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Developing chiral phosphorus ligands for asymmetric hydrogenations*

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Abstract: Chiral rigid and electron-donating phosphocyclic phosphine ligands and modular atropisomeric biaryl phosphine ligands were designed and synthesized. The performance of these chiral ligands in the asymmetric hydrogenations of prochiral dehydroamino acid derivatives, enamides, imines, keto esters, and ketones has been demonstrated to be excellent.

Keywords: asymmetric hydrogenation; atropisomerism; chiral enantioselectivity; phosphines; phosphocyclicity.

INTRODUCTION

Transition-metal-catalyzed asymmetric hydrogenation is a highly efficient, selective, and atom-economical method for the asymmetric catalytic reduction of prochiral substrate such as olefins, ketones, and imines [1]. One of the essential factors for the success of asymmetric hydrogenation is the proper combination of a transition metal and a chiral ligand. Exploring new effective chiral ligands has played a fundamental role in the development of asymmetric hydrogenation [2]. Many research groups have devoted their efforts to the discovery of new efficient chiral ligands. Because of their milestone contributions, Knowles, who developed P-chiral ligand DIPAMP [3], and Noyori, who initiated the study work of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) [4], were awarded the 2001 Nobel Prize in Chemistry. We became interested in the design and synthesis of new chiral phosphorus ligands with high reactivity and enantioselectivity for asymmetric hydrogenations. Based on some inspiring prototype ligands and rational ligand designs, our group has developed a large variety of chiral ligands with different electronic and steric features [5]. We report herein the results of our study of synthesis of rigid and electron-donating phosphocyclic phosphines and atropisomeric biaryl phosphines, and their applications in the transition-metal-catalyzed asymmetric hydrogenations.

RESULTS AND DISCUSSION

Design and development of chiral phosphocyclic ligands

The rigid electron-rich phosphocyclic motif was first brought to the phosphorus ligand design and synthesis by Burk in the early 1990s. The excellent performance of Burk's DuPhos and BPE [6] showed the beneficial effect of conformational rigidity in asymmetric catalysis and thus inspired us to also in-

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troduce the phosphocyclic motif into our ligand design. We developed benzene ring-based KetalPhos **1** and ferrocene-based f-KetalPhos **2** [7]. Moreover, chiral phosphocyclic ligands such as Binaphane **7** and f-Binaphane **8** [8] were synthesized by combining the axial chirality of binaphthyl moiety to the cyclic framework. Electron-donating and air-stable PennPhos **5** [9] with a fused phosphobicyclic structure feature also gives a highly hindered chiral environment. Our early results of these phosphocyclic ligands implied that the electron-donating property and conformational rigidity are the most important elements for ligand designs (Fig. 1).

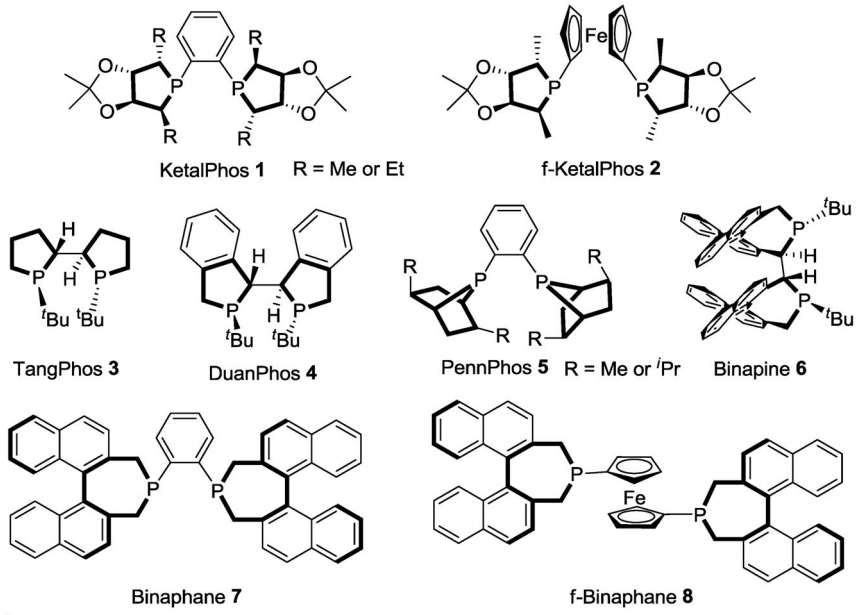


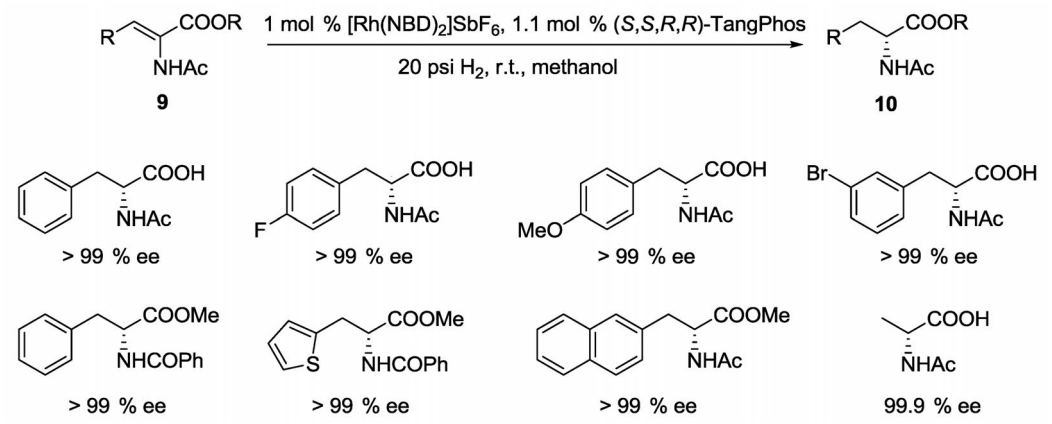
Fig. 1

Considering the fact that the P atoms in the ligands are directly connected to the catalytically active metal center, we attempted to incorporate P chirality into the cyclic framework to bring the stereogenic centers to the closest vicinity of the coordination site. This design motif would consequently make a well-defined chiral environment at the metal center which serves as the essential factor of excellent enantioselectivity in asymmetric catalysis. Inspired by the work of Imamoto et al. on BisP* and MiniPhos, the size difference in the two P substitutes is also a key factor for chiral induction [10]. Our first P-chiral bisphospholane ligand TangPhos **3** was conveniently synthesized and exhibited excellent enantioselectivity and reactivity toward a broad spectrum of various substrates, including functional olefins, β-keto esters, and imines [11]. The success of TangPhos encouraged us to develop more rigid P-chiral bisphospholanes such as Binapine **6** [12] and DuanPhos **4** [13]. Both enantiomers of Binapine and DuanPhos were conveniently synthesized and have been explored to be superior in asymmetric hydrogenations and more air-stable than TangPhos.

Asymmetric hydrogenation of dehydroamino acid derivatives using chiral phosphocyclic ligands

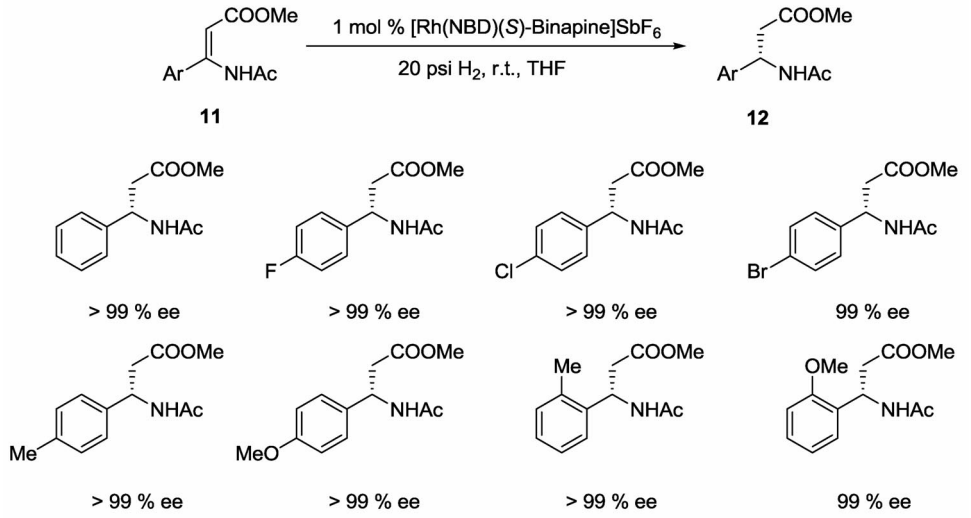
Asymmetric hydrogenation of α-dehydroamino acid derivatives has been extensively studied by using Rh catalysts and regarded as a model reaction to reveal the performance of chiral ligands. Rh–TangPhos complex catalyzed the hydrogenation of α-(acylamino)acrylic acids and esters under mild conditions

with 1 mol % of catalyst loading [11]. It was noteworthy that over 99 % ee were obtained for all substrates tested, tolerating various substituent groups and heteroaromatic rings. High turnovers (TON = 10 000) were also observed in the hydrogenation of *N*-acetyl-1-phenylethenamine, yielding *N*-acetyl-1-phenylethylamine in over 99 % yield and with 99.3 % ee (Scheme 1).



Scheme 1

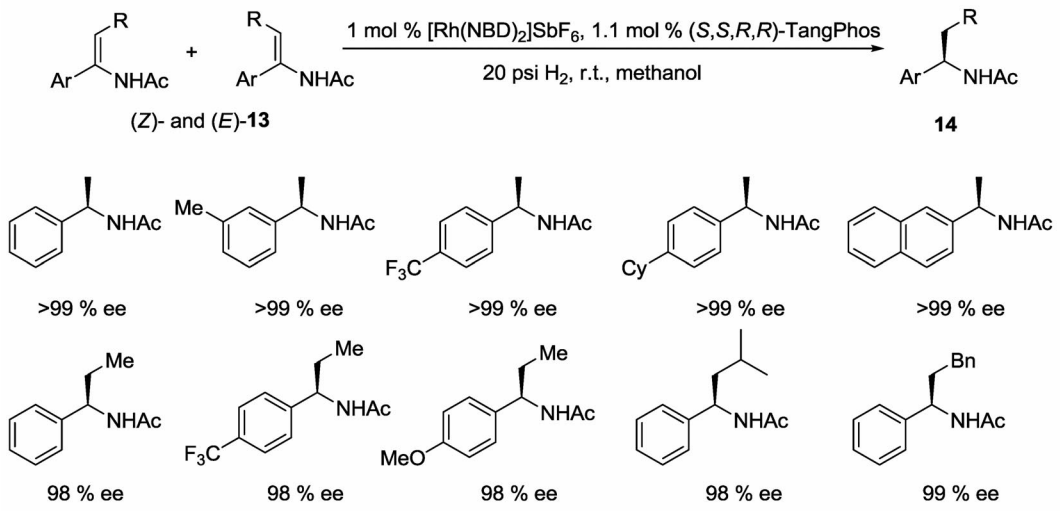
We further studied the asymmetric hydrogenation of (*Z*)-β-aryl-β-(acylamino)-acrylic acid derivatives. In this reaction, the Rh complexes of our Binapine ligand were found to give high enantioselectivities [12]. A series of methyl (*Z*)-β-aryl-β-(acetylamino)acrylates were smoothly hydrogenated by Rh–Binapine catalyst under mild conditions (20 psi H_2, r.t.) to give corresponding β-amino acid esters with quantitative yield. 99 % ee or higher was obtained for most of these β-(acetylamino)acrylate substrates regardless of the electronic properties of the aryl group on the substrate (Scheme 2).



Scheme 2

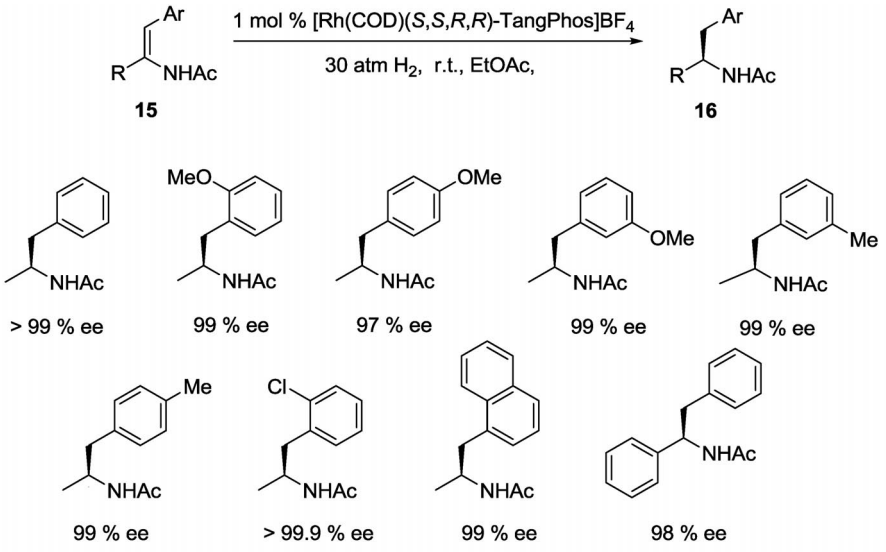
Asymmetric hydrogenation of enamides using chiral phosphocyclic ligands

The asymmetric hydrogenation of enamide substrate is of great significance because the products of this transformation could easily give enantiomerically pure amines which are important chiral building blocks in the synthesis of many chiral drugs. Using 1 mol % of Rh–TangPhos catalyst, a variety of α-arylenamides were hydrogenated to form chiral amides with excellent enantioselectivities [11]. More than 99 % ee were observed in the hydrogenation of α-phenylenamides without β-substituents. It was noteworthy that high enantiomeric excesses were also obtained for β-substituted isomeric enamide mixtures (*Z*/*E*) and β-methyl-substituted enamides with various substituents on the 1-aryl group (Scheme 3).



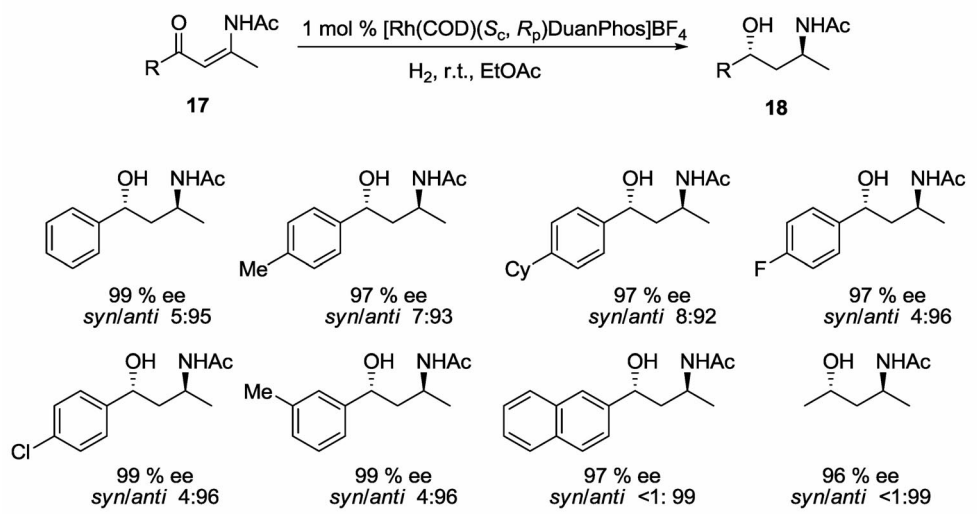
Scheme 3

Recently, we have investigated more enamide substrates. The asymmetric hydrogenation of β-arylenamides has attracted less attention. Thus, we synthesized a series of (*E*)- and (*Z*)-β-arylenamides and explored the performance of our rigid electron-donating ligands in Rh-catalyzed hydrogenation of β-arylenamides [14]. To our delight, using 1 mol % Rh–TangPhos catalyst, the hydrogenation reactions gave excellent enantioselectivities for all (*Z*)-enamide substrate in quantitative yield. Under the same reaction conditions, the (*Z*)-enamide substrate was successfully hydrogenated with only 0.1 % catalyst (Scheme 4).



Scheme 4

Chiral 1,3-amino alcohols are interesting structural motifs prevalent in pharmaceutical products as well as in important chiral auxiliaries and ligands for asymmetric synthesis. Recently, we have studied the asymmetric hydrogenation of β-ketoenamide as a highly efficient route to prepare chiral 1,3-amino alcohols with a high level of enantiocontrol. We subjected a series of β-ketoenamide substrates prepared conveniently from readily available 1,3-diketones, to asymmetric hydrogenation with Rh–DuanPhos complex [15]. In ethyl acetate, excellent enantioselectivities (up to 99 % ee) and high diastereoselectivities (up to >99:1 *anti*:*syn*) were observed for a variety of β-ketoenamide substrates. The hydrogen pressure was found to be critical for the formation of the desired product in good yield without compromising the enantioselectivity (Scheme 5).

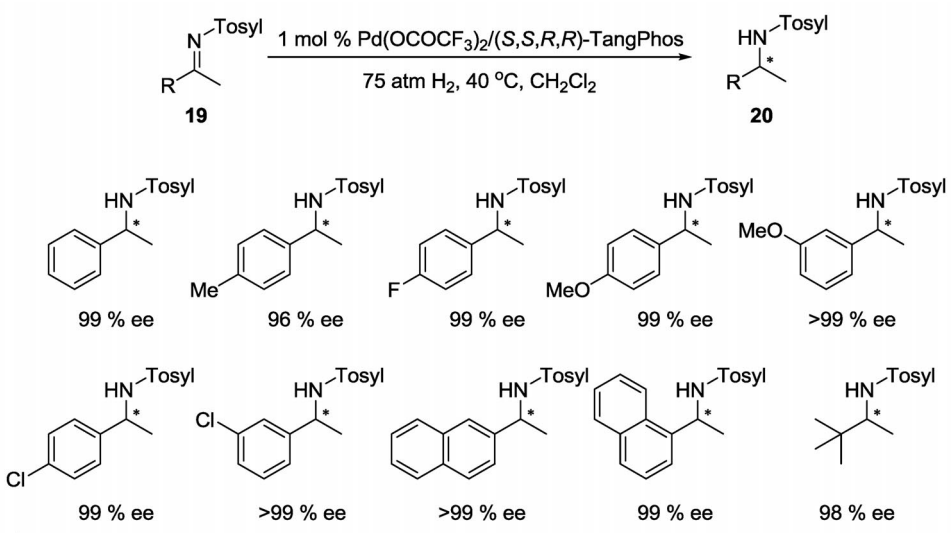


Scheme 5

Asymmetric hydrogenation of imines using chiral phosphocyclic ligands

Although significant progress has been made in the catalytic asymmetric reduction of ketones and olefins over the last few decades, the asymmetric reduction of imines still remains a major challenge. Based on the previous studies of asymmetric hydrogenation of imine using a number of transition-metal-based catalysts, we were prompted to apply the highly rigid and electron-donating phosphocyclic ligands in the hydrogenation of imine substrates.

N-tosylimines were selected as the hydrogenation substrates since they are relatively stable and can be easily obtained from the corresponding ketones exclusively as the *E*-isomer. Moreover, the electron-withdrawing character of the *N*-tosyl group reduces the inhibitory effect of the hydrogenation product on the catalysts, which might lead to higher reactivity and enantioselectivity. A study of using different bisphosphine ligands and transition-metal precursors showed that $Pd(OCOCF_3)_2$ and TangPhos was the best combination. Under the optimized conditions, a series of *N*-tosylimines prepared from corresponding ketones were successfully hydrogenated in the presence of $Pd(OCOCF_3)_2$–TangPhos, achieving up to 99 % ee enantioselectivities and more than 99 % conversions (Scheme 6) [16].



Scheme 6

The substrate scope was also extended to examples of cyclic tosyl imines or sultams. Excellent enantioselectivities were also obtained (Fig. 2).

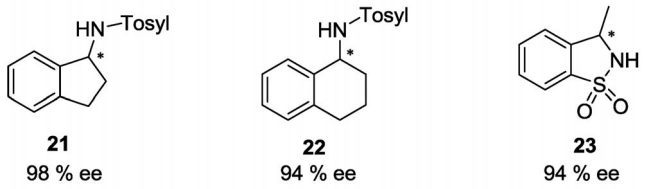
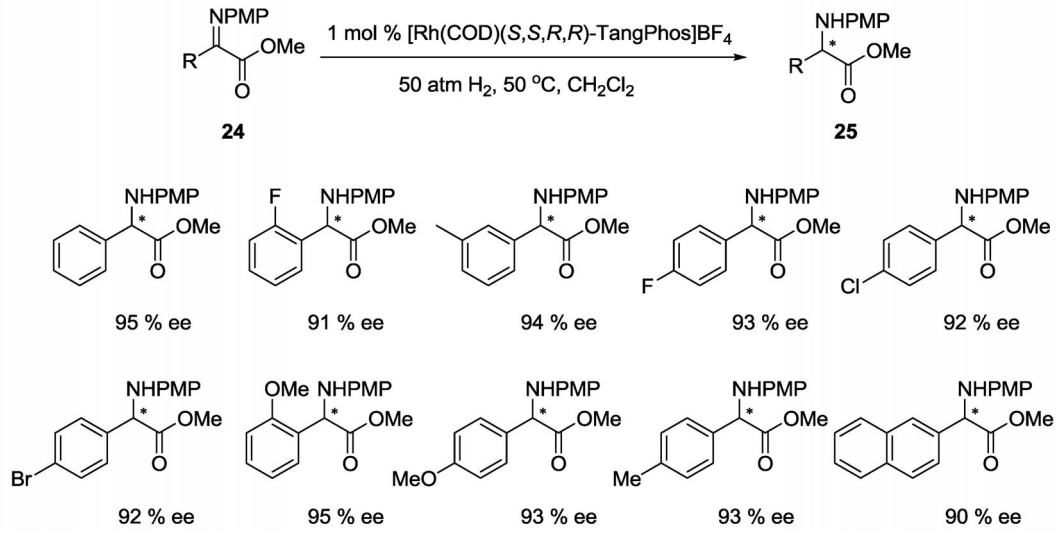


Fig. 2

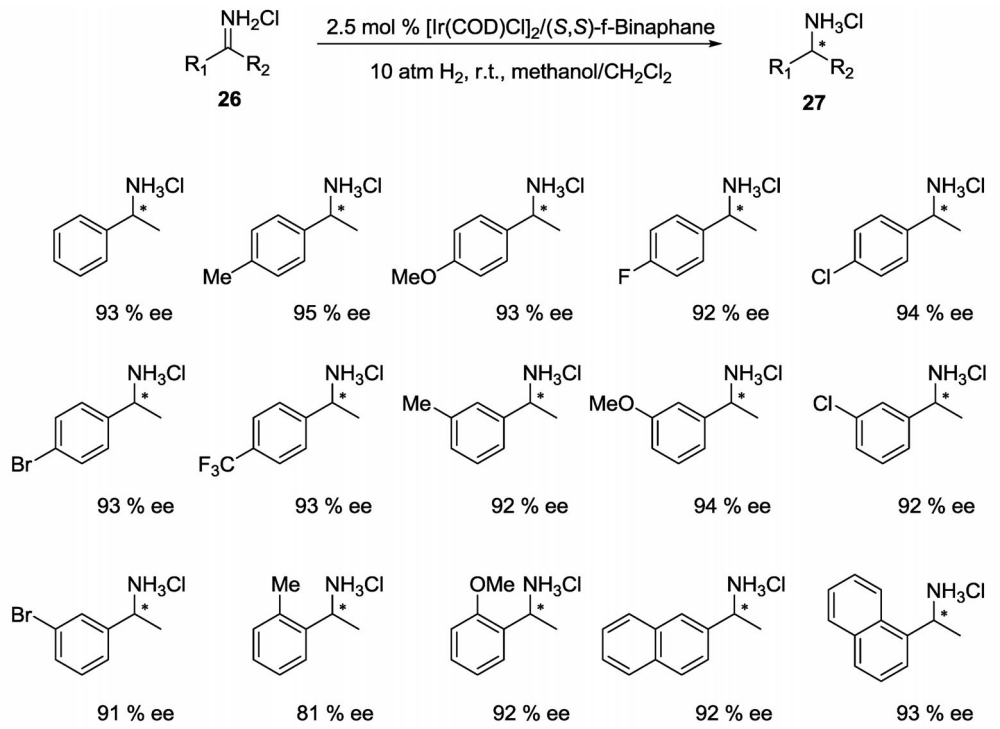
Asymmetric hydrogenation of α-aryl imino ester is of importance in organic synthesis because it produced chiral aryl glycines, which are important building blocks for many bioactive molecules such as amoxicillins, nocardicins, cephalecins, and glycopeptide antibiotics. We explored and found a highly enantioselective synthesis method of chiral aryl glycine derivatives by using the asymmetric hydrogenation of PMP-protected (PMP = *p*-methoxyphenyl) α-aryl imino esters with a Rh–TangPhos catalyst [17]. The substrate scope we examined in this reaction included a number of amino esters with various substituents on the aromatic ring or the ester group. Excellent enantiomeric excesses were achieved when all substrates were converted with high yields. These made this method potentially useful for the preparation of a variety of chiral aryl glycines (Scheme 7).



Scheme 7

In our recent research, we have come to study one class that has been overlooked in the asymmetric hydrogenations, unprotected N–H imines.

Without involving any protecting group manipulations like other available methods, this first method could produce chiral amines in a highly efficient, atom-economical, and enantioselective fashion. We were delighted to find that Ir–f-Binaphane was the best catalyst for this operationally simple and mild asymmetric hydrogenation [18]. A variety of N–H imine substrates were prepared in the form of hydrochloride salts as single isomer and bench-stable solids. Substrates with substituents of different electronic properties and bulkiness on the aryl group were uniformly reduced with high enantioselectivities (Scheme 8).



Scheme 8

Design and development of chiral atropisomeric ligands

We were inspired to develop effective ligands with an atropisomeric backbone in asymmetric hydrogenation due to the great success of Noyori's BINAP. The pioneering studies on the axially chiral BINAP demonstrated that the ruthenium metal complex of this atropisomeric biaryl ligand could catalyze the asymmetric hydrogenation of functional ketones as well as simple ketones with remarkably high enantioselectivity and reactivity [4a]. However, due to the fact that the two naphthyl moieties in BINAP structure can rotate around the connecting axial sp^2–sp^2 bond with little restriction, we designed modular Cn-TunePhos **28** and Cn*-TunePhos **29** by connecting the two aryl moieties with a tunable linking bridge (Fig. 3) [19].

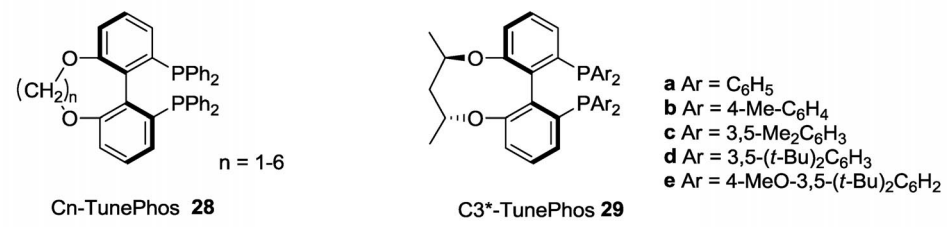
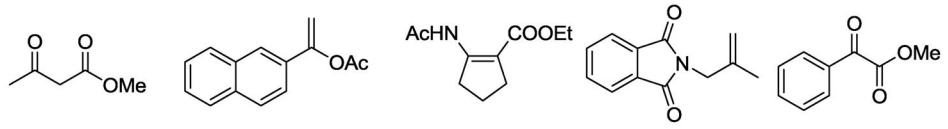


Fig. 3

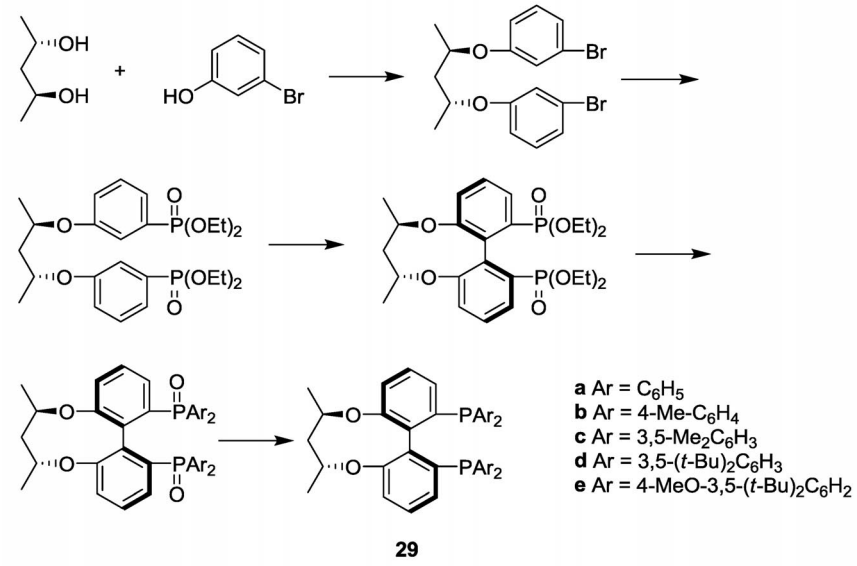
This additional linkage not only minimizes the conformational rotation of the two aryl moieties but also defines the bite angle of the atropisomeric ligand with improved precision. By adjusting the linkage length between the two aryl moieties, for example, from C1 to C6, the bite angle of the ligand can be finely tuned and optimized for different substrates [19a]. The hydrogenation with Cn-TunePhos allowed us to study the effect of the bite angle on enantioselectivity for different classes of substrate in a systematic way (Fig. 4) [5].



Catalytc system	$RuCl_2(\eta^6$-benzene)(**28**)	$[NH_2Me_2][RuCl($**28**$)(\mu$-$Cl)_3]$	Rh(methallyl)$_2$[**28**]+HBF_4	$[RuCl_2($**28**$)](DMF)_m$	$[RuCl_2($**28**$)](DMF)_m$
Optimal linkage	C4	C1,C2	C2 - C5	C3	C3
Ee	99 % ee	96 % ee	99 % ee	94 % ee	97 % ee

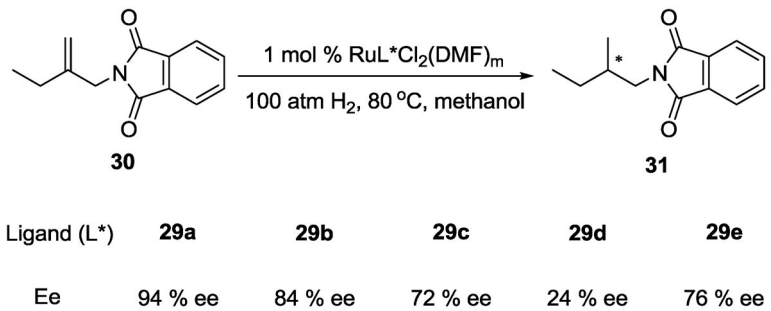
Fig. 4

Apart from optimization in the length of these alkyl linkers, another obvious strategy to modulate the atropisomeric biaryl ligand is to replace the phosphorus substituents. This important structural modification would endow the TunePhos ligands with unique steric and electronic properties. We established a remarkably versatile route for the synthesis of a family of C3-TunePhos derivative diphosphine ligands without involving cumbersome individual resolution procedures for each derivative (Scheme 9) [19b].



Scheme 9

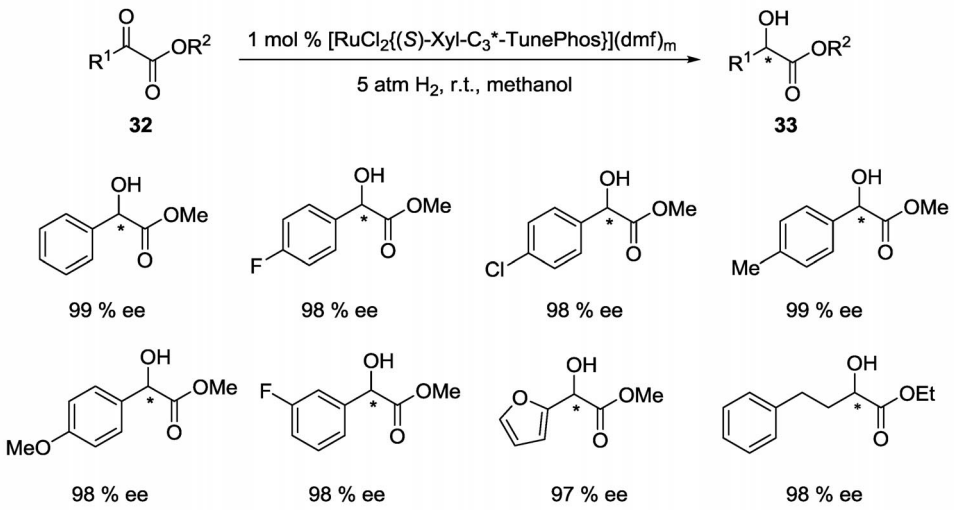
A systematic investigation of the effects of different aryl substituent groups on TunePhos ligands indicated that the introduction of groups of different steric hindrance and electronic properties significantly affects the enantioselectivities. For example, in the asymmetric hydrogenation of *N*-2-ethylallylphthalimide, using ligands with more bulky aryl groups such as 4-methyl (**29b**) and 3,5-dimethyl (**29c**) groups or even more hindered 3,5-di-*tert*-butyl (**29d**) and 4-methoxyl-3,5-di-*tert*-butyl (**29e**) groups other than phenyl groups would decreased the enantioselectivities dramatically from 94 to 24 % ee (Scheme 10) [19b].



Scheme 10

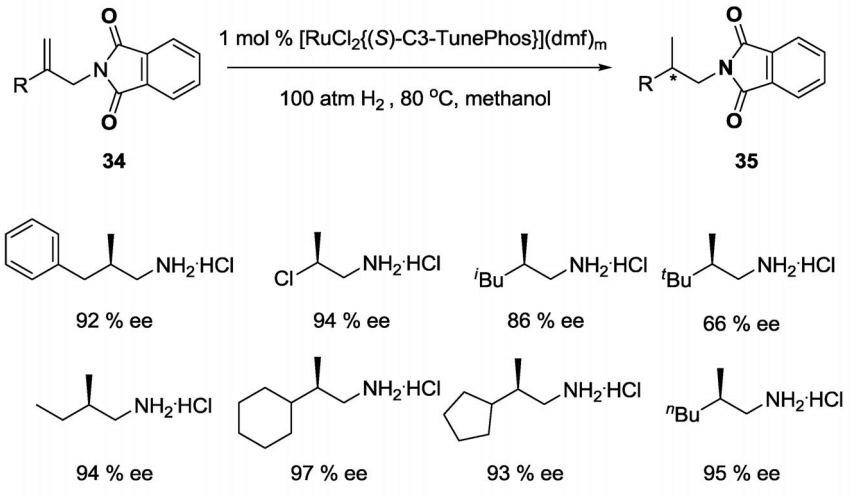
Asymmetric hydrogenation using chiral atropisomeric ligands

Asymmetric hydrogenation of the corresponding α-keto esters provides one of the most efficient approaches to enantiomerically pure α-hydroxy acid derivatives, which are very important structural motifs in numerous biologically active compounds and are often utilized as resolving agents. Optimization proved that ruthenium complex of C3*-TunePhos showed superior efficiency in the asymmetric hydrogenation of α-keto esters at room temperature under low hydrogen pressure [19b]. Achieving the excellent enantioselectivity (ranging from 96 to 99 % ee) for a wide scope of α-keto ester substrates demonstrated the Ru–C3*-TunePhos to be potentially applicable catalyst for the key intermediate synthesis for angiotensin converting enzyme (ACE) inhibitors Benazepril and Delapril hydrochloride via asymmetric hydrogenation (Scheme 11).



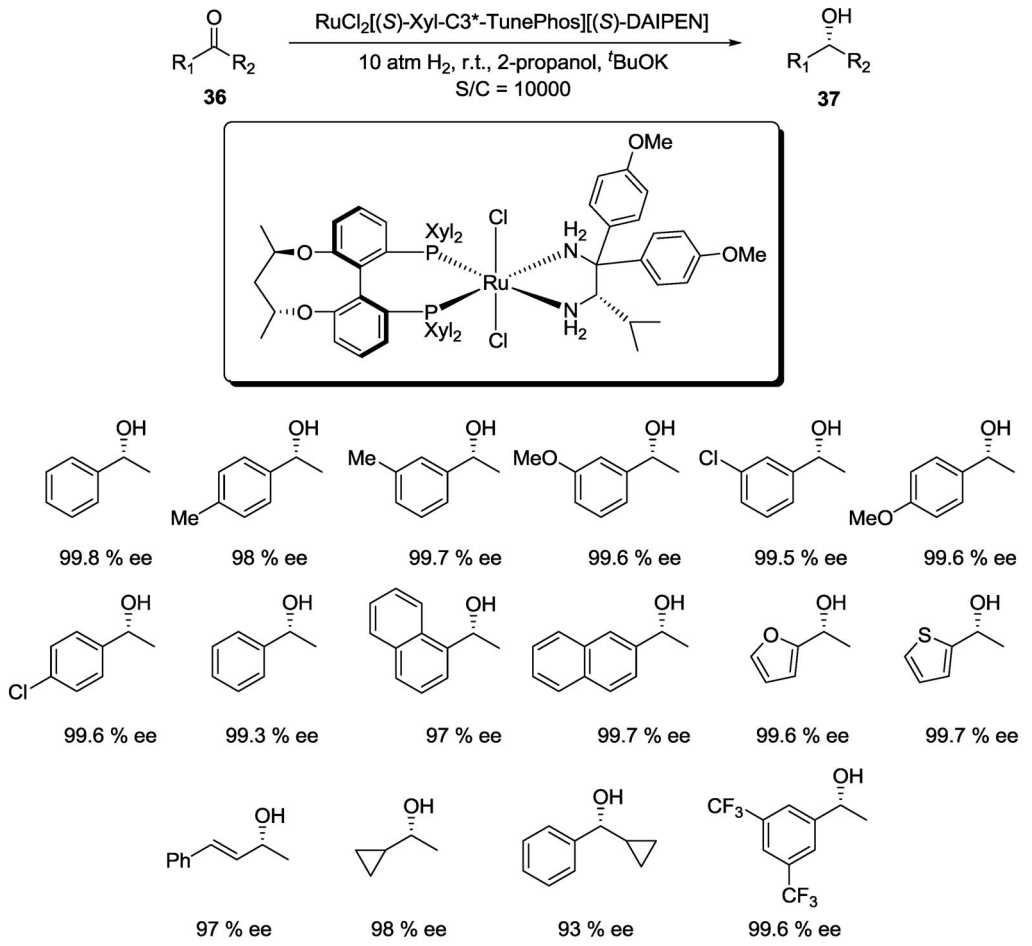
Scheme 11

Chiral amines bearing a β-methyl group on the chiral center, and their derivatives, are key structural elements in natural products and pharmaceuticals. In our investigation, we found that the disubstituted allylphthalimides are subject to highly enantioselective catalytic asymmetric hydrogenation using Ru–TunePhos, to form corresponding chiral phthalimides and subsequently the β-methyl chiral primary amines [20]. In the asymmetric hydrogenation reaction that was carried out on a variety of allylphthalimide substrates, substrates with a primary *n*-alkyl substituent such as ethyl, *n*-butyl, or benzyl group at the 2-position afforded products with high ee values (92–96 % ee), although a decrease of enantiomeric excess was observed when steric hindrance of the substituents increased (Scheme 12).



Scheme 12

Catalytic enantioselective hydrogenation of prochiral ketones has been a powerful method to prepare enantiomerically pure secondary alcohols, which are key structural elements in a large number of pharmaceutical products. Many effective catalysts available for asymmetric hydrogenation of ketones to date are derived from the milestone discoveries of BINAP–ruthenium–diamine complexes by Noyori and co-workers [4a]. The Ru complexes of C3*-TunePhos ligands were highly effective catalyst in the asymmetric hydrogenation of simple ketones. By screening the different P substituents, we found that the formation of ruthenium complex consisting of (*S*)-Xyl-C3*-TunePhos and (*S*)-DAIPEN proved to be the best catalyst [21]. A wide range of simple ketones, including aromatic, heteroaromatic, α,β-unsaturated, and cyclopropyl ketones can be smoothly hydrogenated, affording high reactivity (up to 1 000 000 TON) and excellent enantioselectivities (Scheme 13) (>99 % ee).



Scheme 13

CONCLUSION

Highly rigid and electron-donating phosphocyclic ligands and highly tunable axially atropisomeric biaryl phosphines were designed and synthesized for asymmetric hydrogenations. Phosphocyclic ligands are extremely efficient for asymmetric hydrogenations such as Rh-catalyzed hydrogenations of dehydroamino acid derivatives, enamides, and imines. Modular atropisomeric biaryl phosphines were successfully applied to Ru-catalyzed asymmetric hydrogenations of keto esters, allylphthalimides, and unfunctionalized ketones. Their success has undoubtedly demonstrated the value of rigid and well-defined structure in ligand design and will provide inspirations for our ongoing efforts in developing more chiral phosphorus ligands for extensive applications in the field of asymmetric hydrogenation and many other catalytic transformations.

ACKNOWLEDGMENTS

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