Developing Chiral Ligands for Asymmetric Hydrogenation

WEICHENG ZHANG, YONGXIANG CHI, AND XUMU ZHANG*

Department of Chemistry, 104 Chemistry Research Building, The Pennsylvania State University, University Park, Pennsylvania 16802

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ABSTRACT

This Account outlines our efforts in ligand development for asymmetric hydrogenation. The successful development of three classes of ligands is presented, including (1) ligands with phosphocyclic motifs, (2) ligands with atropisomeric backbones, and (3) bisphosphine ligands inspired by the structure of 2,3-*O*-isopropylidene-2,3-dihydroxyl-1,4-bis(diphenylphosphino)butane (DIOP). With this large ligand toolbox, we have prepared many pharmaceutically valuable chiral products efficiently.

Introduction

Transition-metal-mediated asymmetric hydrogenation is an efficient method for the catalytic reduction of prochiral alkenes, ketones, and imines into the corresponding chiral products with hydrogen gas.[1] Several salient advantages, such as broad substrate scope, high reactivity and selectivity, as well as minimum generation of by-products and wastes, render this transformation highly desirable for both academia and industry. The success of hydrogenation relies primarily on the proper combination of a metal and a ligand. Whereas the choice of transition metals is limited within the periodic table, a myriad of organic backbones may be employed as ligand structures. In fact, exploring new effective chiral ligands has played a fundamental role in the history of asymmetric hydrogenation.

Since Knowles[2a] and Horner[2b] reported the first chiral versions of Wilkinson's catalyst $[Rh(PPh_3)_3]Cl$ for homogeneous hydrogenation, several historically important ligands[3–9] (Figure 1) have been developed over the past decades, providing extremely valuable insights into ligand design. In the early 1970s, Kagan developed C_2-symmetric chelating bisphosphine DIOP **1** and showed the importance of backbone chirality in the ligand structure.[3] In a landmark work, Knowles demonstrated the equal importance of P chirality by applying 1,2-bis(phenyl-*o*-anisoylphosphino)ethane (DIPAMP) **2** in the first industrial-scale synthesis of L-DOPA.[4] To illustrate the spatial distribution of steric hindrance around the catalytic metal–ligand complex, Knowles also introduced the widely accepted "quadrant diagram" concept.[4b] Then, a major breakthrough came in 1980 when Noyori et al. initiated pioneering studies on axially chiral 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) **3**.[5a] Operating through a novel metal–ligand bifunctional mechanism, the combination of ruthenium and this atropisomeric biaryl ligand has greatly expanded the substrate scope from olefins to not only functional ketones but also simple ketones.[5b,c] Because of their milestone contributions to this important area, Knowles[4c] and Noyori[5c] were awarded the 2001 Nobel Prize. In 1991, Burk designed rigid strongly electron-donating bis(phospholane) DuPhos **4** and BPE **5** as versatile ligands for Rh-catalyzed hydrogenation of various functional olefins.[6] The modular nature of **4** and **5** allows their steric environment to be optimized through structural modification. The significance of modularity in ligand design was also embodied in the C_1-symmetric planar chiral ferrocene-based JosiPhos **6** ligand family.[7a] Because its two chelating donors can be easily changed, a large ligand series has been prepared to fit the steric and electronic requirements of various catalytic reactions.[7b] Meanwhile, Pfaltz and others developed modular P,N-ligand PHOX **7** with two sterically and electronically unequivalent donors, attaining unprecedented Ir-catalyzed asymmetric hydrogenation of imines and unfunctionalized olefines.[8] Recently, the discovery of modular monodentate phosphorous ligands **8** made another conceptual breakthrough, showing that not only bidentate but also monodentate ligands are viable candidates for hydrogenation reactions.[9]

As Knowles pointed out,[4b] "Since achieving 95% ee only involves energy differences of about 2 kcal, which is no more than the barrier encountered in a simple rotation of ethane, it is unlikely that before the fact one can predict what kind of ligand structures will be effective." Indeed, thus far, ligand design remains an empirical rather than rational approach, where a useful ligand can only be discovered through extensive trial and error. Fortunately, the success of these seminal ligands **1**–**8** have served as

Weicheng Zhang obtained his M.S. degree in 2002 under the guidance of Professor Fu-Mian Li at Peking University. Then, he enrolled in the Chemistry Department of the Pennsylvania State University as a doctoral candidate. Intrigued by the power of asymmetric catalysis, he joined Professor Zhang's group and is working on developing new chiral ligands for asymmetric catalysis.

Yongxiang Chi was born in 1973 in the Sichuan Province, China. He received his Ph.D. degree in 2000 from the Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, under the supervision of Professor Yaozhong Jiang. Then, he joined Professor Zhang's group at the Pennsylvania State University as a postdoctoral fellow. His research interests include asymmetric synthesis and catalysis, particularly, the development of efficient chiral ligands and catalysts.

Xumu Zhang was born in 1961 in the Hubei Province, China. He received his B.S. degree (1982) from Wuhan University and his M.S. degree (1985) from the Chinese Science Academy, Fuzhou, China, under the supervision of Professors Jinling Huang and Jiaxi Lu. After a short stay at the University of California, San Diego, he received his Ph.D. degree in chemistry in 1992 from Stanford University under the guidance of Professor James P. Collman. After 2 years of postdoctoral work at Stanford, he joined the Department of Chemistry at the Pennsylvania State University in 1994 as an Assistant Professor. He was promoted to an Associate Professor in 1999 and then a full Professor in 2003. In 2007, he moved to Rutgers University as a Professor in the Departments of Chemistry and Chemical Biology and Pharmaceutical Chemistry. His research interests include the development of chiral phosphine ligands for asymmetric catalysis, the investigation of asymmetric hydrogenation and carbon–carbon bond-forming reactions, the synthesis of biologically active compounds, and the discovery of new synthetic methods.

* To whom correspondence should be addressed. E-mail: xumu@chem.psu.edu.

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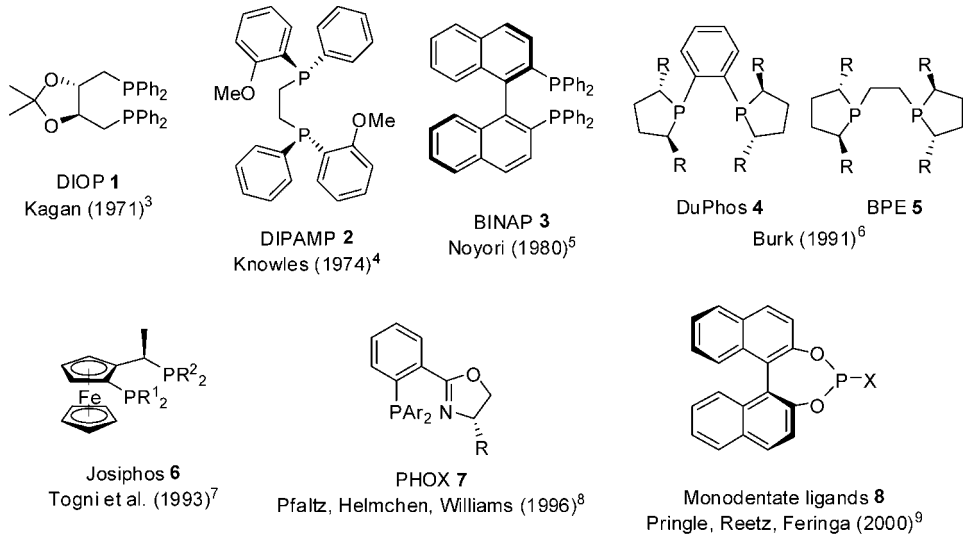


FIGURE 1. Historically important ligands for asymmetric hydrogenation.

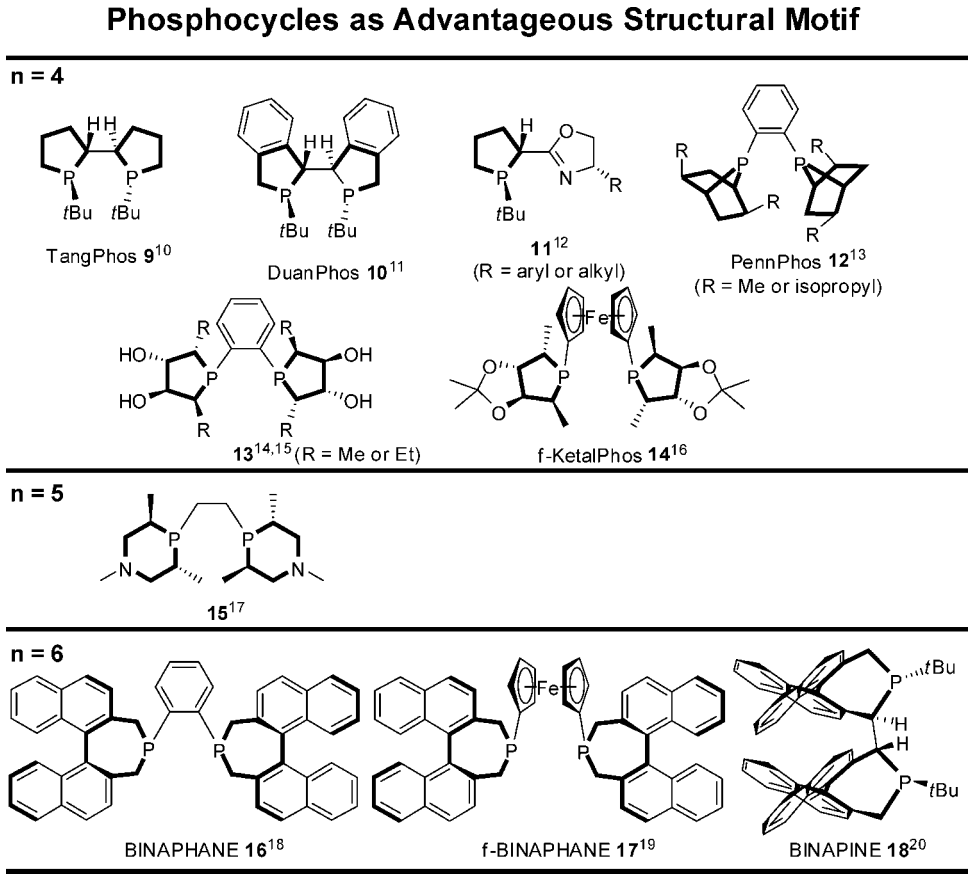


FIGURE 2. Phosphocyclic ligands.

inspiring prototypes based on which further modification can often lead to improved catalytic efficiency. Hence, thousands of effective chiral ligands have been reported today, via either de novo design or structural modification of the proven motifs.

Dedicated to the advancement of asymmetric hydrogenation, our group has developed a large variety of chiral ligands in the past decade. Behind their diverse structures are some strategic considerations that proved extremely important during the course of our research. Herein, we will share our experience in ligand development, together with the application of our ligand toolbox for the preparation of pharmaceutically valuable products.

Phosphocyclic Motif

A summary of phosphocyclic ligands **9**–**18** developed in our lab is given in Figure 2.[10–20] It is noted that the merit of rigid electron-rich phosphocyclic motif was first appreciated in Burk's DuPhos **4** and BPE **5**.[6] Their modular

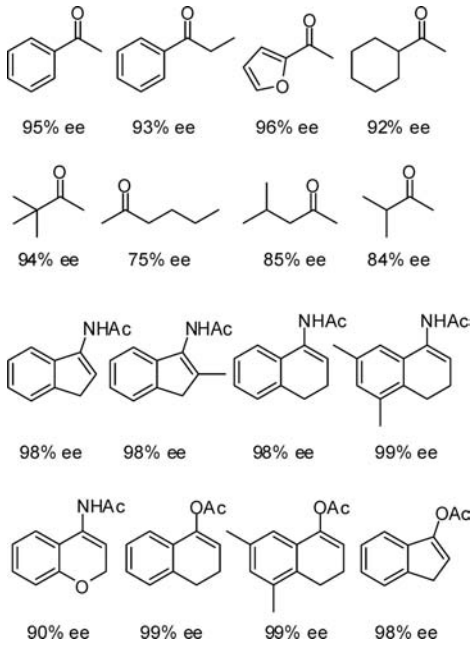


FIGURE 3. Selected hydrogenation results by the Rh/**12** system.

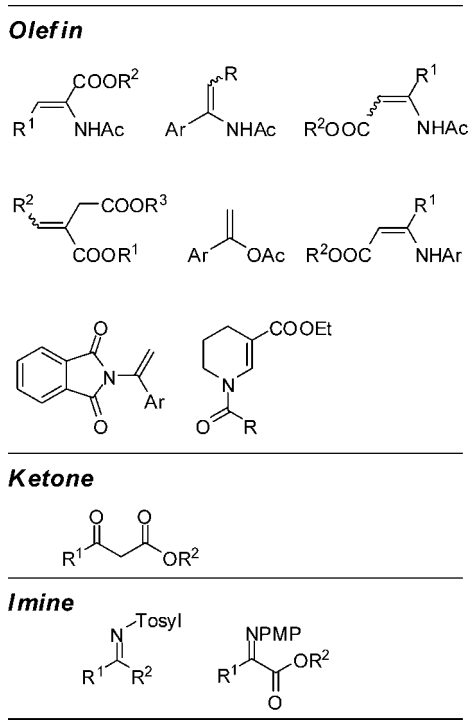


FIGURE 4. Substrate scope of **9**.

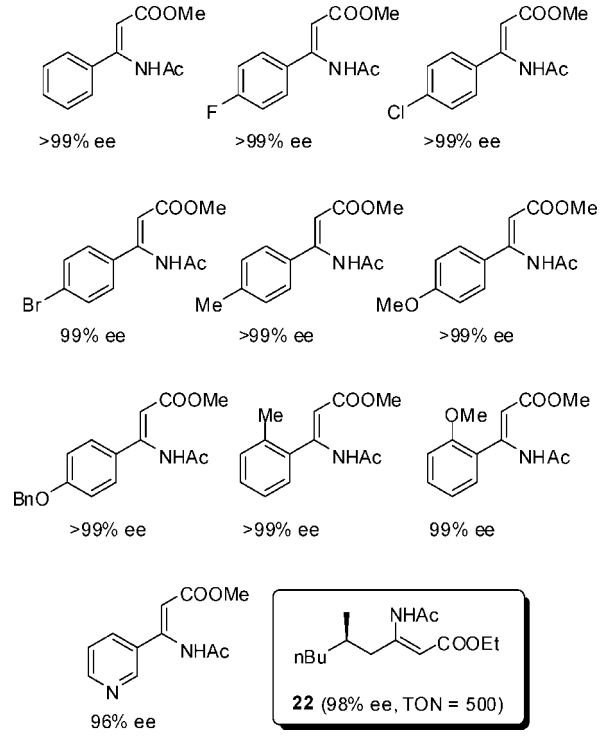
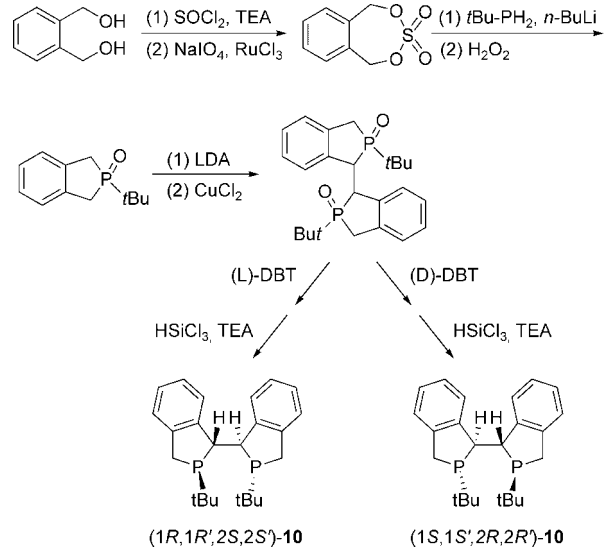


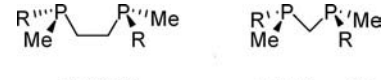
FIGURE 5. Hydrogenation of (*Z*)-*β*-aryl-*β*-(acylamino)acrylates by the Rh/**18** system.

Scheme 1. Synthesis of 10 as Both Enantiomers



structures inspired us to develop analogous hydroxyl(bisphospholane) **13**[14a,b,15] and its related KetalPhos,[14c] ferrocene-based f-KetalPhos **14**,[16] and the six-membered bis(azaphosphorinane) **15**.[17] Moreover, attaching seven-membered phosphepine moieties[21] onto the benzene or ferrocene backbone led to BINAPHANE **16**[18] and f-BINAPHANE **17**,[19] respectively.

Because our earlier results[22] showed the beneficial effect of conformational rigidity in asymmetric catalysis, we introduced a fused phosphabicyclic motif to eliminate conformational flexibility of five-membered rings in the design of PennPhos **12**,[13] which maintains desirable electron-donating and air-stable properties but gives a more hindered chiral environment. While asymmetric hydrogenation of unfunctionalized aryl alkyl and alkyl alkyl ketones remains a considerable challenge, we found that the combination of $[Rh(COD)Cl]_2$ and **12** in the presence of KBr and 2,6-lutidine reduced this type of substrate with excellent enantioselectivity.[13a] Moreover, **12** gave superior results for the challenging cyclic enamides[13b] and cyclic enol acetates[13c] (Figure 3).



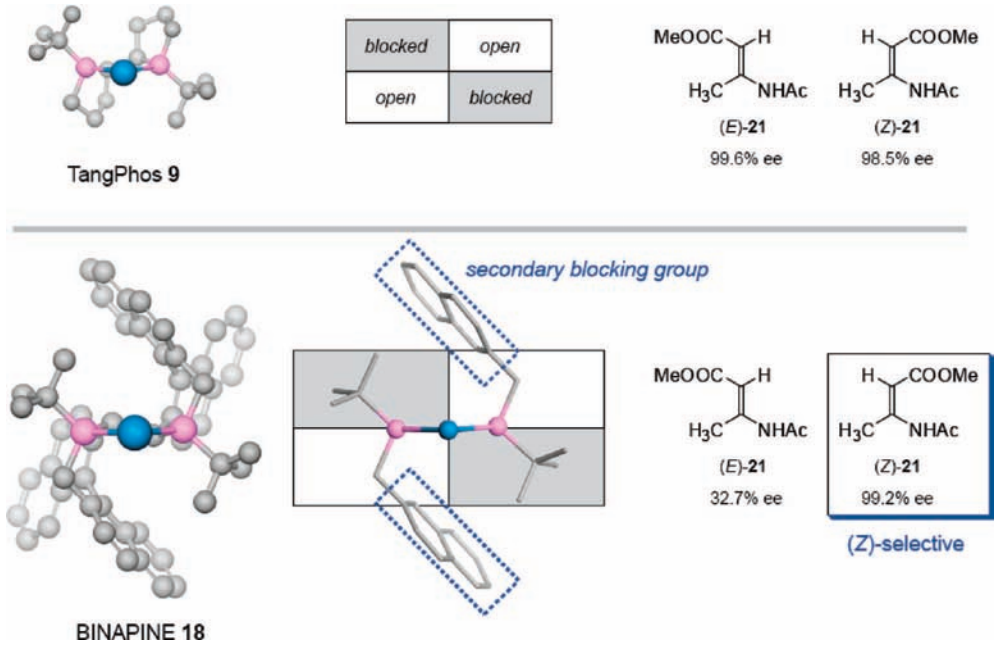


FIGURE 6. MM2 calculations of Rh/**9** and Rh/**18** complexes and comparative hydrogenation results for (*E*)-**21** and (*Z*)-**21**.

With stereogenic centers located closest to the coordination site, P-chiral ligands are preferred for the formation of a definite chiral environment. As shown by the work of Imamoto et al. on BisP* **19** and MiniPhos **20**,[23] the size difference in the two P substitutes is a key factor for chiral induction. Having witnessed the importance of conformational rigidity in **12**, we designed TangPhos **9** by incorporating P chirality within the cyclic motif.[10a] In combination with suitable transition metals, **9** exhibits excellent enantioselectivity and reactivity toward a broad range of substrates, including functional olefins, [10a–e] β-keto esters,[10f] and imines[10g,h] (Figure 4). In addition, **9** was reported to give excellent results in asymmetric hydroformylation reactions.[24]

The synergic combination of P chirality and the cyclic motif, as seen in the success of **9**, encouraged us to explore BINAPINE **18** through further integration of axial chirality.[20] Comparative hydrogenation of isomeric methyl 3-acetylamino-2-butenoates **21** revealed a superior selectivity of **18** toward the *Z* isomer. In contrast, although **9** tolerates both *E* and *Z* isomers of most aliphatic substrates, unsatisfactory results were observed for aromatic substrates bearing *ortho* functionality.[10b] Because (*Z*)-β-aryl-β-(acylamino)acrylates can be prepared from the corresponding β-keto esters, many pharmaceutically important β-aryl-β-amino acids, regardless of the substitution mode on the aryl moiety, can be prepared via the Rh/**18**-catalyzed hydrogenation route (Figure 5).[20] For example, extensive screening of many well-known chiral ligands determined **18** as the most selective ligand [98% enantiomeric excess (ee), at 500 turnover number (TON) for (*R*,*Z*)-ethyl 3-acetamido-5-methylnon-2-enoate **22**, affording the key precursor to a chiral drug for the treatment of various disorders.[25]

Because rigid structures are subject to minimum conformational distortion during transition states, the MM2

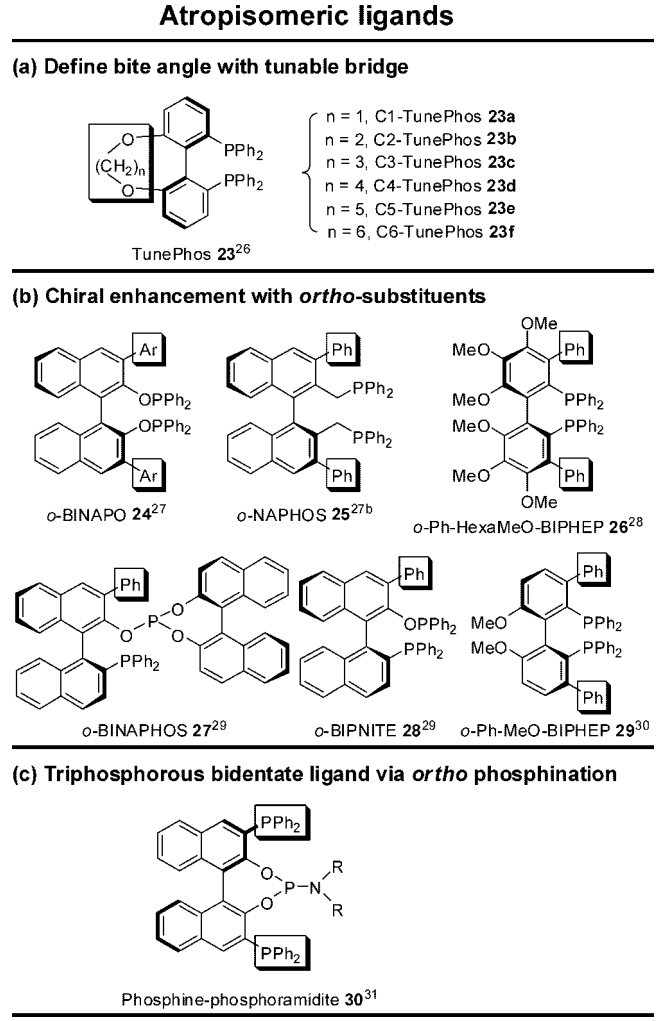


FIGURE 7. Development of ligands with an atropisomeric backbone.

Chart 1. Defined Bite Angle of 23 with a Tunable Bridge from C1 to C6

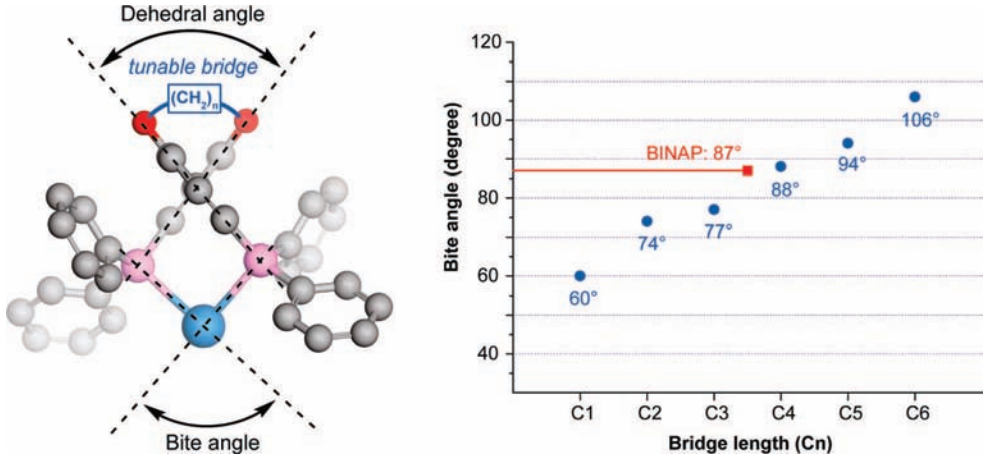
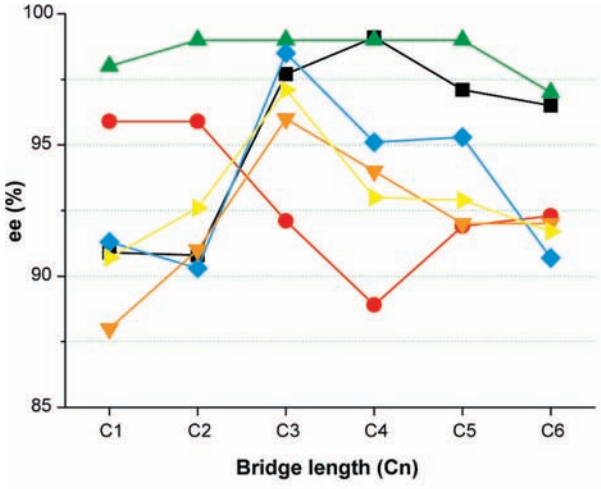


Chart 2. Bite Angle Effect of 23 in Ru-Catalyzed Hydrogenation Reactions



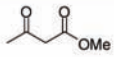
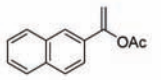
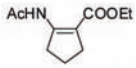
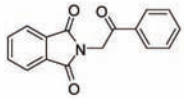
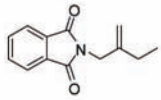
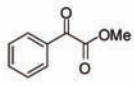
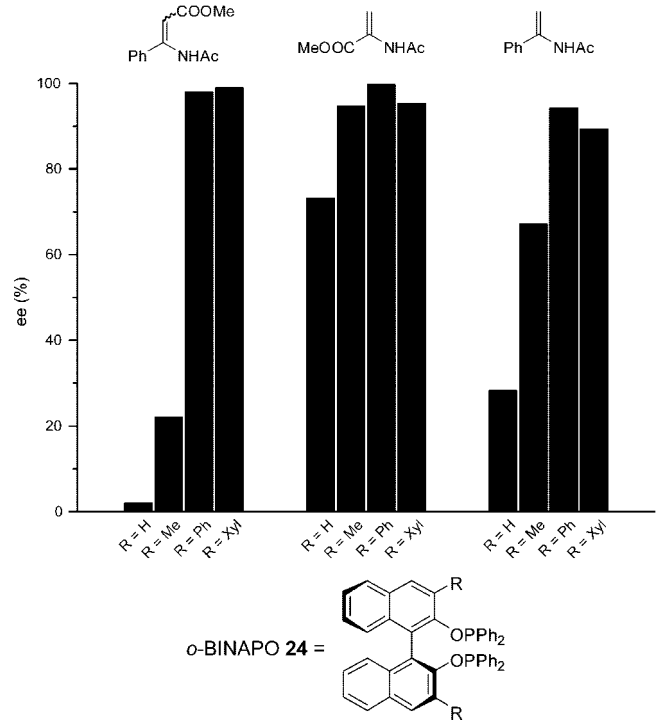
Symbol	Substrate	Catalytic system	Optimal linkage
■		$RuCl_2(\eta^6\text{-benzene})$[19]	C4
●		$[NH_2Me_2][\{RuCl[19]\}_2(\mu\text{-}Cl)_3]$	C1, C2
▲		$Rh(methallyl)_2$[19] + HBF_4	C2 ~ C5
◆		$[NH_2Me_2][\{RuCl[19]\}_2(\mu\text{-}Cl)_3]$	C3
▼		$(RuCl_2[19])(DMF)_m$	C3
▶		$(RuCl_2[19])(DMF)_m$	C3

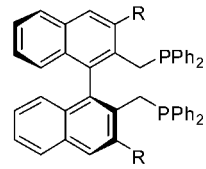
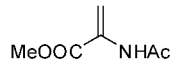
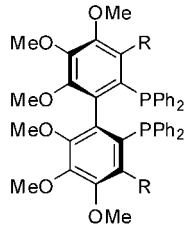
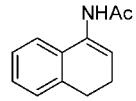
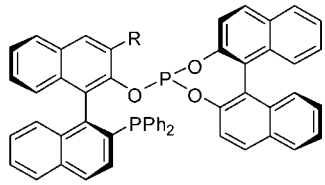
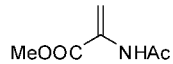
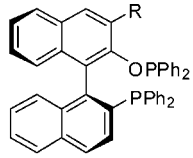
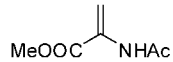
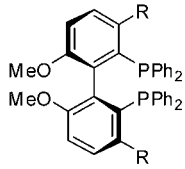
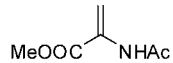
Chart 3. Chiral Enhancement of the BINAPO Ligand through *ortho* Substitution



calculation of such metal–ligand complexes at the ground state may provide valuable information on the origin of chiral induction. The unique *Z* selectivity of **18** prompted us to investigate its chiral environment in terms of a quadrant diagram (Figure 6). Similar to the P-chiral **9**, two nonadjacent quadrants are blocked by the sterically hindered *tert*-butyl P substituents; a distinct feature of **18**, however, is the presence of two bulky naphthyl moieties extending beyond the original quadrants and shielding the coordination plane from the top and the bottom. Before more detailed studies come out, we currently attribute its unusual *Z* selectivity to these secondary blocking groups.

Because the chirality of **9** originates from (–)-sparteine-mediated asymmetric protonation, it exists as only one enantiomer.[10a] To address this issue, we developed DuanPhos **10** that can be synthesized as both enantiomers via a convenient route (Scheme 1).[11a] It turned out that the appended benzene rings of **10** enhance its reactivity, selectivity, and air-stability compared with **9**. Our recent study revealed that hydrogenation of β-methylcinnamic acids by the Rh/**10** system gave

Table 1. *ortho* Enhancement of Chiral Induction in the Atropisomeric Ligands 25–29

Ligand	Substrate	ee (%) R = H	ee (%) R = Ph	Reference
		54.0	98.7	27b
		65	98	28
		96	99	29
		77	99	29
		25	99	30

excellent results even at reduced catalyst loading (97% ee, TON = 5000).[11c]

Atropisomeric Backbone

The great success of BINAP in asymmetric hydrogenation[5b,c] inspired us to develop effective ligands with an atropisomeric backbone (Figure 7). Although replacing P substitutes is an obvious strategy, profound effects will be observed via the modification of the axially chiral backbone. The fact that the two naphthyl moieties of BINAP can rotate around the connecting sp^2–sp^2 bond with little restriction raised the questions (1) whether this rotational freedom, instead of a restricted conformation, is a prerequisite for the observed high enantioselectivity and, (2) if not, whether a bite angle or a certain bite-angle range exists that is optimal for each individual substrate. To answer these questions, we designed modular TunePhos **23** by connecting the two aryl moieties with a tunable bridge (Figure 7a).[26a] The additional linkage not only minimizes the conformational rotation but also defines the dihedral angle and further the bite angle with improved precision. Moreover, optimization of the bite angle can be accomplished by adjusting the length of the linking bridge, for example, from C1 to C6. MM2 calculations indicated that the whole series of C*n*–TunePhos **23a–f** covers a wide range of the bite angle (from 60° to 106°); to each ligand, a discrete value is assigned by the restrictive tether (Chart 1). Thus, hydrogenation with **23a–f** allowed us to study the effect of the bite angle on enantioselectivity in a systematic way.[26] Thus far, a number of different substrates have been tested, giving excellent results comparable or superior to those obtained with BINAP. For each substrate, there is an optimal bite angle or an angle range for maximum selectivity (Chart 2): **23c** (n = 3) gives the best results for α-phthalimide ketone,[26d] allylphthalimides,[26e] and α-keto esters;[26f] **23a** (n = 1) and **23b** (n = 2) give the best results for enol acetates;[26b] **23a** gives the best results for β-keto esters;[26a] and **23b–e** (n = 2–5) give the best results for cyclic β-dehydroamino esters.[26c] Our results showed that no single ligand gives consistently superior results for all of

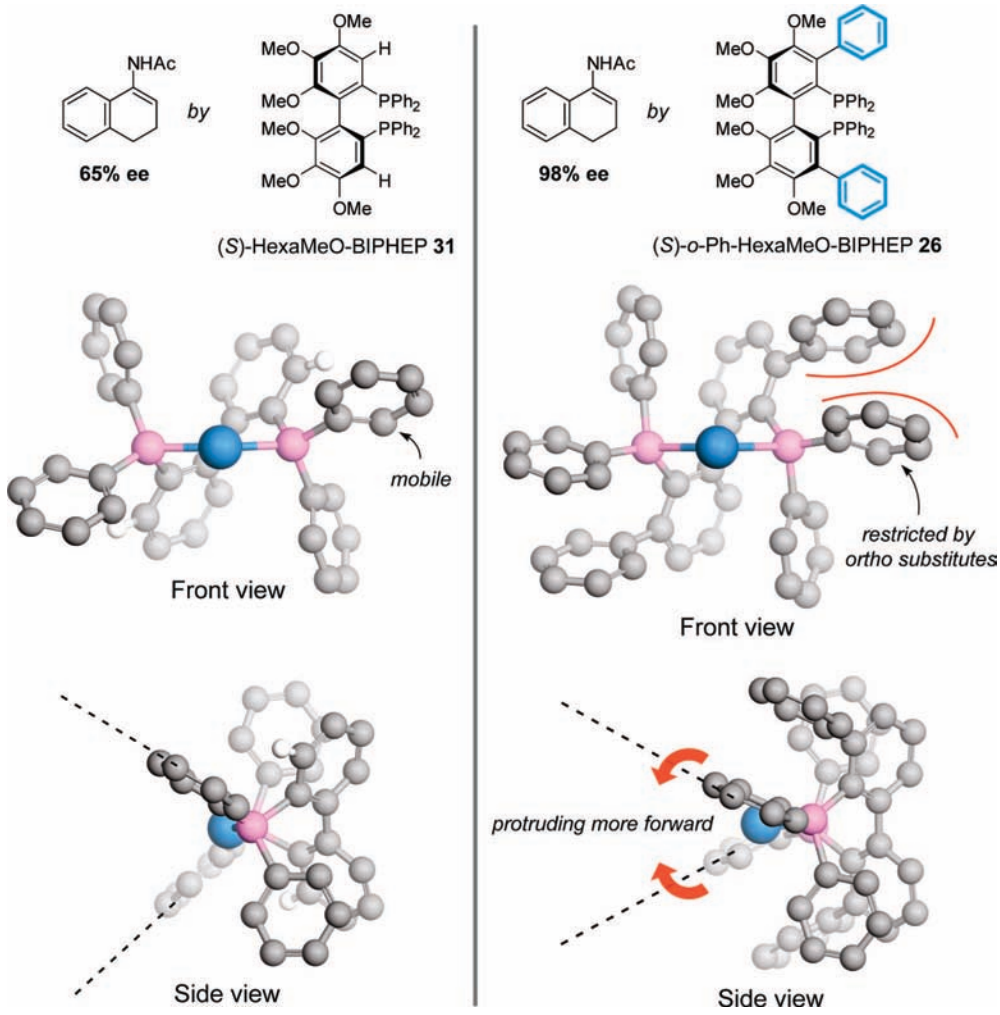


FIGURE 8. MM2 calculations of Rh/**31** and Rh/**26** complexes (methoxy groups and non-3,3′-hydrogen atoms are omitted for clarity).

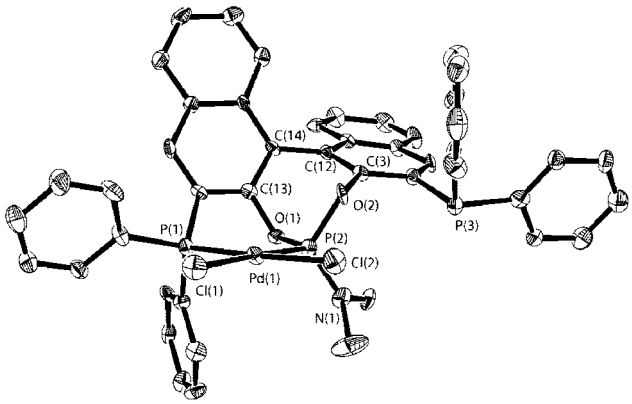
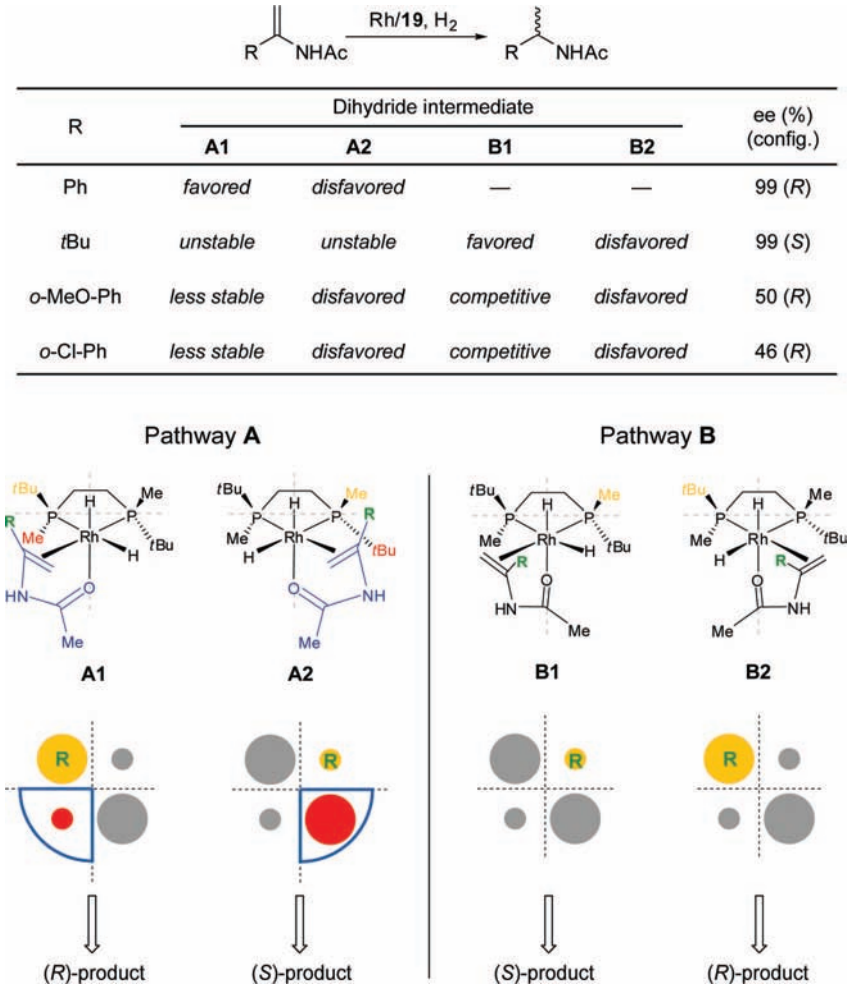


FIGURE 9. Single-crystal structure of $PdCl_2$·**30a** (R = CH_3) (hydrogen and the solvent are omitted for clarity).

those substrates. Therefore, optimization of the bite angle is necessary for biaryl-type ligands.

Because structural analysis of BINAP has shown the crucial role of equatorial P substitutes for chiral induction,[32] we envisioned that enantiodifferentiation originating from the biaryl backbone can be strengthened through implementation of hindered groups on the proximate 3,3′ positions (Figure 7b). Consistent with this postulation, a significant chiral enhancement was observed in the flexible BINAPO ligand when it was modified with various *ortho* substitutes (Chart 3).[27] Of particular importance is the planar phenyl group in our development of *o*-NAPHOS **25**,[27b] *o*-Ph-HexaMeO-BIPHEP **26**,[28] *o*-BINAPHOS **27**,[29] *o*-BIPNITE **28**,[29] and *o*-Ph-BIPHEP **29**,[30] all of which gave much better enantioselectivity than the parent ligands (Table 1). To understand the remarkable "*ortho* effect", we have preformed computational studies to compare **26** with the corresponding unsubstituted HexaMeO-BIPHEP **31**.[28] In contrast to the unrestrained equatorial P-phenyl groups of **31**, those of **26** are compressed and acccordingly oriented parallel to the *ortho* substituents, protruding more forward with a decreased conformational mobility (Figure 8).

The discovery of monophosphorous ligands **8**[9] has become a recent highlight in hydrogenation research.[33] From a practical viewpoint, their highly modular structure and short synthesis from cheap starting materials are indispensable advantages for high throughput synthesis and screening. Inspired by the success of Feringa et al. in combining phosphoramidite **8** (X = NR_2) and achiral PPh_3,[34] we designed a modular pseudo-C_2-symmetric phosphine–phosphoramidite **30** via double *ortho* phosphination of the chiral BINOL backbone.[31a] As evidenced by ^{31}P nuclear magnetic resonance (NMR)



R	Dihydride intermediate				ee (%) (config.)
	A1	A2	B1	B2	
Ph	*favored*	*disfavored*	—	—	99 (*R*)
*t*Bu	*unstable*	*unstable*	*favored*	*disfavored*	99 (*S*)
o-MeO-Ph	*less stable*	*disfavored*	*competitive*	*disfavored*	50 (*R*)
o-Cl-Ph	*less stable*	*disfavored*	*competitive*	*disfavored*	46 (*R*)

FIGURE 10. Mechanism of stereoselection in the Rh/**19**-catalyzed hydrogenation of enamides.[36b]

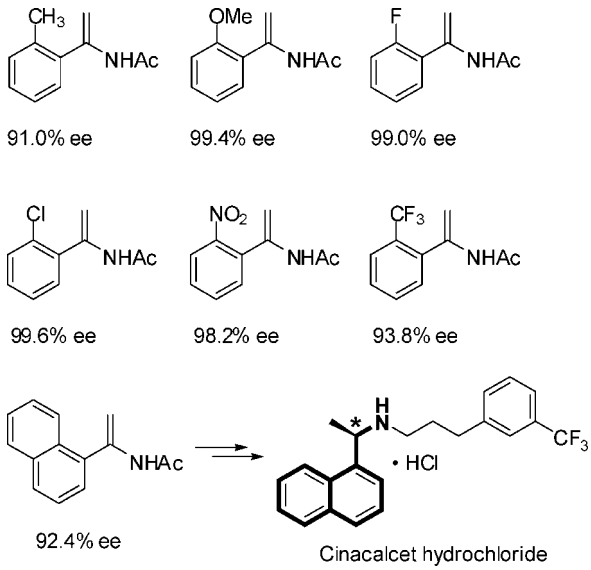


FIGURE 11. Hydrogenation of *ortho*-substituted arylenamides and 1-naphthylenamide by the Rh/**30a** system.

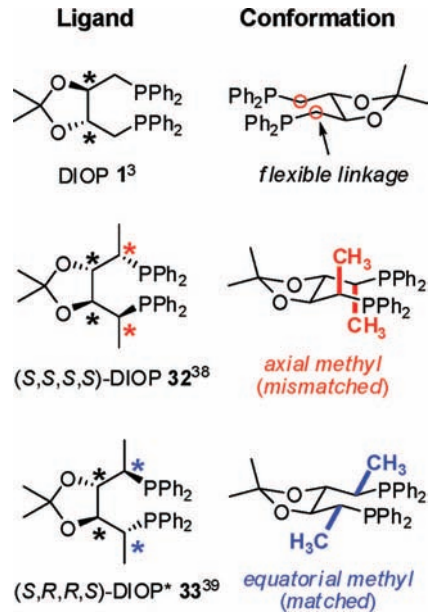


FIGURE 12. Interplay of dual stereogenic centers in the backbones of **32** and **33** is critical for chiral induction.

and X-ray diffraction experiments, among the three potential donors, only two properly oriented phosphines form effective chelation with metal, leaving a third spectator phosphine. The single-crystal structure of $PdCl_2$·**30a** (R = CH_3) indicated that its chiral induction relies on the quasi-equatorial phenyl of the peripheral phosphine P(1) and the dimethylamino group of the central phosphoramidite P(2) (Figure 9).[31b] Characterized by a stepwise-assembly synthesis, the overall steric

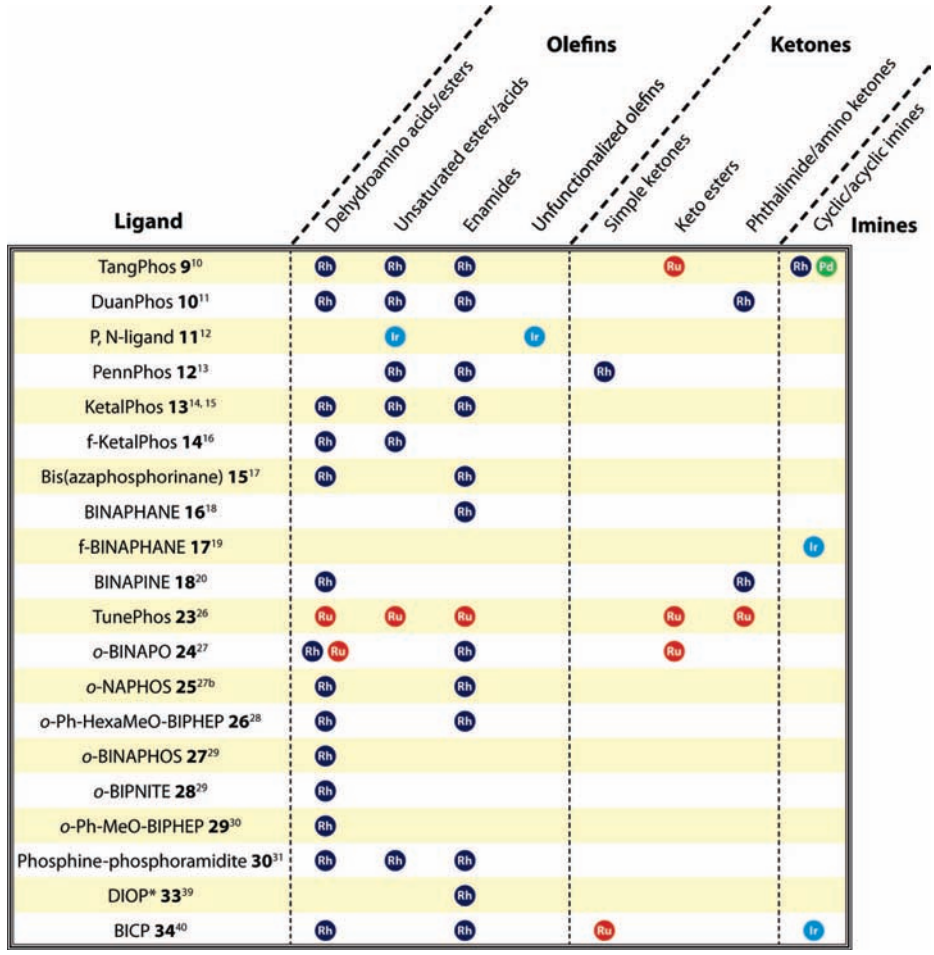


FIGURE 13. Development of a chiral ligand toolbox for asymmetric hydrogenation.

and electronic environment of **30** can be tailored for different substrates by individual optimization of the two distinct modules.[35]

Although enantioselective hydrogenation of α-arylenamides has been fulfilled with many ligands available today, those bearing *ortho* functionalities remained unsolved. Imamoto and coworkers have conducted thorough mechanistic studies on the Rh/**19** system, leading to the "dihydride mechanism" that involves migratory insertion as the key enantiodifferentiating step.[36] In the hydrogenation of enamides,[36b] they identified two competing hydride insertion pathways **A** and **B** (Figure 10): for a common arylenamide, minimization of the steric interaction between the substrate-made chelation ring and the P substitutes of **19** favors the formation of the *R* product via intermediate **A1**; on the other hand, a hindered R substituent, such as the *tert*-butyl group, on the substrate will switch the pathway for a less congested dihydride intermediate **B1**, thus affording the opposite *S* selectivity. In the case of *ortho*-substituted enamides, the efficiency of hydrogenation through pathway **A** is partially compromised because of the increased steric hindrance of the R substituent, so that remarkably low ee values are observed compared with otherwise substituted enamides. This rationale is in agreement with our preliminary experiments using C_2-symmetric TangPhos **9**, DuPhos **4** (R = Et), and BINAPHANE **16**. In particular, the Rh/**9** system gave reversed enantioselectivity for *ortho*-methyl-substituted arylenamide, which further confirms the proposed role of pathway **B**.

Interestingly, we found that the unsymmetrical ligand **30** gave superior selectivity toward these challenging substrates, including 1-naphthylenamide (Figure 11).[31a] If we suppose that the Rh/**30** system works via a similar dihydride mechanism, it is obvious that the undesired hydrogenation pathway **B** has been suppressed effectively. Practically, the hydrogenation of 1-naphthylenamide may be applied for the synthesis of (*R*)-1-(1-naphthyl)ethylamine, a key precursor to Cinacalcet hydrochloride for the treatment of hyperparathyroidism and hypercalcemia.[37] Recently, a series of **30** with a varying phosphoramidite donor has been applied in the highly enantioselective hydrogenation of α-dehydroamino esters and itaconates.[31b] An interesting phenomenon associated with the Rh/**30** system is the strong solvent effect: during the hydrogenation of itaconates, the switch of product chirality was observed simply by the use of different solvents.[31b]

DIOP-Inspired Ligands

Kagan's creative work on DIOP **1**[3] has launched intensive studies for C_2-symmetric chelating bisphosphine ligands. However, its flexible methylene linkage has reduced the

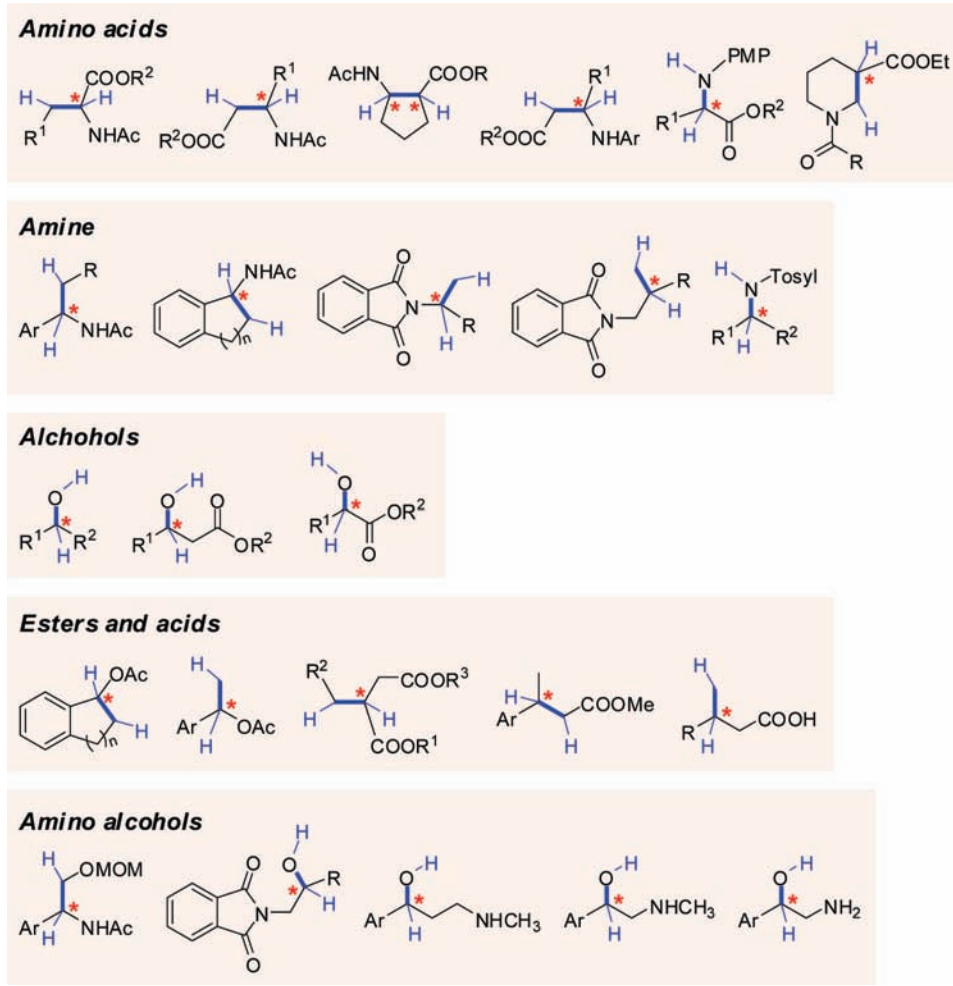
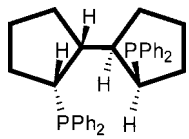


FIGURE 14. Chiral building blocks prepared via asymmetric hydrogenation.

efficiency of transferring chirality from the backbone. One solution to this problem is the introduction of additional stereogenic centers close enough to eliminate conformational ambiguity. Thus, an extra methyl group was placed near the donor site to form a modified ligand (*S*,*S*,*S*,*S*)-DIOP **32**, albeit with eroded selectivity.[38] Because the deteriorative result suggested a mismatching between the backbone chirality and the axially oriented methyl group, we devised a diastereomeric (*S*,*R*,*R*,*S*)-DIOP* **33** by inverting the methyl chirality (Figure 12). In this way, all substituents on the metal–ligand chelate ring are located in an equatorial position, giving much better results than **1** and **32** in the hydrogenation of enamides.[39]

Alternatively, the removal of conformational flexibility inherent to **1** can be realized with the help of a rigid cyclic structure, such as a five-membered cyclopentane ring. Thus, we designed rigid bisphosphine BICP **34** and successfully applied it in Rh-, Ru-, and Ir-catalyzed hydrogenation reactions.[40]



BICP **34**[39]

Development of a Ligand Toolbox for Asymmetric Hydrogenation

No universal ligands exist. However, given a ligand library with sufficient structural diversity, it is still possible to find out the desired catalytic system for a specific substrate (a ligand toolbox approach).[41] Thus far, we have developed a large variety of ligands with different structural motifs. As shown in the tabular survey (Figure 13), the combination of these ligands with suitable transition metals enabled the hydrogenation of various substrates with excellent enantioselectivity. When new ligands and their combination with transition metals are explored, this ligand toolbox can be expanded to a broader substrate scope.

In practice, asymmetric hydrogenation offers an economical method for the large-scale preparation of chiral products, such as the famous Monsanto's L-DOPA synthesis,[4c] Takasago's carbapenem synthesis,[5b,c] and Syngenta's (*S*)-Metolachlor synthesis.[42] Thus far, we have been able to synthesize many pharmaceutically important chiral building blocks, including amino acids, amines, alcohols, esters, acids, and amino alcohols, in a highly efficient way (Figure 14). For example, chiral γ-amino alcohols **36** are key intermediates to the antidepressants **35a–d**, which can be prepared by asymmetric hydrogena-

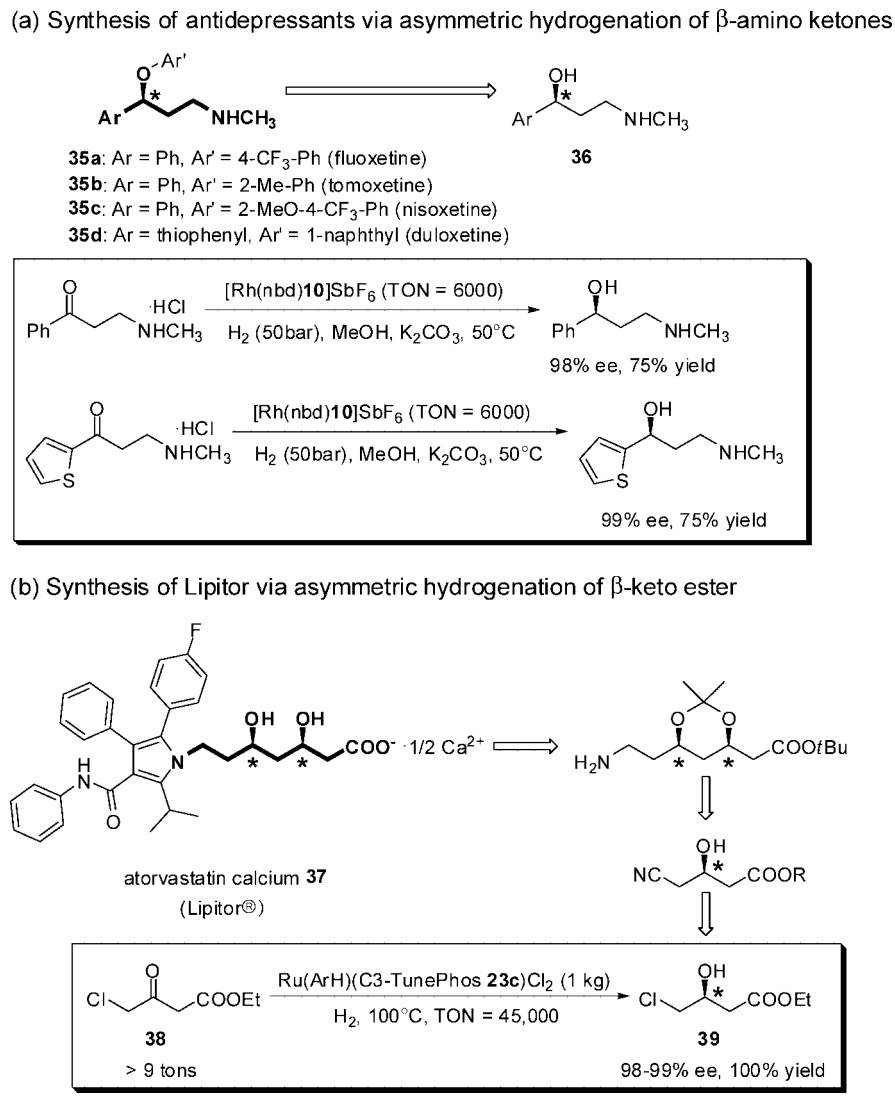


FIGURE 15. Practical applications of asymmetric hydrogenation for pharmaceutical products.

tion of amino ketones. We found that the Rh/**10** system showed excellent results for this transformation: up to 6000 turnovers and 98% ee have been achieved (Figure 15a).[11b] As the most wanted drug (>10 billion dollar sales per year) for the treatment of hypercholesterolemia, atorvastatin calcium (Lipitor) **37** functions as a single enantiomer. In the convergent synthesis of **37**,[43] enantiomerically pure (*S*)-ethyl 4-chloro-3-hydroxybutanoate **39** is the key chiral intermediate, which can be prepared via Ru-catalyzed asymmetric hydrogenation of ethyl 4-chloroacetoacetate **38**. Using the Ru/**23c** system, excellent enantioselectivity (>98% ee) has been achieved at 45 000 turnovers in complete conversion (Figure 15b).

Conclusion

In this Account, we have reviewed our works on ligand development, from which some insightful experiences can be learned for future research. With few exceptions, ligands listed in Figure 13 benefit from conformational rigidity or reduced conformational flexibility. Their success has undoubtedly demonstrated the value of rigid structures in ligand design. Nevertheless, overemphasis on this principle will cause inevitable neglect of several other key factors, including accessibility (whether the designed ligand can be prepared easily), stability (whether it is stable under various conditions), reactivity and scope (whether and how it will form reactive catalytic species with transition metals, and what type of substrates it will be good for), and modularity (whether the structural motif can be evolved into a broad ligand series for fine-tuning its steric and/or electronic properties). The past has witnessed tremendous progress in asymmetric hydrogenation because of the development of many powerful chiral ligands. As more useful ligands and their applications are discovered, our knowledge of ligand design will continue to grow.

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References

(1) (a) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York, 1994. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. *1–3*. (c) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (d) Tang, W.; Zhang, X. New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003**, *103*, 3029–3069.

(2) (a) Knowles, W. S.; Sabacky, M. J. Catalytic Asymmetric Hydrogenation Employing a Soluble, Optically Active, Rhodium Complex. *Chem. Commun.* **1968**, 1445–1446. (b) Horner, L.; Siegel, H.; Buthe, H. Asymmetric Catalytic Hydrogenation with an Optically Active Phosphinerhodium Complex in Homogeneous Solution. *Angew. Chem., Int. Ed.* **1968**, *7*, 942.

(3) Kagan, H. B.; Dang, T.-P. Asymmetric Catalytic Reduction with Transition Metal Complexes. I. A Catalytic System of Rhodium(I) with (–)-2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, a New Chiral Diphosphine. *J. Am. Chem. Soc.* **1972**, *94*, 6429–6433.

(4) (a) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, O. J. Asymmetric Hydrogenation. Rhodium Chiral Bisphosphine Catalyst. *J. Am. Chem. Soc.* **1977**, *99*, 5946–5952. (b) Knowles, W. S. Asymmetric Hydrogenation. *Acc. Chem. Res.* **1983**, *16*, 106–112. (c) Knowles, W. S. Asymmetric Hydrogenations (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002**, *41*, 1998–2007.

(5) (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. Synthesis of 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), an Atropisomeric Chiral Bis(triaryl)phosphine, and Its Use in the Rhodium(I)-Catalyzed Asymmetric Hydrogenation of α-(Acylamino)acrylic Acids. *J. Am. Chem. Soc.* **1980**, *102*, 7932–7934. (b) Noyori, R.; Ohkuma, T. Asymmetric Catalysis by Architectural and Functional Molecular Engineering: Practical Chemo- and Stereoselective Hydrogenation of Ketones. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73. (c) Noyori, R. Asymmetric Catalysis: Science and Opportunities (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022.

(6) (a) Burk, M. J. C_2-Symmetric Bis(phospholanes) and Their Use in Highly Enantioselective Hydrogenation Reactions. *J. Am. Chem. Soc.* **1991**, *113*, 8518–8519. (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. Preparation and Use of C_2-Symmetric Bis(phospholanes): Production of α-Amino Acid Derivatives via Highly Enantioselective Hydrogenation Reactions. *J. Am. Chem. Soc.* **1993**, *115*, 10125–10138. (c) Burk, M. J. Modular Phospholane Ligands in Asymmetric Catalysis. *Acc. Chem. Res.* **2000**, *33*, 363–372.

(7) (a) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. A Novel Easily Accessible Chiral Ferrocenyldiphosphine for Highly Enantioselective Hydrogenation, Allylic Alkylation, and Hydroboration Reactions. *J. Am. Chem. Soc.* **1994**, *116*, 4062–4066. (b) Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A. Solvias Josiphos Ligands: From Discovery to Technical Applications. *Top. Catal.* **2002**, *19*, 3–16.

(8) (a) Helmchen, G.; Pfaltz, A. Phosphinooxazolines—A New Class of Versatile, Modular P,N-Ligands for Asymmetric Catalysis. *Acc. Chem. Res.* **2000**, *33*, 336–345. (b) Pfaltz, A.; Drury, W. J., III. Design of Chiral Ligands for Asymmetric Catalysis: From C_2-symmetric P,P- and N,N-Ligands to Sterically and Electronically Nonsymmetrical P,N-Ligands. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5723–5726. (c) Bell, S.; Wustenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. Asymmetric Hydrogenation of Unfunctionalized, Purely Alkyl-Substituted Olefins. *Science* **2006**, *311*, 642–644.

(9) (a) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. Biarylphosphonites: a Class of Monodentate Phosphorus(III) Ligands that Outperform Their Chelating Analogues in Asymmetric Hydrogenation Catalysis. *Chem. Commun.* **2000**, 961–962. (b) Reetz, M. T.; Mehler, G. Highly Enantioselective Rh-Catalyzed Hydrogenation Reactions Based on Chiral Monophosphite Ligands. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889–3890. (c) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. Highly Enantioselective Rhodium-Catalyzed Hydrogenation with Monodentate Ligands. *J. Am. Chem. Soc.* **2000**, *122*, 11539–11540.

(10) (a) Tang, W.; Zhang, X. A Chiral 1,2-Bisphospholane Ligand with a Novel Structural Motif: Applications in Highly Enantioselective Rh-Catalyzed Hydrogenations. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612–1614. (b) Tang, W.; Zhang, X. Highly Efficient Synthesis of Chiral β-Amino Acid Derivatives via Asymmetric Hydrogenation. *Org. Lett.* **2002**, *4*, 4159–4161. (c) Tang, W.; Liu, D.; Zhang, X. Asymmetric Hydrogenation of Itaconic Acid and Enol Acetate Derivatives with the Rh-TangPhos Catalyst. *Org. Lett.* **2003**, *5*, 205–207. (d) Dai, Q.; Yang, W.; Zhang, X. Efficient Rhodium-Catalyzed Asymmetric Hydrogenation for the Synthesis of a New Class of *N*-Aryl β-Amino Acid Derivatives. *Org. Lett.* **2005**, *7*, 5343–5345. (e) Yang, Q.; Gao, W.; Deng, J.; Zhang, X. Highly Enantioselective Hydrogenation of *N*-Phthaloyl Enamides. *Tetrahedron Lett.* **2006**, *47*, 821–823. (f) Wang, C.; Tao, H.; Zhang, X. Highly Enantioselective Ru-Catalyzed Hydrogenation of β-Keto Esters Using Electron-Donating Bis(trialkylphosphine) Ligand-TangPhos. *Tetrahedron Lett.* **2006**, *47*, 1901–1903. (g) Yang, Q.; Shang, G.; Gao, W.; Deng, J.; Zhang, X. A Highly Enantioselective, Pd-TangPhos-Catalyzed Hydrogenation of *N*-Tosylimines. *Angew. Chem., Int. Ed.* **2006**, *45*, 3832–3835. (h) Shang, G.; Yang, Q.; Zhang, X. Rh-Catalyzed Asymmetric Hydrogenation of α-Aryl Imino Esters: An Efficient Enantioselective Synthesis of Aryl Glycine Derivatives. *Angew. Chem., Int. Ed.* **2006**, *45*, 6360–6362. (i) Lei, A.; Chen, M.; He, M.; Zhang, X. Asymmetric Hydrogenation of Pyridines: Enantioselective Synthesis of Nipecotic Acid Derivatives. *Eur. J. Org. Chem.* **2006**, 4343–4347.

(11) (a) Liu, D.; Zhang, X. Practical P-Chiral Phosphane Ligand for Rh-Catalyzed Asymmetric Hydrogenation. *Eur. J. Org. Chem.* **2005**, 646–649. (b) Liu, D.; Gao, W.; Wang, C.; Zhang, X. Practical Synthesis of Enantiopure γ-Amino Alcohols by Rhodium-Catalyzed Asymmetric Hydrogenation of β-Secondary-Amino Ketones. *Angew. Chem., Int. Ed.* **2005**, *44*, 1687–1689. (c) Sun, X.; Zhou, L.; Wang, C.-J.; Zhang, X. Rh-Catalyzed Highly Enantioselective Synthesis of β-Methylcinnamic Acids. *Angew. Chem., Int. Ed.* **2007**, *46*, 2623–2626.

(12) Tang, W.; Wang, W.; Zhang, X. Phospholane-Oxazoline Ligands for Ir-Catalyzed Asymmetric Hydrogenation. *Angew. Chem., Int. Ed.* **2003**, *42*, 943–946.

(13) (a) Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. High Enantioselective Hydrogenation of Simple Ketones Catalyzed by a Rh-PennPhos Complex. *Angew. Chem., Int. Ed.* **1998**, *37*, 1100–1103. (b) Zhang, Z.; Zhu, G.; Jiang, Q.; Xiao, D.; Zhang, X. Highly Enantioselective Hydrogenation of Cyclic Enamides Catalyzed by a Rh-PennPhos Catalyst. *J. Org. Chem.* **1999**, *64*, 1774–1775. (c) Jiang, Q.; Xiao, D.; Zhang, Z.; Cao, P.; Zhang, X. Highly Enantioselective Hydrogenation of Cyclic Enol Acetates Catalyzed by a Rh-PennPhos Complex. *Angew. Chem., Int. Ed.* **1999**, *38*, 516–518.

(14) (a) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. Rhodium-Hydroxyl Bisphospholane Catalyzed Highly Enantioselective Hydrogenation of Dehydroamino Acids and Esters. *Tetrahedron Lett.* **1999**, *40*, 6701–6704. (b) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. Synthesis of Chiral Hydroxyl Phospholanes from D-Mannitol and Their Use in Asymmetric Catalytic Reactions. *J. Org. Chem.* **2000**, *65*, 3489–3496. (c) Dai, Q.; Wang, C.; Zhang, X. Chiral Bisphospholane Ligands (Meketalphos): Synthesis of their Rh(I) Complexes and Applications in Asymmetric Hydrogenation. *Tetrahedron* **2006**, *62*, 868–871.

(15) Parallel to our work, other groups also carried out independent studies on D-mannitol-derived bisphospholane ligands, see (a) Carmichael, D.; Doucet, H.; Brown, J. M. Hybrid P-Chiral Diphosphines for Asymmetric Hydrogenation. *Chem. Commun.* **1999**, 261–262. (b) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stürmer, R.; Börner, A. Synthesis of a New Class of Functionalized Chiral Bisphospholane Ligands and the Application in Enantioselective Hydrogenations. *J. Org. Chem.* **1998**, *63*, 8031–8034. (c) Holz, J.; Heller, D.; Stürmer, R.; Börner, A. Synthesis of the First Water-Soluble Chiral Tetrahydroxy Diphosphine Rh(I) Catalyst for Enantioselective Hydrogenation. *Tetrahedron Lett.* **1999**, *40*, 7059–7062. (d) Yan, Y.-Y.; Rajanbabu, T. V. Ligand Tuning in Asymmetric Catalysis: Mono- and Bis-phospholanes for a Prototypical Pd-Catalyzed Asymmetric Allylation Reaction. *Org. Lett.* **2000**, *2*, 199–202. (e) Yan, Y.-Y.; Rajanbabu, T. V. Highly Flexible Synthetic Routes to Functionalized Phospholanes from Carbohydrates. *J. Org. Chem.* **2000**, *65*, 900–906.

(16) Liu, D.; Li, W.; Zhang, X. A Novel Chiral Ferrocenyl Phosphine Ligand from Sugar: Applications in Rh-Catalyzed Asymmetric Hydrogenation Reactions. *Org. Lett.* **2002**, *4*, 4471–4474.

(17) Yan, Y.; Zhang, X. Six-Membered Bis(azaphosphorinane), Readily Available Ligand for Highly Enantioselective Asymmetric Hydrogenations. *Tetrahedron Lett.* **2006**, *47*, 1567–1569.

(18) Xiao, D.; Zhang, Z.; Zhang, X. Synthesis of a Novel Chiral Binaphthyl Phospholane and Its Application in the Highly Enantioselective Hydrogenation of Enamides. *Org. Lett.* **1999**, *1*, 1679–1681.

(19) (a) Xiao, D.; Zhang, X. Highly Enantioselective Hydrogenation of Acyclic Imines Catalyzed by Ir-f-Binaphane Complexes. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425–3428. (b) Chi, Y.; Zhou, Y.-G.; Zhang, X. Highly Enantioselective Reductive Amination of Simple Aryl Ketones Catalyzed by Ir-f-Binaphane in the Presence of Titanium(IV) Isopropoxide and Iodine. *J. Org. Chem.* **2003**, *68*, 4120–4122.

(20) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. A Bisphosphepin Ligand with Stereogenic Phosphorus Centers for the Practical Synthesis of β-Aryl-β-amino Acids by Asymmetric Hydrogenation. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509–3511.

(21) Gladiali, S.; Dore, A.; Fabbri, D.; De Lucchi, O.; Manassero, M. Novel Atropisomeric Phosphorus Ligands: 4,5-Dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine Derivatives. *Tetrahedron: Asymmetry* **1994**, *5*, 511–514.

(22) (a) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. Asymmetric [3 + 2] Cycloaddition of 2,3-Butadienoates with Electron-Deficient Olefins Catalyzed by Novel Chiral 2,5-Dialkyl-7-phenyl-7-phosphabicyclo[2.2.1]heptanes. *J. Am. Chem. Soc.* **1997**, *119*, 3836–3837. (b) Chen, Z.; Jiang, Q.; Zhu, G.; Xiao, D.; Cao, P.; Guo, C.; Zhang, X. Syntheses of Novel Chiral Monophosphines, 2,5-Dialkyl-7-phenyl-7-phosphabicyclo-[2.2.1]heptanes, and Their Application in Highly Enantioselective Pd-Catalyzed Allylic Alkylations. *J. Org. Chem.* **1997**, *62*, 4521–4523.

(23) (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. P-Chiral Bis(trialkylphosphine) Ligands and Their Use in Highly Enantioselective Hydrogenation Reactions. *J. Am. Chem. Soc.* **1998**, *120*, 1635–1636. (b) Yamanoi, Y.; Imamoto, T. Methylene-Bridged P-Chiral Diphosphines in Highly Enantioselective Reactions. *J. Org. Chem.* **1999**, *64*, 2988–2989.

(24) (a) Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider, P. J. A Highly Enantioselective Catalyst for Asymmetric Hydroformylation of [2.2.1]-Bicyclic Olefins. *Tetrahedron Lett.* **2005**, *46*, 7831–7834. (b) Axtell, A. T.; Klosin, J.; Abboud, K. A. Evaluation of Asymmetric Hydrogenation Ligands in Asymmetric Hydroformylation Reactions. Highly Enantioselective Ligands Based on Bis-phosphacycles. *Organometallics* **2006**, *25*, 5003–5009.

(25) (a) Hoge, G. Technology Development at Pfizer: "Real World" Asymmetric Hydrogenation. Conference: Modern Synthetic Methods, Reaction to Reality and Chiral USA 2005. July 12–14, 2005, Princeton, NJ. (b) Conway, B. G.; Nanninga, T. N.; Wu, H.; Hoge, G.; Pearlman, B. A.; Winkle, D. D. Preparation of β-Amino Acids Having Affinity for the α-2-δ Protein. *PCT Int. Appl.* 2006, WO 2006008612.

(26) (a) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. Synthesis of Chiral Bisphosphines with Tunable Bite Angles and Their Applications in Asymmetric Hydrogenation of β-Ketoesters. *J. Org. Chem.* **2000**, *65*, 6223–6226. (b) Wu, S.; Wang, W.; Tang, W.; Lin, M.; Zhang, X. Highly Enantioselective Hydrogenation of Enol Acetates Catalyzed by Ru-TunaPhos Complexes. *Org. Lett.* **2002**, *4*, 4495–4497. (c) Tang, W.; Wu, S.; Zhang, X. Enantioselective Hydrogenation of Tetrasubstituted Olefins of Cyclic β-(Acylamino)acrylates. *J. Am. Chem. Soc.* **2003**, *125*, 9570–9571. (d) Lei, A.; Wu, S.; He, M.; Zhang, X. Highly Enantioselective Asymmetric Hydrogenation of α-Phthalimide Ketone: An Efficient Entry to Enantiomerically Pure Amino Alcohols. *J. Am. Chem. Soc.* **2004**, *126*, 1626–1627. (e) Wang, C.; Sun, X.; Zhang, X. Enantioselective Hydrogenation of Allylphthalimides: An Efficient Method for the Synthesis of β-Methyl Chiral Amines. *Angew. Chem., Int. Ed.* **2005**, *44*, 4933–4935. (f) Wang, C.; Sun, X.; Zhang, X. Highly Enantioselective Hydrogenation of α-Keto Esters Catalyzed by Ru-Tunephos Complexes. *Synlett* **2006**, 1169–1172.

(27) (a) Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. Highly Effective Chiral *ortho*-Substituted BINAPO Ligands (*o*-BINAPO): Applications in Ru-Catalyzed Asymmetric Hydrogenations of β-Aryl-Substituted β-(Acylamino)acrylates and β-Keto Esters. *J. Am. Chem. Soc.* **2002**, *124*, 4952–4953. (b) Zhou, Y.-G.; Zhang, X. Synthesis of Novel BINOL-Derived Chiral Bisphosphorus Ligands and Their Applications in Catalytic Asymmetric Hydrogenation. *Chem. Commun.* **2002**, 1124–1125.

(28) Tang, W.; Chi, Y.; Zhang, X. An *ortho*-Substituted BIPHEP Ligand and Its Applications in Rh-Catalyzed Hydrogenation of Cyclic Enamides. *Org. Lett.* **2002**, *4*, 1695–1698.

(29) Yan, Y.; Chi, Y.; Zhang, X. Novel Phosphine–Phosphite and Phosphine–Phosphinite Ligands for Highly Enantioselective Asymmetric Hydrogenation. *Tetrahedron: Asymmetry* **2004**, *15*, 2173–2175.

(30) Wu, S.; He, M.; Zhang, X. Synthesis of *ortho*-Phenyl Substituted MeO-BIPHEP Ligand and its Application in Rh-Catalyzed Asymmetric Hydrogenation. *Tetrahedron: Asymmetry* **2004**, *15*, 2177–2180.

(31) (a) Zhang, W.; Zhang, X. Synthesis of Triphosphorous Bidentate Phosphine–Phosphoramidite Ligands: Application in the Highly Enantioselective Hydrogenation of *ortho*-Substituted Aryl Enamides. *Angew. Chem., Int. Ed.* **2006**, *45*, 5515–5518. (b) Zhang, W.; Zhang, X. Highly Enantioselective Hydrogenation of α-Dehydroamino Esters and Itaconates with Triphosphorous Bidentate Ligands and the Unprecedented Solvent Effect thereof. *J. Org. Chem.* **2007**, *72*, 1020–1023.

(32) Shimizu, H.; Nagasaki, I.; Saito, T. Recent Advances in Biaryl-Type Bisphosphine Ligands. *Tetrahedron* **2005**, *61*, 5405–5432.

(33) Komarov, I. V.; Borner, A. Highly Enantioselective or Not?—Chiral Monodentate Monophosphorus Ligands in the Asymmetric Hydrogenation. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197–1200.

(34) Hoen, R.; Boogers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meetsma, A.; Tiemersma-Wegman, T. D.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. Achiral Ligands Dramatically Enhance Rate and Enantioselectivity in the Rh/Phosphoramidite-Catalyzed Hydrogenation of α,β-Disubstituted Unsaturated Acids. *Angew. Chem., Int. Ed.* **2005**, *44*, 4209–4212.

(35) Inoguchi, K.; Sakuraba, S.; Achiwa, K. Design Concepts for Developing Highly Efficient Chiral Bisphosphine Ligands in Rhodium-Catalyzed Asymmetric Hydrogenations. *Synlett* **1992**, 169–178.

(36) (a) Gridnev, I. D.; Higashi, N.; Asakura, K.; Imamoto, T. Mechanism of Asymmetric Hydrogenation Catalyzed by a Rhodium Complex of (*S*,*S*)-1,2-Bis(*tert*-butylmethylphosphino)ethane. Dihydride Mechanism of Asymmetric Hydrogenation. *J. Am. Chem. Soc.* **2000**, *122*, 7183–7194. (b) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. Asymmetric Hydrogenation of Enamides with Rh-BisP* and Rh-MiniPHOS Catalysts. Scope, Limitations, and Mechanism. *J. Am. Chem. Soc.* **2001**, *123*, 5268–5276. (c) Gridnev, I. D.; Imamoto, T. On the Mechanism of Stereoselection in Rh-Catalyzed Asymmetric Hydrogenation: A General Approach for Predicting the Sense of Enantioselectivity. *Acc. Chem. Res.* **2004**, *37*, 633–644.

(37) van Wagenen, B. C.; Moe, S. T.; Balandrin, M. F.; DelMar, E. G.; Nemeth, E. F. Calcium Receptor-Active Compounds. U.S. Patent 2001, 6,211,244.

(38) Kagan, H. B.; Fiaud, J. C.; Hoornaert, C.; Meyer, D.; Poulin, J. C. Synthesis of New Chiral Phosphines for Asymmetric Catalysis. *Bull. Soc. Chim. Belg.* **1979**, *88*, 923–931.

(39) Li, W.; Zhang, X. Synthesis of 3,4-*O*-Isopropylidene-(3*S*,4*S*)-dihydroxy-(2*R*,5*R*)-bis(diphenylphosphino)hexane and its Application in Rh-Catalyzed Highly Enantioselective Hydrogenation of Enamides. *J. Org. Chem.* **2000**, *65*, 5871–5874.

(40) (a) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. High Enantioselective Rh-Catalyzed Hydrogenations with a New Chiral 1,4-Bisphosphine Containing a Cyclic Backbone. *J. Am. Chem. Soc.* **1997**, *119*, 1799–1800. (b) Zhu, G.; Zhang, X. Asymmetric Rh-Catalyzed Hydrogenation of Enamides with a Chiral 1,4-Bisphosphine Bearing Diphenylphosphino Groups. *J. Org. Chem.* **1998**, *63*, 9590–9593. (c) Zhu, G.; Casalnuovo, A. L.; Zhang, X. Practical Syntheses of β-Amino Alcohols via Asymmetric Catalytic Hydrogenation. *J. Org. Chem.* **1998**, *63*, 8100–8101. (d) Zhu, G.; Zhang, X. Additive Effects in Ir-BICP Catalyzed Asymmetric Hydrogenation of Imines. *Tetrahedron: Asymmetry* **1998**, *9*, 2415–2418. (e) Zhu, G.; Chen, Z.; Zhang, X. Highly Efficient Asymmetric Synthesis of β-Amino Acid Derivatives via Rhodium-Catalyzed Hydrogenation of β-(Acylamino)Acrylates. *J. Org. Chem.* **1999**, *64*, 6907–6910. (f) Cao, P.; Zhang, X. Ru-BICP-Catalyzed Asymmetric Hydrogenation of Aromatic Ketones. *J. Org. Chem.* **1999**, *64*, 2127–2129.

(41) Zhang, X. Developing a Chiral Toolbox for Asymmetric Catalytic Reactions. *Enantiomer* **1999**, *4*, 541–555.

(42) Blaser, H.-U. The Chiral Switch of (*S*)-Metolachlor: A Personal Account of an Industrial Odyssey in Asymmetric Catalysis. *Adv. Synth. Catal.* **2002**, *344*, 17–31.

(43) Baumann, K. L.; Butler, D. E.; Deering, C. F.; Mennen, K. E.; Millar, A.; Nanninga, T. N.; Palmer, C. W.; Roth, B. D. The Convergent Synthesis of CI-981, an Optically Active, Highly Potent, Tissue Selective Inhibitor of HMG-CoA Reductase. *Tetrahedron Lett.* **1992**, *33*, 2283–2284.

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