P-Phos: A Family of Versatile and Effective Atropisomeric Dipyridylphosphine Ligands in Asymmetric Catalysis

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ABSTRACT
This Account outlines our efforts in the design and synthesis of a family of highly effective atropisomeric dipyridylphosphine ligands (P-Phos and its variants) and in the development of their widespread applications in transition-metal-catalyzed asymmetric reactions including hydrogenation, hydrosilylation, and C−C bond formation. Desirable attributes, such as air stability, broad substrate scope, fast rates of reaction, excellent enantioselectivities, low catalyst loading, and mild conditions, make the catalyst systems highly attractive and thus may provide excellent opportunities for practical applications.

Introduction

The quest for new chiral ligands and their related transition metal catalysts with improved utility, activity, and selectivity is a major effort in the study of asymmetric catalysis. Among the efficient ligands reported to-date, chiral diphosphines account for a considerable share.[1,2] Over the last two decades, tremendous success has been achieved in the use of chiral diarylphosphine ligands, such as BINAP, BIPHEMP, and MeO-BIPHEP,[3] in numerous asymmetric reactions, especially in Rh- or Ru-catalyzed asymmetric hydrogenation.[1,2] In contrast, the catalytic property of transition-metal complexes with chiral phosphine ligands embodying heterocyclic moieties such as pyridyl ring has been relatively unexplored even though the expansion of the scope of metal phosphine chemistry with the rich chemistry of heterocyclic functionalities is obvious.

The diphosphine ligands using biheteroaryls as supporting scaffolds were initially introduced in the mid-1990s.[4a] A series of five-membered biheteroaromatic diphosphines such as tetraMe-BITIANP,[4a] tetraMe-BITIOP,[4b] and N-Me-2-BINP[4c] have been synthesized by Sannicolò and co-workers. These ligands exhibited comparably high enantioselectivities to BINAP in the Ru-catalyzed asymmetric hydrogenations of α- and β-keto esters,[4,5] as well as excellent regio- and enantioselectivities in the Pd-catalyzed asymmetric Heck reactions.[6] The desirable features of using diheteroaryls to replace traditional carbocyclic biaryl as backbones in chrial phosphine ligands are that (1) the added functionality of the heteroaryl rings in the ligand may introduce more interesting chemistry and (2) the recycle of catalysts derived from heteroaryls possessing basic sites may be realized by a simple acidic extraction process.[7,8]

The purpose of this Account is to report our efforts in the design and synthesis of a family of highly effective atropisomeric dipyridylphosphine ligands and in the development of their widespread applications in transition-metal-catalyzed asymmetric reactions.

Atropisomeric Dipyridylphosphine Ligands, P-Phos

In 1980, Wilkinson et al. reported that ruthenium and rhodium complexes containing tris(2-pyridyl)phosphine were inactive in the homogeneous hydrogenation of alkenes.[9] This was thought to be attributed to the coordination of the nitrogen atom of the pyridyl group to the metal center, which rendered the complexes coordinately saturated. Having envisaged this, we commenced our research in this area with the design and synthesis of a series of phosphine ligands (Figure 1, **1**−**3**)[8,10] encompassing 2,6-dimethoxypyridyl groups, in which more hindered substituents were introduced to the *ortho* positions of the nitrogen atom to block the access of the pyridyl ring to the metal center. The resulting Rh complexes were found to be effective for the hydrogenation of aldehydes, imines, and prochiral olefins.[10]

After solving this important problem, we set out to tailor a novel atropisomeric dipyridylphosphine ligand, P-Phos (Figure 2, **4a**),[11] which furnished very high levels of absolute stereocontrol in the Ru-catalyzed enantioselective hydrogenations of 2-(6′-methoxy-2′-naphthyl)propenoic acid and β-keto esters.

For the optimization of nonracemic diphosphines, the P-substituents represent an important structural or elec-

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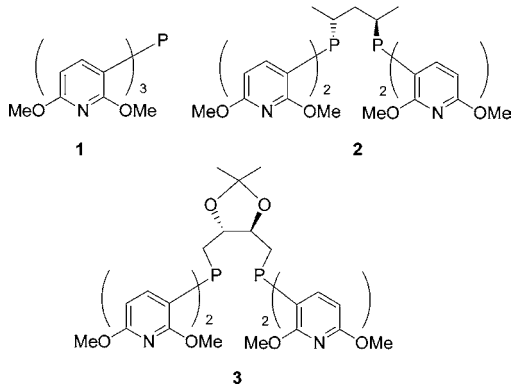


FIGURE 1. Phosphine ligands containing 2,6-dimethoxypyridyl groups.

tronic module that can be systematically adjusted to create a diverse range of chiral diphosphine ligands and therefore may lead to interesting or improved results. In this context, we designed two P-Phos analogues, Tol-P-Phos[12] (Figure 2, **4b**) and Xyl-P-Phos[13] (**4c**), by attaching different

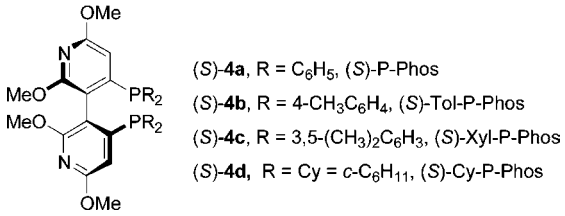


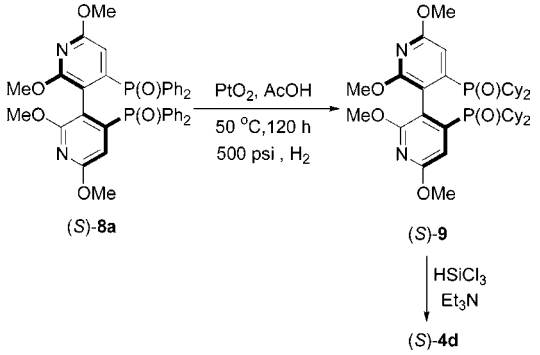
FIGURE 2. P-Phos and its variants.

P-substituents onto the dipyridyl skeleton rather than changing the backbone itself. This is a simple and straightforward strategy of modifying P-Phos. Additionally, with the understanding that dicyclohexylphosphino ligands are sometimes better than their diphenylphosphino analogues,[14] we also developed a convenient synthetic pathway to another P-Phos analogue, Cy-P-Phos (**4d**).[15]

The approach for each P-Phos member **4a**−**4c** entailed the introduction of the phosphinyl group at the *para*-position of 3-bromo-2,6-dimethoxypyridine followed by an oxidation process to afford the monophosphine oxide **7**, which was transformed to the racemic C_2-symmetric diphosphine dioxide **8** via a Cu-mediated Ullmann coupling reaction. Optical resolution of the racemate **8** with enantiopure dibenzoyltartaric acid (DBTA) followed by reduction with trichlorosilane gave the corresponding diphosphine enantiomer in overall six steps from the commercially available 2,6-dimethoxypyridine as delineated in Scheme 1.[11−13] This method represents one of the two major synthetic strategies for biheteroaryl diphosphines.[7]

With enantiopure P-Phos oxide (*S*)-**8a** on hand, the axially chiral bis(aryldicyclohexylphosphine) dioxide (*S*)-**9** (Scheme 2) was easily prepared via PtO_2-catalyzed hydrogenation.[15] Similarly, (*R*)-**9** could be easily prepared from (*R*)-**8a**.

Scheme 2. The Synthetic Route toward 4d

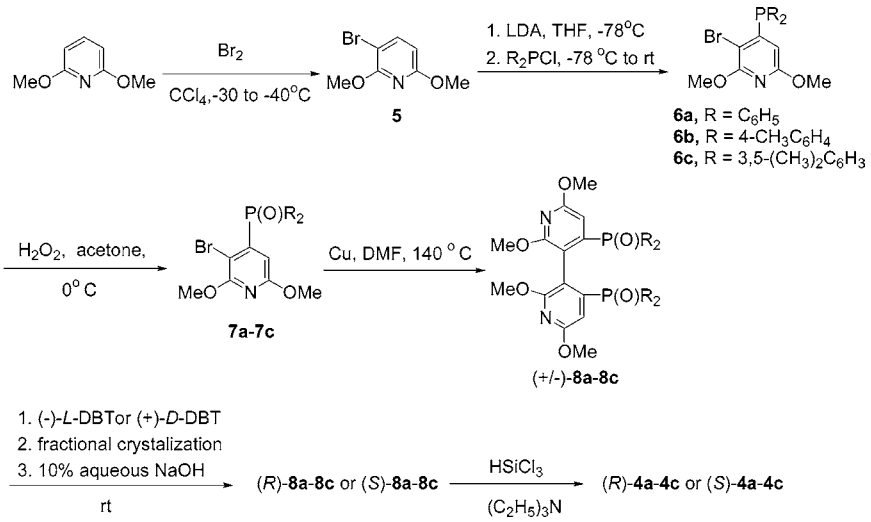


Asymmetric Catalytic Hydrogenations

Catalytic asymmetric hydrogenation is probably the simplest and yet the most powerful and economically attractive method for the production of amino acid derivatives, chiral amines, chiral alcohols, etc., which comprise a large proportion of enantiomerically pure pharmaceuticals. By utilization of various catalyst systems based on the P-Phos family of ligands, a broad scope of unsaturated substrates can be hydrogenated with high ee's, which clearly shows the versatility of this new class of ligands.

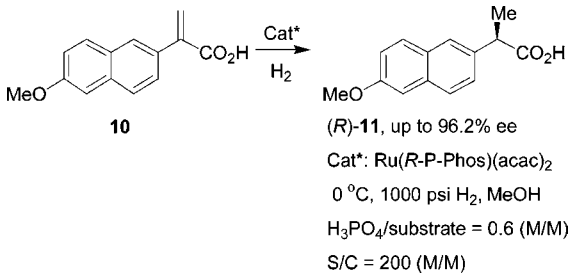
Hydrogenation of Prochiral Olefins. 2-(6′-Methoxy-2′-naphthyl)propenoic Acid. P-Phos was highly effective in the Ru-catalyzed asymmetric hydrogenation of 2-(6′-

Scheme 1. The Synthetic Route toward 4a−4c



methoxy-2′-naphthyl)propenoic acid **10** leading to a highly valued antiinflammatory drug naproxen **11** (Scheme 3).[11]

Scheme 3. Hydrogenation of 2-(6′-Methoxy-2′-naphthyl)propenoic Acid Leading to Naproxen



Higher initial hydrogen pressure and lower reaction temperature were beneficial for the enhancement of the enantioselectivity. Besides, the ee was increased by 1−2% upon the addition of 0.6 equiv of phosphoric acid to the reaction mixture. Thus, when Ru(P-Phos)(acac)$_2$ complex was used as catalyst, the best result was achieved in up to 96.2% ee, which was superior to that obtainable with the corresponding Ru(BINAP) system (94.8% ee) in a side-by-side comparison study.

(*Z*)-β-Aryl-Substituted α-(Acylamino)acrylates. In the past three decades, Rh-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids and their esters has been developed to be a standard procedure for the synthesis of optically active α-amino acids with high enantioselectivities.[1,2a] Nevertheless, the corresponding chemistry mediated by ruthenium catalysts has been relatively less investigated,[16] although ruthenium catalysts were widely applied in the enantioselective hydrogenation of other types of substrates.

The parent ligand P-Phos proved to be more efficacious than its analogues in the Ru-catalyzed low-pressure hydrogenation of (*Z*)-β-aryl-substituted α-(acylamino)-acrylates **12** (Scheme 4) in methanol, affording a multitude of α-amino acid derivatives **13** with 90−97% ee.[17]

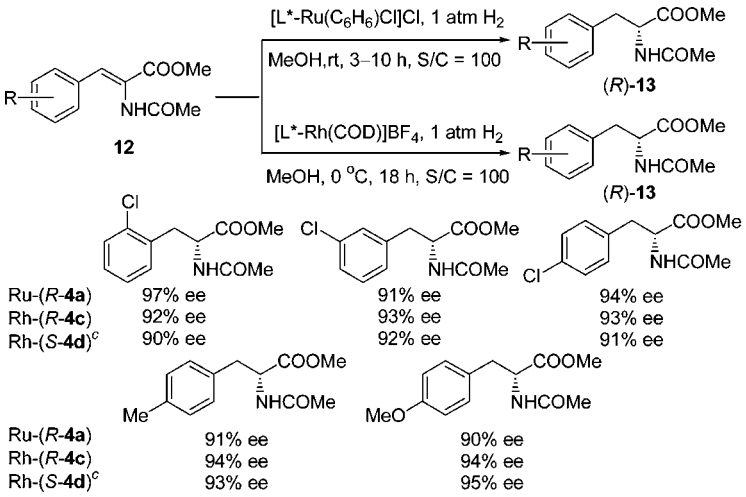
In contrast, in the same hydrogenation reactions catalyzed by cationic Rh(I) complexes ligated by **4a**−**4c**, a sterically more encumbered catalyst was required for higher enantioselectivities. Quantitative yield of products could be easily realized in a range of common organic solvents, while methanol was found to be the most suitable solvent. Therefore, a number of methyl (*Z*)-2-acetamidocinnamate derivatives **12** were hydrogenated quantitatively with consistently high enantioselectivities (92−94% ee) in methanol for 18 h by using Rh-(*R*-Xyl-P-Phos) as catalyst at 0 °C under 1 atm hydrogen pressure.

To evaluate the efficacy of Cy-P-Phos **4d**, this ligand was also applied to the Rh-catalyzed asymmetric hydrogenation of **12**.[15] Under the aforementioned preferred conditions as in the employment of **4a**−**4c**, **4d** possessed similar enantioselectivity but substantially higher activity as compared to the optimal ligand **4c**. In addition, acetone appeared to be the best choice of solvent, although the reactions could proceed smoothly in an assortment of aprotic or protic organic solvents.

(*Z*)-β-Alkyl-Substituted β-(Acylamino)acrylates. Recently, the asymmetric hydrogenation of β-(acylamino)-acrylates as one of the most facile methods for the preparation of β-amino acids has gained considerable attention. By use of chiral diphosphine−rhodium complexes (such as Rh complexes of BICP, DuPhos, MiniPhos, BDPMI, and TangPhos) in the catalytic enantioselective hydrogenation of β-alkyl-substituted β-(acylamino)acrylates, good to excellent ee's have been attained.[2a,18a] However, the studies on ruthenium-catalyzed hydrogenation of this type of prochiral substrates are comparatively limited. A few such substrates have been examined by Noyori and co-workers[18b] based on the Ru(OCOCH$_3$)$_2$-(BINAP) catalyst system, and the highest ee for the (*E*)-isomers of substrates was 96%.

In terms of both activity and enantioselectivity, Ru complexes of the P-Phos series displayed remarkably better utility in the enantioselective hydrogenation of (*E*)-**14** than the corresponding Rh complexes irrespective of the ligand incorporated (Scheme 5).[19] Interestingly, opposite enantiomers of hydrogenation products **15** were furnished, respectively, by Ru and Rh complexes with an identical chiral ligand. In the cases of Ru catalysts, the sterically hindered ligand provided higher ee's and reac-

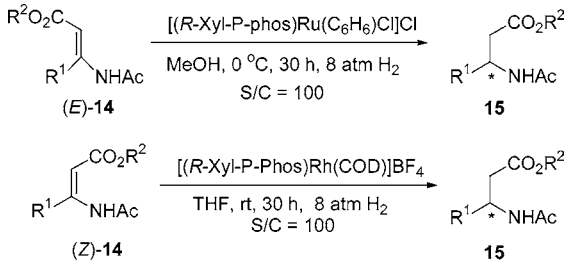
Scheme 4. Hydrogenation of (*Z*)-β-Aryl-Substituted α-(Acylamino)acrylates



cat*	conv. (%)[a]	ee (%)[a]
Ru-(*R*-**4a**)	>99.9	90
R-**4b**	>99.9	85
R-**4c**	64	73
Rh-(*R*-**4a**)	>99.9	38
R-**4b**	70	46
R-**4c**	>99.9	90 (93)[b]
S-**4d**	>99.9	90 (97)[c]

[a] rt, 2–3 h. [b] 0 °C, 18 h. [c] Reaction in acetone, 0 °C, 8 h

Scheme 5. Hydrogenation of β-Alkyl-Substituted β-(Acylamino)acrylates



Substrate	R^1	R^2	ee(%)[a]	ee(%)[b]
14a	Me	Et	97.9 (*S*)	68.3 (*R*)
14b	Me	Me	98.1 (*S*)	71.9 (*R*)
14c	Et	Me	98.2 (*S*)	79.7 (*R*)
14d	*i*-Pr	Me	98.3 (*R*)	82.3 (*S*)
14e	*n*-Pr	Et	98.5 (*S*)	78.5 (*R*)
14f	*t*-Bu	Me	99.7 (*R*)	–

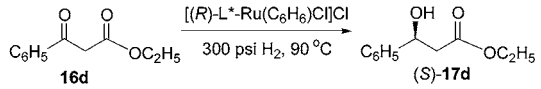
[a] (*E*)-**14** as substrates. [b] (*Z*)-**14** as substrates.

tion rates. In a like fashion for Ru-catalyzed hydrogenation of α-dehydroamino acids, the reaction was strongly solvent-dependent, and methanol was found to be the best choice of solvent. Hence, a diverse selection of β-amino acid derivatives of extremely high enantiopurities (97.9−99.7%) were obtained by using Ru-Xyl-P-Phos catalyst under the preferred conditions. To the best of our knowledge, these results, along with those from the Ru complexes containing a bridged C_2-symmetric biphenyl phosphine,[20] represent the best enantioselectivities obtained by using Ru catalysts in the hydrogenation of this type of substrates.

Regarding the hydrogenation of (*Z*)-isomers of **14**, the enantioselectivity of Ru-Xyl-Phos complex in methanol was markedly inferior to that for the (*E*)-isomers under otherwise identical conditions. Rh complexes compared more favorably than Ru complexes in this transformation. Likewise, Rh and Ru complexes with the same enantiomer of ligands have an opposite sense of asymmetric control. THF was the preferred solvent in the Rh-catalyzed reactions.

Hydrogenation of Ketones. Functionalized Ketones: β-Ketoesters. The excellent chiral recognition ability of a vast spectrum of Ru−biarylbisphosphine catalysts can be evinced by the hydrogenation of β-ketoesters to afford optically active β-hydroxy carboxylic esters,[2a,2c] which are important synthetic intermediates of various bioactive compounds, such as carbacephem antibiotics.[21,22] Several different Ru complexes with P-Phos family ligands have been employed in this process, and high enantioselectivities (up to 99%) were accomplished (Schemes 6 and 7).[11b,12,13]

Scheme 7. Studies on the Activity and Air Stability of Ru-(P-Phos) Catalysts

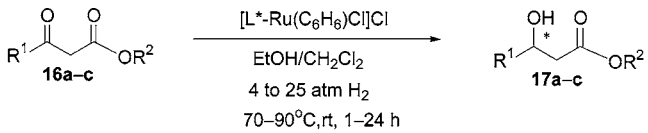


recction conditions	P-Phos ee% (time, conv.%)	Tol-P-Phos ee% (time, conv.%)	Xyl-P-Phos ee% (time, conv.%)	BINAP ee% (time, conv.%)
A[a,b] S/C = 800	96.1 (3h, 100) —(2h, 96.8)	96.2 (2h, 100) —(1.5h, 95.4)	**96.2** (2h, 100) —(1.5h, 98.4)	92.6 (2h, 98.6)
B[b,c] S/C = 7500	90.6 (15h, 84)	91.3 (15h, 90)	93.2 (15h, 98)	
C[a,d] S/C = 800	95.5 (3h, 98.6)	96.4 (2h, 100)	**96.1** (2h, 100)	90.0 (3h, 100)
D[a,e] S/C = 800	93.9 (3h, 94.4)	95.7 (3h, 100)	**95.5** (2h, 100)	66.6 (3h, 95.5)

[a] 200 mg substrate, 1.73 M in EtOH/CH_2Cl_2. [b] N_2 atmosphere. [c] 30 g substrate, 4.11 M in EtOH/CH_2Cl_2. [d] System without being degassed or dried . [e] Catalyst solution was exposed to air for 10 h prior to the reaction.

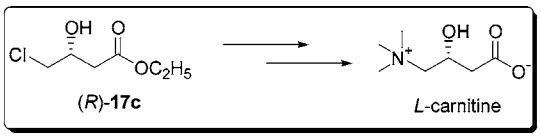
In the hydrogenation of substrate **16c** bearing a chloride atom at the contiguous site of the carbonyl group, Ru−BINAP failed to give desired product **17c** in satisfactory enantiopurity at room temperature, probably due to the competitive coordination of the ester group and the halogen atom. Surprisingly, higher temperature (100 °C) led to excellent chiral efficiency (97% ee) under 100 atm H_2 pressure.[23] In contrast, the employment of Ru complexes of P-Phos[11b] or Tol-P-Phos[12] furnished higher enantioselectivity (98% ee) under milder conditions (80 °C, 4−20 atm H_2). The chiral product **17c** has been further

Scheme 6. Hydrogenation of β-Ketoesters



	17a	17b	17c
(*S*)-P-Phos[a]	S/C = 400, 98.6 % ee	S/C = 2800, 96.6 % ee	S/C = 2800, 98.0 % ee
(*R*)-Tol-P-Phos	S/C = 400, 98.0 % ee	S/C = 400, 98.0 % ee	S/C = 400, 97.9 % ee
(*R*)-Xyl-P-Phos	S/C = 400, 97.1 % ee	S/C = 2800, 94.5 % ee	S/C = 400, 94.8 % ee

[a] (*S*-P-Phos)-$RuCl_2$(DMF)n



applied to the practical synthesis of L-carnitine (Scheme 6), an important agent responsible for the transport of long-chain fatty acid through human metabolism.[23]

Activity and Air Stability of the Ru-(P-Phos) Catalyst System.[12,13] The hydrogenation of **16d** leads to a useful pharmaceutical intermediate, (*S*)-3-hydroxy-3-phenyl propionate (**17d**).[24] Ru-BINAP showed only moderate enantioselectivity for this kind of β-aryl-β-ketoesters (85% ee),[25] unlike its generally excellent performance for β-alkyl-β-ketoester substrates. Gratifyingly, excellent activity and enantioselectivity were achieved by using Ru-(P-Phos) complexes (Scheme 7). In the presence of Ru(*R*-Xyl-P-Phos)$(C_6H_6)Cl_2$, the reaction with a substrate-to-catalyst molar ratio (S/C) of 800 was completed in 2 h, giving the desired product in up to 96.2% ee.[13] Even with a substrate-to-catalyst ratio as high as 7500, the hydrogenation can be conveniently conducted on a 30 g substrate scale leading to 98% conversion within 15 h with the retention of high enantioselectivity (93.2% ee).

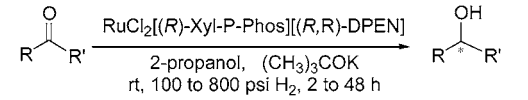
Besides the enantioselectivity, reactivity, and productivity, which are important factors of consideration in determining the commercial feasibility of a reaction, other desirable features of a good catalyst system include the ease of catalyst preparation and handling as well as the operational simplicity of the experimental procedures. A frequently encountered problem associated with the use of metal phosphine catalysts is that most of them are air sensitive, especially in solution, and trace amounts of air in the reaction system may often deactivate the catalysts and thus make irreproducible results. This problem is even more severe in industrial applications in which the rigorous degassing of the reaction system with N_2 is frequently more difficult than in the laboratory-scale operations. To our delight, Ru complexes of the P-Phos family of ligands have been found to be highly air stable. When experimental procedures prior to the charging of hydrogen were performed in air and solvents without predegassing and drying, or even when the catalyst solution was exposed to air for 10 h before its application, both the catalyst activity and enantioselectivity for the hydrogenation of **16d** remained unchanged (Scheme 7, >94% conversion, 94.4−96.4% ee) from the air-proved system (96.2% ee), while the ee obtained from Ru(*R*-BINAP)-$(C_6H_6)Cl_2$ catalyst precursor, in a side by side comparison study, sharply dropped from 92.0% to 66.6%.

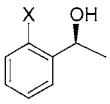
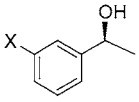
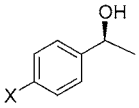
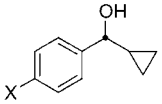
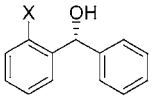
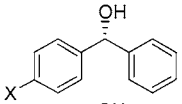
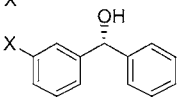
Simple Ketones. The catalytic asymmetric hydrogenation of prochiral ketones provided an excellent path for the synthesis of enantiomerically pure secondary alcohols. An important breakthrough in this area was achieved by Noyori and co-workers using a XylBINAP/DAIPEN/Ru complex (DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine) in conjunction with an inorganic base in 2-propanol in the hydrogenation of an extensive range of unfunctionalized ketones.[21]

During the course of our studies to broaden the application scope of P-Phos ligands, we attempted to employ a substantially less expensive chiral diamine, DPEN (1,2-diphenylethylenediamine), instead of the expensive fancy diamine DAIPEN. The preformed complex *trans*-[$RuCl_2${(*R*)-Xyl-Phos}{(*R*,*R*)-DPEN}] proved to be an extremely versatile catalyst precursor for the asymmetric hydrogenation of a wide spectrum of prochiral ketones.[26] The reactions worked efficiently at room temperature under atmospheric to 600 psig hydrogen pressure in 2-propanol containing an alkaline base such as *t*-BuOK or K_2CO_3. The use of chiral Xyl-P-Phos generally provided far more favorable ee's to those obtainable with the parent ligand P-Phos or Tol-P-Phos.

Schemes 8 and 9 reveal a broad spectrum of ring-substituted acetophenones, *ortho*-substituted unsymmetrical benzophenones, substituted phenyl cyclopropyl ketones, α,β-unsaturated ketones, and heteroaromatic methyl ketones that are tolerated by the catalyst system in the rapid and productive access to multifarious chiral secondary alcohols with consistently excellent enantiopurities (up to >99.9%) even with S/C ratios as high as 100 000. Particularly noteworthy was the observation that the Xyl-P-Phos-Ru-DPEN catalyst was air stable even in solution, which highlighted its attractive attributes from the viewpoint of practical applications.

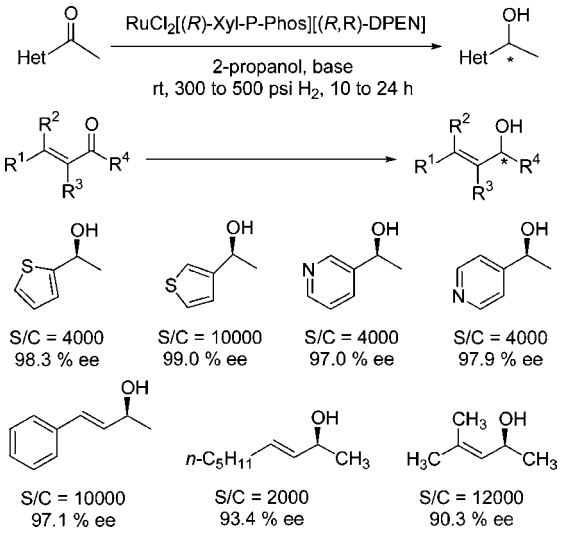
Scheme 8. Hydrogenation of Aromatic Ketones, Cyclopropyl Ketones, and Unsymmetrical Benzophenones



alcohol	X	S/C	ee (%)
	H	**100,000**	**99.1**
	Me	4000	97.7
	OMe	4000	93.3
	Br	10000	**>99.9**
	Me	12000	97.7
	OMe	4000	98.8
	Br	4000	99.5
	Me	20000	98.8
	OMe	20000	98.7
	Br	50000	**>99.9**
	CF_3	12000	97.7
	H	5000	97.6
	OMe	1000	96.1
	F	2000	92.0
	Cl	5000	92.3
	Me	2000	95.9
	F	2000	97.6
	Cl	10000	97.4
	Me	2000	3.9
	Cl	2000	47.3
	CF_3	2000	77.2
	Me	2000	43.2

Hydrogenation of Quinolines with Recoverable Catalysts. The catalytic asymmetric hydrogenation of easily accessible and less expensive quinoline derivatives is doubtless the most direct and convenient access toward enantiomerically enriched tetrahydroquinoline derivatives,

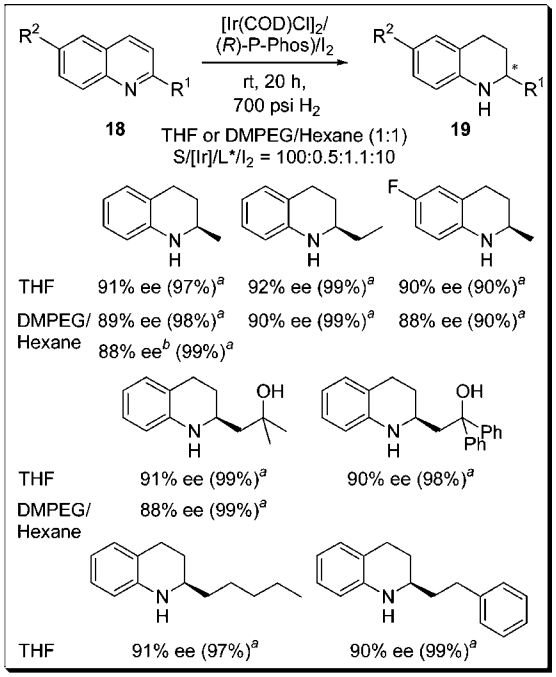
Scheme 9. Hydrogenation of Heteroaromatic Methyl Ketones and α,β-Unsaturated Ketones



which are significant synthetic intermediates for biologically active compounds.[27] Reports on this methodology are rather scarce. Zhou and co-workers recently discovered that iridium complexes bearing MeO-BIPHEP or ferrocenyloxazoline-derived P,N-ligand performed effectively for this conversion into optically active tetrahydroquinolines containing a chiral carbon at the 2-position.[28]

Iridium complex generated in situ from $[Ir(COD)Cl]_2$ and P-Phos in combination with 0.1 equiv of I_2 in THF served as a highly efficient catalyst system for the hydrogenation of this class of challenging substrates, **18**, at room temperature (Scheme 10),[29] furnishing hydrogenation products **19** in 90−92% ee. In the meanwhile, we were delighted to find that the Ir-(P-Phos) catalyst was particularly robust and air stable. No variation was detected in the ^{31}P NMR spectrum of the catalyst solution even after 2 weeks in air. The reactivity and enantioselectivity for the hydrogenation of 2-methylquinoline were virtually retained notwithstanding the catalyst solution being exposed to air for 24 h. In contrast, sharp diminutions both in conversion (from 99% to 21%) and in ee (from 94% to 28%) occurred if Ir-(MeO-BIPHEP) was used under the same conditions.

Scheme 10. Hydrogenation of Quinolines



[a] Data in parenthesis were isolated yields. [b] Data obtained with the catalyst reused for eight times.

Given the high efficiency and the air stability of the Ir-(P-Phos) catalyst system, we have further explored the recyclability of this catalyst using 2-methylquinoline as a model substrate. By use of a two-phase reaction medium, 1:1 mixture of hexane and poly(ethylene glycol) dimethyl ether (DMPEG), complete conversion and high enantioselectivity were essentially maintained (89% ee vs 91% ee in THF). Most importantly, the product was conveniently separated by simple decantation of the hexane layer. Upon extraction of the product residue with hexane, the DMPEG phase encompassing the Ir-(P-Phos) catalyst could be reused. In a catalyst-reusability study, we observed essentially no loss of ee after eight times of recycle.[29]

Asymmetric Catalytic Hydrosilylation of Simple Ketones

The development of asymmetric hydrosilylation of prochiral ketones as a desirable alternative to asymmetric hydrogenation could be highly rewarding due to the mild reaction conditions employed and the technical simplicity. However, the high cost of catalyst and the low substrate-to-catalyst ratio (50−500) rendered previous hydrosilylation work not competitive with hydrogenation.[30]

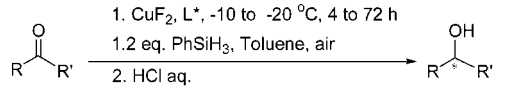
By using Buchwald's protocol for conjugate reduction,[31] Lipshutz and co-workers disclosed a highly active $Cu^{I}Cl$/diphosphine [e.g., 3,5-xyl-MeO-BIPHEP or DTBM-SEGPHOS]/*t*-BuONa/polymethylhydrosiloxane (PMHS) system for the enantioselective hydrosilylations of both aryl alkyl and heteroaromatic ketones even at a substrate-to-ligand ratio (S/L) of over 100 000.[32] Very recently, they also described a robust $Cu(OAc)_2 \cdot H_2O$/DTBM-SEGPHOS/PMHS hydrosilylation system (CuH in a bottle),[33] which furnished a new opportunity for asymmetric hydrosilylation in consideration of practical applications.

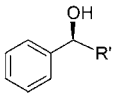
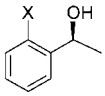
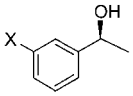
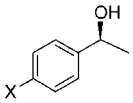
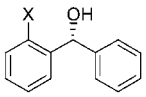
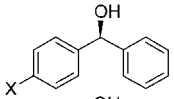
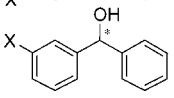
At the time that we initiated our investigation in this area, we noted an air-accelerated and base-free CuF_2/BINAP/$PhSiH_3$ system demonstrated by Riant et al., which catalyzed the hydrosilylation of some aryl alkyl ketones in moderate to good ee's at lower S/L ratios of 100−200 under ambient conditions.[34]Although the mechanism of this air-accelerated system remained elusive at that stage, it appeared that air played a key role in the formation of the active catalyst precursor during the catalytic cycle, and the much less air-sensitive diphosphine ligands would therefore be very crucial to the generation of the active catalyst systems. We consequently conjectured that our P-Phos-type ligands embracing unique air stability might be especially suited for this important reaction.

Much to our delight, the dipyridylphosphine/CuF_2/$PhSiH_3$ system served as an extraordinarily efficient system

rendering competitive levels of enantioselectivities of up to 97% ee for the hydrosilylation of *meta*- and *para*-substituted acetophenones (Scheme 11).[35] Moreover, the

Scheme 11. Hydrosilylation of Simple Ketones



alcohol	X or R'	S/L	(*S*)-Xyl-P-Phos ee (%)	(*S*)-P-Phos ee (%)
	Me	100	87	89
	Et	100	93	
	Me	100	72	
	Cl	100	77	
	Br	100	70	
	Me	100	87	
	OMe	100	92	
	Br	100	89	
	CF_3	100	91	
	Me	100	91	
	Cl	100	94	
	Br	100	96	
	Br	**50000**	93	
	CF_3	100	94	96
	NO_2	100	**97**	
	NO_2	50000	93	
	NO_2	**100,000**	90 (rt)	
	Me	25	83	75
	F	25	63	75
	Cl	25	91	90
	CF_3	25	95	**98**
	Me	25	39	27
	Cl	25	43	36
	CF_3	25	41	25
	Me	25	6	

excellent practical viability of this catalyst system was evinced by its remarkably high activities (S/L ratio up to 100 000) and very mild reaction conditions such as normal atmosphere, moderately low temperatures (ambient temperature to −20 °C) and compatibility with traces of moisture.

Polymethylhydrosiloxane (PMHS) is an attractive reducing reagent for environmentally benign reductive processes since it is inexpensive, nontoxic, and stable to air and moisture.[36] In light of this, we also probed the efficiency of the present catalyst system by switching the hydride source from $PhSiH_3$ to PMHS. The sense of enantioselective induction appeared to be independent of silane irrespective of the use of P-Phos or Xyl-P-Phos, but PMHS was less reactive than $PhSiH_3$. For instance, when the hydrosilylation of acetophenone was carried out with 1 mol % CuF_2 and 0.05 mol % (*S*)-Xyl-P-Phos with 1.2 equiv of $PhSiH_3$ at room temperature under air atmosphere, complete conversion was observed in 10 min with 76.7% ee, whereas, in the case of PMHS, 76.8% conversion was achieved within 25 min with 75.3% ee under otherwise identical conditions.

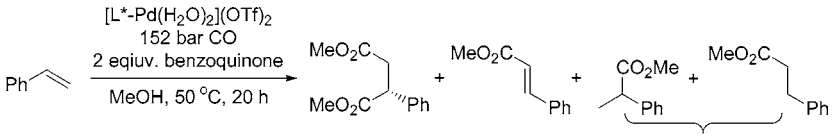
In addition, the enantioselective hydrosilylation of unsymmetrical diaryl ketones to benzhydrol had remained a formidable challenge, and the highest enantioselectivity reported in the literature prior to our study was around 20%.[37] In this regard, the P-Phos catalyst system was found to be surprisingly effective in the stereoselective hydrosilylation of *ortho*-substitued benzophenones with good to excellent ee's (up to 98%, Scheme 11). As expected, because of the lack of steric bias, *meta*- and *para*-substituted benzophenones were converted to the corresponding alcohols in low to moderate ee's.

Asymmetric Catalytic C−C Bond Formation

Bis-alkoxycarbonylation of Styrene. Pd(II)-catalyzed asymmetric bis-alkoxycarbonylation of styrene for the synthesis of optically active butanedioic acid derivatives with high chemoselective, enantioselective control, or both represents a significant challenge.[38] Hydrated palladium(II) triflate complexes containing the (*R*)-P-Phos family of ligands have been synthesized and applied to this reaction as depicted in Scheme 12.[39] With the use of 0.8 mol % of catalyst and 2 equiv of benzoquinone (as oxidant), the reaction was carried out in methanol under 152 bar initial CO pressure with 56−67% conversion. The best chemoselectivity of 79% and enantioselectivity of 84% for the desired product dimethyl-2-phenylsuccinate (DMPS) was achieved in the presence of chiral P-Phos with a catalyst loading of 1.6% mol.

1,4-Addition of Boronic Acids to α,β-Unsaturated Ketones. Since Hayashi et al. reported the first asymmetric version of 1,4-addition of organoboronic acids to α,β-unsaturated ketones mediated by rhodium(I)-BINAP catalyst,[40] impressive chemical yields and enantioselectivities have also been observed in reactions involving a variety

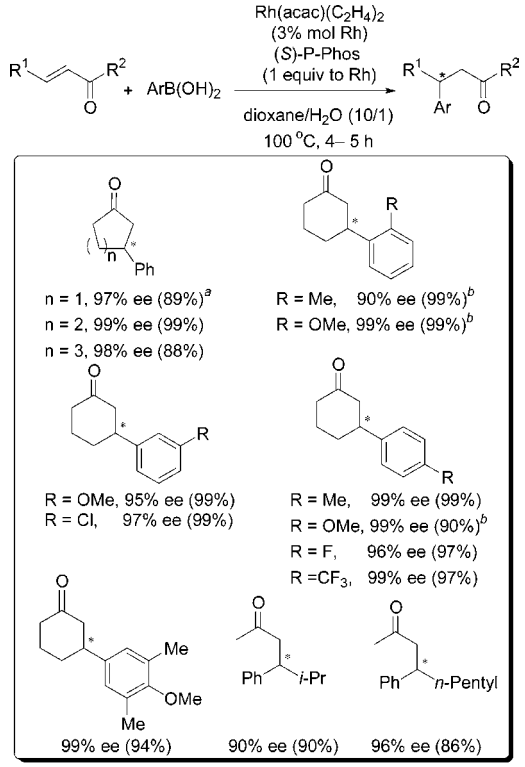
Scheme 12. Asymmetric Bis-alkoxycarbonylation of Styrene



	S/C		DMPS	MC	MP
(*R*)-P-Phos	125	67% conv.	71% (83% ee)	20%	2.7%
(*R*)-P-Phos	63	67% conv.	**79**% (**84**% ee)	18%	1.5%
(*R*)-Tol-P-Phos	125	58% conv.	52% (82% ee)	24%	4.4%
(*R*)-Xyl-P-Phos	125	56% conv.	42% (82% ee)	28%	1.7%

of other electron-deficient olefins.[41] [Rh(acac)((*S*)-P-Phos)] complex, generated in situ from equimolar of Rh(acac)-$(CH_2{=}CH_2)_2$ and (*S*)-P-Phos in dioxane/H_2O (10/1) at 100 °C, has also been found to be well-suited for this transformation (Scheme 13).[42] In the presence of excess of

Scheme 13. 1,4-Addition of Boronic Acids to α,β-Unsaturated Ketones



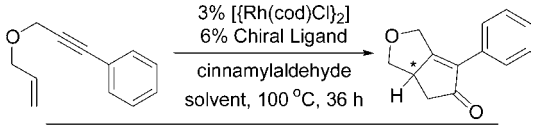
[a] Data in parenthesis were isolated yields. [b] dioxane/H_2O = 20:1

arylboronic acids (1.4−5.0 equiv), a vast selection of aryl groups with either electron-donating or electron-withdrawing substituents on the *ortho*-, *meta*- or *para*-position have been readily incorporated onto the β-position of several kinds of cyclic and acyclic enones with exceptionally good yields and ee's (up to 99%) in most cases, which are either comparable to or better than the relevant Rh−BINAP system.

Asymmetric Aqueous Pauson−Khand-Type Reaction. Extensive efforts have been devoted to the asymmetric transition-metal-catalyzed/mediated [2 + 2 + 1] carbonylative cycloaddition of an alkene and an alkyne (Pauson−Khand-type reaction or PKR), which offers an excellent opportunity for the preparation of various optically active cyclopentenones.[43] Nevertheless, no catalytic asymmetric aqueous PKR systems had been developed prior to our study. Recently, we discovered that P-Phos was highly effective in an interesting rhodium-catalyzed PKR in the use of aldehydes as nontoxic "carbon monoxide" reagents and water as the only solvent without a surfactant. Interestingly, this protocol allowed the handling of both the catalyst and the reactants under air without special precautions.[44]

The higher concentration of reactants in conventional organic solvents proved to offer higher rates in the PKR. This significant finding prompted us to use water as the sole solvent, which was expected to increase the effective concentration of the reactants according to the aqueous micellar concept[45] and thereby to accelerate the reaction. In this regard, we found water to be much more conducive than organic solvents for higher reactivity and ee's (Scheme 14). P-Phos displayed far superior efficacy to the other

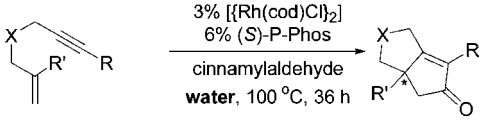
Scheme 14. Ligand and Solvent Effects on the Asymmetric Pauson−Khand-Type Reaction

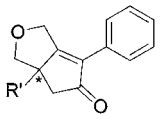
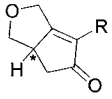
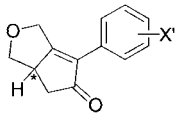
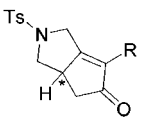
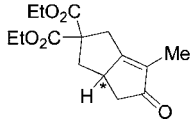


ligand*	solvent	yield (%)	ee (%)
P-Phos	toluene	65	80
P-Phos	dioxane	63	74
P-Phos	DMF	6	0
P-Phos	water	**82**	**84**
BINAP	water	23	61
tol-BINAP	water	33	79
Et-DuPHOS	water	5	22
PHANEPHOS	water	6	15
FerroTANE	water	21	30

screened chiral ligands.[46] Aldehydes as CO surrogates also appeared influential in determining both optical and chemical outcomes, and cinnamylaldehyde gave the best results among the aldehydes examined. Additionally, these attractive aqueous PKR conditions were also well-adapted to a broad assortment of other oxygen-, nitrogen-, and carbon-tethered enynes providing excellent isolated yields in most cases and 74−95% ee (Scheme 15).

Scheme 15. Asymmetric Catalytic Pauson−Khand-Type Reactions



product	R, R', X or X'	yield (%)	ee (%)
	H	82	84
	Me	71	90
	Me	82	**95**
	Et	60	**95**
	*o*-Me	49	74
	m-OMe	88	81
	p-F	90	82
	p-Cl	91	77
	p-Me	92	88
	p-OMe	93	93
	Ph	96	80
	Me	98	88
		91	77

Conclusions

In conclusion, during the past several years, we have established that atropisomeric dipyridylphosphine P-Phos family of ligands served as highly effective and versatile ligands for an array of transition-metal-catalyzed asymmetric reactions including the hydrogenation of structurally diverse unsaturated compounds, hydrosilylation of simple ketones, bis-alkoxycarbonylation of styrene, 1,4-addition of organoboronic acids to α,β-unsaturated ketones, and aqueous Pauson−Khand-type reactions. Desirable attributes, such as air stability, broad substrate scope, fast rates of reaction, excellent enantioselectivities, low catalyst loading, and mild reaction conditions, rendered the catalysts based on the P-Phos family of ligands excellent choices for practical applications.

We are deeply indebted to a highly talented group of co-workers whose names are in the relevant references. We also thank the University Grants Committee Areas of Excellence Scheme in Hong Kong (Grant AoE P/10-01), the Hong Kong Research Grants Council (Project Number N_PolyU 506/04), and the Hong Kong Polytechnic University Area of Strategic Development Fund for financial support.

References

(1) (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley & Sons: New York, 2000. (b) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds. *Comprehensive Asymmetric Catalyses*; Springer: Berlin, 1999. (c) Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; Wiley & Sons: New York, 2001.

(2) For some recent reviews, see: (a) Tang, W.; Zhang, X. New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003**, *103*, 3029−3070. (b) Shimizu, H.; Nagasaki, I.; Saito, T. Recent Advances in Biaryl-Type Bisphosphine Ligands. *Tetrahedron* **2005**, *61*, 5405−5432.

(3) BINAP = 2,2-bis(diphenylphosphanyl)-1,1-binaphthyl; BIPHEMP = (6,6′-dimethylbiphenyl-2,2′-diyl)bis(diphenylphosphine); MeO-BIPHEP = (6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine).

(4) tetraMe-BITIANP = 2,2′-bis(diphenylphosphino)-4,4′,6,6′-tetramethyl-3,3′-bibenzo[*b*]thiophene; tetraMe-BITIOP = 2,2′,5,5′-tetramethyl-4,4′-bis(diphenylphosphino)-3,3′-bithiophene; N-Me-2-BINP = 3,3′-bis(diphenylphosphino)-1,1′-dimethyl-2,2′-biindole. (a) Benincori, T.; Brenna, E.; Sannicolò, F.; Trimarco, L.; Antognazza, P.; Cesarotti E. (Diphenylphosphino)-Biheteroaryls: The First Example of a New Class of Chiral Atropisomeric Chelating Diphosphine Ligands for Transition Metal Catalysed Stereoselective Reactions. *J. Chem. Soc., Chem. Commun.* **1995**, 685−686. (b) Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicolò, F. 2,2′,5,5′-Tetramethyl-4,4′-bis(diphenylphoshino)-3,3′-bithiophene: A New, Very Efficient, Easily Accessible, Chiral Biheteroaromatic Ligand for Homogeneous Stereoselective Catalysis. *J. Org. Chem.* **2000**, *65*, 2043−2047. (c) Benincori, T.; Piccolo, O.; Rizzo, S.; Sannicolò, F. 3,3′-Bis(diphenylphosphino)-1,1′-disubstituted-2,2′-biindoles: Easily Accessible, Electron-Rich, Chiral Diphosphine Ligands for Homogeneous Enantioselective Hydrogenation of Oxoesters. *J. Org. Chem.* **2000**, *65*, 8340−8347.

(5) Spino, C.; Mayes, N.; Desfossés, H.; Sotheeswaran, S. Enantioselective Synthesis of (+)- and (−)-Dihydrokawain. *Tetrahedron Lett.* **1996**, *37*, 6503−6506.

(6) (a) Tietze, L. F.; Thede, K.; Sannicolò, F. Regio- and Enantioselective Heck Reactions of Aryl and Alkenyl Triflates with the New Chiral Ligand (*R*)-BITIANP. *Chem. Commun.* **1999**, 1811−1812. (b) Tietze, L. F.; Thede, K.; Schimpf, R.; Sannicolò, F. Enantioselective Synthesis of Tetrahydroisoquinolines and Benzazepines by Silane Terminated Heck Reactions with the Chiral Ligands (+)-TMBTP and (*R*)-BITIANP. *Chem. Commun.* **2000**, 583−584.

(7) Au-Yeung, T. T.-L.; Chan, A. S. C. Biheteroaromatic Diphosphines and Their Transition Metal Complexes: Synthesis, Characterisation and Applications in Asymmetric Catalysis. *Coord. Chem. Rev.* **2004**, *248*, 2151−2164.

(8) Chan, A. S. C.; Chen, C.-C.; Cao, R. New Rhodium Pyridylphosphine Complexes and Their Application in Hydrogenation Reactions. *Organometallics* **1997**, *16*, 3469−3473.

(9) Kurtev, K.; Ribola, D.; Jones, R. A.; Cole-Hamilton, D. J.; Wilkinson, G. Tris(2-pyridyl)phosphine Complexes of Ruthenium(II) and Rhodium(I). Hydroformylation of Hex-1-ene by Rhodium Complexes. *J. Chem. Soc., Dalton Trans.* **1980**, 55−58.

(10) (a) Hu, W.; Pai, C. C.; Chen, C. C.; Xue, G.; Chan, A. S. C. Synthesis of a Chiral Pyridylphosphine Ligand and a Comparison of Its Rhodium Complex with the Structurally Similar Arylphosphine Rhodium Catalysts in the Asymmetric Hydrogenation of 2-(6′-Methoxy-2′-naphthyl)propenoic Acid. *Tetrahedron: Asymmetry* **1998**, *9*, 3214−3246. (b) Hu, W.; Chen, C. C.; Xue, G.; Chan, A. S. C. Synthesis of (−)-(4*R*,5*R*)-4,5-Bis[di-3′-(2′,6′-dimethoxypyridyl)-phosphinomethyl]-2,2-dimethyl-1,3-dioxolane and Its Application in the Rh-Catalyzed Asymmetric Hydrogenation Reactions. *Tetrahedron: Asymmetry* **1998**, *9*, 4183−4192.

(11) (a) Chan, A. S. C.; Pai, C.-C. Chiral Pyridylphosphines and Their Application in Asymmetric Catalytic Hydrogenation of 2-Arylpropenoic Acids. U.S. Patent 5,886,182, 1999. (b) Pai, C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C.; Wong, W. T. Highly Effective Chiral Dipyridylphosphine Ligands: Synthesis, Structural Determination, and Applications in the Ru-Catalyzed Asymmetric Hydrogenation Reactions. *J. Am. Chem. Soc.* **2000**, *122*, 11513−11514.

(12) Wu, J.; Chen, H.; Zhou, Z.-Y.; Yeung, C.-H.; Chan, A. S. C. Synthesis and Structural Characterization of a Highly Effective Chiral Dipyridylphosphine Ligand and Its Application in the Ru-Catalyzed Asymmetric Hydrogenation of β-Ketoesters. *Synlett* **2001**, 1050−1054.

(13) Wu, J.; Chen, H.; Kwok, W.-H.; Lam, K.-H.; Zhou, Z.-Y.; Yeung, C.-H.; Chan, A. S. C. A New Chiral Dipyridylphosphine Ligand Xyl-P-Phos and Its Application in the Ru-Catalyzed Asymmetric Hydrogenation of β-Ketoesters. *Tetrahedron Lett.* **2002**, *43*, 1539−1543.

(14) (a) 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 and references therein. (b) Yin, J.; Buchwald, S. L. A Catalytic Asymmetric Suzuki Coupling for the Synthesis of Axially Chiral Biaryl Compounds. *J. Am. Chem. Soc.* **2000**, *122*, 12051−12052.

(15) Wu, J.; Au-Yeung, T. T.-L.; Kwok, W.-H.; Ji, J.-X.; Zhou, Z.-Y.; Yeung, C.-H.; Chan, A. S. C. A Convenient Synthesis of 2,2′,6,6′-Tetramethoxy-4,4′-bis(dicyclohexylphosphino)-3,3′-bipyridine (Cy-P-Phos): Application in Rh-Catalyzed Asymmetric Hydrogenation of α-(Acylamino)acrylates. *Adv. Synth. Catal.* **2005**, *347*, 507−511.

(16) Kitamura, M.; Tsukamoto, M.; Bessho, Y.; Yoshimura, M.; Kobs, U.; Widhalm, M.; Noyori, R. Mechanism of Asymmetric Hydrogenation of α-(Acylamino)acrylic Esters Catalyzed by BINAP-Ruthenium(II) Diacetate. *J. Am. Chem. Soc.* **2002**, *124*, 6649 and references therein.

(17) Wu, J.; Pai, C.-C.; Kwok, W. H.; Guo, R. W.; Au-Yeung, T. T. L.; Yeung, C. H.; Chan, A. S. C. Studies on the Rhodium- and Ruthenium-Catalyzed Asymmetric Hydrogenation of α-Dehydroamino Acids Using a Family of Chiral Dipyridylphosphine Ligand (P-Phos). *Tetrahedron: Asymmetry* **2003**, *14* (8), 987−992.

(18) (a) (*R*,*R*)-BICP = (2*R*,2′*R*)-bis(diphenylphosphino)-(1*R*,1′*R*′)-dicyclopentane; Et-DuPHOS = 1,2-bis(2,5-diethylphospholano)benzene; MiniPHOS = 1,2-bis(alkylmethylphosphino)methanes; BDPMI = 4,5-bis(diphenylphosphanylmethyl)imidazolidin-2-ones; TangPhos = (1*S*,1*S*′,2*R*,2*R*′)-1,1′-di-*tert*-butyl-[2,2′]-diphospholanyl. (b) Lubell, W. D.; Kitamura, M.; Noyori, R. Enantioselective Synthesis of β-Amino Acids Based on BINAP−Ruthenium(II) Catalyzed Hydrogenation. *Tetrahedron: Asymmetry* **1991**, *2*, 543−554.

(19) Wu, J.; Chen, X.; Guo, R.; Yeung, C.-H.; Chan, A. S. C. Ru-Catalyzed Highly Enantioselective Hydrogenation of β-Alkyl-Substituted β-(Acylamino)acrylates. *J. Org. Chem.* **2003**, *68* (6), 2490−2493.

(20) Qiu, L.; Wu, J.; Chan, S.; Au-Yeung, T. T.-L.; Ji, J.-X.; Guo, R.; Pai, C.-C.; Zhou, Z.; Li, X.; Fan, Q.-H.; Chan, A. S. C. Remarkably Diastereoselective Synthesis of a Chiral Biphenyl Diphosphine Ligand and Its Application in Asymmetric Hydrogenation. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5815−5820.

(21) Ager, D. J.; Laneman, S. A. Reductions of 1,3-Dicarbonyl Systems with Ruthenium-Biarylbisphosphine Catalysts. *Tetrahedron: Asymmetry* **1997**, *8*, 3327−3355.

(22) 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.

(23) Kitamura, M.; Ohkuma, T.; Takaya, H.; Noyori, R. A Practical Asymmetric Synthesis of Carnitine. *Tetrahedron Lett.* **1988**, *29*, 1555−1556.

(24) Kumar, A.; Ner, D. H.; Dike, S. Y. A New Chemoenzymatic Enantioselective Synthesis of R-(−)-Tomoxetine, (*R*)- and (*S*)-Fluoxetine. *Tetrahedron Lett.* **1991**, *32*, 1901−1904.
(25) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. Asymmetric Hydrogenation of β-Keto Carboxylic Esters. A Practical, Purely Chemical Access to β-Hydroxy Esters in High Enantiomeric Purity. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858.
(26) (a) Wu, J.; Chen, H.; Kwok, W.; Guo, R.; Zhou, Z.; Yeung, C.; Chan, A. S. C. Air-Stable Catalysts for Highly Efficient and Enantioselective Hydrogenation of Aromatic Ketones. *J. Org. Chem.* **2002**, *67*, 7908−7910. (b) Wu, J.; Ji, J.-X.; Guo, R.; Yeung, C.-H.; Chan, A. S. C. Chiral [$RuCl_2$(dipyridylphosphane)-(1,2-diamine)] Catalysts: Applications in Asymmetric Hydrogenation of a Wide Range of Simple Ketones. *Chem.—Eur. J.* **2003**, *9*, 2963−2968.
(27) Katritzky, A. R.; Rachwal, S.; Rachwal, B. Recent Progress in the Synthesis of 1,2,3,4,-Tetrahydroquinolines. *Tetrahedron* **1996**, *52*, 15031−15070 and references therein.
(28) (a) Wang, W.; Lu, S.; Yang, P.; Han, X.; Zhou, Y. Highly Enantioselective Iridium-Catalyzed Hydrogenation of Heteroaromatic Compounds, Quinolines. *J. Am. Chem. Soc.* **2003**, *125*, 10536−10537. (b) Yang, P.; Zhou, Y. The Enantioselective Total Synthesis of Alkaloid (−)-Galipeine *Tetrahedron: Asymmetry* **2004**, *15*, 1145−1149. (c) Lu, S.; Han, X.; Zhou, Y. Asymmetric Hydrogenation of Quinolines Catalyzed by Iridium with Chiral Ferrocenyloxazoline Derived N, P Ligands. *Adv. Synth. Catal.* **2004**, *346*, 909−912.
(29) Xu, L.; Lam, K. H.; Ji, J.-X.; Wu, J.; Fan, Q.-H.; Lo, W.-H.; Chan, A. S. C. Air-Stable Ir-(P-Phos) Complex for Highly Enantioselective Hydrogenation of Quinolines and Their Immobilization in Poly(ethyleneglycol) Dimethyl Ether (DMPEG). *Chem. Commun.* **2005**, 1390−1392.
(30) (a) Nishiyama, H.; Itoh, K. Asymmetric Hydrosilylation and Related Reactions. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley VCH: New York, 2000; Chapter 2. (b) Carpentier, J.-F.; Bette, V. Chemo- and Enantioselective Hydrosilylation of Carbonyl and Imino Groups. An Emphasis on Non-Traditional Catalyst Systems. *Curr. Org. Chem.* **2002**, *6*, 913−936.
(31) (a) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. Asymmetric Conjugate Reduction of α,β-Unsaturated Esters Using a Chiral Phosphine-Copper Catalyst *J. Am. Chem. Soc.* **1999**, *121*, 9473−9474. (b) Hughes, G.; Kimura, M.; Buchwald, S. L. Catalytic Enantioselective Conjugate Reduction of Lactones and Lactams. *J. Am. Chem. Soc.* **2003**, *125*, 11253−11258.
(32) (a) Lipshutz, B. H.; Noson, K.; Chrisman, W. Ligand-Accelerated, Copper-Catalyzed Asymmetric Hydrosilylations of Aryl Ketones. *J. Am. Chem. Soc.* **2001**, *123*, 12917−12918. (b) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. Asymmetric Hydrosilylation of Aryl Ketones Catalyzed by Copper Hydride Complexed by Nonracemic Biphenyl Bis-Phosphine Ligands. *J. Am. Chem. Soc.* **2003**, *125*, 8779−8789. (c) Lipshutz, B. H.; Lower, A.; Noson, K. Copper(I) Hydride-Catalyzed Asymmetric Hydrosilylation of Heteroaromatic Ketones. *Org. Lett.* **2002**, *4*, 4045−4048.
(33) (a) Lipshutz, B. H.; Frieman, B. A. CuH in a Bottle: A Convenient Reagent for Asymmetric Hydrosilylations *Angew. Chem., Int. Ed.* **2005**, *44*, 6345−6348. (b) Rainka, M. P.; Aye, Y.; Buchwald, S. L. Copper-Catalyzed Asymmetric Conjugate Reduction as a Route to Novel β-Azaheterocyclic Acid Derivatives. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5821−5823.
(34) Sirol, S.; Courmarcel, J.; Mostefai, N.; Riant, O. Efficient Enantioselective Hydrosilylation of Ketones Catalyzed by Air Stable Copper Fluoride-Phosphine Complexes. *Org. Lett.* **2001**, *3*, 4111−4113.
(35) Wu, J.; Ji, J.-X.; Chan, A. S. C. A Remarkably Effective Copper(II)-Dipyridylphosphine Catalyst System for the Asymmetric Hydrosilylation of Ketones in Air. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 3570−3575.
(36) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. Polymethylhydrosiloxane: A Versatile Reducing Agent for Organic Synthesis. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381.
(37) Brunner, H.; Kürzinger, A. Asymmetric catalysis XL. Enantioselective Hydrosilylation of Ketones by Diphenylsilane with [Rh(cod)Cl]$_2$/Pyridinethiazolidine Catalysts. *J. Organomet. Chem.* **1988**, *346*, 413−424.
(38) Nefkens, S. C. A.; Sperrle, M.; Consiglio, G. Palladium-Catalyzed Enantioselective Bis-alkoxycarbonylation of Olefins. *Angew. Chem., Int. Ed. Engl.* **1993**, *2*, 1719−1720.
(39) Wang, L.; Kwok, W.; Wu, J.; Guo, R.; Au-Yeung, T. T.-L.; Zhou, Z.; Chan, A. S. C.; Chan, K.-S. Enantioselective Bis-Alkoxycarbonylation of Styrene Catalyzed by Novel Chiral Dipyridylphosphine Cationic Palladium(II) Complexes. *J. Mol. Catal. A* **2003**, *196*, 171−178.
(40) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryl- and Alkenylboronic Acids to Enones. *J. Am. Chem. Soc.* **1998**, *120*, 5579−5580.
(41) Hayashi, T.; Yamasaki, K. Rhodium-Catalyzed Asymmetric 1,4-Addition and Its Related Asymmetric Reactions. *Chem. Rev.* **2003**, *103*, 2829−2844.
(42) Shi, Q.; Xu, L.; Li, X.; Jia, X.; Wang, R.; Au-Yeung, T. T.-L.; Chan, A. S. C.; Hayashi, T.; Cao, R.; Hong, M. Bipyridyl-Based Diphosphine as an Efficient Ligand in the Rhodium-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids to α,β-Unsaturated Ketones. *Tetrahedron Lett.* **2003**, *44*, 6505−6508.
(43) Boñaga, L. V. R.; Krafft, M. E. When the Pauson-Khand and Pauson-Khand Type Reactions Go Awry: A Plethora of Unexpected Results. *Tetrahedron* **2004**, *60*, 9795−9833.
(44) Kwong, F. Y.; Li, Y. M.; Lam, W. H.; Qiu, L.; Lee, H. W.; Yeung, C. H.; Chan, K. S.; Chan, A. S. C. Rhodium-Catalyzed Asymmetric Aqueous Pauson-Khand-Type Reaction. *Chem.—Eur. J.* **2005**, *11*, 3872−3880.
(45) Lindstrom, U. M. Stereoselective Organic Reactions in Water. *Chem. Rev.* **2002**, *102*, 2751−2772 and references therein.
(46) tol-BINAP = 2,2-bis(di-*p*-tolylphosphanyl)-1,1-binaphthyl; (*R*,*R*)-Et-DUPHOS = (−)-1,2-bis((2*R*,5*R*)-2,5-diethylphospholano)benzene; (*S*)-PHANEPHOS = (*S*)-(+)-4,12-bis(diphenyl-phosphano)-[2.2]-paracyclophane; (*S*,*S*)-Et-FerroTANE = (−)-1,1-bis((2*S*,4*S*)-2,4-diethylphospholano)ferrocene.

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