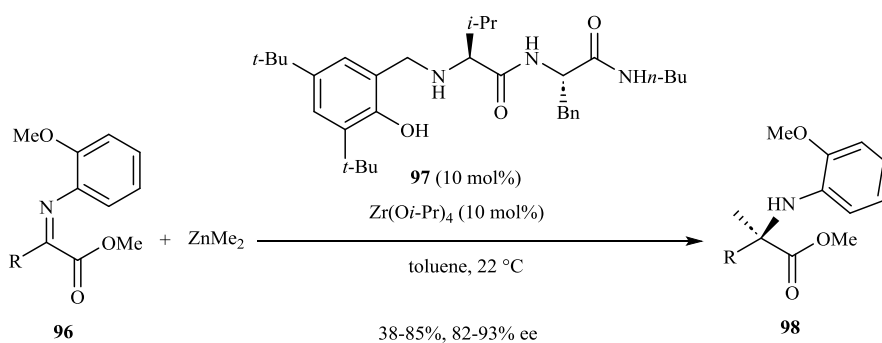


Scheme 29. Addition of alkynylzinc reagents to aromatic aldimines.

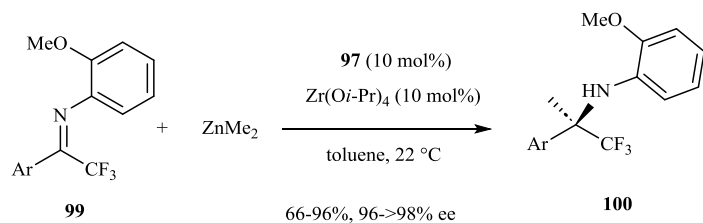
Later in 2008, these authors employed the same ligand **90** to develop the first enantioselective alkylation of α -ketoimine esters with ZnMe_2 (Scheme 30) [55]. ZnMe_2 was added at $-15\text{ }^\circ\text{C}$ in toluene to aryl-substituted α -ketoimine esters **94** in the presence of only 5 mol% of chiral ligand **90** and 5 mol% of $\text{Zr}(\text{O}i\text{-Pr})_4$ to afford chiral quaternary aromatic α -aminoesters **95** in 34-98% yields and 94-97% ee. Actually, the yields were $\geq 71\%$ in all cases of substrates excepted for a *t*-butyl ester ($\text{R} = t\text{-Bu}$) which reacted with only 34% yield. With the aim of extending the scope of this methodology to alkyl-substituted α -ketoimine esters **96**, the authors found that the use of 10 mol% of related chiral ligand **97** at 4 or $22\text{ }^\circ\text{C}$ allowed the addition of ZnMe_2 to be achieved, leading to the desired chiral quaternary aliphatic α -aminoesters **98** with 38-85% yields and 82-93% ee, as shown in Scheme 30. Furthermore, the methodology could also be applied to aryl-substituted trifluoromethylketoimines **99**, which reacted at $22\text{ }^\circ\text{C}$ under the same catalyst loading with ZnMe_2 to give chiral trifluoromethyl-containing quaternary α -aminoesters **100** with 66-96% yields and 96->98% ee, as presented in Scheme 30. The authors proposed transition state **G** in which the aryl/alkyl imine was chelated to the zirconium center through its nitrogen and oxygen atoms. Then, ZnMe_2 chelated to the amide carbonyl group of the chiral ligand added to the activated $\text{C}=\text{N}$ bond of the imine. Similarly, the stereoselectivity of the alkylation of aryl-substituted trifluoromethylketoimines **99** was explained by related transition state **H** which exhibited a supplementary chelation of the zirconium center with a fluoride atom.



Ar = Ph, *o*-MeOC₆H₄, *p*-MeOC₆H₄, *p*-F₃CC₆H₄, *o*-BrC₆H₄, ,
 1-Naph, 2-Naph, 2-furyl, *p*-BrC₆H₄, *m*-ClC₆H₄, *p*-IC₆H₄
 R = Me, Et, Bn, *t*-Bu

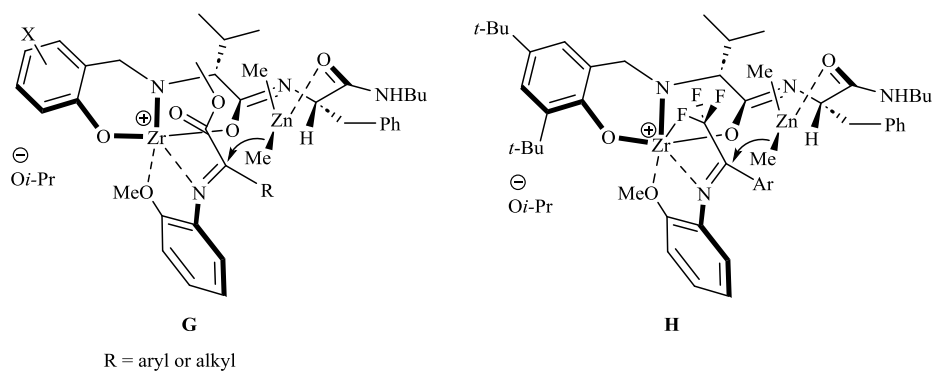


R = *n*-Pr, allyl(CH₂)₂, BnCH₂, *i*-Bu, *i*-Pr, Cy



Ar = Ph, *p*-BrC₆H₄, *p*-MeO₂CC₆H₄, *p*-MeOC₆H₄,

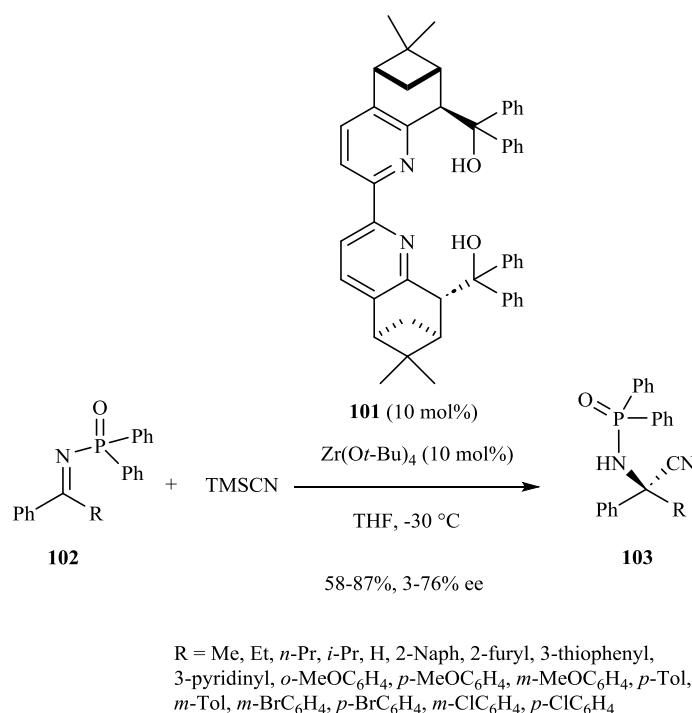
proposed transition states for aryl-/alkyl-substituted α -ketoimines and trifluoromethylketoimines:



Scheme 30. Additions of ZnMe_2 to aryl/alkyl-substituted α -ketoimine esters and aryl-substituted trifluoromethylketoimines.

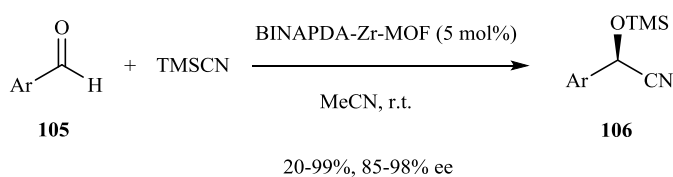
8. ENANTIOSELECTIVE ZIRCONIUM-CATALYZED CYANATIONS

The catalytic asymmetric Strecker reaction represents a powerful methodology to reach chiral amino nitriles [56] among other cyanation reactions [57]. It deals with the addition of TMSCN or HCN to aldimines in the presence of a chiral catalyst. In 1998, Kobayashi et al. described the first highly enantioselective Strecker reaction of aldimines promoted by a chiral zirconium catalyst generated from $\text{Zr}(\text{O}t\text{-Bu})_4$ and a chiral BINOL-derived ligand, allowing the corresponding products to be achieved with enantioselectivities of up to 98% ee [58]. Later in 2008, Chen and Chen investigated chiral bipyridyldiol ligand **101** in enantioselective zirconium-catalyzed Strecker reaction of *N*-diphenylphosphinoyl ketimines **102** with TMSCN (Scheme 31) [59]. The optimal conditions involved the use of a chiral catalyst in situ formed from 10 mol% of this ligand and 10 mol% of $\text{Zr}(\text{O}t\text{-Bu})_4$ in THF as solvent at $-30\text{ }^\circ\text{C}$. A series of aliphatic and (hetero)aromatic quaternary amino nitriles **103** were synthesized in 58-87% yields and 3-76% ee. Aliphatic, and (hetero)aromatic substrates reacted with homogeneously good yields, since 68-73% yields were obtained for aliphatic substrates; 52-87% yields for aromatic ones, and 58-79% for heteroaromatic ones. Aliphatic substrates generally provided the lowest ee values (10-42% ee) along with heteroaromatic ones (3-24% ee). It was found that the electronic nature of aromatic substrates dramatically influenced the enantioselectivity of the reaction (34-72% ee).



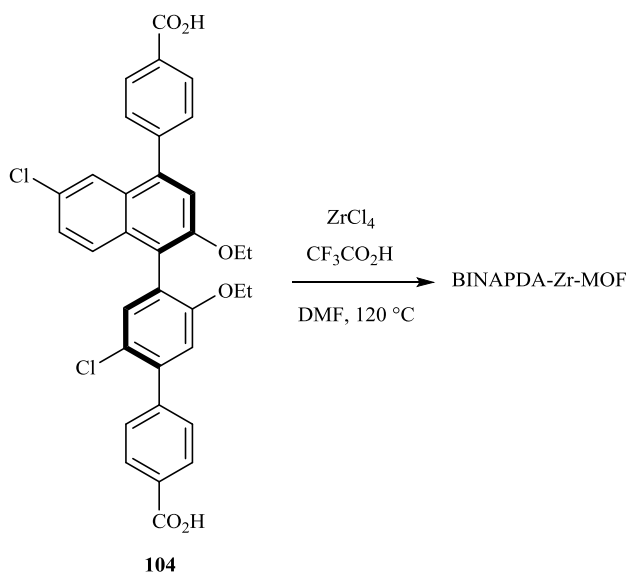
Scheme 31. Strecker reaction of *N*-diphenylphosphinoyl ketimines.

In 2019, Dong and Chen reported the synthesis of novel metal-organic frameworks based on zirconium, such as BINAPDA-Zr-MOF, which was generated by heating at $120\text{ }^\circ\text{C}$ chiral dicarboxylic acid ligand **104** and ZrCl_4 (Scheme 32) [60]. The use of 5 mol% of this MOF to promote in acetonitrile at room temperature the enantioselective cyanosilylation of (hetero)aromatic aldehydes **105** with TMSCN (Scheme 32). Chiral products **106** were obtained in 20-99% yields and 85-98% ee. Actually, the yields were $\geq 75\%$ in all cases of substrates substituted by either electron-withdrawing or electron-donating groups on the phenyl ring excepted for sterically hindered 9-anthryl-substituted aldehyde ($\text{Ar} = 9\text{-anthryl}$) which reacted with only 20% yield.



Ar = Ph, *p*-Tol, *p*-MeOC₆H₄, *p*-O₂NC₆H₄, *p*-FC₆H₄, *m*-Tol, *p*-BrC₆H₄, *m*-ClC₆H₄, *m*-MeOC₆H₄, 2-Naph, 9-anthryl

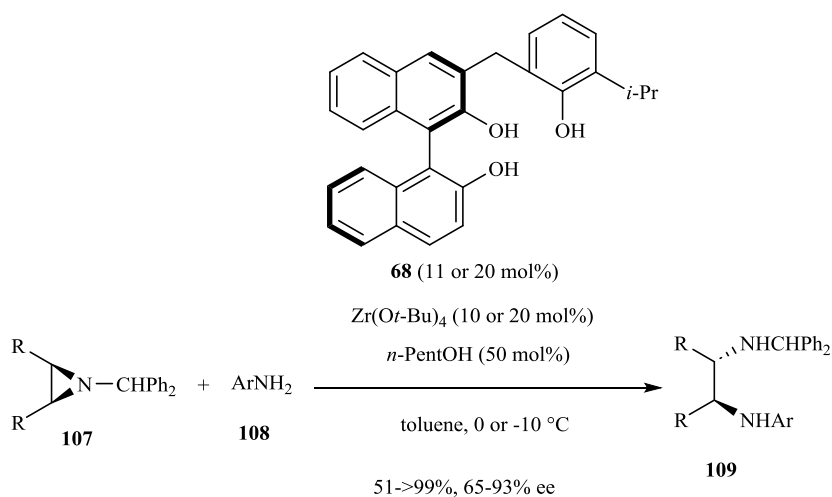
preparation of BINAPDA-Zr-MOF:




Scheme 32. Cyanosilylation of (hetero)aromatic aldehydes in the presence of BINAPDA-Zr-MOF.

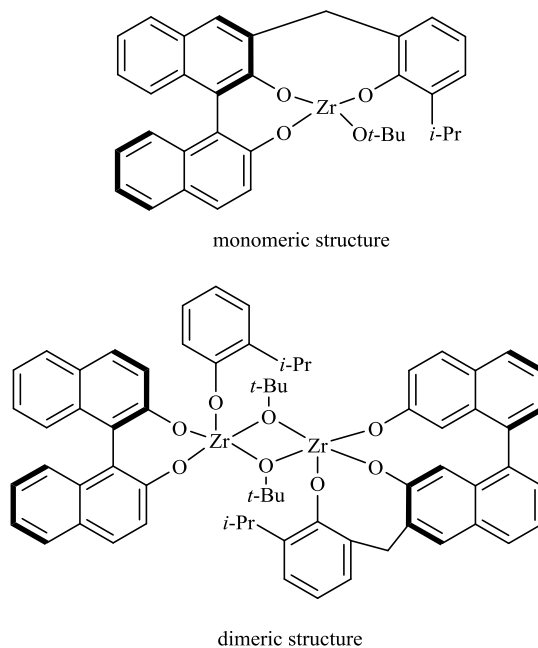
9. ENANTIOSELECTIVE ZIRCONIUM-CATALYZED RING-OPENING REACTIONS

In 1992, Nugent disclosed the first desymmetrization of *meso*-epoxides, evolving through ring-opening with azides, by using a chiral zirconium catalyst in situ prepared from Zr(*Ot*-Bu)₄ and a chiral trialkanolamine, which furnished chiral azido silyl ethers with up to 93% ee [9]. Ever since, asymmetric *meso*-epoxide ring-opening reactions have been intensively investigated [61], although the corresponding reactions using aziridines as electrophiles have been less studied [Erreur ! Signet non défini.e,62]. In 2009, Kobayashi developed a rare example of enantioselective zirconium-catalyzed ring-opening reaction of *meso*-aziridines **107** with anilines **108** (Scheme 33) [63]. It involved 10 or 20 mol% of Zr(*Ot*-Bu)₄ as precatalyst and 11 or 20 mol% of chiral BINOL-derived tridentate ligand **68** in toluene. Carried out at 0 or -10 °C in the presence of 50 mol% of pentanol as an additive, the reaction of a range of *meso*-*N*-benzhydryl aziridines **107** with variously substituted anilines **108** led to chiral 1,2-diamines **109** with 51->99% yields and 65-93% ee. The lowest ee value (65% ee) was observed in the reaction of a sterically hindered 2-substituted aniline (Ar = *o*-Tol). The authors proposed two different possible structures for the active catalyst, which were monomeric or dimeric (Scheme 33).



Ar = Ph, *p*-Tol, *m*-Tol, *o*-Tol, *m*-MeOC₆H₄, *m*-O₂NC₆H₄, *m*-ClC₆H₄,
m-BrC₆H₄, *m*-IC₆H₄, *m*-NCC₆H₄, *m*-EtO₂CC₆H₄, *m*-F₃CC₆H₄, 
 R = Me, Et
 R,R = (CH₂)₄, (CH₂)₃, CH₂CH=CHCH₂,

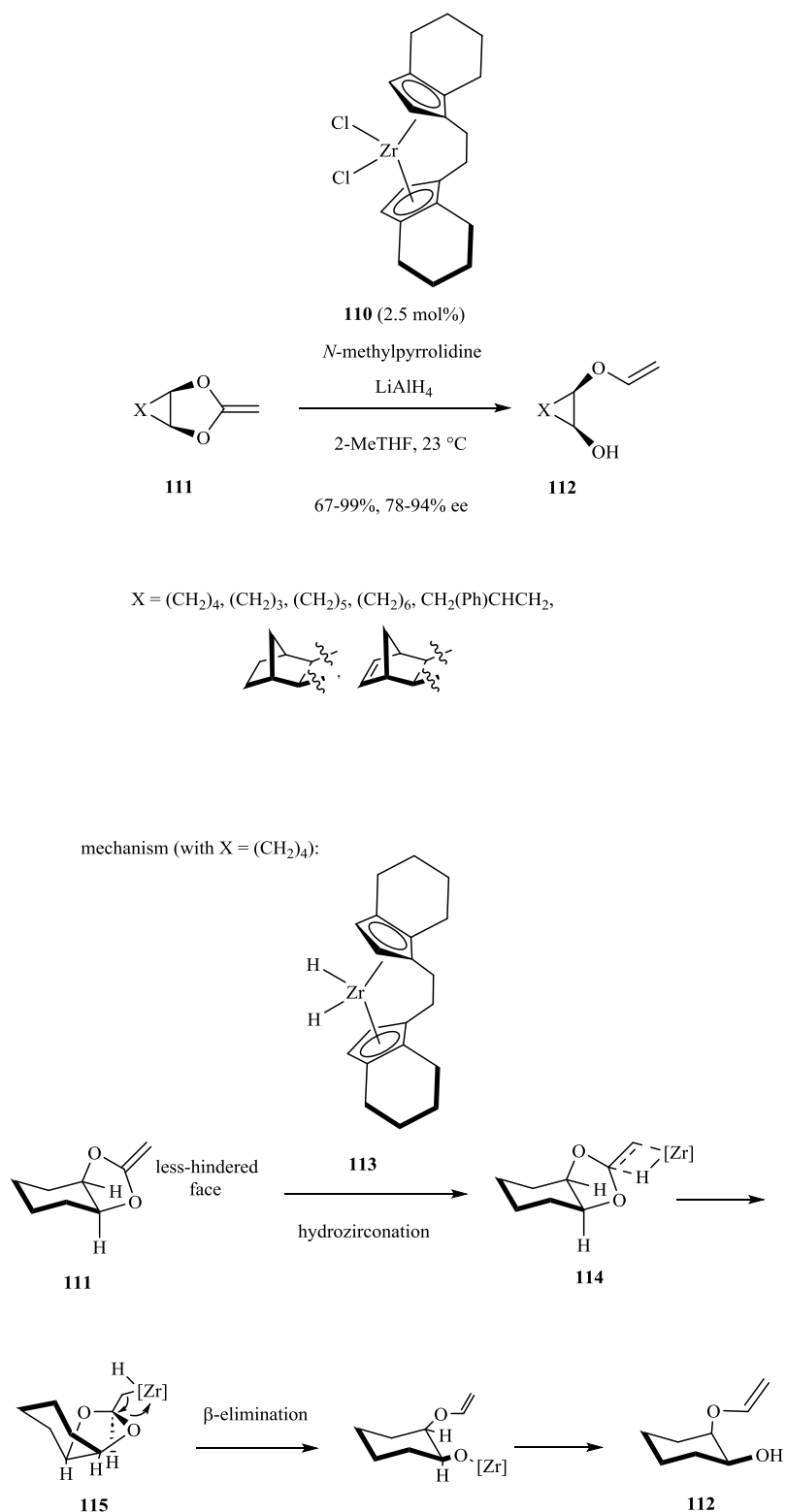
possible structures for active catalyst:



Scheme 33. Ring-opening reaction of *meso*-*N*-benzhydryl aziridines with anilines.

In another area, an enantioselective ring-opening of cyclic *meso*-ketene acetals **156** was disclosed in 2022 by Streuff et al. on the basis of an asymmetric zirconium catalysis [64]. The process, evolving through a β -oxygen elimination, was promoted at 23 °C by a low catalyst loading (2.5 mol%) of chiral preformed zirconium catalyst **110** in 2-MeTHF as solvent in the presence of LiAlH₄ and *N*-methylpyrrolidine. Under these mild reaction conditions, a range of *meso*-ketene acetals **111** afforded chiral β -vinyloxy alcohols **112** with 67-99% yields and 78-94% ee, as illustrated in Scheme 34. Especially, a variety of ketene acetals including fused five to eight-membered rings were compatible, leading to desired products with 83-93% ee. The authors proposed that the in situ generated active catalyst was chiral zirconium hydride complex **113**. The latter promoted the hydrozirconation of the alkene from the less-hindered side which led to transition state **114**. Then, this

intermediate evolved into transition state **115** which underwent a β -elimination to afford the product (Scheme 34).

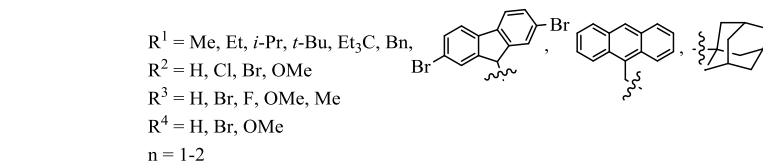
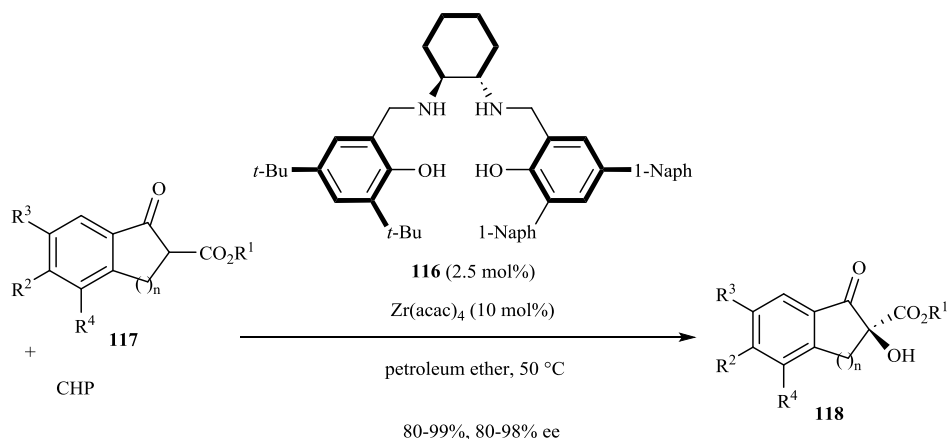


Scheme 34. Ring-opening of cyclic *meso*-ketene acetals.

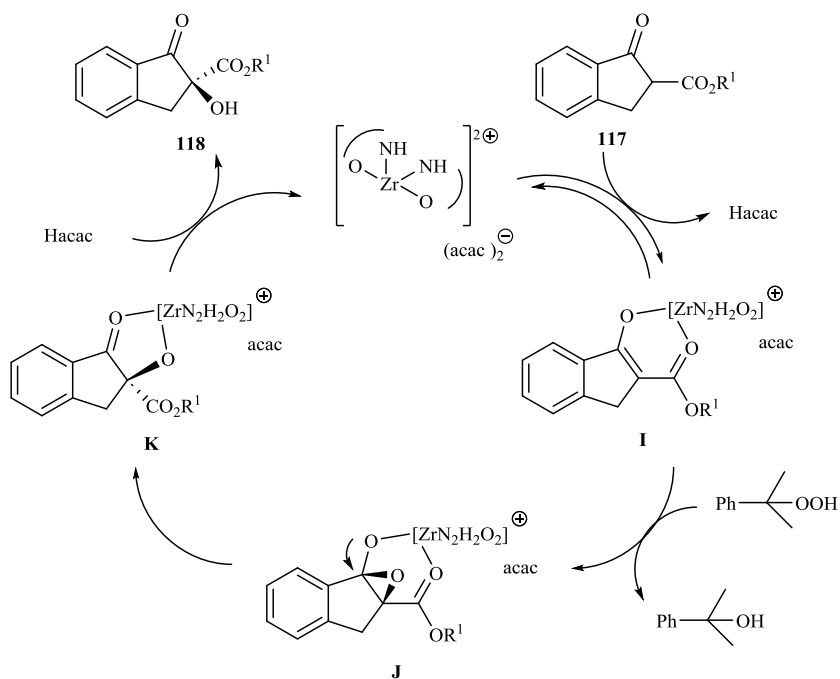
10. ENANTIOSELECTIVE ZIRCONIUM-CATALYZED HYDROXYLATIONS

In 2017, asymmetric zirconium catalysis was applied by Meng et al. to develop a highly efficient route to challenging chiral α -hydroxy β -keto esters [65]. With this aim, novel chiral tetradentate *C1*-symmetric salan

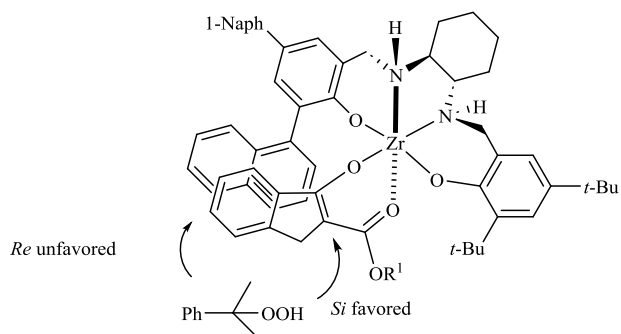
ligands were synthesized from chiral 1,2-diamines. Among them, ligand **116** was found optimal in the enantioselective α -hydroxylation of 1-indanone-derived β -keto esters **117** with cumene hydroperoxide (CHP) as oxidant (Scheme 35). Indeed, the use of 11 mol% of this ligand associated to 10 mol% of $\text{Zr}(\text{acac})_4$ in petroleum ether as solvent to catalyze the hydroxylation of a variety of β -keto esters **117** afforded chiral α -hydroxy β -keto esters **118** with 80-99% yields and 80-98% ee. In the mechanism proposed in Scheme 35, there is formation of zirconium enolate complex **I**. Subsequently, the oxidant attacks the C=C double bond to give zirconium epoxide intermediate **J**. Then, the latter is rearranged into alkoxide intermediate **K** which delivers the final product after protonation. A transition state (Scheme 35) shows that the *Re*-face of the enolate intermediate is hampered by one naphthyl group of the ligand, thus favoring the attack of the oxidant through the *Si*-face of the enolate.



proposed mechanism (with $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$ and $n = 1$):

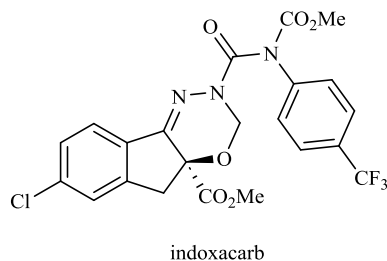
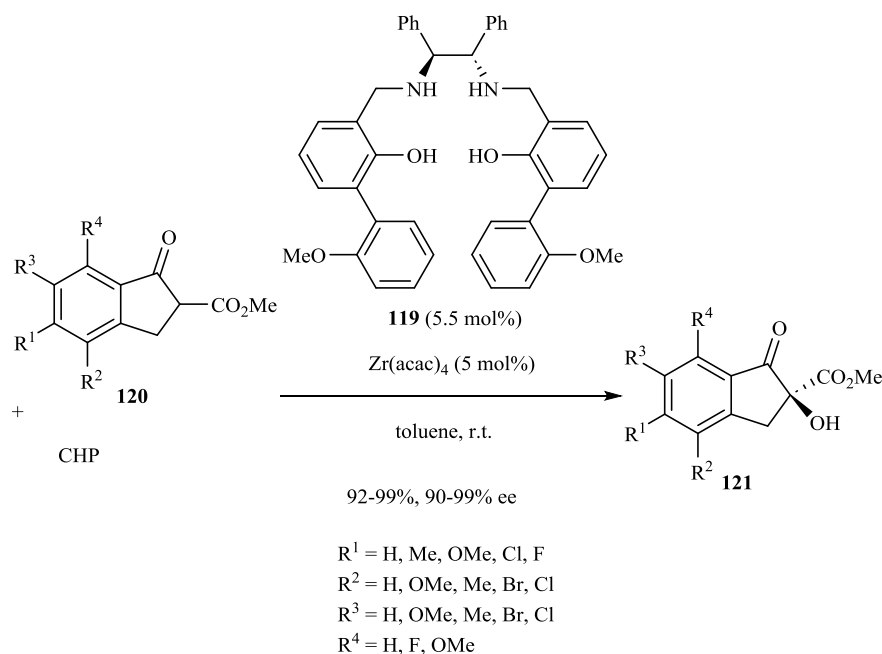


proposed transition state:



Scheme 35. α -Hydroxylation of 1-indanone-derived β -keto esters in the presence of salan ligand **116**.

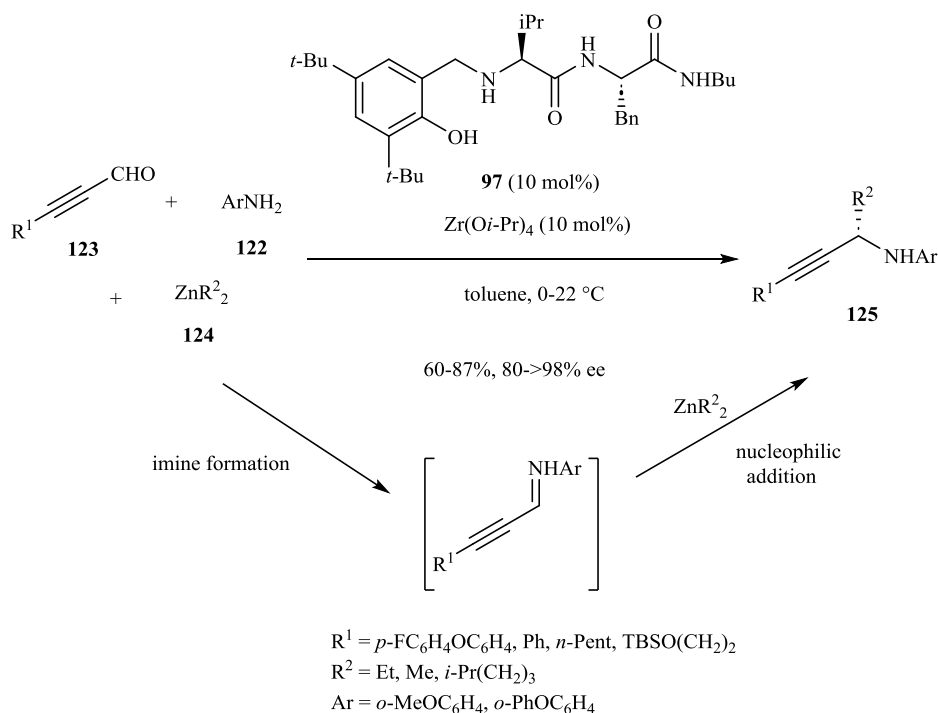
Later in 2020, Nam and Wang reinvestigated this methodology by using more readily available *C*₂-symmetric chiral salan ligand **119** (Scheme 36) [66]. In this case, 5.5 mol% of this ligand was combined with 5 mol% of the same precatalyst $\text{Zr}(\text{acac})_4$ in toluene at room temperature. A range of 1-indanone-derived β -keto methyl esters **120** bearing different types of substituents on the phenyl ring were compatible, affording chiral α -hydroxy β -keto methyl esters **121** with 92-99% yields and 90-99% ee. The utility of this methodology was demonstrated by its application in the synthesis of a key intermediate to prepare insecticide indoxacarb.



Scheme 36. α -Hydroxylation of 1-indanone-derived β -keto methyl esters in the presence of salan ligand **164**.

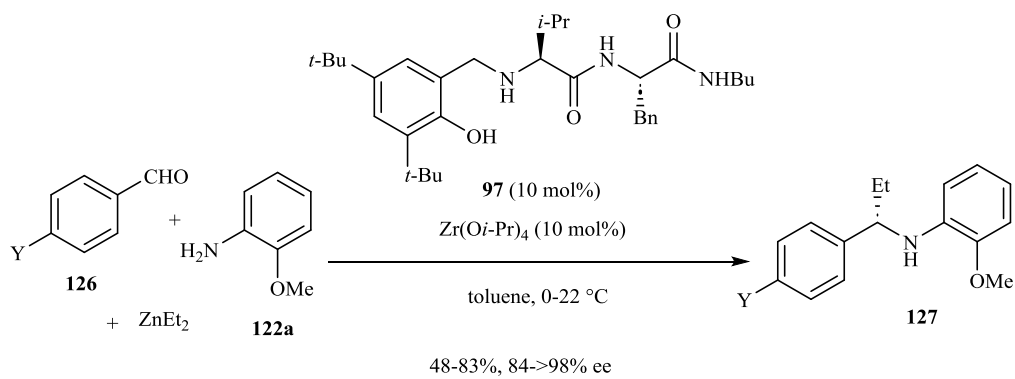
11. ENANTIOSELECTIVE ZIRCONIUM-CATALYZED DOMINO AND TANDEM REACTIONS

Economic asymmetric domino and tandem reactions allow highly complex chiral products to be simply synthesized through one-pot methodologies without isolating and purifying intermediates as well as costly protection-deprotection steps. In spite of the success of these reactions [67], only a limited number of zirconium-catalyzed domino reactions have been described in the last two decades. In 2003, Hoveyda and Snapper employed a chiral zirconium catalyst in situ formed from 10 mol% of $\text{Zr}(\text{O}i\text{-Pr})_4$ and 10 mol% of chiral peptidic ligand **97** to promote the enantioselective alkylation of alkynylimines with alkyl zinc reagents [68]. The alkynylimines were in situ generated from the reaction between the corresponding *o*-substituted anilines **122** and aldehydes **123**. As depicted in Scheme 37, the three-component domino imine formation/nucleophilic addition reaction of aromatic or aliphatic alkynylaldehydes **123**, anilines **122**, and alkyl zinc reagents **124** performed at 0-22 °C in toluene led to chiral propargylamines **125** with 60-87% yields and 80->98% ee.

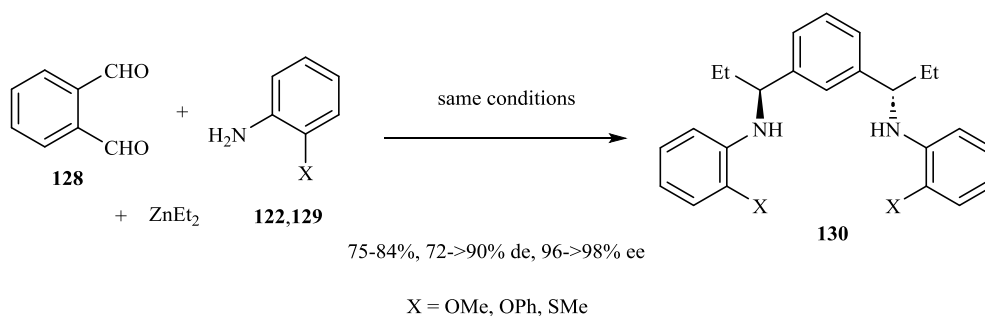


Scheme 37. Three-component reaction of alkynylaldehydes, anilines and alkyl zinc reagents.

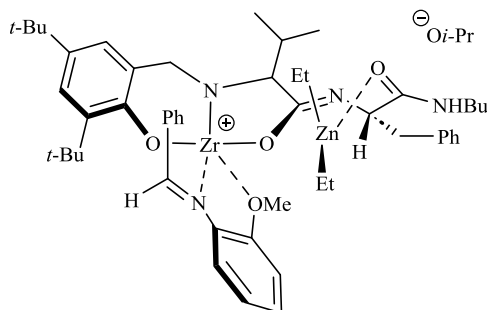
In 2005, the same conditions were applied to develop enantioselective alkylations of aromatic aldimines, in situ generated from the corresponding aldehydes **126** and anilines **122a**, with ZnEt_2 (Scheme 38) [69]. The three-component domino imine formation/nucleophilic addition reaction afforded in toluene at 0 °C to room temperature desired chiral amines **127** in 48-83% yields and 84->98% ee. Moreover, the reaction of dialdehydes **128** with anilines **122,129** and ZnEt_2 led to chiral diamines **130** as mixtures of two diastereomers (72->90% de) with 75-84% yields and 96->98% ee. Imines in situ generated from *o*-anisidine (X = OMe) provided the desired product with only 72% de while those derived from *o*-phenoxy- (X = OPh) and *o*-thiomethylanilines (X = SMe) afforded almost single diastereomers (>90% de). The stereoselectivity in the formation of products **127** can be explained by the transition state depicted in Scheme 38 in which the zirconium atom was chelated to the aryl imine through a N,O-bidentate association. Then, ZnEt_2 added to the imine through chelation with the carbonyl group of the peptidic ligand.



Y = CH(OEt)₂, CO₂Me, TBSOCH₂, *i*-PrO₂C(CH₂)₄

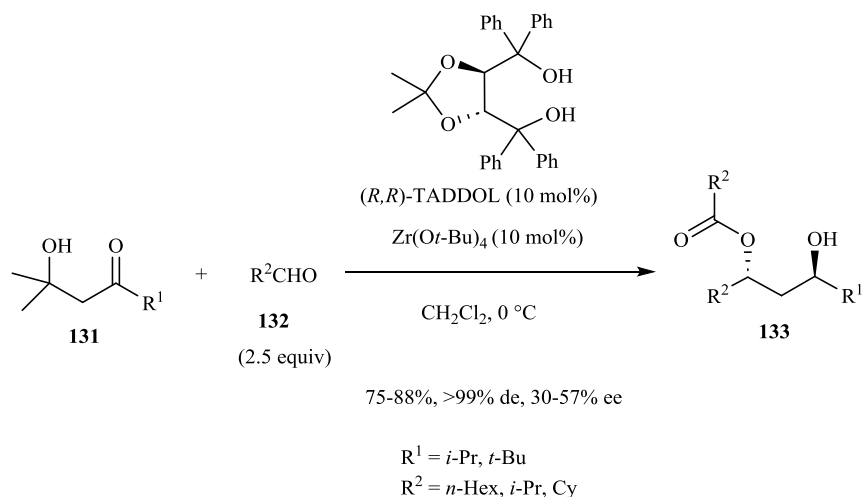


proposed transition state (with Y = H):

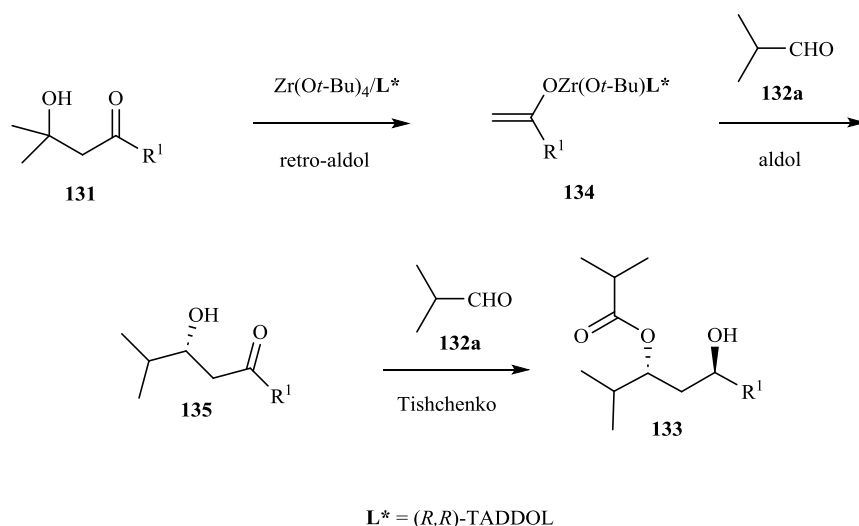


Scheme 38. Three-component reactions of aromatic aldehydes, anilines and ZnEt₂.

Earlier in 2003, Hansch and Schneider disclosed the first enantioselective zirconium-catalyzed domino aldol/Tishchenko reaction involving ketone aldols as enol equivalents [70]. As illustrated in Scheme 39, 10 mol% of a chiral zirconium complex in situ generated from Zr(*Ot*-Bu)₄ and (*R,R*)-TADDOL was found capable to promote at 0 °C in dichloromethane as solvent a domino aldol/Tishchenko reaction between aliphatic ketone aldol adducts **131** and aldehydes **132**, affording chiral 1,3-*anti*-diol monoesters **133** as single diastereomers in 75-88% yields and 30-57% ee. The pseudo-three-component reaction evolved through the mechanism detailed in Scheme 39. In the presence of the chiral catalyst, the ketone aldol substrate underwent a retro-aldol reaction to give zirconium enolate intermediate **134** (R² = *i*-Pr). Then, an aldol condensation between this intermediate and aldehyde **132** occurred to afford β-hydroxy ketone **135**. Subsequently, the latter reacted with a second equivalent of aldehyde **132** through an *anti*-diastereoselective Tishchenko reaction to produce final product **133**.

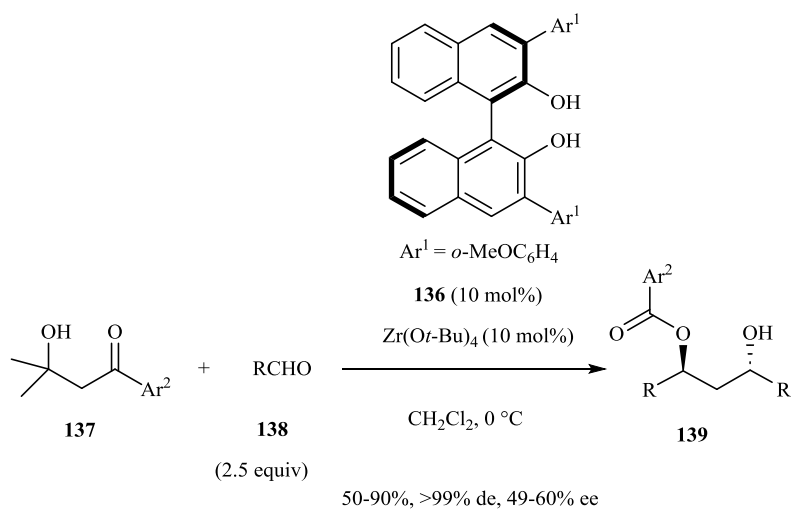


possible mechanism (with $R^2 = i\text{-Pr}$):



Scheme 39. Pseudo-three-component reaction of aliphatic ketone aldols with aldehydes in the presence of (R,R) -TADDOL.

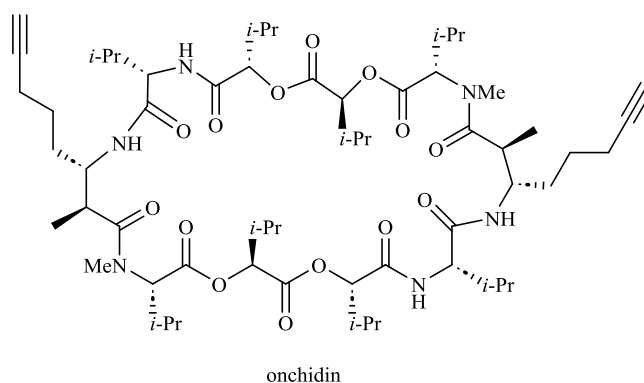
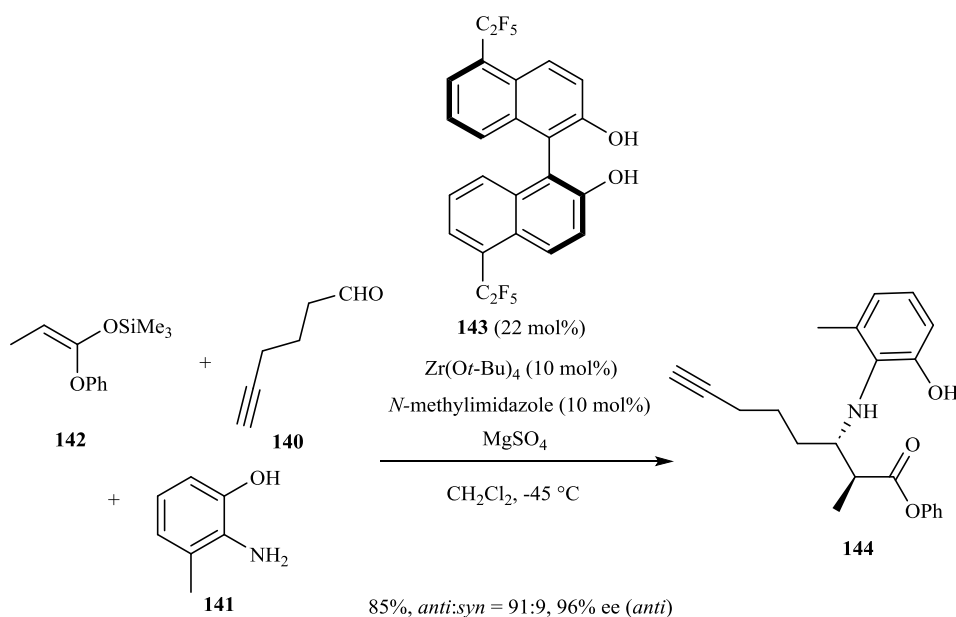
In 2006, the same authors reinvestigated this type of reaction in the presence of another catalyst system composed of 10 mol% of chiral BINOL-derived ligand **136** and the same quantity of $Zr(Ot-Bu)_4$ [71]. As presented in Scheme 40, in this case the domino aldol/Tishchenko reaction occurred between aromatic ketone aldols **137** and two equivalents (2.5) of aliphatic aldehydes **138** which afforded chiral products **139** as single *anti*-diastereomers with 50-90% yields and 49-60% ee.



$\text{R} = i\text{-Pr}, i\text{-Bu}, \text{Cy}, n\text{-Hex}, 2\text{-Et-Pr}$
 $\text{Ar}^2 = \text{Ph}, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, m\text{-Tol}$

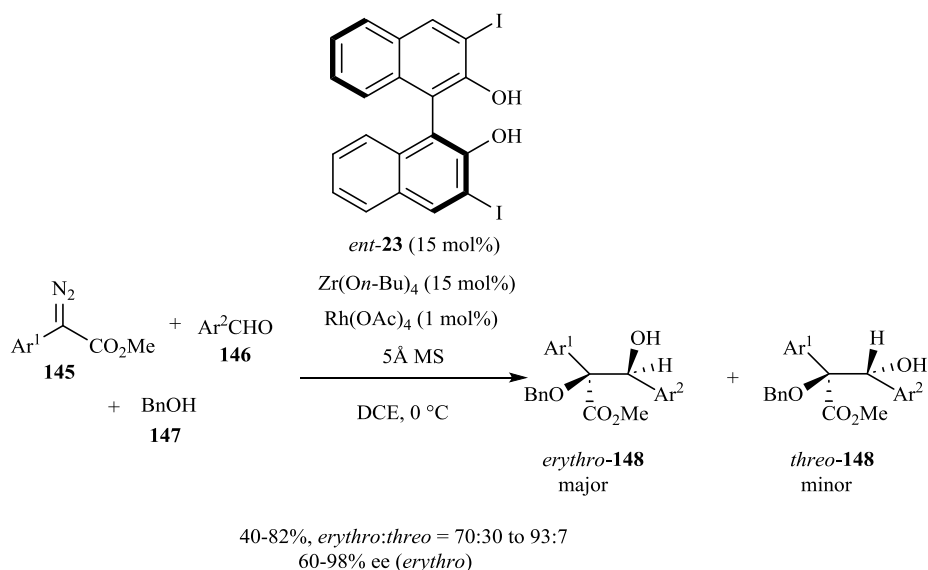
Scheme 40. Pseudo-three-component reaction of aromatic ketone aldols with aldehydes in the presence of a BINOL-derived ligand.

In 2007, Kobayashi et al. described an enantioselective three-component Mannich-type reaction between 5-hexynal **140**, 2-amino-*m*-cresol **141**, and ketene silyl acetal **142** catalyzed by a chiral zirconium complex in situ produced from 10 mol% of $\text{Zr}(\text{O}t\text{-Bu})_4$ and 22 mol% of chiral BINOL-derived ligand **143** (Scheme 41) [72]. The process performed at $-45\text{ }^\circ\text{C}$ in dichloromethane in the presence of 10 mol% of *N*-methylimidazole as an additive afforded chiral Mannich product **144** as major *anti*-diastereomer in 85% yield, good diastereoselectivity (*anti:syn* = 91:9) and 96% ee. The utility of this methodology was demonstrated by converting product **144** into cytotoxic depsipeptide onchidin.



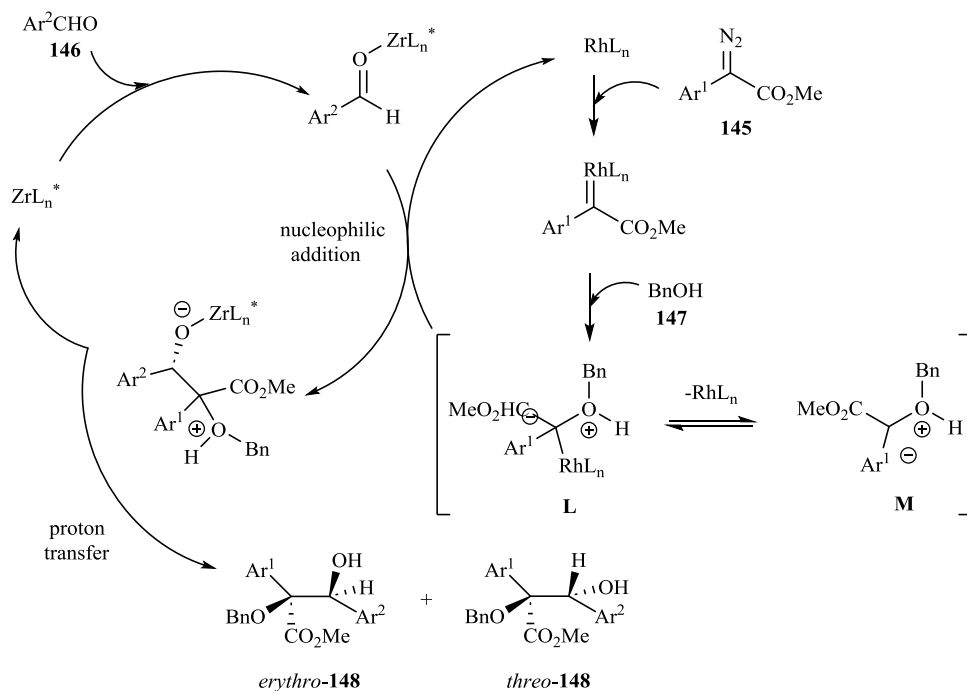
Scheme 41. Three-component Mannich-type reaction of 5-hexynal, 2-amino-*m*-cresol and a ketene silyl acetal.

In 2008, Hu et al. reported the use of a combination of 15 mol% of a chiral zirconium catalyst derived from Zr(On-Bu)_4 and chiral BINOL-derived ligand *ent*-**23** with 1 mol% of Rh(OAc)_4 to promote an enantioselective three-component aldol-type reaction between aryl diazoacetates **145**, aromatic aldehydes **146**, and benzyl alcohol **147** [73]. As detailed in Scheme 42, the process evolved through the generation of oxonium ylide intermediates **L** or **M** from the reaction between the aryl diazoacetate, Rh(OAc)_4 , and benzyl alcohol. These intermediates were trapped by the chiral zirconium complex to give through an aldol-type addition the final product **148**. This reaction afforded chiral α,β -dihydroxy acid derivatives **148** with 40-82% yields and good to high diastereoselectivities (*erythro:threo* = 70:30 to 93:7) combined with 60-98% ee for the major diastereomers.



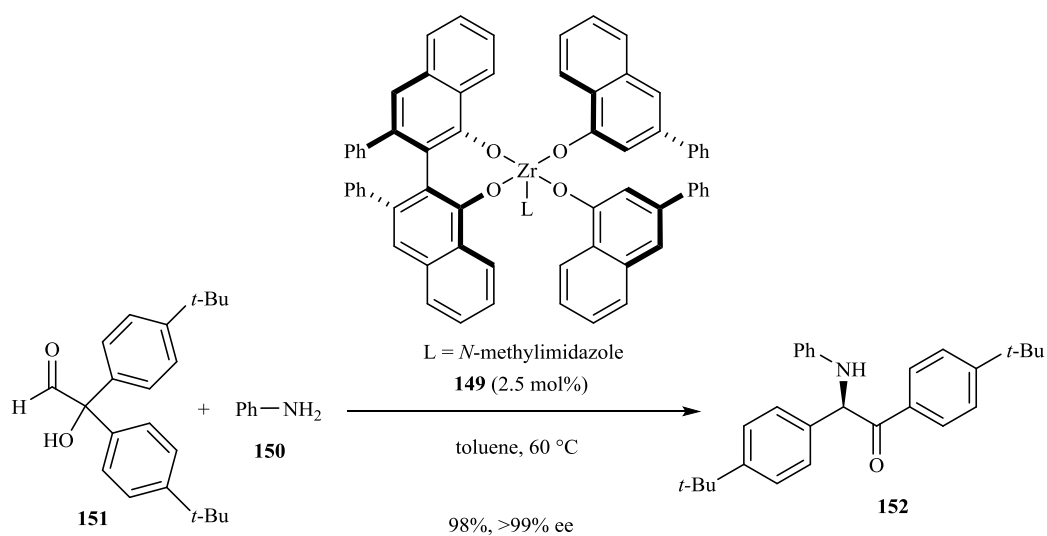
$\text{Ar}^1 = \text{Ph, } p\text{-BrC}_6\text{H}_4, m\text{-Tol}$
 $\text{Ar}^2 = \text{Ph, } p\text{-MeOC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4,$
 $3,4\text{-(OCH}_2\text{O)C}_6\text{H}_3, 1\text{-Naph, 2-furyl, } p\text{-O}_2\text{NC}_6\text{H}_4$

proposed mechanism:



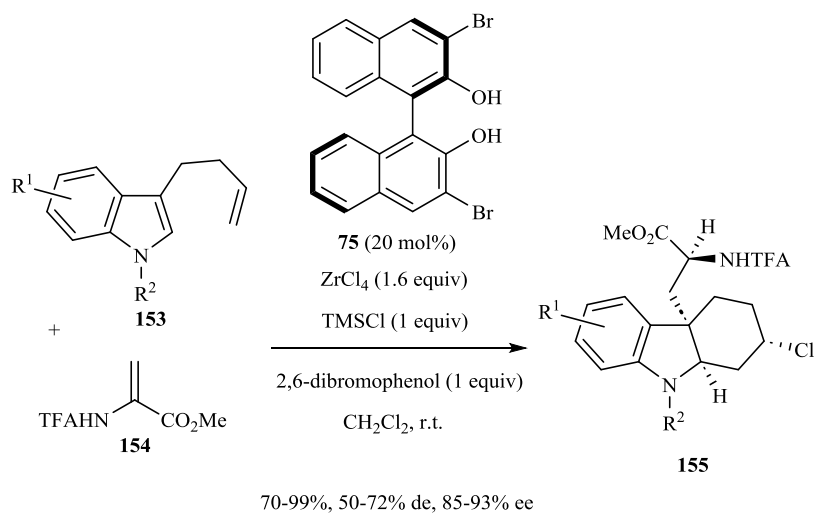
Scheme 42. Three-component reaction of aromatic aldehydes, aryl diazoacetates and benzyl alcohol.

In 2014, Wulff et al. developed an enantioselective domino imine formation/rearrangement reaction catalyzed by chiral preformed zirconium complex **149** exhibiting a VANOL ligand (Scheme 43) [74]. The reaction evolved through the formation of an imine from the reaction between aniline **150** and α -hydroxyaldehyde **151**. Then, the latter underwent a rearrangement to deliver enantiopure α -aminoketone **152** in 98% yield.

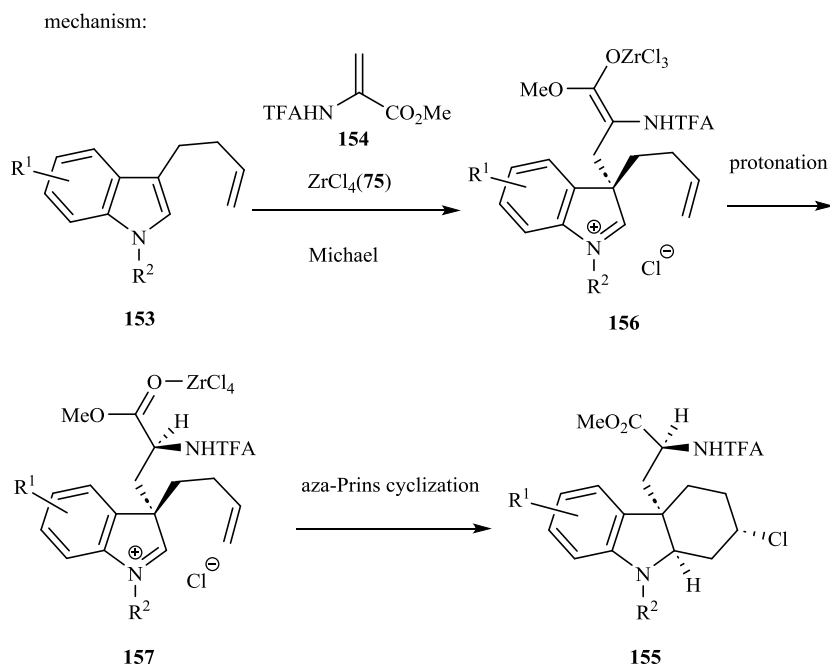


Scheme 43. Domino imine formation/rearrangement reaction of an α -hydroxyaldehyde with aniline.

In 2016, Reisman et al. reported an asymmetric zirconium-mediated domino Michael/protonation/aza-Prins reaction of C3-substituted indoles **153** with amidoacrylate **154**, affording chiral tricyclic indoles **155** (Scheme 44) [75]. The reaction required the use of 1.6 equivalent of $ZrCl_4$ combined with 20 mol% of chiral BINOL-derived ligand **75** as catalyst system, and also that of stoichiometric additives, such as $TMSCl$ and 2,6-dibromophenol. It allowed a variety of chiral indoles **155** to be synthesized with 70-99% yields, 85-93% ee, and 50-72% de. The mechanism proposed in Scheme 44 shows that the Michael addition of the indole to the acrylate generated intermediate **156**, which subsequently underwent protonation to give intermediate **157**. Then, the final product was formed through an aza-Prins cyclization.

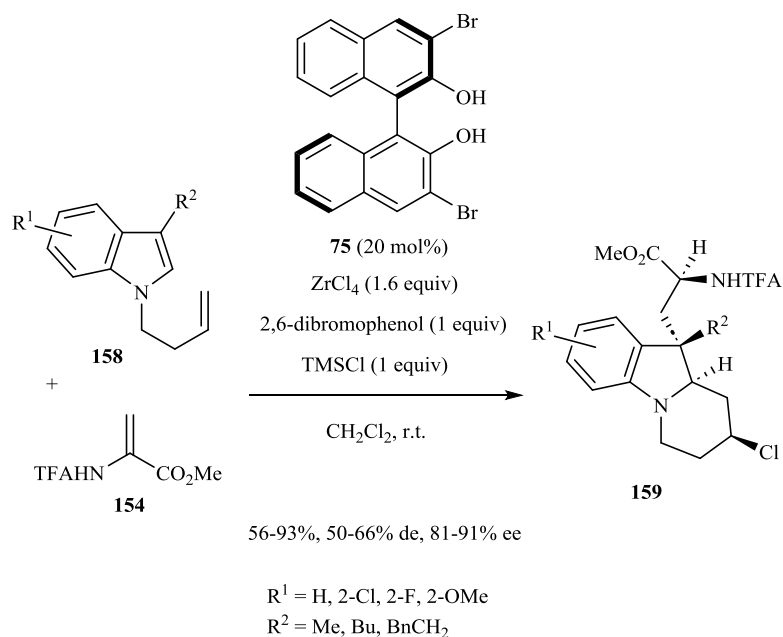


R¹ = H, 1-Me, 2-Me, 3-Me, 4-Me, 2-OMe, 2-Br
R² = Me, allyl, Bn



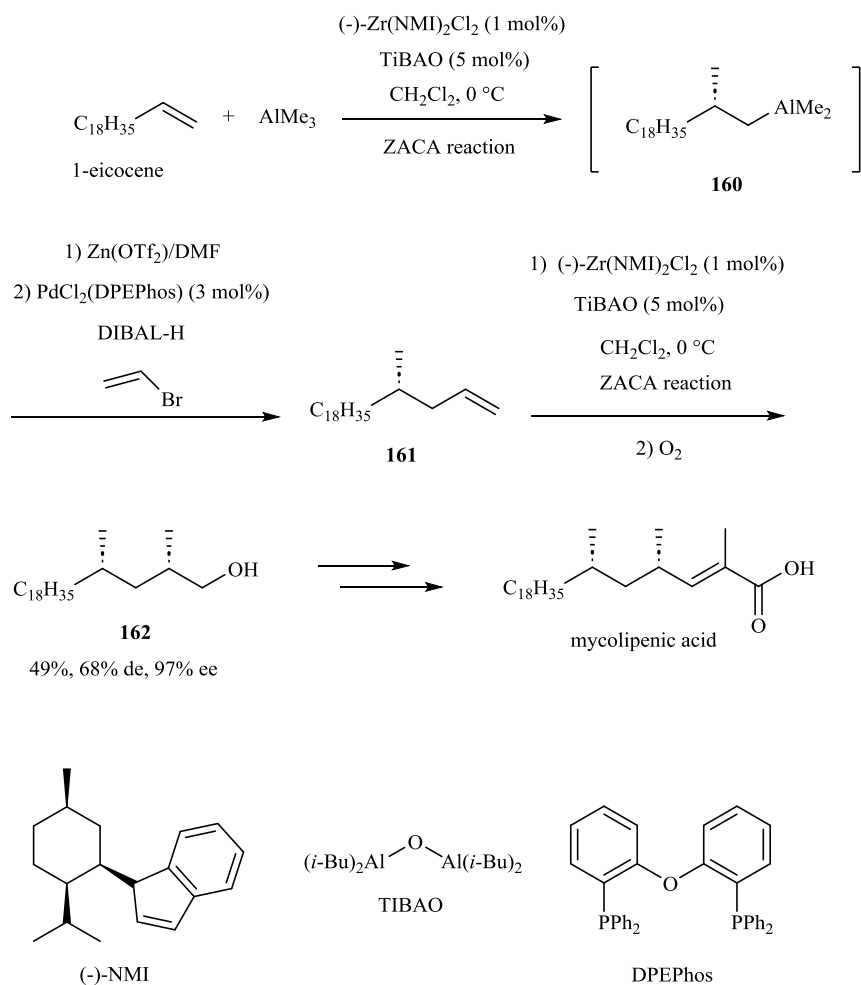
Scheme 44. Domino Michael/protonation/aza-Prins reaction of C3-alkene-linked indoles with an amidoacrylate.

Another type of substrates, such as indoles **158** in which the pendant alkene was linked through the indole nitrogen atom, were also submitted to the same reaction conditions (Scheme 45) [75]. In this case, the reaction of indoles **158** with amidoacrylate **154** led to tricyclic chiral indolines **159** in 56-93% yields, 50-66% de, and 81-91% ee.



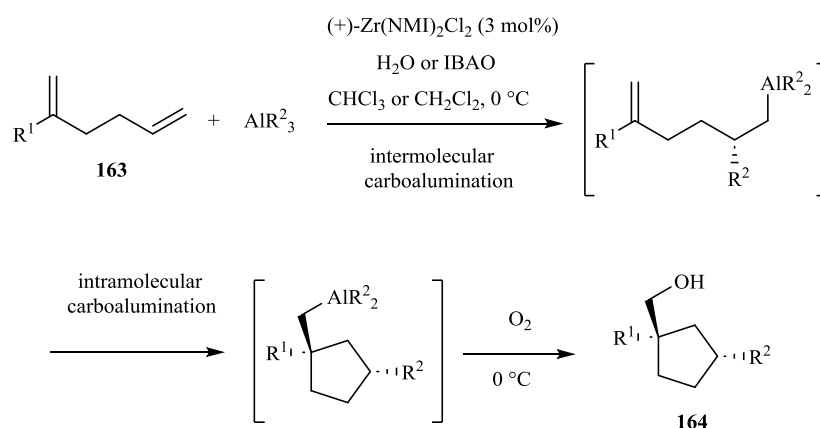
Scheme 45. Domino Michael/protonation/aza-Prins reaction of *N*-alkene-linked indoles with an amidoacrylate.

In 1978, Negishi et al. discovered the zirconium-catalyzed carboalumination of alkynes [5]. Ever since, the asymmetric zirconium-catalyzed carboalumination of alkenes (ZACA reaction) has been widely developed by this group, becoming a powerful tool for the synthesis of many important chiral products especially when included in tandem processes [76]. For example, Negishi et al. reported in 2017 a synthesis of mycolipenic acid based on an asymmetric tandem ZACA/palladium-catalyzed vinylation reaction between 1-eicocene and vinylbromide (Scheme 46) [77]. The synthesis began with the ZACA reaction of 1-eicocene with AlMe_3 performed at 0 °C in the presence of only 1 mol% of preformed chiral zirconium catalyst (-)- $\text{Zr}(\text{NMI})_2\text{Cl}_2$ and tetraisobutyldialuminumoxane (TIBAO) as an additive in dichloromethane as solvent to give the corresponding chiral aluminum compound **160**. Then, this intermediate underwent a palladium-catalyzed vinylation with vinylbromide to give chiral alkene **161**. Subsequently, the latter was submitted to a novel ZACA reaction followed by oxidation which delivered chiral alcohol **162** with 49% yield, 68% de and 97% ee. This key intermediate was further converted through three additional steps into desired enantiopure mycolipenic acid.



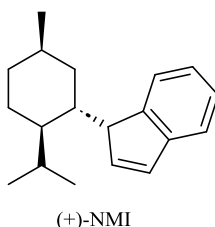
Scheme 46. Tandem ZACA/palladium-catalyzed vinylation reaction of 1-eicocene with vinylbromide and synthesis of mycolipenic acid.

In the same year, these authors also developed enantioselective zirconium-catalyzed tandem double carboalumination/oxidation reaction of unactivated 2-substituted 1,5-dienes **163** [78]. The double carboalumination was promoted by 3 mol% of preformed chiral zirconium catalyst $(+)\text{-Zr(NMI)}_2\text{Cl}_2$ in chloroform or dichloromethane as solvent in the presence of water or isobutylaluminumoxane (IBAO) as additives, leading after subsequent oxidation to chiral cyclopentanes **164** (Scheme 47). A range of these functionalized products were readily synthesized with 40-85% yield, 34->98% de and 82-97% ee. Remarkably, the first intermolecular ZACA reaction proceeded exclusively at the monosubstituted alkene, which was followed by the second intramolecular carboalumination.



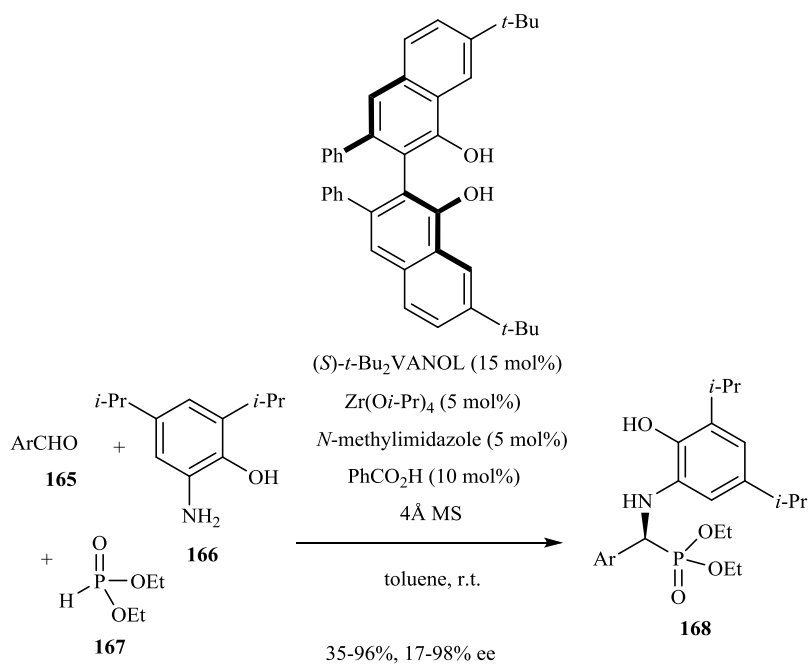
40-85%, 34->98% de, 82-97% ee

R¹ = Ph, *p*-FC₆H₄, *p*-ClC₆H₄, *m*-ClC₆H₄, *p*-MeOC₆H₄, 2-Naph, 2-furyl,
Cy, Me, Bn, HOCH₂, TBDPSOCH₂, TBDPSO(CH₂)₂, HO(CH₂)₂
R² = Me, Et, *n*-Pr

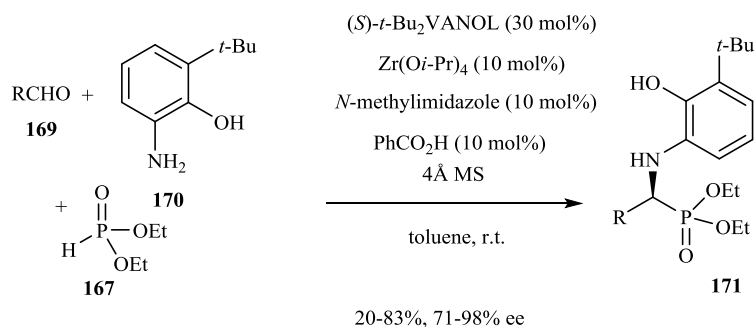


Scheme 47. Tandem double carboalumination/oxidation reaction of unactivated 2-substituted 1,5-dienes.

An efficient zirconium catalyst was developed in 2021 by Wulff et al. to be applied as promotor in the asymmetric three-component Kabachnik–Fields reaction between aldehydes, anilines, and diethyl phosphite, affording the corresponding chiral α -aminophosphonates (Scheme 48) [79]. The domino process was mediated at room temperature in toluene as solvent by a chiral zirconium catalyst in situ generated from one equivalent of Zr(O*i*-Pr)₄, three equivalents of chiral BINOL-derived ligand (*S*)-*t*-Bu₂VANOL, and one equivalent of *N*-methylimidazole. The catalyst system was compatible to either aromatic or aliphatic aldehydes, providing good results when employed in the presence of 10 mol% of benzoic acid as an additive. In the reaction of aromatic aldehydes **165** with 3,5-disubstituted-2-hydroxyanilines **166**, and diethyl phosphite **167**, the best results were achieved when employing 15 mol% of (*S*)-*t*-Bu₂VANOL, 5 mol% of Zr(O*i*-Pr)₄, and 5 mol% of *N*-methylimidazole. Under these conditions, chiral aryl α -aminophosphonates **168** were obtained in 35-96% yields and 17-98% ee with the best results obtained for 3,5-diisopropyl-2-hydroxyaniline (R = *i*-Pr). In the reaction of aliphatic aldehydes **169** with 3-*t*-butyl-2-hydroxyaniline **170** and diethyl phosphite **167**, the desired phosphonates **171** were obtained with 20-83% yields and 71-98% ee. These results were obtained by performing the reaction in the presence of 30 mol% of (*S*)-*t*-Bu₂VANOL, 10 mol% of Zr(O*i*-Pr)₄, 10 mol% of *N*-methylimidazole, and 10 mol% of benzoic acid in toluene at room temperature. On the basis of X-ray analysis, the authors proposed that the active catalyst depicted in Scheme 48 exhibited three VANOL ligands chelated to the zirconium center with two protonated *N*-methylimidazoles.

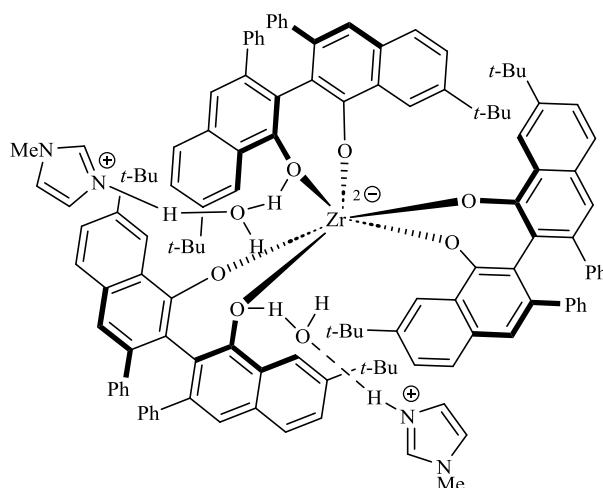


Ar = Ph, 2-Naph, *p*-MeOC₆H₄, *p*-*t*-BuC₆H₄, *p*-Tol, *p*-ClC₆H₄,
p-BrC₆H₄, *p*-Br-2-Naph, *p*-F₃CC₆H₄, 4-pyridyl,



R = *n*-Bu, *t*-Bu, *i*-Pr, *n*-Pr, *n*-Oct, allyl(CH₂)₂, HC≡C(CH₂)₄, Br(CH₂)₅,
 TBSO(CH₂)₂, TBSO(CH₂)₄, BocNH(CH₂)₂, PhthNH(CH₂)₃, N₃(CH₂)₃,
 N₃(CH₂)₅, MeO₂C(CH₂)₂, Cy, *c*-Pent, *i*-Bu

structure of active catalyst:



Scheme 48. Three-component Kabachnik–Fields reactions between aromatic/aliphatic aldehydes, anilines and diethyl phosphite.

CONCLUSIONS

As a non-toxic and abundant metal, zirconium has gained a significant importance especially in asymmetric catalysis. In the last three decades, a range of chiral zirconium catalysts mostly derived from BINOL have been successfully applied to promote many types of economic and ecologic highly enantioselective transformations, spanning from basic ones, such as Friedel–Crafts reactions, cycloadditions, aldol reactions, Mannich reactions, epoxidations, nucleophilic additions to carbonyl compounds and derivatives, cyanations, ring-opening reactions, hydroxylations, hydroformylations, carboaluminations among others, to more modern and complex domino and tandem reactions. This review updates the field of enantioselective zirconium-catalyzed reactions reported since the beginning of 2003, illustrating the power of these catalysts to provide high stereoselectivity in many types of asymmetric transformations. The non-toxicity and abundance of zirconium makes its application in 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. Despite the impressive advances made in this field, many challenges remain, such as more applications in the total synthesis of important biologically active and natural products to be achieved as well as the investigation of other types of (novel) ligands.

LIST OF ABBREVIATIONS

acac: acetylacetone

Ar: aryl

BINOL: 1,1'-bi-2-naphthol

Bn: benzyl

Boc: *tert*-butoxycarbonyl

Bz: benzoyl

CHP: cumene hydroperoxide

Cy: cyclohexyl

DBTA: dibenzyltartramide

de: diastereomeric excess

DIBAL-H: diisobutylaluminum hydride

DIPT: diisopropyltartrate

DME: dimethoxyethane

DMF: dimethylformamide

DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

ee: enantiomeric excess

Hex: hexyl

IBAO: isobutylaluminumoxane

L: ligand

MOF: metal organic framework

MS: molecular sieves
MTBE: methyl*tert*-butylether
Naph: naphthyl
NMI: neoisomethylindene
Oct: octyl
Pent: pentyl
Phth: phthalimido
PMB: *para*-methylbenzyl
r.t.: room temperature
TADDOL: α , α , α' , α' -tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol
TBDPS: *tert*-butyldiphenylsilyl
TBS: *tert*-butyldimethylsilyl
TEA: trimethylamine
TFA: trifluoroacetic acid
THF: tetrahydrofuran
TIBAO: tetraisobutyldialuminoxane
TMS: trimethylsilyl
Tol: tolyl
VANOL: 3,3'-diphenyl-2,2'-bi-(1-naphthol)
ZACA: zirconium-catalyzed asymmetric carboalumination

CONSENT FOR PUBLICATION

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

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