# BINOLs modified at the 3,3′-positions: chemists' preferred choice in asymmetric catalysis

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**Abstract**

This article provides a general overview of the most relevant topics in the applications of BINOL modified at the 3 and 3′-positions in asymmetric catalysis. A brief introduction to the chiral BINOL backbone so modified is given. A selection of the most outstanding uses of the catalysts according to the functional groups at the 3,3′-positions of BINOL backbones such as 3,3′-disubstituents of BINOLs, phosphoric acid derivatives and phosphoramidites is then presented. This review aims to introduce the latest developments of this active field, including the literature since 2008.

**Keywords:** BINOLs modified at 3,3′- positions, chiral ligand, asymmetric catalysis

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## 1. Introduction

According to Cram and coworkers′ precursory work, BINOL (1,1′-Bi-2-naphthol) **1** ( Figure 1) and modified BINOLs have the potential ability to realize high chiral recognition.[1] Especially after Noyori first reporting about the application of BINOL in asymmetric catalysis in 1979,[2] BINOL whose chirality is derived from the restricted rotation around its 1,1′-bond is often served as the starting material to obtain chiral BINOL derived compounds.[3-11] In a word, BINOL derivatives have played a very important role in asymmetric catalysis, and have attracted a great deal of interest.[10-13] On the other hand, only a limited number of reactions are induced by BINOL derivatives due to their lower Brønsted acidity.[14] To make them able to catalyze more asymmetric reactions, they are usually employed as chiral ligands and Lewis bases to bind with metals to form complexes. Many modified BINOL ligands have been successfully synthesized and applied to a wide range of chemical transformations. BINOL modified at the 3,3′-positions can be readily obtained via a two-step protocol that includes treatment of a suitably protected BINOL (usually protected by methoxymethyl chloride) with an organolithium reagent (usually n-BuLi), followed by reaction with an electrophile (Scheme1), although there are other limited expensive methods.[15]

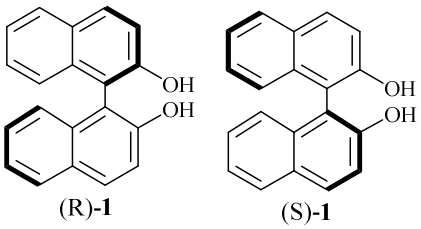
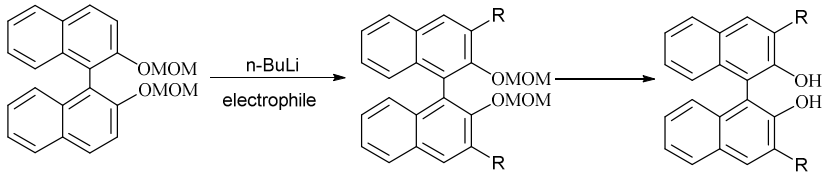



**Figure 1.** The structures of two enantiomers of BINOL.

Modification at the 3,3′-positions can also dramatically tune its steric and/or electronic properties.[16] So we mainly pay attention to the 3,3′-positions in this review. For convenience, it will be carried out according to the class of functional groups introduced at the 3,3′-positions.




**Scheme 1.** The representative synthesis route of 3,3′-BINOLs.

## 2. Some Representative Applications of BINOLs Modified at 3,3′-Positions

### 2.1 BINOLs 3,3′-disubstituted by acyclic functional groups

The fact that there are only few examples of BINOLs 3,3′-disubstituted by acyclic functional groups in asymmetric catalysis may be due to the fact that acyclic functional groups can rotate more freely

than other functional groups. Of the structures depicted in Figure 2, compound **2** was first used in the enantioselective asymmetric allylboration of ketones in 2006 (Scheme 2) and then by Schaus in 2011 in the asymmetric propargylation of ketones (Scheme 3).[17,18]

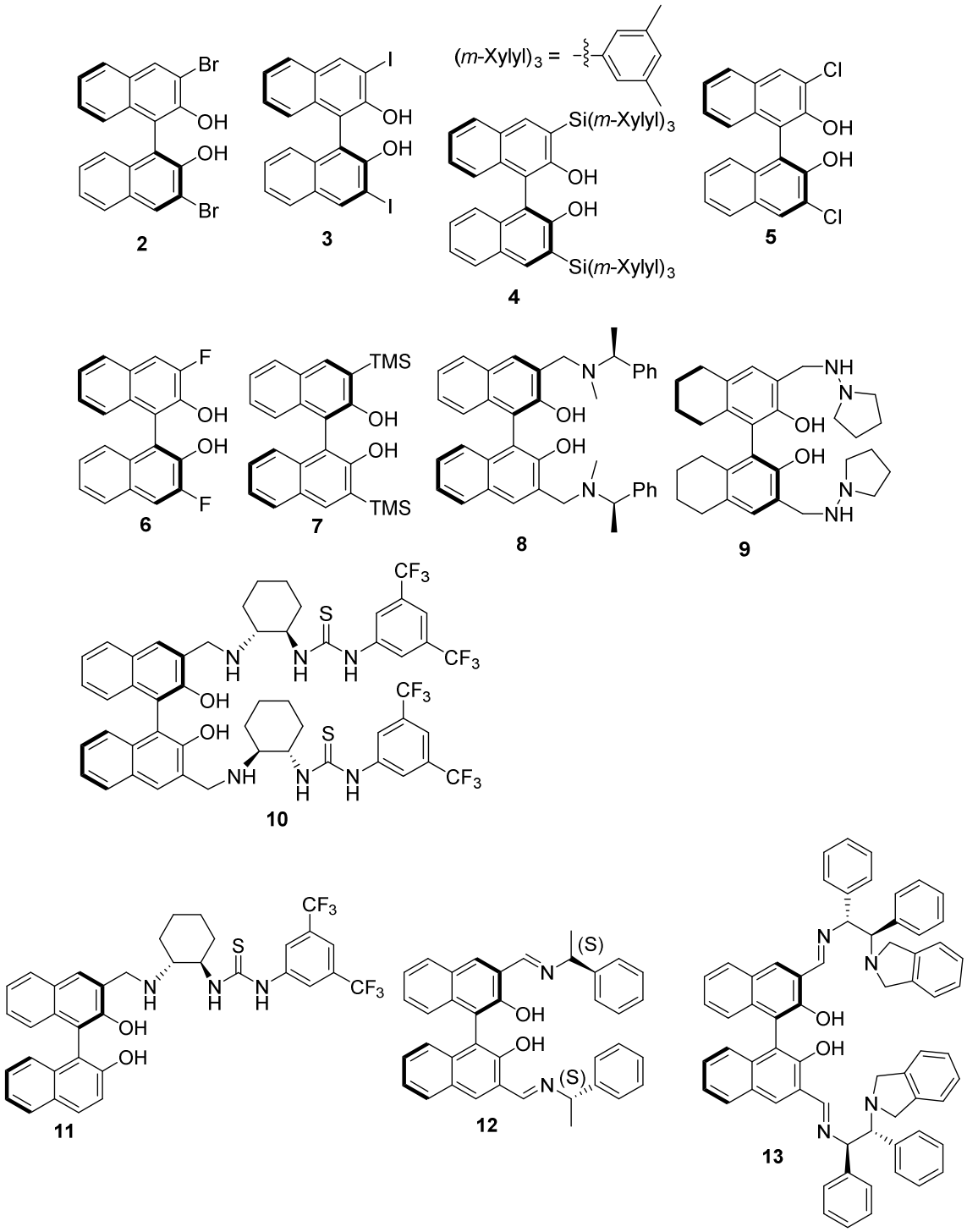
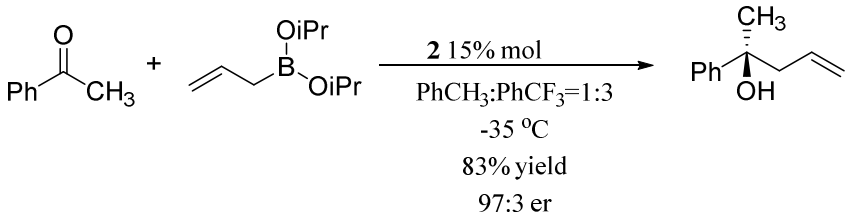
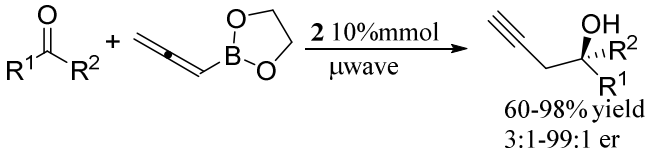



**Figure 2.** Representative list of BINOLs modified at 3,3′-positions by acyclic functional groups.




**Scheme 2.** Asymmetric allylboration of ketones catalyzed by **2.**




**Scheme 3.** Asymmetric propargylation ofketones using allenylboronates catalyzed by **2.**

In Scheme 2 Schaus and co-workers developed a ligand-accelerated protocol which is a closely related and highly enantioselective catalyst for the catalytic asymmetric allylboration of ketones. In their proposed catalytic cycle (Figure 3), A ligand exchange process which is not only at the beginning but at the end of the catalytic cycle was thought to be the efficient catalytic process.

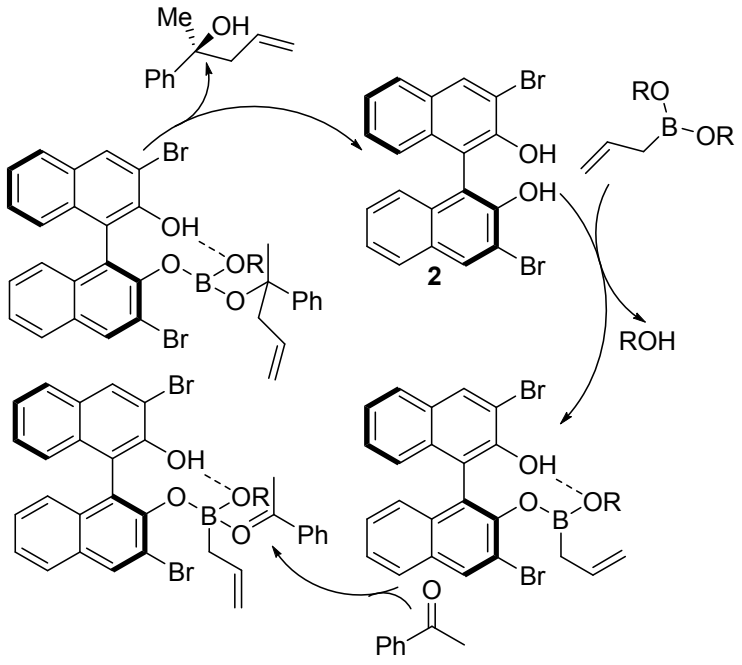



**Figure 3.** Proposed catalytic cycle of asymmetric allylboration of ketones catalyzed by **2.**

The mechanism of Scheme 2 was studied by Goodman and Pellegrinet[19] in 2008, who showed that the design of new ligand-accelerated boron reactions can be aided by studying this type reaction

catalyzed by **2**.Their result indicates that the most reactive species is a cyclic Lewis acid-activated boronate rather than Brønsted acid-activated (Figure 4).

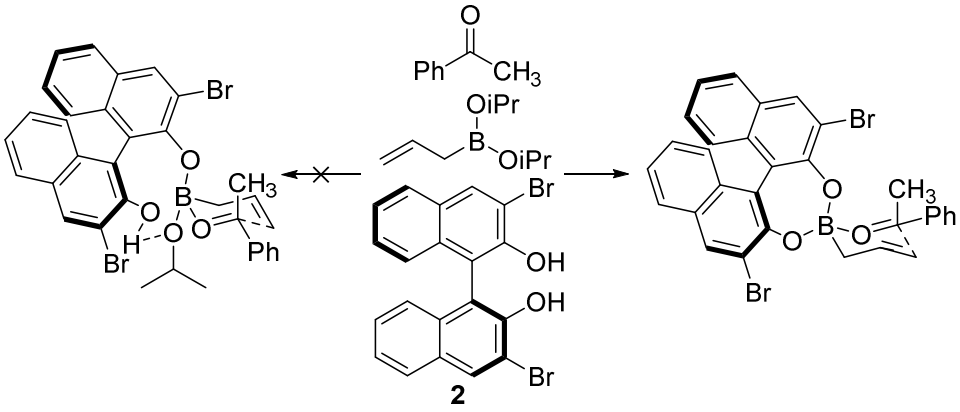
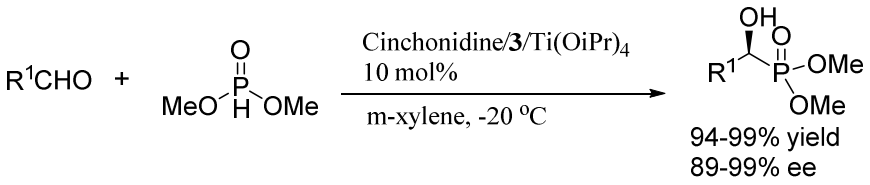



**Figure 4.** Proposed transition state.

Compound **3** was used in self-assembled bifunctional catalysis of enantioselective hydrophosphonylation by You *et al.* in 2008.[20] And the α-hydroxy phosphonates they got can be reached up to 99% ee and 99% yield (Scheme 4). Besides that, they also proposed a reasonable transition-state model (Figure 5).

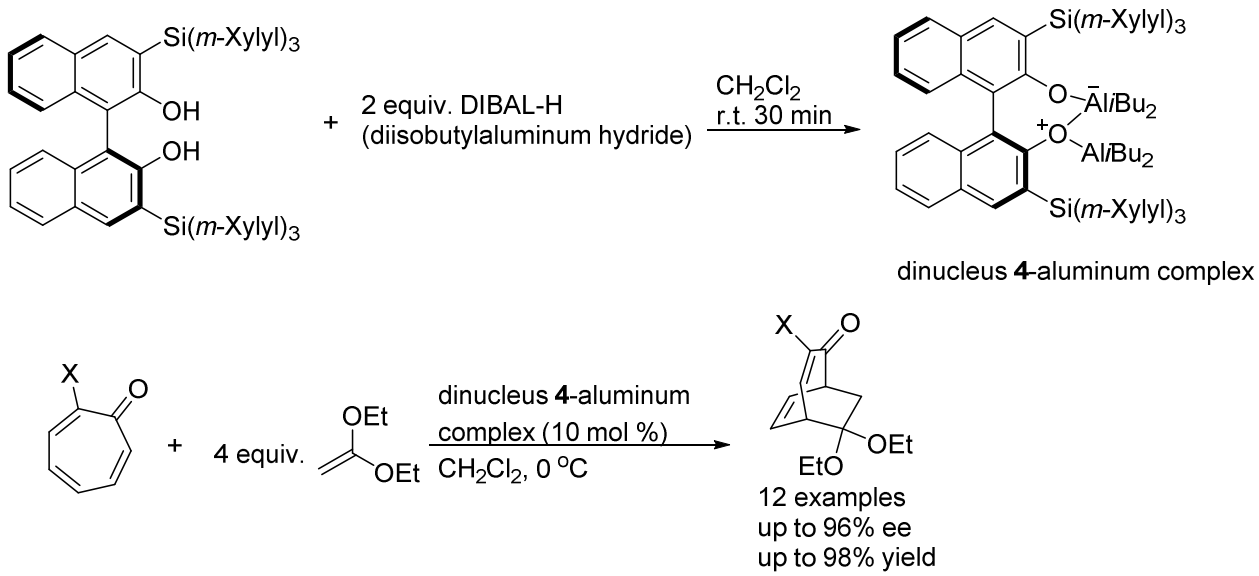



**Scheme 4**. Self-assembled bifunctional catalysis of enantioselective hydrophosphonylation.

You′s work is important because the modular nature of **3** and cinchonidine enables easy tuning of the steric and electronic properties. Furthermore, the components of these self-assembled catalysts are commercially available, thus making this process much more accessible. This strategy is to provide a powerful method for searching new types of bifunctional catalysts.

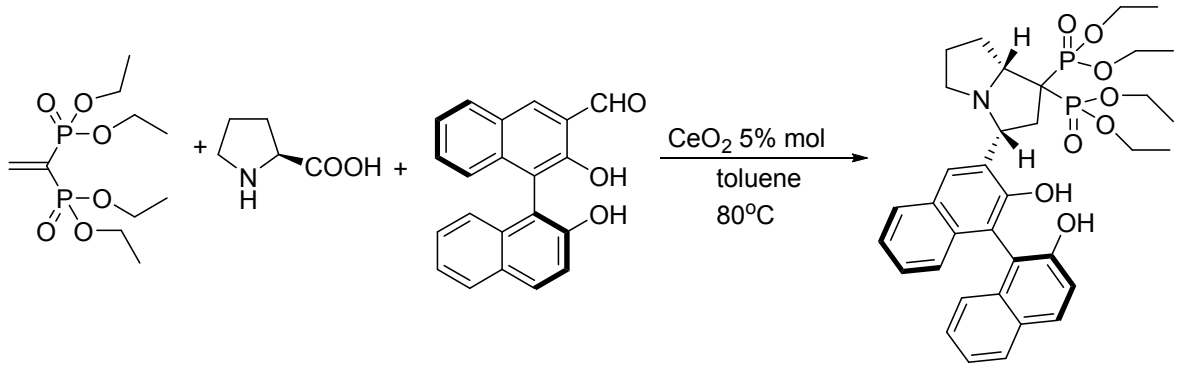
In 2009, Yamamoto *et al.* used the dinucleus **4**-aluminum complex to obtain the Diels-Alder adducts exclusively without other types of cycloadducts in high enantioselectivity (Scheme 5).[21] They argued that they have developed an asymmetric version using chiral aluminum catalyst to give functionalized bicyclo[3.2.2] ring structures with high enantioselectivities which should be widely applicable for asymmetric synthesis of highly substituted chiral seven-membered rings.




**Scheme 5.** Asymmetric Diels-Alder reaction between tropone derivatives and ketene diethyl acetal catalysed by dinucleus 4-aluminum complex.

We are always doing the research about asymmetric catalysis employing BINOLs modified at 3,3′-positions as catalysts. We also believe that BINOLs can also be utilized as chiral substrates to synthesize chiral compounds. Our primary results have been published,[22] although there is only one example in our paper (Scheme 6).




**Scheme 6.** BINOLs modified at 3,3′-positions utilized as chiral substrates to synthesize chiral compound.

Similarly, in 2011, Michael used **5** to the conjugate addition of arylboronates to α,β-unsaturated ketones with enantioselectivities of up to 99:1 (Scheme 7),[23] and above all, this method was applied to synthesize intermediates for syntheses of (+)-indatraline and (+)-tolterodine.

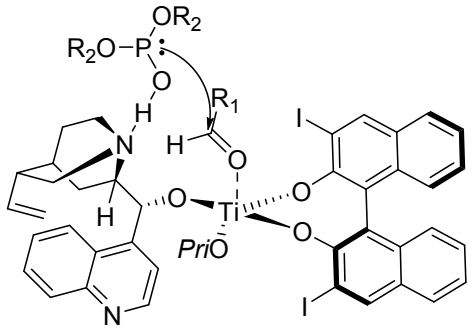
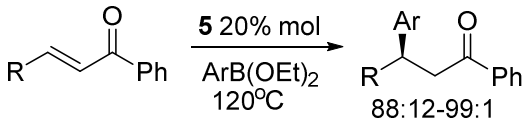
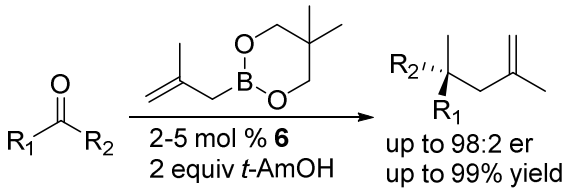


**Figure 5.** Proposed transition-state model of enantioselective hydrophosphonylation.



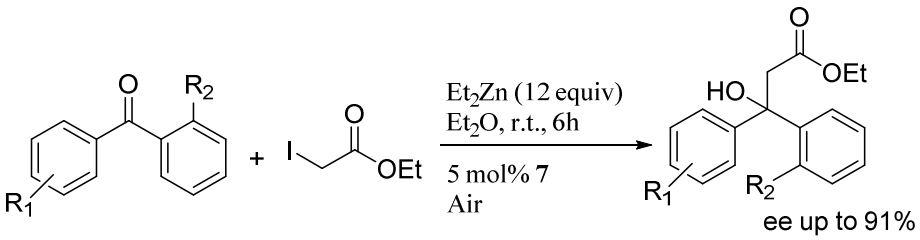

**Scheme 7.** Asymmetric conjugate arylboration of enones catalyzed by **5.**

Zhang and coworkers synthesized **6** for the first time in 2013, and used it for asymmetric methallylation of ketones.[24] Up to 98:2 enantioselectivity and 99% yield were obtained with 5 mol % catalyst loading and The catalyst could be easily recovered and reused (Scheme 8).




**Scheme 8.** Asymmetric methallylation of ketones catalysed by **6.**

Ligand **7** was used as a ligand in the first catalytic enantioselective Reformatsky reaction using the ortho-substituted diaryl ketones (Scheme 9) in a radical mechanism (Figure 6). Chiral tertiary alcohols with two aryl groups were gotten with good enantioselectivities and moderate to good yields was obtained.[25]




**Scheme 9.** First catalytic enantioselective Reformatsky reaction using the ortho-substituted diaryl ketones catalyzed by **7.**

Ligand **8** was developed by Feng *et al.* in 2008, and that **8** coordinated with $Et_2AlCl$ formed a new bifunctional chiral Al(III) complex.[26] This bifunctional catalyst has been developed for the effective enantioselective hydrophosphonylation of aldehydes. The reaction can employ a variety of aromatic, heteroaromatic, condensed-ring, α,β-unsaturated, and aliphatic aldehydes.The desired α-hydroxy phosphonate was obtained in moderate to good enantioselectivities (up to 87% ee) and with good to excellent yields (up to 99%) under mild conditions (at 0 °C) (Scheme 10). They also proposed a possible catalytic cycle based on the experimental results (Figure 7).

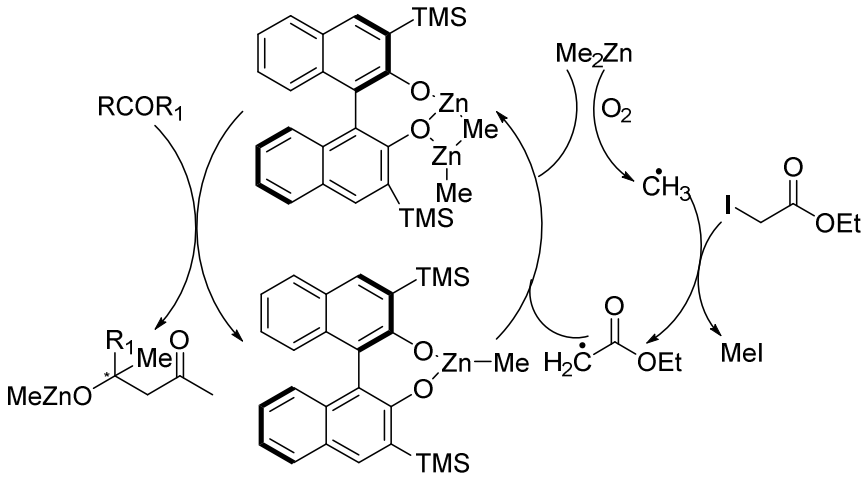
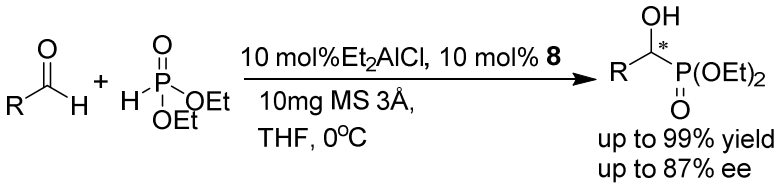
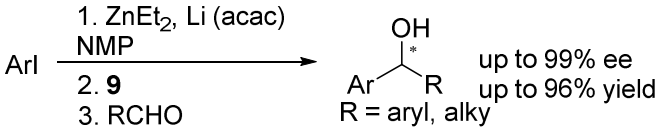



**Figure 6.** Proposed catalytic cycle for the Reformatsky reaction promoted by **7**




**Scheme 10.** Effective enantioselective hydrophosphonylation of aldehydes catalyzed by **8**.

Compound **9** was employed in the addition of heteroarylzinc reagent to an aldehyde with good enantioselectivity by Pu in 2010 (Scheme 11).[27,28]




**Scheme 11.** Asymmetric arylzinc addition to aldehydes catalysed by **9.**

Pu also found for the first time that an aryl bromide, 2-bromothiophene, could be used to prepare a heteroarylzinc reagent by reaction with $ZnEt_2$.

In 2011, Yuan *et al.* employed **10** and **11** which are newly designed thiourea-BINOL catalysts to catalyse an enantioselective three-component Petasis reaction among salicylaldehydes, amines and organoboronic acids.[29] A wide range of alkylaminophenols can be obtained in good to high enantioselectivity (up to 95% ee) and good yield (up to 92%) (Scheme 12).

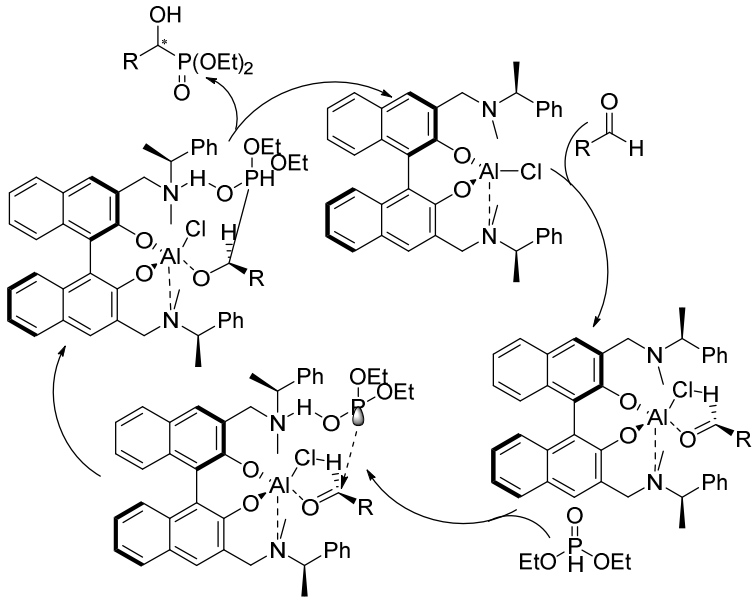
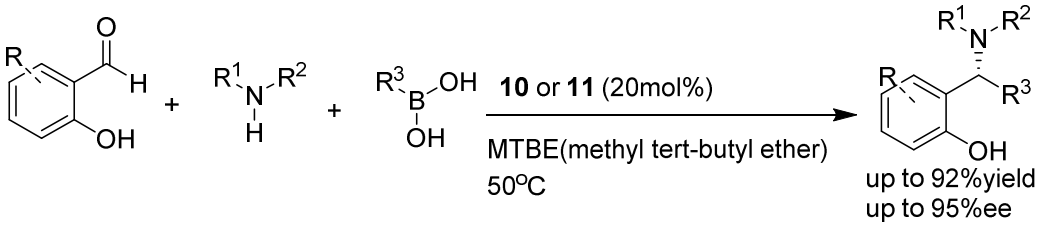
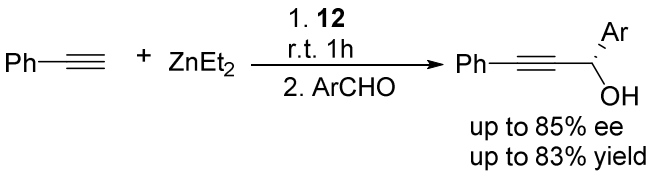


**Figure 7.** A possible catalytic cycle for the effective enantioselective hydrophosphonylation of aldehydes.




**Scheme12.** Enantioselective organocatalytic three-component petasis reaction among salicylaldehydes, amines, and organoboronic acids catalyzed by **10** or **11.**

They also tentatively proposed a possible reaction pathway for this catalytic enantioselective Petasis reaction (Figure 8).




**Scheme 13.** Asymmetric alkyne addition to aldehydes catalyzed by **12.**

In 2014, Pu used **12**, a BINOL-chiral benzylic amine-based Schiff base to catalyze the reaction of phenylacetylene with aldehydes in the presence of $ZnEt_2$ with up to 85% ee and 83% yield (Scheme 13) .[30] The results show that various propargylic alcohols could be obtained with encouraging results by utilizing the readily prepared **12** as a catalyst.

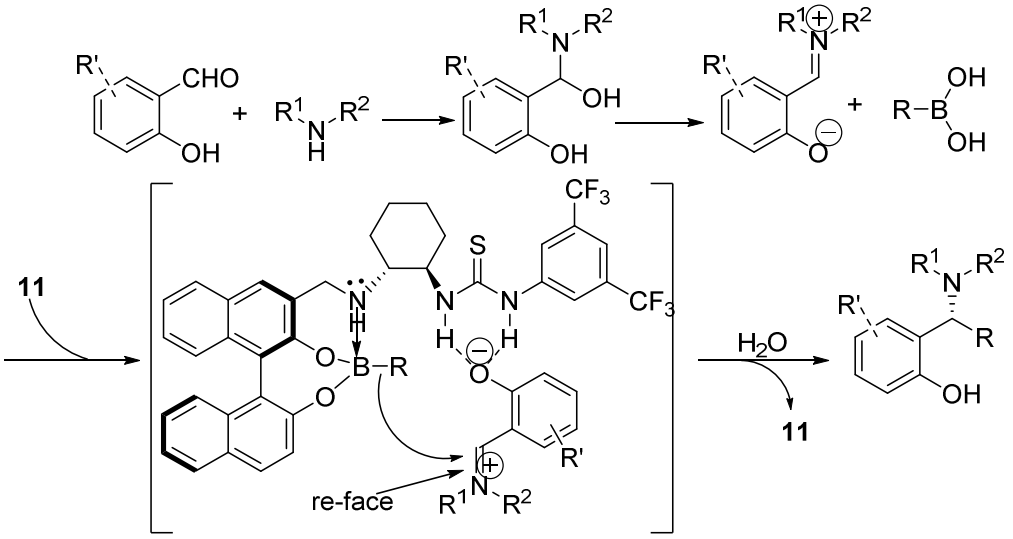
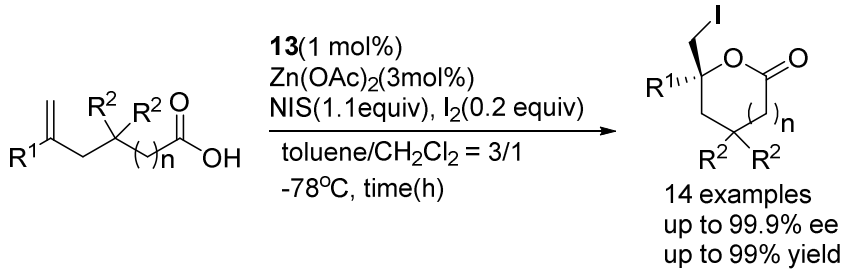



**Figure 8.** A possible reaction pathway for the catalytic enantioselective Petasis reaction.

Meanwhile, Arai *et al.* designed a newly ligand **13** which showed excellent catalytic activity for the iodolactonization reaction to yield products in quantitative yields with outstanding enantioselectivity after forming complex **13**–$Zn_3(OAc)_4$ with $Zn(OAc)_2$.[31] Using this trinuclear Zn complex, 1 mol% Zn3(OAc)4-**13** catalyzed asymmetric iodolactonization in up to 99.9% ee (Scheme 14)




**Scheme 14.** Catalytic asymmetric iodolactonization using a **13**–$Zn_3(OAc)_4$ catalyst.

### 2.2 BINOLs 3,3′-disubstituted by aromatic rings

Compounds **14-16** were utilized to catalyze the asymmetric reaction of alkynes with aldehydes to get chiral propargylic alcohols at room temperature in 2009 by Pu *et al.*[32]

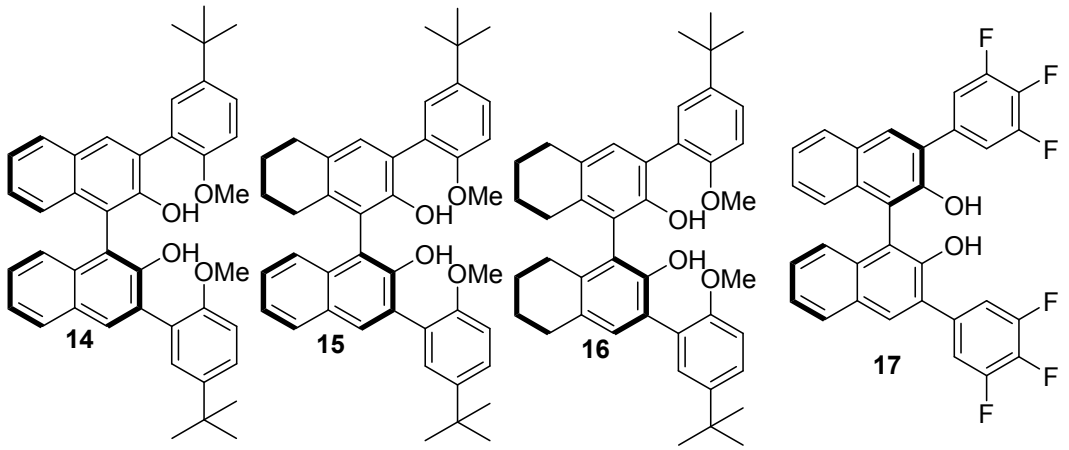
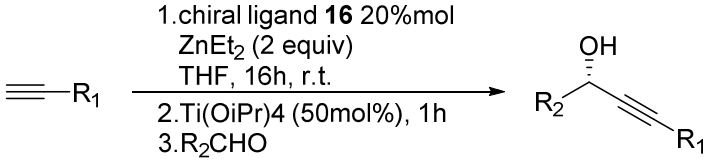



**Figure 9.** Typical examples of BINOLs 3,3′-disubstituted by aromatic rings.

Chiral ligands **15** and **16** were obtained through modification of the dihedral angle of BINOL. With the optimized system, **16** was the best. When combined with $ZnEt_2$ and $Ti(OiPr)_4$, **16** catalyzed the reactions of alkyl propiolates with 88-99% ee; the reactions of phenylacetylene with 81-87% ee; the reactions of 4-phenyl-1-butyne, an alkyl alkyne, with 77-89% ee; and the reactions of trimethylsilylacetylene with 92-97% ee (Scheme 15).



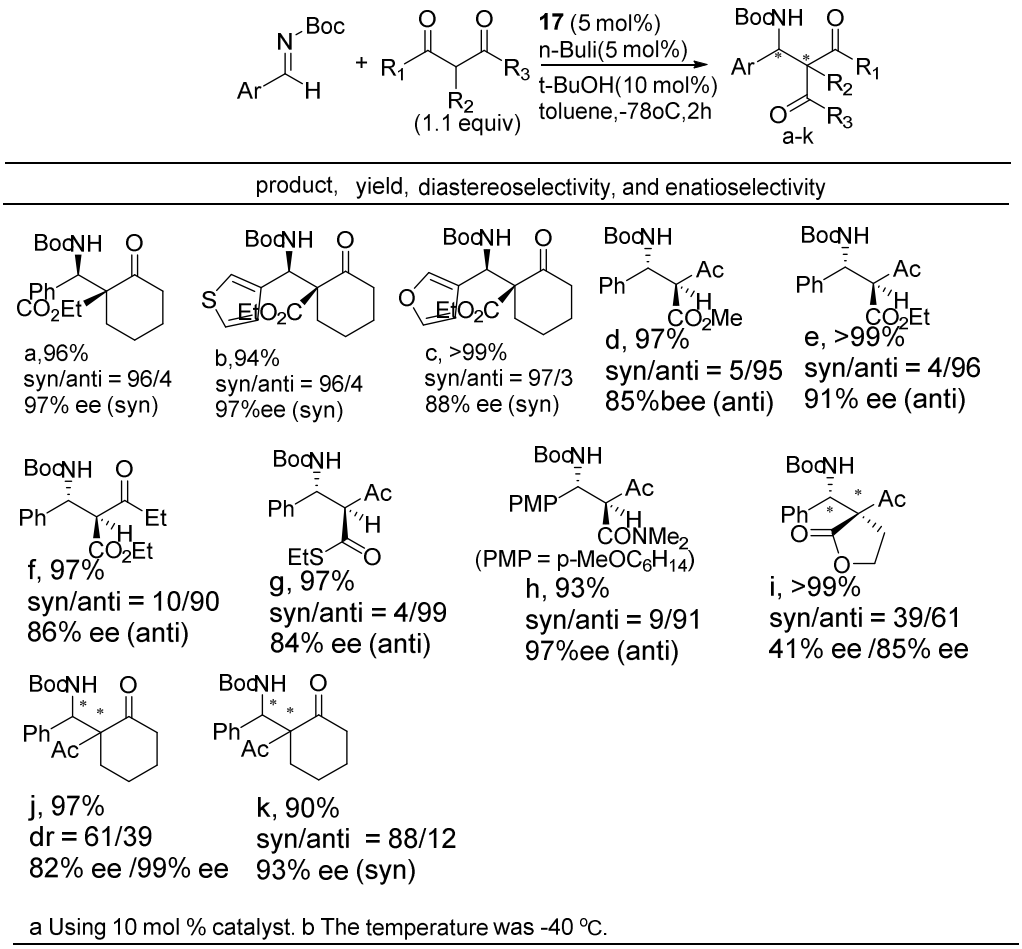

**Scheme 15.** Asymmetric synthesis of diverse propargylic alcohols promoted by **16.**

Pu′s work shows that modification of the dihedral angle of BINOL is also very crucial compared with the tune of steric and/or electronic properties of BINOL.

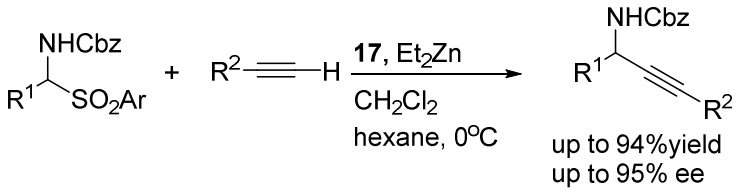
In 2010, Ishihara *et al.* used **17** to get a simple Li(I) BINOLate salt to promote a highly enantioselective direct Mannich-type reaction of aldimines with 1,3-dicarbonyl compounds.[33] Compound **17** was effective to selectively synthesize *syn* adducts from cyclic reagents and unreported *anti* adducts from acyclic reagents (Scheme 16).

Two years later, Pedro *et al.* reported they employed **17** in a new procedure to obtain N-Cbz-protected propargylic amines which is optically active building blocks for organic synthesis and essential backbones in biologically active compounds as well as natural products.[34] The 3,3′-disubstituted ligands contribute to high enantioselectivities because of their vital steric effect. The reactions can undergo different alkynes, and with a variety of aromatic as well as heteroaromatic starting materials, providing the very products with good yields and high enantiomeric excesses (Scheme 17). A plausible concise catalytic cycle for the alkynylation of α-amido sulfones in the presence of Zn–BINOL complexes was given by the author, too. (Figure 10).




**Scheme 16.** A highly enantioselective direct Mannich-type reaction of aldimines with 1,3-dicarbonyl compounds.




**Scheme 17.** Enantioselective Zinc/BINOL-catalysed alkynylation of aldimines generated insitu from α-amido sulfones.

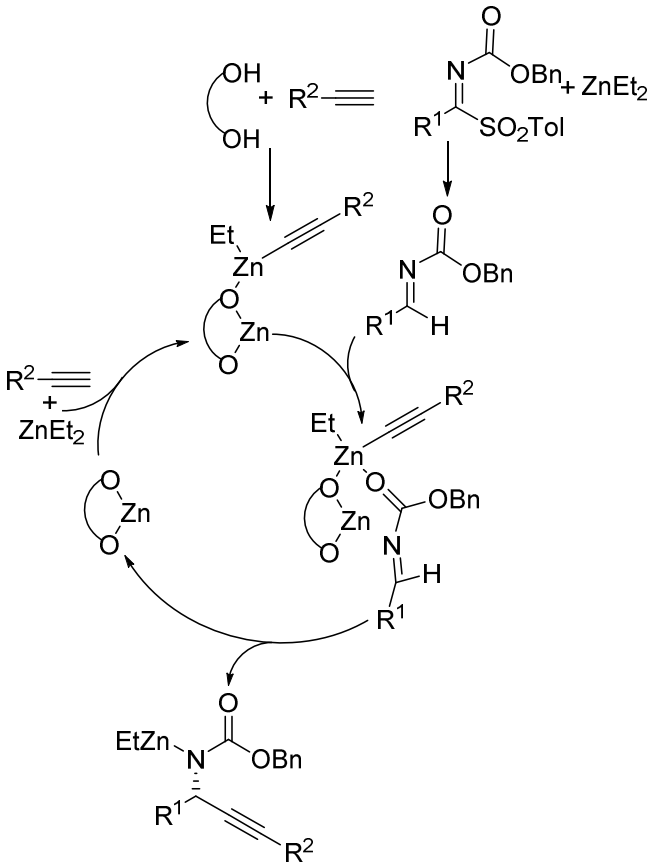


**Figure 10**. A plausible concise catalytic cycle for the alkynylation of α-amido sulfones in the presence of Zn-BINOL complexes.

### 2.3 BINOLs 3,3′-disubstituted by heterocyclic rings.

As described in Figure 11, there are mainly three compounds of BINOLs 3,3′-disubstituted by heterocyclic rings. In 2008, Feng *et al.* reported the Strecker reaction of ketoimines with fairly wide range of substrate scopes and excellent enantioselectivities (up to 99% ee) catalysed by **18** (Scheme 18).[35]

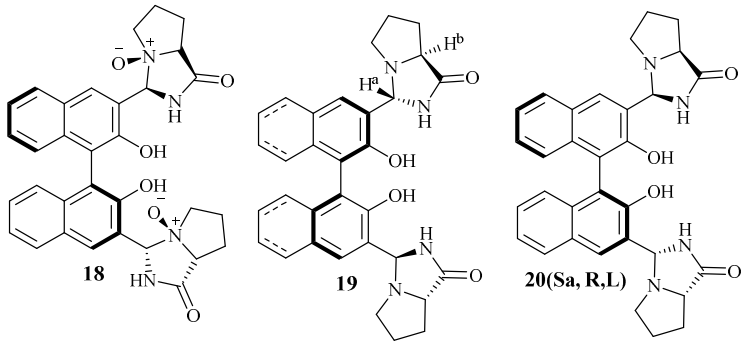
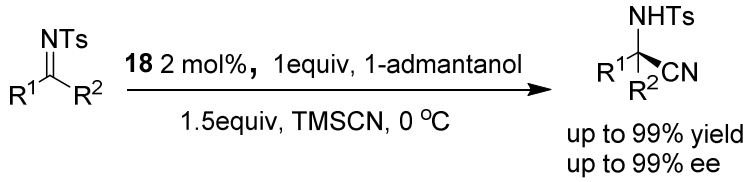


**Figure 11.** Representative compounds of BINOLs 3,3′-disubstituted by heterocyclic rings.

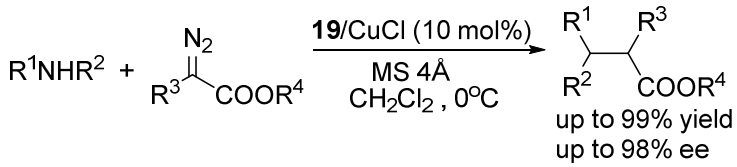
 

This strategy can be useful in the organic synthesis because of low catalyst loading (2 mol%), mild reaction conditions, and operational simplicity. The author claimed that further investigation of the reaction mechanism is underway.



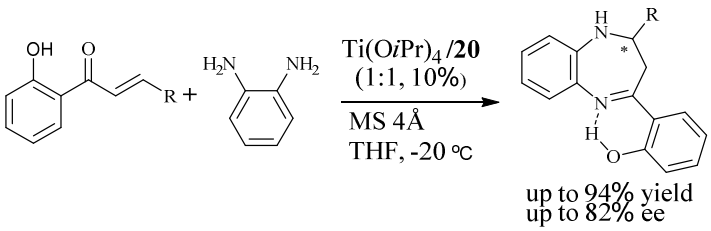

**Scheme 18.** Highly enantioselective Strecker reaction of ketoimines catalyzed by **18.**

Two years later, they (Feng *et al.*) developed a novel and easily available BINOL-type copper(I) catalyst obtained from **19** that is highly enantioselective in the catalytic insertion reaction of α-diazoesters into N-H bonds of the amines under mild reaction conditions.[36] Moderate to good results were also obtained when reacting with secondary amine as well as the excellent ee values and yields observed for primary amines. According to this method, they can readily prepare a variety of useful chiral α-amino esters with different *N*-substituted groups in excellent yields and enantiomeric excesses (Scheme 19). And they intend to take further studies on the potent catalytic N-H insertion of secondary amine with diazoesters and mechanistic studies.




**Scheme 19.** Copper(I)-**19**-catalyzed asymmetric insertion of diazoesters into the N-H bond of amine.

From then on, they (Feng *et al.*) used a titanium complex from a similar ligand **20** to enhance the domino reaction of *o*-phenylenediamine and chalcone derivatives to synthesize 2-substituted-1,5-ben-zodiazepine derivatives for the first time in 2011.[37] The products obtained are in good yields with up to 82% ee (Scheme 20).




**Scheme 20.** Enantioselective synthesis of 2-substituted-1,5-benzodiazepines enhanced by **20.**

Given the essential role of the hydroxyl group at the 2′-position of chalcone, they rationalized a possible simplified catalytic cycle (Figure 12).

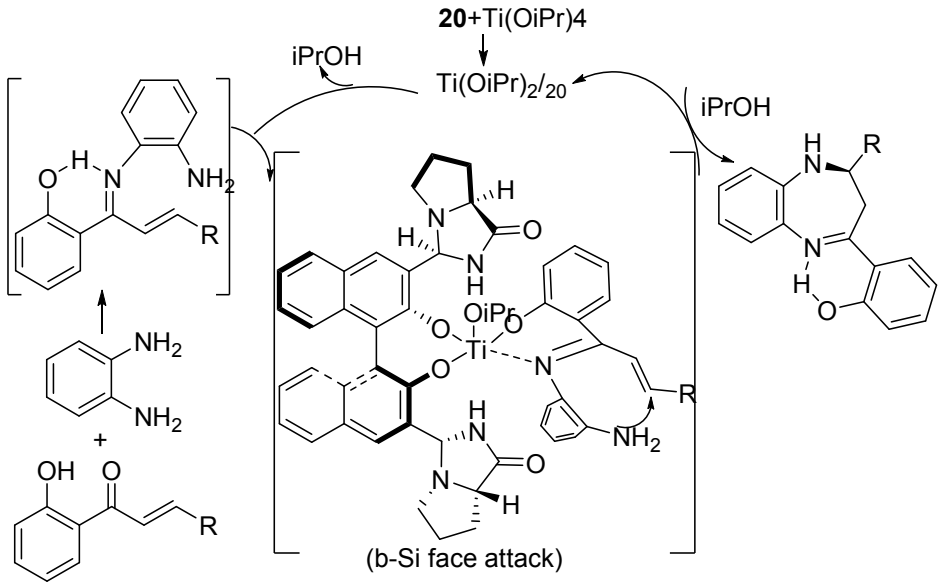



**Figure 12.** Proposed catalytic cycle of enantioselective synthesis of 2-substituted-1,5-benzo diazepines enhanced by **20.**

## 3. The Coming Trend and Ongoing Results to Convert Potent 3,3′-Disubstituted BINOLs into Chiral Phosphoric Acids

That 3,3′-disubstituted BINOLs were converted into chiral phosphoric acids is one of the most successful achievements in organocatalysis (Figure 13).[38] The key for high enantioselectivity is to introduce a sterically hindered aromatic ring or silyl group into 3,3′-positions of BINOL backbones which was independently discovered by Akiyama[39] and Terada.[40-42]

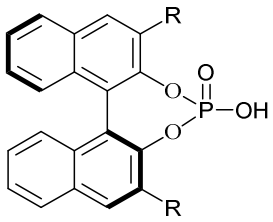
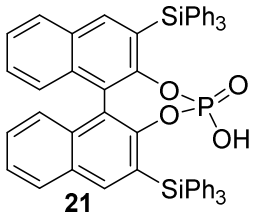


**Figure 13.** The structure of chiral monophosphoric acids derived from 3,3′-disubstituted BINOLs.

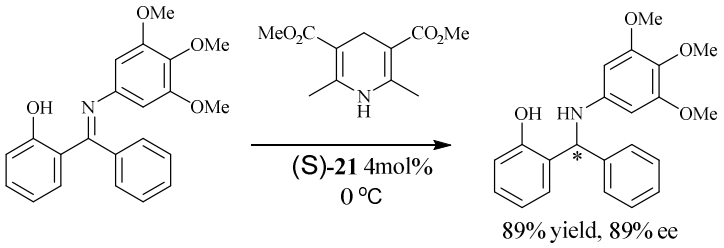
 



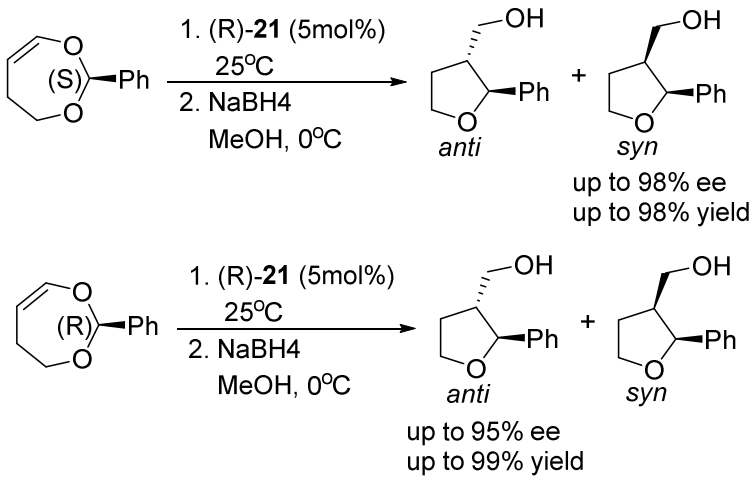

**21**

### 3.1 BINOLs-derived phosphoric acids 3, 3′-disubstituted by acyclic functional groups

In 2011, Wang *et al.* reported the transfer hydrogenation of N-arylortho-hydroxybenzophenone ketimines first catalysed by chiral phosphoric acid (S)-**21.**[43] Chiral diarylmethylamines can be obtained in high yields as well as enantioselectivities (Scheme 21).




**Scheme 21.** Enantioselective transfer hydrogenation of *N*-aryl-*ortho*-hydroxybenzophenone ketimines promoted by (S)-**21.**



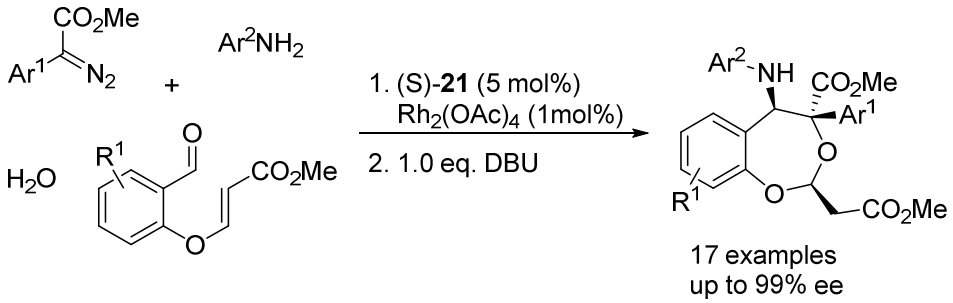

**Scheme 22.** Petasis–Ferrier-type rearrangement of cyclic vinyl acetals catalyzed by (R)-**21.**

In 2014, Terada *et al.* studied the Petasis–Ferrier-type rearrangement of a 7-membered cyclic vinyl acetal catalyzed by (R)-**21,** through which the high anti- or syn-selectivity is obtained (Scheme 20) and their DFT calculations suggested that non-classical C–H/O hydrogen bonds between the catalyst and the substrate play an important role in determining the stereoselectivity.[44]

At the same year, Liu and Hu *et al.* used (S)-**21** as catalyst to develop a four-component

Mannich reaction subsequently followed by an intramolecular oxo-Michael addition to efficiently produce chiral cyclic acetals with high diastereoselectivity and enantioselectivity (Scheme 23).[45]

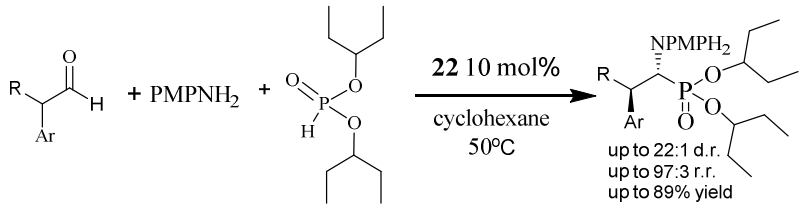



**Scheme 23.** Enantioselective four-component Mannich reactions of aryldiazoacetates with water, anilines and methyl 3-(2-formylphenoxy) propenoates catalysed by (S)-**21.**

### 3.2 BINOLs-derived phosphoric acids 3,3′-disubstituted by aromatic rings

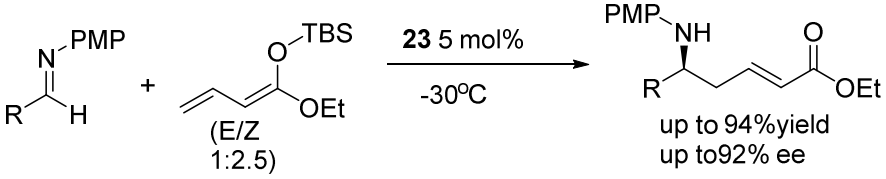
Figure14 depicts structures of representative BINOLs-derived phosphoric acids 3,3′-disubstituted by aromatic rings in recent years.

List *et al.* employed **22** (Figure 14) to catalyse Kabachnik–Fields reaction to asymmetrically synthesize mimics of a-amino acids and a-amino phosphonates in 2008. [46]The desired products which have great promise as antibacterial and anti-HIV drugs[47] were obtained with moderate to good enantioselectivity and yields (Scheme 24).




**Scheme 24.** Direct asymmetric three-component Kabachnik-Fields reaction catalysed by **22.**

Meanwhile, **23** was used in the first catalytic, enantioselective, vinylogous Mukaiyama–Mannich reactions of acyclic silyl dienolates and imines by Schneider et al.[48] They got the highly valuable δ-amino-α,β-unsaturated carboxylic esters in high yields, complete regioselectivity and good to excellent enantioselectivities ( Scheme 25).




**Scheme 25.** First catalytic, enantioselective, vinylogous Mukaiyama-Mannich reactions of acyclic silyl dienolates and imines.

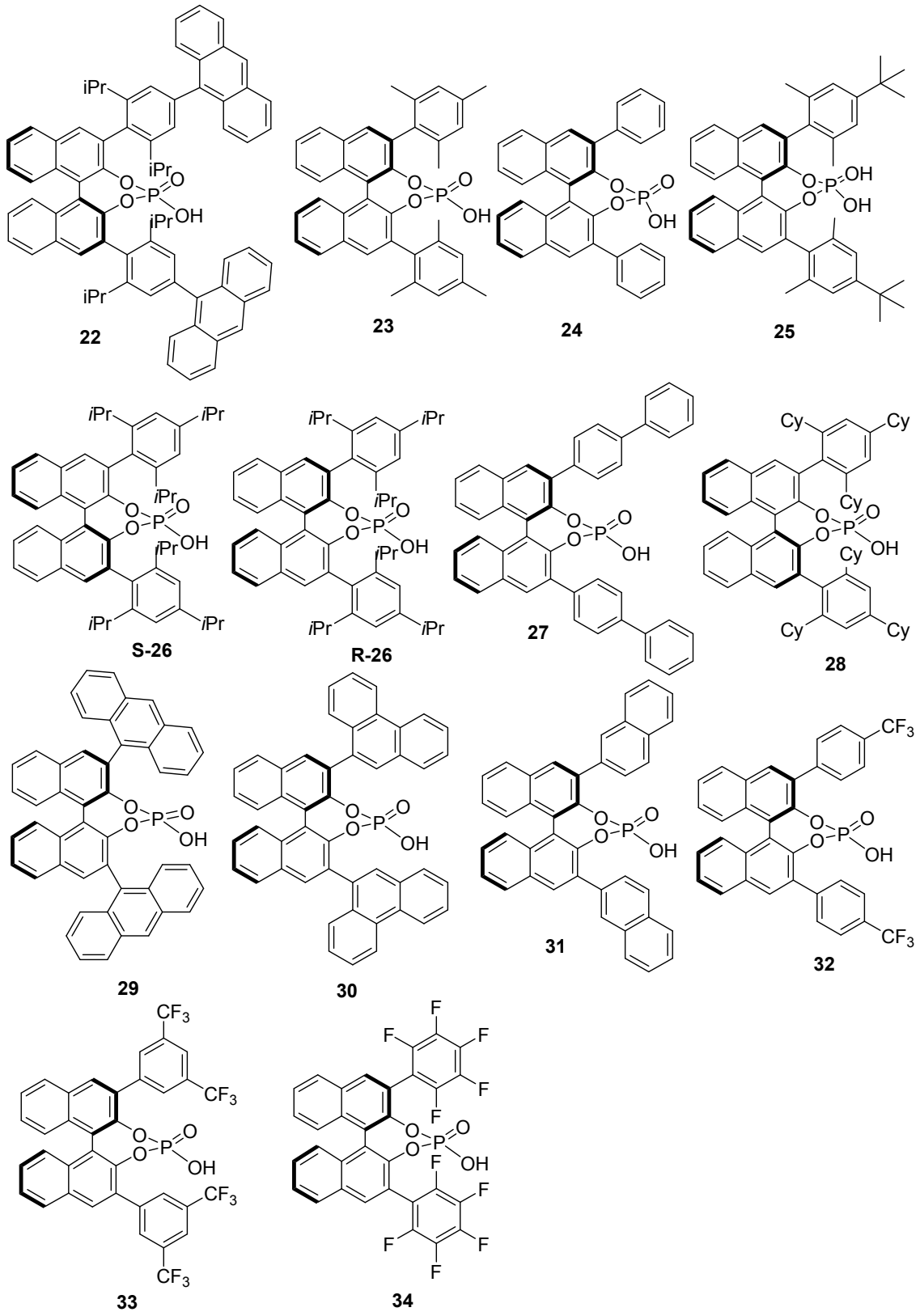
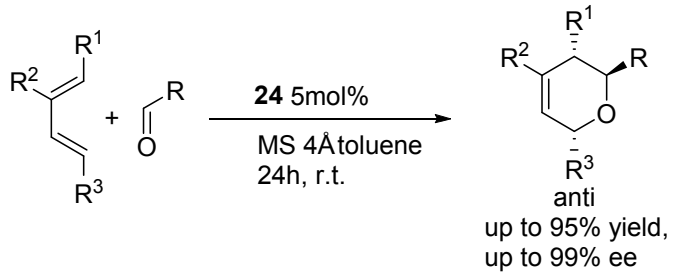



**Figure 14.** Typical BINOLs derived phosphoric acid catalysts 3,3′-disubstituted by aromatic rings.

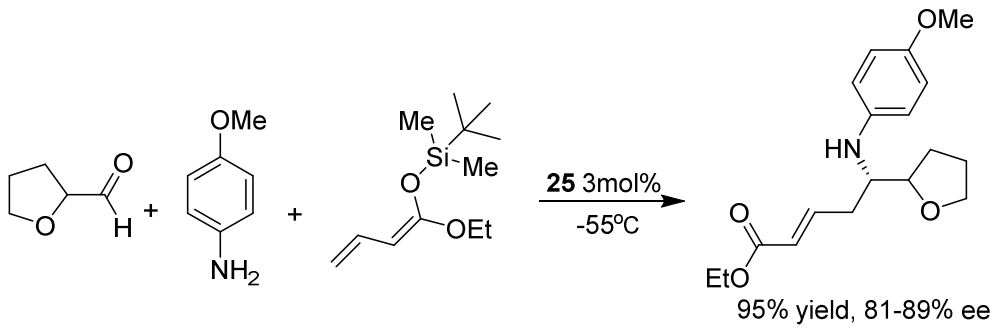
 

Some time thereafter, Terada *et al.* reported that they used **24** to catalyse the first example of a hetero-Diels-Alder reaction which is highly enantio and anti-selective between a glyoxylate and siloxy- or methoxydienes.[49] Initial results with **24** suggested that chiral Lewis acids have typically provided the optically active syn adduct, but chiral phosphoric acid **24** was unparalleled efficient in producing anti adducts in high yields with high ee value as single diastereomers (Scheme 26). Their results indicates the steric demand of the catalyst is likely to be the main factor in increasing the syn selectivity.




**Scheme 26.** The first example of a hetero-Diels-Alder reaction catalysed by **24.**

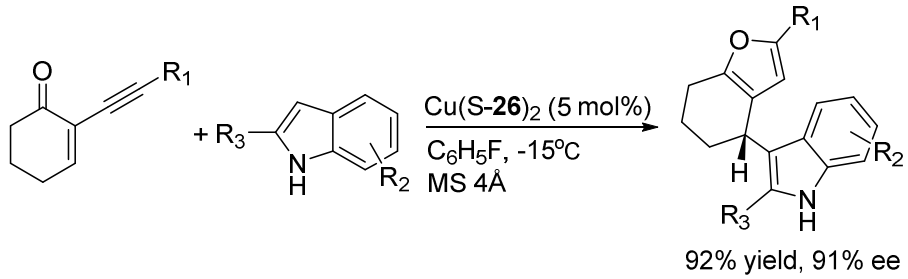
In 2011, Bräse *et al.* employed **25** a to promote the vinylogous Mukaiyama–Mannich reaction to obtain hydroindole derivatives.[50] The highly diastereoselective δ-amino-α,β-unsaturated carboxylic esters were obtained (Scheme 27).




**Scheme 27.** The vinylogous Mukaiyama-Mannich reaction catalysed by **25.**

**(S)-26** was used as a catalyst in the enantioselective synthesis of highly substituted furans through cycloisomerization in 2011 by Toste.[51] Bräse *et al.* think copper(II)-(S)-**26** catalyst catalyses the intramolecular heterocyclization of 2-(1-alkynyl)-2-alkene-1-ones and furnishes high levels of enantioselectivity in the subsequent nucleophile attack (Scheme 28).




**Scheme 28.** Copper(II)-(S)-**26**-catalyzed indole addition reaction.

A proposed mechanism was suggested by Bräse *et al.* (Figure 15).

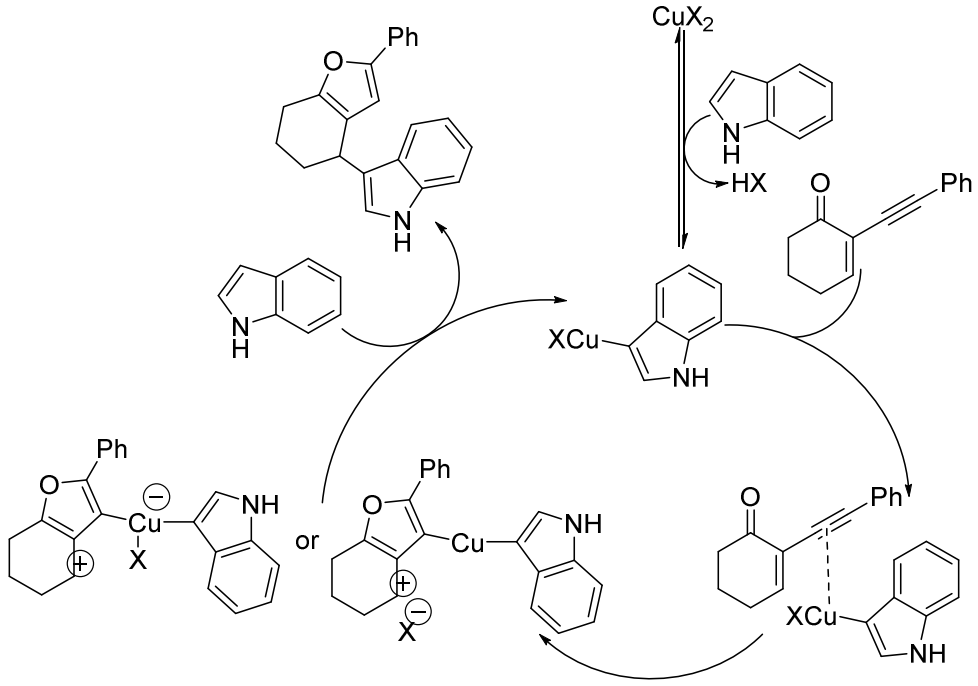
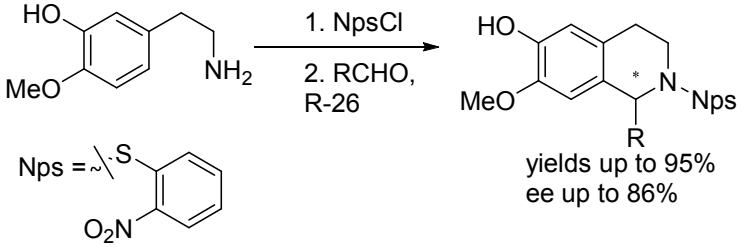



**Figure 15.** A proposed mechanism of copper(II)-(S)-**26**-catalyzed indole addition reaction.

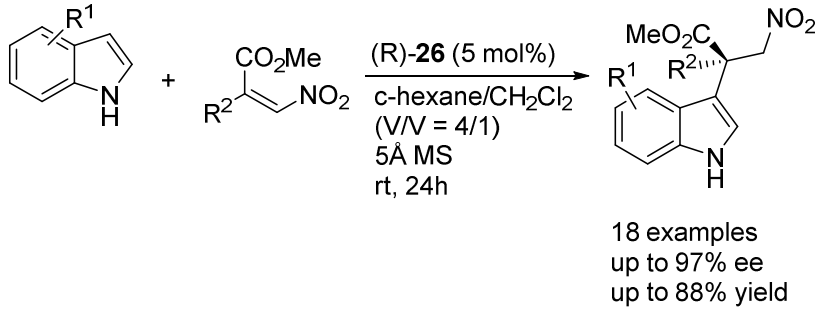
Three years later, a symmetric Pictet−Spengler reaction catalyzed by (R)-**26** was reported by Hiemstra.[52] The Pictet−Spengler products were obtained in good ee values and yields (Scheme 29).




**Scheme 29.** Organocatalytic enantioselective Pictet-Spengler Reactions promoted by (R)-**26.**

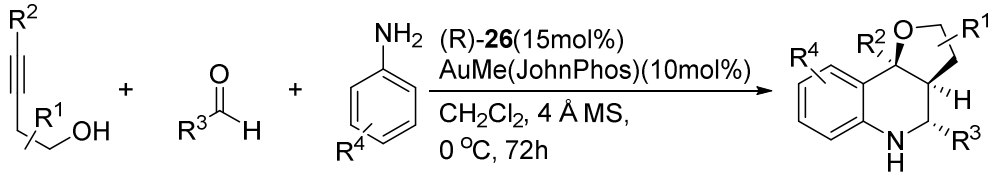
 

Meanwhile, Akiyama *et al.* described the Friedel–Crafts reaction of indoles with β-alkoxycarbonyl-β-disubstituted nitroalkenes in which a wide variety of substrates participated to afford indoles having all-carbon quaternary centers with excellent selectivities catalyzed by (R)-**26** (up to 97% ee) (Scheme 30).[53]



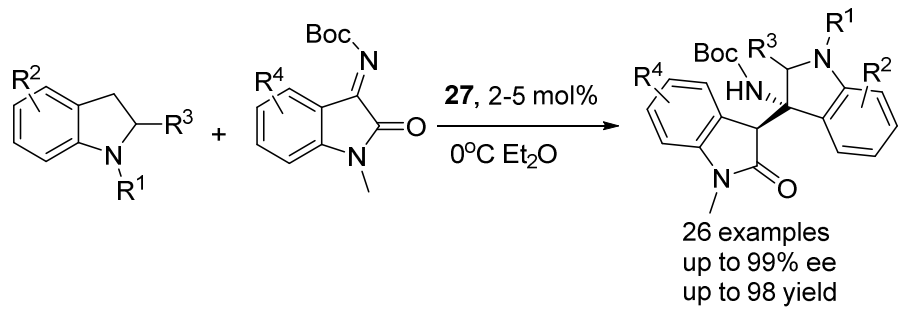

**Scheme 30.**The Friedel–Crafts reaction of indoles with β-alkoxycarbonyl-β-disubstituted nitroalkenes catalyzed by (R)-**26.**

Meanwhile, Álvarez and Rodríguez et al. reported the enantioselective synthesis of hexahydrofuro[3,2-c]quinolines catalysed by (R)-**26**.[54] The heterocyclic product was obtained in high enantioselection and good yield (Scheme 31).




**Scheme 31.** The enantioselective synthesis of hexahydrofuro[3,2-c]quinolines catalysed by (R)-**26.**

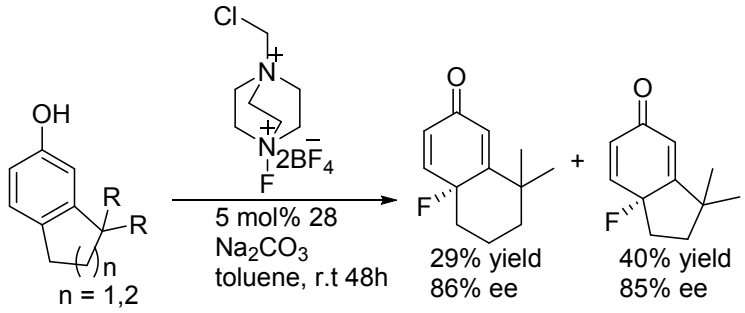
In 2012, Wang *et al.*demonstrated the first asymmetric aza-Friedel–Crafts reaction of indoles and pyrroles with isatin-derived N-Boc ketimines catalyzed by chiral phosphoric acids **27**.[55] The reaction was conducted under mild conditions to yield a variety of adducts generally in high yields and excellent enantiomeric excess (Scheme 32).




**Scheme 32.** the first asymmetric aza-Friedel–Crafts reaction of indoles and pyrroles with isatin-derived N-Boc ketimines catalyzed by chiral phosphoric acids **27.**

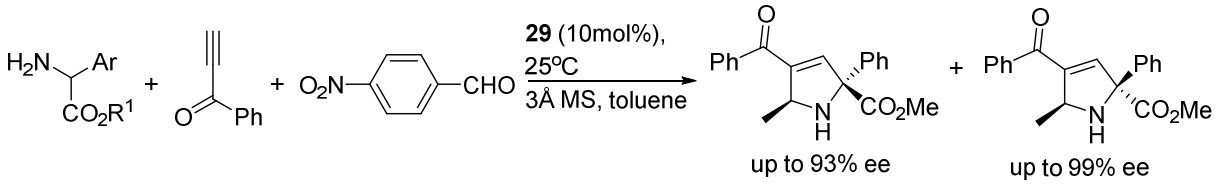
 

In 2013, **28** derived chiral anion phase-transfer catalyst has enabled the direct and highly enantioselective fluorinative dearomatization of phenols reported by Toste.[56] The fluorinated chiral small molecules bearing reactive functionality can be obtained efficiently from simple, readily available phenols under ambient reaction conditions with high enantioselectivity (Scheme 33).



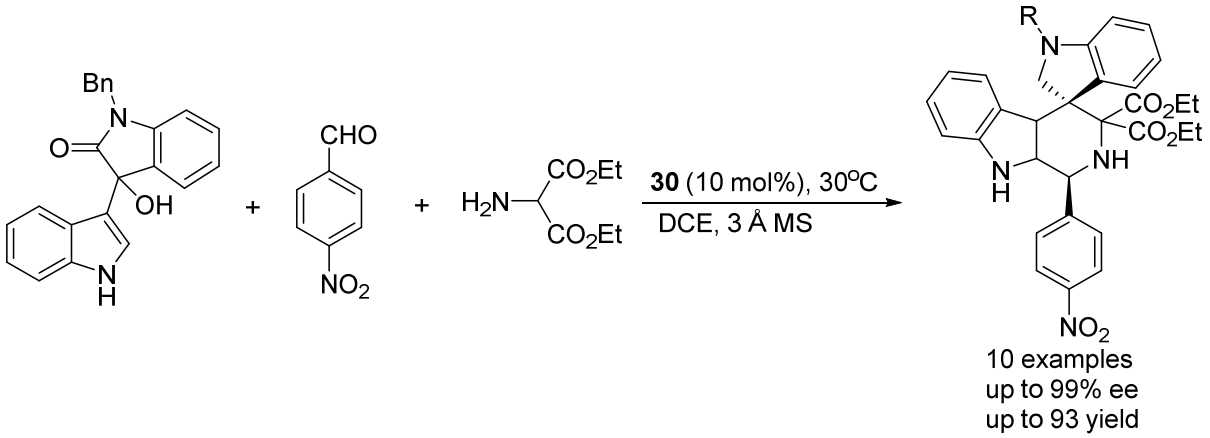

**Scheme 33.** The Direct enantioselective fluorinative dearomatization of phenols catalysed by **28** derived chiral anion phase-transfer catalyst.

In 2013, Shi and Tu *et al.* successfully constructed 2,5-dihydropyrrole scaffolds which is synthetically and biologically important in high yields (up to 99%) and excellent enantioselectivities (up to 99% ee) via a 1,3-dipolar cycloaddition using α-arylglycine esters as azomethine precursors catalysed by **29** (Scheme 34).[57] Meanwhile, They reported the construction of a chiral six-membered piperidine framework with two stereogenic centers via catalytic asymmetric formal [3+3] cycloaddition of 3-indolylmethanol and an in situ-generated azomethine ylide catalysed by **30**.[58] The desired spiro-products were obtained in high yields (67–93%) and with excellent enantioselectivities (97–>99% ee) (Scheme 35).



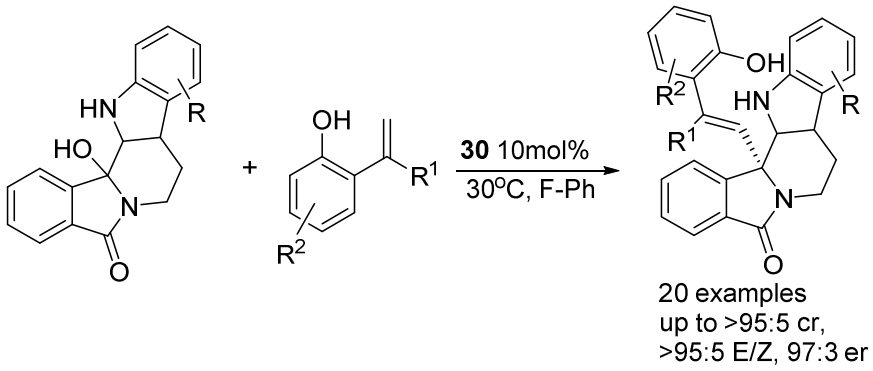

**Scheme 34.** Enantioselective construction of 2,5-dihydropyrrole skeleton with quaternary stereogenic center via asymmetric 1,3-dipolar cycloaddition catalysed by **29.**




**Scheme 35.** Enantioselective construction of a six-membered piperidine structure catalysed by **30.**

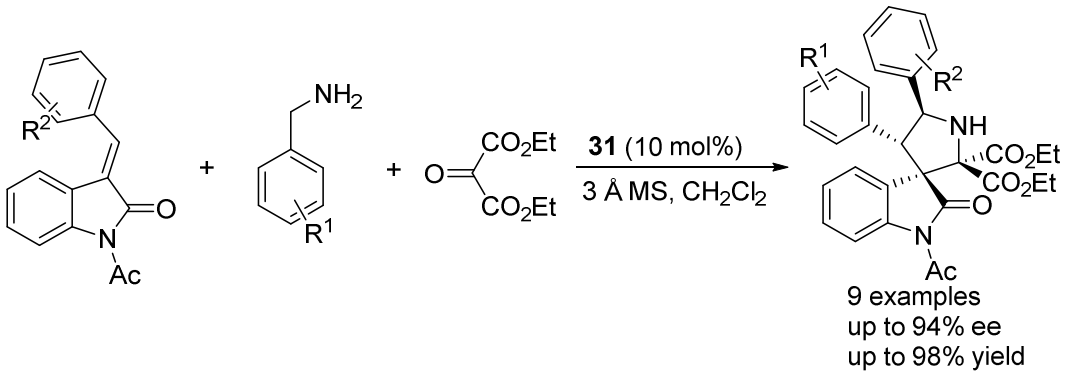
In 2014, Shi *et al.* again used **30** to catalyze the first organocatalytic asymmetric formal alkenylation of multicyclic alcohols and they used non-metal-based alkenes instead of alkenyl metals as the alkenyl group source.[59] This transformation offers a convenient access to functionalized chiral isoindolo-β-carbolines with one quaternary stereogenic center in high chemo-, (E/Z)-, and enantioselectivities (Scheme 36). (up to >95:5 cr, >95:5 E/Z, 97:3 er).




**Scheme 36.** The first organocatalytic asymmetric formal alkenylation of multicyclic alcohols catalyzed by **30**.

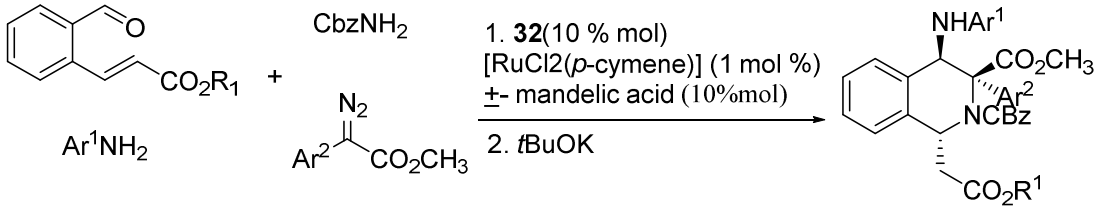
At the same year, Gong *et al.* developed the first asymmetric catalytic biomimetic three-component 1,3-dipolar cycloaddition of α-keto esters and benzylamine with electron-deficient olefins promoted by **31**.[60] The pyrrolidine derivatives are obtained in high yields and excellent enantioselectivities (up to 99% ee) undermild conditions (Scheme 37).



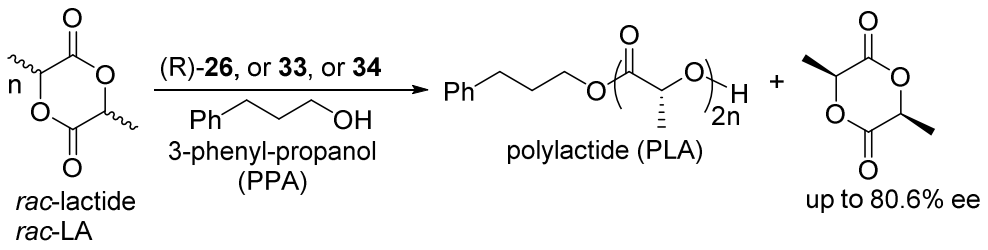

**Scheme37.** 1,3-dipolar cycloaddition of R-keto esters and benzylamine with electron-deficient olefins catalysed by **31.**

In 2014, compound **32** was developed for a four-component Mannich/cascade aza-Michael reaction by Hu.[61] This is an example of a synergistic combination of organocatalyst and transition metal and led to the synthesis of 1,3,4-tetrasubstituted tetrahydroisoquinolines in moderate yields with high diastereo- and enantioselectivity (Scheme 38).




**Scheme 38.** A four-component Mannich/cascade aza-Michael reaction catalysed by **32.**

In 2014, Terada and Satoh achieved a high enantiomer-selectivity for the polymerization of *rac*-LA using (R)-**26**, **33**, **34** (Scheme 39).[62] And the ROP (ring-opening polymerization) of DLA (D-lactide) preferentially proceeded employing (R)-**26** at 75 $^{o}$C, as well as the $k_D/k_L$ was 28.3 at a monomer conversion of 49.0% which is the highest value for the enantiomer-selective ROP of *rac*-LA. Their results showed that the electronic nature of the substituent at 3, 3′-positions strongly influenced the ee compared to the steric hindrance and the highest ee was achieved by (R)-**26**.

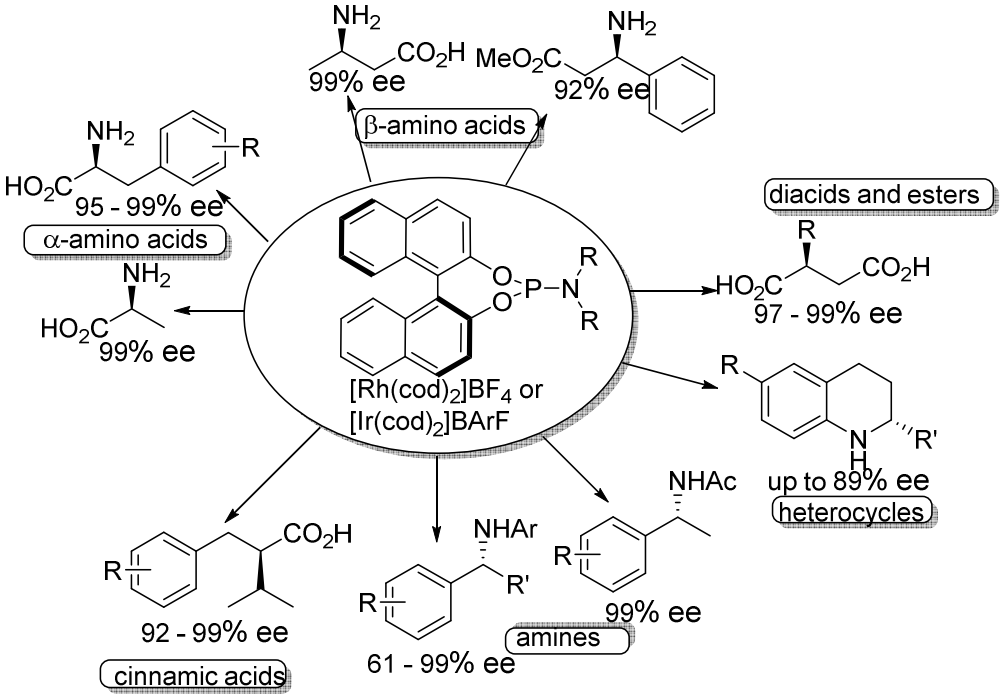



**Scheme 39**. Enantiomer-selective ring-opening polymerization of *rac*-lactide catalysed by (R)-**26**, **33**, **34.**

## 4. Some Seminal Applications of the Conversion of 3, 3′-Disubstituted BINOLs into Phosphoramidites

BINOL-derived phosphoramidite ligands were originally used for the asymmetric Cu-catalyzed conjugate addition of dialkylzinc reagents to enones reported by Feringa in 1997.[63]




**Scheme 40.** Phosphoramidites as ligands for asymmetric hydrogenation[64].

That phosphoramidites usually show excellent levels of stereocontrol as well as monodentate nature is essential in combinatorial catalysis, where a ligand-combination strategy is frequently used. Phosphoramidite ligands have turned out to be specially versatile in asymmetric hydrogenation, and the transformations listed in Scheme 40 are illustrative of the wide scope and exceptional ee values obtained with these monodentate ligands. These ligands have been found to have comprehensive applications in asymmetric catalysis.[64]

Figure16 lists structures of representative phosphoramidite ligands appeared in recent years.

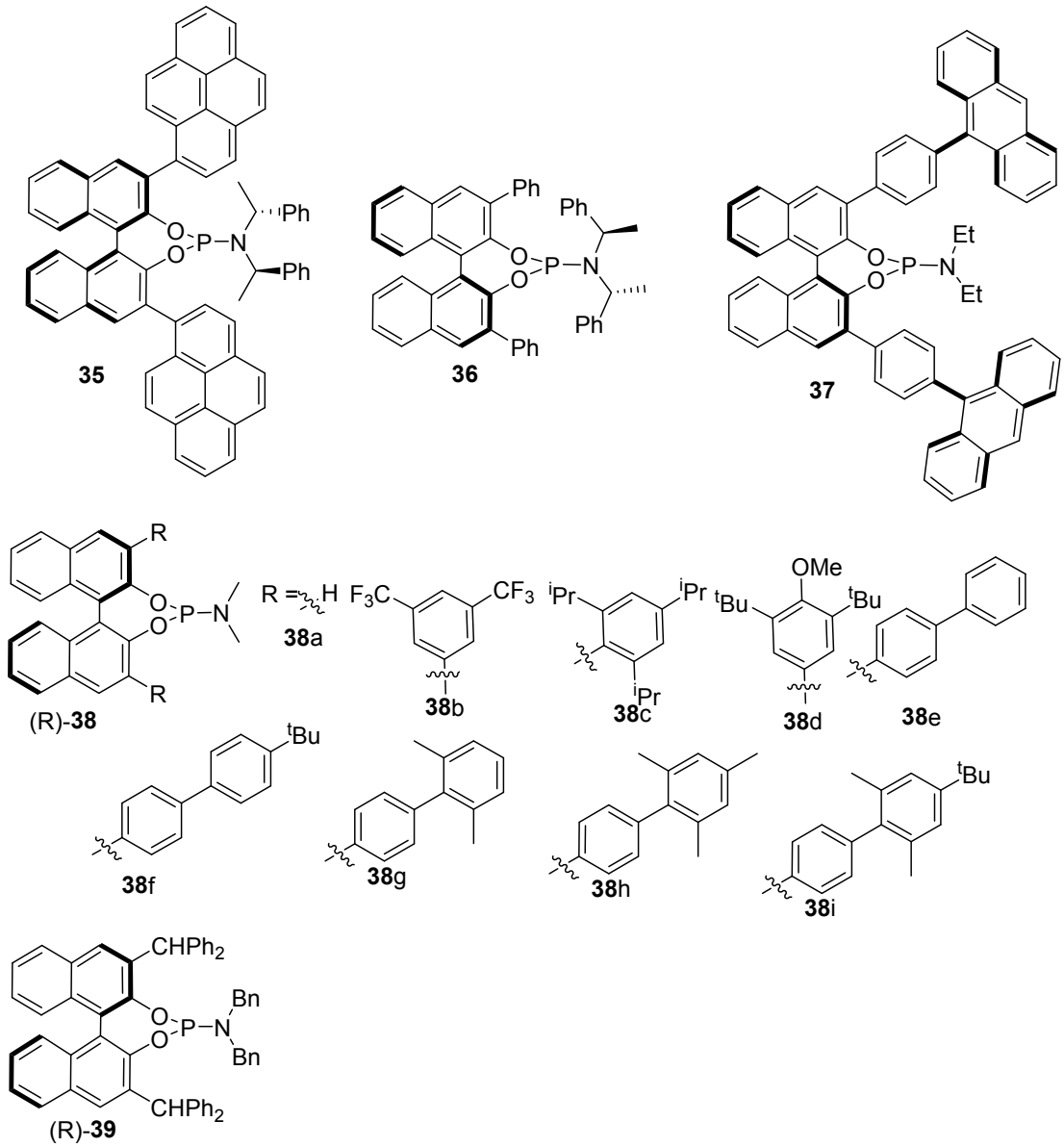
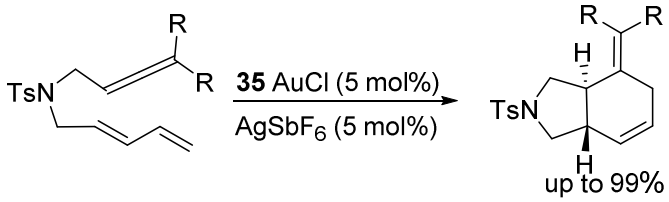



**Figure 16.** Structures of representative phosphoramidite ligands.

In 2010, González *et al.* reported a [4 + 2]-cycloaddition of allenes and dienes catalysed by **35**.[65] The reactions induced by *ortho*-arylphosphoramiditegold(I) complexes allow for the asymmetric synthesis of pyrrolidine products (Scheme 41).




**Scheme 41.** Enantioselective [4 + 2]-cycloaddition of allene-dienes catalysed by **35.**

Two years later, González *et al.* gained some insight into the underlying mechanisms of these cycloadditions through a computational study (DFT) (Figure 17).[66]

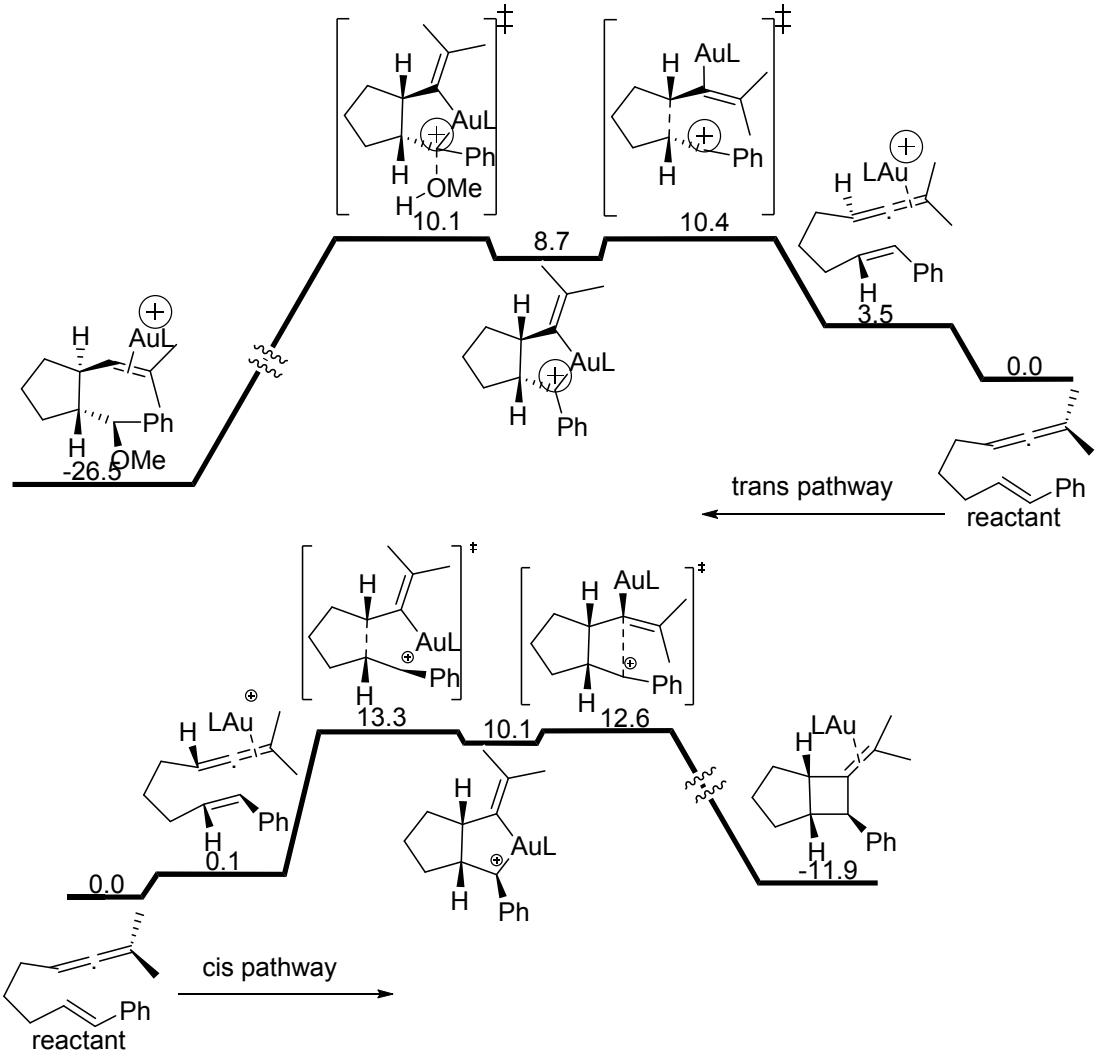
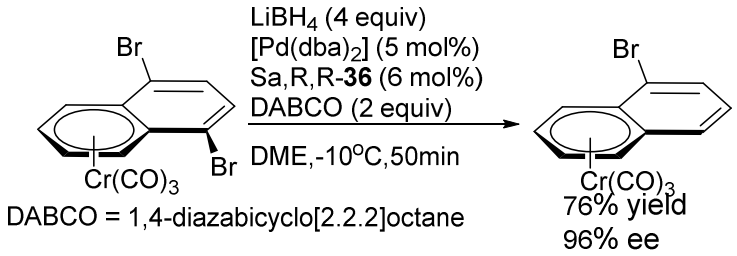



**Figure 17.** DFT profile for the potential free energy surface for the cis and trans cyclization pathways at the M06/LACV3P**++ level of theory corrected for $CH_2Cl_2$ as solvent in kcal/mol. L = $P(OMe)_2(NMe_2)$.

In 2010, Mercier *et al.* got the highly enantioenriched planar chiral [Cr(5-bromonaphthalene)$(CO)_3$] using asymmetric hydrogenolysis of [Cr(5,8-dibromonaphthalene)$(CO)_3$] promoted by **36**.[67] The products they got can be in high ee values (Scheme 42). They also illustrated the proposed mechanism (Figure 18).




**Scheme 42.** Asymmetric catalytic hydrogenolysis of aryl halide bonds in fused arene chromium and ruthenium complexes catalysed by **36.**

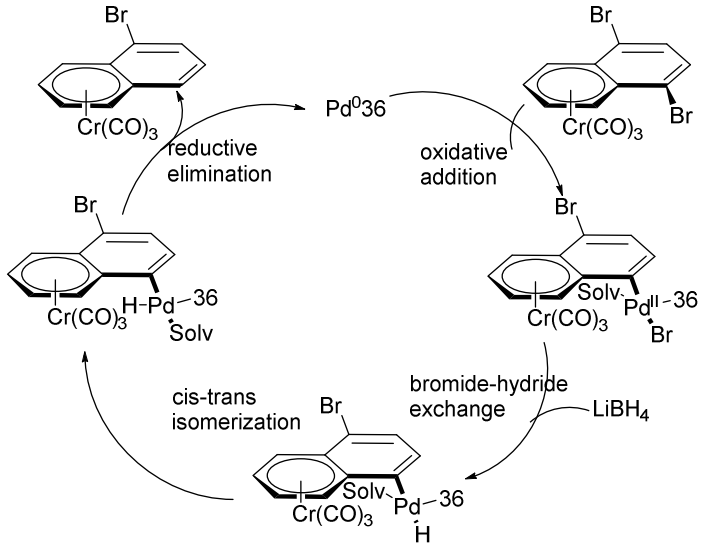
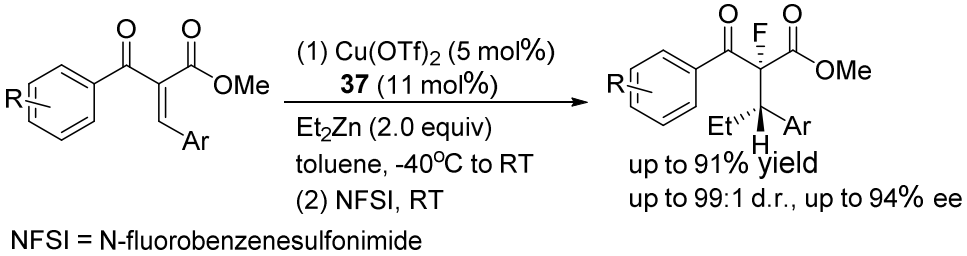



**Figure 18.** Proposed mechanism of the asymmetric hydrogenolysis of aryl halide bonds in fused arene chromium and ruthenium complexes.

Ma *et al.* used **37** for diastereo- and enantioselectivity of the tandem 1,4-addition / fluorination in 2011.[68] The tandem reaction can tolerate many kinds of dialkylzinc reagents as well as a range of acyclic alkylidene β-ketoesters to afford the cascade fluorinated products with adjacent carbon- and fluorine-substituted quaternary and tertiary stereocenters (Scheme 43).

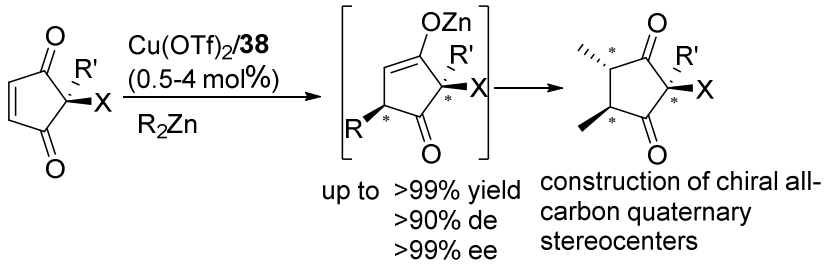



**Scheme 43.** The diastereo- and enantioselectivity of the tandem 1,4-addition/fluorination catalysed by **37.**

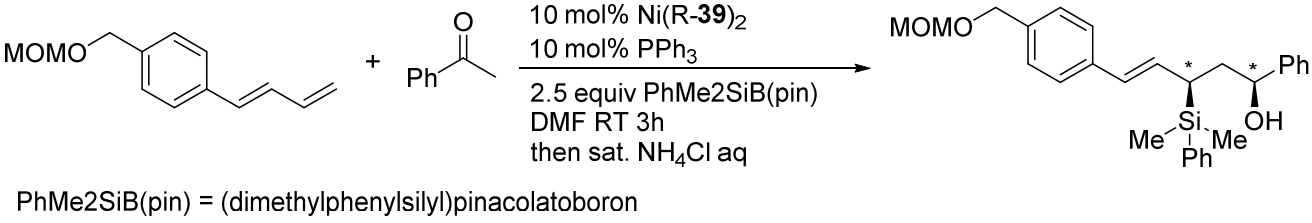
Particularly, the structural diversity of the BINOL-derived monodentate phosphoramidite ligands are enlarged by Ma′s new class of modular phosphorus compounds.

One year later, Mikami *et al.* developed a highly stereoselective catalytic alkylation sequence for the formation of highly functionalized and multifunctional five-membered-ring materials which bear all-carbon quaternary stereocenters in a one-pot strategy.[69] Enantioselective desymmetrization of achiral cyclopentene-1,3-diones was therefore accomplished by chiral Cu-**38** catalysts (Scheme 44).




**Scheme 44.** Synthesis of five-membered-ring compounds containing all-carbon quaternary stereocenters promoted by **38.**

Besides that, in 2011, Saito *et al.* have successfully developed a three-component coupling which is enantioand diastereoselective of 1,3-dienes, aldehydes, and a silylborane catalyzed by BINOL backbone-derived phosphoramidite nickel ligand **39**.[70] It is the first example that an asymmetric coupling occurs between two different classes of unsaturated compounds with a bimetallic reagent and represents a new synthesis strategy to get access to optically active α-chiral derivatives of allylsilane (Scheme 45).




**Scheme 45.** Diastereoselective three-component coupling of 1,3-dienes, aldehydes, and a silylborane leading to a-chiral allylsilanes catalysed by **39.**

## 5. Conclusions

In this review, we intend to summarize exactly both the origins of and recent progress in the development of reactions catalyzed by 3,3′-disubstituted chiral BINOL derivatives, including 3,3′-disubstituted BINOL, 3,3′-disubstituted BINOL Backbone-derived Phosphoric Acids and 3,3′-disubstituted BINOL Backbone-derived Phosphoramidites. These classes of catalysts has turned out

to be very efficient. It has not only provided organic chemists with a highly stereodefined, bifunctional catalyst platform, but also crucially encouraged its users to think in term of potent factors in these reactions. Even though the enantiocontrolling step of a certain transformation may not always be unambiguous, this could not prevent chemists expanding the frontiers of the capabilities of these catalysts or ligands. The discovery of new chemical transformations is surely driven by hypothesis, but the ultimate legitimacy of the beginning hypothesis should be integrate to the discovery of exciting novel modes of reactivity or selectivity. Bhadury *et al.* have discusseed the application of 3,3′-disubstituted axially dissymmetric BINOLs derivates serving as potent strong Brønsted acids.[14] They reviewed some suitably substituted and sterically demanding BINOLS, their use in organic transformations and possibility to convert them into stronger Bronsted acids as more effective organocatalysts. However, reports about BINOLs are always increasing, so we intend to illustrate the current development of BINOLs according to groups at 3,3′-positions. We hope this short review can further promote collective thinking about new strategies for chiralcentre-forming transformations including reagents and catalysts.

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