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Ligand Design

Electron-Donating and Rigid P-Stereogenic Bisphospholane Ligands for Highly Enantioselective Rhodium-Catalyzed Asymmetric Hydrogenations**

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Development of chiral phosphorus ligands has drawn intensive interest owing to their significant role in transition-metal-catalyzed asymmetric reactions.[1] Catalytic asymmetric hydrogenation has been widely used as a practical and efficient method in the synthesis of chiral molecules.[2] Although excellent enantioselectivities have been obtained by using benchmark ligands such as dipamp (1,2-ethanediyl-bis[(2-methoxyphenyl)phenylphosphane]),[3] binap (2,2′-bis-(diphenylphosphanyl)-1,1′-binaphthyl),[4] DuPhos (1,2-bis(phospholano)benzene derivatives),[5] and more recently TangPhos[6] **1** and DuanPhos[7] **2** (Figure 1), it is still highly desirable to develop ligands that can be prepared easily and have high enantioselectivity, reactivity, and with broad substrate scope for asymmetric hydrogenation. Herein, we report a new highly electron-donating and conformationally rigid P-stereogenic bisphospholane ligand **3** (named ZhangPhos; Figure 1) where both enantiomers can be synthesized conveniently. High enantioselectivities and reactivities have been achieved at room and elevated temperature in rhodium-catalyzed hydrogenation of various functionalized alkene derivatives.

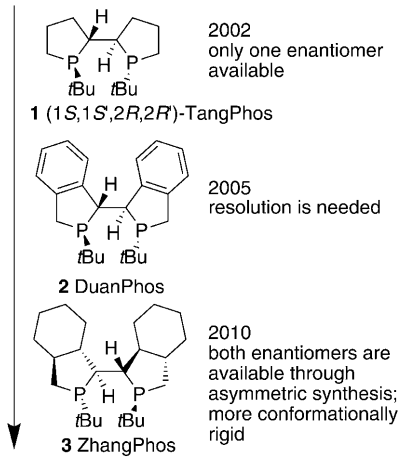

Figure 1. Structure of the three P-stereogenic phosphorus ligands.

Since the discovery of the landmark ligand dipamp, more attention has been paid to P-stereogenic phosphorus ligands because the chiral environment induced by the ligands is close to the transition metal centers. For example, BisP* (1,2-bis(alkylmethylphosphino)ethane),[8] miniphos (1,2-bis(alkylmethylphosphino)methane),[9] and trichickenfootphos (*tert*-butylmethylphosphino-di-*tert*-butylphosphinomethane)[10] provide excellent enantioselectivities in asymmetric hydrogenation, especially for the challenging tetra-substituted olefins. However, the development of P-stereogenic ligands is still limited owing to difficulty with synthesizing them. Our research group has ever reported a P-stereogenic ligand **1**, TangPhos, which is one of the most efficient ligands for asymmetric hydrogenation.[6] More recently, many other groups found that TangPhos exhibited the highest enantioselectivities for diverse transition-metal-catalyzed asymmetric reactions such as arylcyanation and alkylation of imidazoles at high temperatures.[11] However, only one enantiomer of TangPhos (1*S*,1*S*′,2*R*,2*R*′-**1**) is readily available owing to the requisition of chiral induction from (−)-sparteine. Later on, we introduced another P-stereogenic phosphorus ligand **2**, DuanPhos, with both enantiomers being available.[7] But the synthesis of DuanPhos requires resolution in the final step and its electron-donating ability is not as strong as that of TangPhos. The wide applications of TangPhos[11] and DuanPhos[12] encourage us to develop a more synthetically practical and conformationally rigid P-stereogenic bisphospholane scaffold **3**, ZhangPhos. The two five-membered phospholane rings in the backbone of **3** are believed to restrict the conformational flexibility and lead to high enantioslectivity. It is envisioned that the electron-rich bis(trialkylphosphane) structure contributes to the high reactivity. In addition to the excellent enantioselective induction, the two chiral cyclohexane rings on the backbone are expected to further benefit the electron-donating ability and conformational rigidity of **3**.

Ligand **3** was synthesized in a straightforward manner in five steps from a commercially available chiral source, (1*S*,2*S*)-1,2-cyclohexanedicarboxylic acid (**4**), which was reduced to chiral diol **5** quantitatively (Scheme 1; see the

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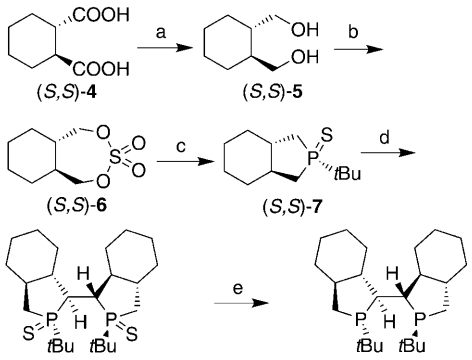


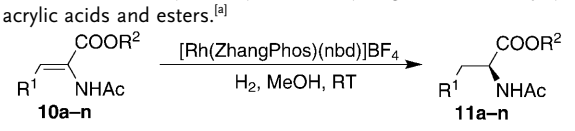
Scheme 1. Synthesis of ligand **3**. Reagents and conditions: a) $LiAlH_4$, 98%; b) 1. $SOCl_2$, NEt_3; 2. $RuCl_3{\cdot}XH_2O$, $NaIO_4$, 88% (over 2 steps); c) *t*$BuPH_2$, *n*BuLi, S, 81%; d) *s*BuLi, $[Fe(acac)_3]$, 50%, e) Si_2Cl_6, benzene, 90%. acac = acetylacetone.

Supporting Information for experimental details and analytical data). Cyclic sulfate **6** was obtained in 88% yield and was synthesized according to a known procedure.[13] Reaction of **6** with lithiated *tert*-butylphosphane, and subsequent in situ protection with sulfur powder afforded enantiomerically pure phosphane sulfide **7** (> 99% *ee* was determined by HPLC on a chiral statioanry phase).[14] A homocoupling mediated by $[Fe(acac)_3]$ in the presence of *sec*-butyllithium provided the C_2-symmetric bisphosphane sulfide **8** in 50% yield, along with recovered starting material **7** (25%). The absolute configuration of **8** was determined by X-ray crystallographic analysis.[15] Desulfuration of **8** with hexachlorodisilane[6a] afforded ligand **3**, (1*S*,1′*S*,2*R*,2′*R*,3a*S*,3′a*S*,7a*S*,7′a*S*)-ZhangPhos, as a white crystalline solid in 90% yield.

Ligand **3** was then used in the rhodium-catalyzed hydrogenation of various prochiral alkene derivatives. The cationic Rh complex, $[Rh(ZhangPhos)(nbd)]BF_4$ (**9**; nbd = 3,5-norbornadiene), was prepared and used directly as the catalyst precursor. α-(Acylamino)acrylic acids and esters were hydrogenated under very mild conditions (in methanol at room temperature under 20 psi of H_2 for 12 h).[16] Full conversions and extremely high enantioselectivities (> 99% *ee* exclusively) were obtained in the hydrogenation of both α-(acylamino)acrylic acids and their ester derivatives (Table 1). The catalyst can tolerate a wide array of substituted phenyl rings and thio ring (Table 1, entries 5–12), as well as the *N*-benzoyl derivative (Table 1, entry 14). To further evaluate the catalytic efficiency of the Rh–ZhangPhos system in asymmetric hydrogenation, methyl 2-acetamido-3-(4-fluorophenyl)acrylate (**10g**) was hydrogenated using 0.002 mol% of complex **9** under the same reaction conditions. In this way, (*S*)-**11g** was obtained with > 99% *ee* in quantitative yield within 4 hours, thus indicating a high turnover number (TON = 50000) and a high turnover frequency (TOF = 12500 h^{-1}) for the Rh–ZhangPhos catalyst.

A variety of α-arylenamides **12** were also hydrogenated with the Rh–ZhangPhos catalyst to afford enantiomerically pure amides (Table 2). *Ee* values of more than 99% were achieved exclusively in the hydrogenation of enamides **12**, regardless of the substituents on the phenyl ring (Table 2, entries 1–8). Rh–ZhangPhos also showed tolerance to the *E*/*Z* mixture of trisubstituted enamides and gave excellent enantioselectivity (Table 2, entries 10 and 11). High turnover (10000) was also obtained in the hydrogenation of *N*-(1-(4-bromophenyl)vinyl)acetamide (**12g**) with > 99% *ee* in quan-

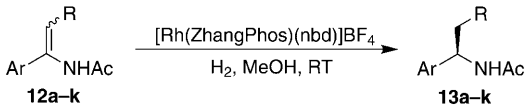
Table 1: Rhodium-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids and esters.[a]



Entry	**10**	R^1	R^2	*ee* [%][b]
1	**a**	H	Me	> 99
2	**b**	*n*Pr	Me	> 99
3	**c**	*i*Pr	H	> 99
4	**d**	Ph	H	> 99
5	**e**	Ph	Me	> 99
6	**f**	*p*-FC_6H_4	H	> 99
7	**g**	*p*-FC_6H_4	Me	> 99
8	**h**	*p*-$MeOC_6H_4$	Me	> 99
9	**i**	*p*-$CF_3C_6H_4$	Me	> 99
10	**j**	*m*-BrC_6H_4	Me	> 99
11	**k**	*o*-ClC_6H_4	Me	> 99
12	**l**	2-thienyl	Me	> 99
13	**m**	2-naphthyl	H	> 99
14[c]	**n**	Ph	Me	> 99

[a] The reactions were carried out at room temperature under 20 psi of H_2 in MeOH for 12 hours with **9** (1 mol%) as the catalyst precursor. Conversions were 100%. [b] The *ee* values were determined by GC or HPLC on a chiral stationary phase using a Chiralsil-VAL III FSOT or a Chiralcel OJ column, respectively. The *ee* values of the acids were determined for the corresponding methyl ester by treatment with $TMSCHN_2$. The absolute configurations of the products were determined as *S* by comparison of the retention times of two enantiomers with reported data.[6a] [c] The protecting group on N was changed form Ac to Bz for this reaction. Bz = benzoyl, TMS = trimethylsilyl.

Table 2: Rhodium-catalyzed asymmetric hydrogenation of α-arylenamide.[a]



Entry	**12**	R^1	R^2	*ee* [%][b]
1	**a**	Ph	H	> 99
2	**b**	*m*-MeC_6H_4	H	> 99
3	**c**	*m*-$MeOC_6H_4$	H	> 99
4	**d**	*m*-BrC_6H_4	H	> 99
5	**e**	*p*-MeC_6H_4	H	> 99
6	**f**	*p*-ClC_6H_4	H	> 99
7	**g**	*p*-BrC_6H_4	H	> 99
8	**h**	*p*-$MeOC_6H_4$	H	> 99
9	**i**	2-naphthyl	H	> 99
10	**j**	Ph	Me	> 99
11	**k**	*p*-$CF_3C_6H_4$	Me	> 99

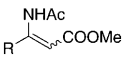
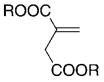
[a] See footnotes of Table 1. For the *E*/*Z* ratio of **12j–k**, see reference [17]. [b] The *ee* values were determined by GC or HPLC on a chiral stationary phase using a Chiral Selective 1000 or a Chiralcel OD-H column, respectively. The absolute configurations of the products were determined as *S* by comparison of their retention times of two enantiomers with reported data.[6a]

titative yield. These results are among the best reported to date.

The two chiral cyclohexane rings fused on the phospholane rings are expected to make ZhangPhos more conformationally rigid and electron-donating than TangPhos. It has been demonstrated that high rigidity and a well-defined structure are beneficial to achieving high enantioselectivity.[2] As shown in Table 3, Rh–ZhangPhos gave higher or comparable enantioselectivities compared to Rh–TangPhos in the hydrogenation of another three types of prochiral olefins: enol acetates **14** (Table 3, entries 1–5), β-(acetylamino)acrylates **15** (Table 3, entries 6–10), and itaconic acid derivatives **16** (Table 3, entries 11 and 12). For the hydrogenation of aromatic enol acetates, which serves as an alternative to direct hydrogenation of ketones, increase of enantioselectivity was observed by using Rh–ZhangPhos as the catalyst, especially for **14b** (from 92% to 98% *ee*; Table 3, entry 2). β-(Acetylamino)acrylates remain challenging substrates for asymmetric hydrogenation, which can form nonnatural chiral β-amino acids. With Rh–ZhangPhos, the hydrogenation of both *E* and *Z* isomers of β-(acetylamino)acrylates derivatives **15** gave high enantioselectivities (from 92% to more than 99% *ee*). In particularly, for *ortho*-substituted substrate **15e**, a significant increase in enantioselectivity (from 74% to 92% *ee*) was obtained with the Rh–ZhangPhos complex (Table 3, entry 10).

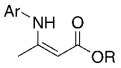
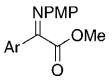
In asymmetric catalysis, the enantioselectivity generally decreases at high temperature as a result of the ligand flexibility. The conformationally rigid cyclohexane rings were expected to reduce the flexibility of ligand **3** and sustain high enantioselectivity at high temperature. Indeed, some preliminary results of hydrogenations requiring higher temperature showed that ZhangPhos has better tolerance to high temperature than TangPhos. As shown in Table 4, the hydrogenation of *N*-aryl β-enamino esters **17**[6d] (Table 4, entries 1–3) and α-aryl imino esters **18**[6e] (Table 4, entries 4 and 5), where a temperature of 50 °C was needed, Rh–ZhangPhos delivered higher enantioselectivities than Rh–TangPhos. It is expected that ZhangPhos will have promising applications in asymmetric catalytic processes, which require elevated temperature.[11a,b]

Table 3: Rhodium-catalyzed asymmetric hydrogenation of enol acetates, β-(acetylamino)acrylates and itaconic acid derivatives.[a]

Entry	Substrate	*ee* [%][b] ZhangPhos	TangPhos
			
1	**14a** Ar = Ph	97(*S*)	96(*R*)[c]
2	**14b** Ar = *p*-FC_6H_4	98(*S*)	92(*R*)[c]
3	**14c** Ar = *p*-ClC_6H_4	97(*S*)	97(*R*)[c]
4	**14d** Ar = *p*-$NO_2C_6H_4$	>99(*S*)	99(*R*)[c]
5	**14e** Ar = 2-naphthyl	99(*S*)	97(*R*)[c]
			
6	**15a** R = Me (*E*)	>99(*S*)	>99(*R*)[d]
7	**15b** R = Me (*Z*)	97(*S*)	97(*R*)[d]
8	**15c** R = Et (*E*)	>99(*S*)	>99(*R*)[d]
9	**15d** R = Ph (*Z*)	95(*R*)	94(*S*)[d]
10	**15e** R = *o*-MeC_6H_4 (*Z*)	**92**(*R*)	**74**(*S*)[d]
			
11	**16a** R = Me	>99(*R*)	99(*S*)[c]
12	**16b** R = H	>99(*R*)	99(*S*)[c]

[a] See footnotes of Table 1. Solvent was ethyl acetate for **14**, THF for **15**, and **16**. [b] The *ee* values were determined by GC or HPLC on a chiral stationary phase (see references [6b,c]). The absolute configurations of the products were determined by comparison of the retention times of two enantiomers with reported data. [c] Data from reference [6c]. [d] Data from reference [6b].

Table 4: Rhodium-catalyzed asymmetric hydrogenation of *N*-aryl β-enamino esters and α-aryl imino esters.[a]

Entry	Substrate	*ee* [%][b] ZhangPhos	TangPhos
			
1	**17a** Ar = Ph, R = Me	93(+)	91(−)[c]
2	**17b** Ar = Ph, R = Et	96(+)	95(−)[c]
3	**17c** Ar = *p*-FC_6H_4, R = Et	98(+)	96(−)[c]
			
4	**18a** Ar = Ph	97(*R*)	95(*S*)[d]
5	**18b** Ar = *o*-$MeOC_6H_4$	97(+)	95(−)[d]

[a] For **17**, the reactions were carried out at 50 °C in TFE under 6 atm of H_2 for 18 hours with **9** (1 mol%). For **18**, the reactions were carried out at 50 °C in CH_2Cl_2 under 50 atm of H_2 for 24 hours with **9** (1 mol%). Conversions were 100%. [b] The *ee* values were determined by GC or HPLC on a chiral stationary phase (see references [6d,e]). [c] Data from reference[6d]. [d] Data from reference [6e]. PMP = *para*-methoxyphenyl, TFE = trifluoroethanol.

In conclusion, we have designed and developed a new highly electron-donating, P-stereogenic bisphospholane ligand **3** (ZhangPhos), which can be synthesized practically and highly enantioselectively from a commercially available chiral reagent. Ligand **3** exhibited extremely high enantioselectivities (up to 99% *ee*) and reactivities (up to 50000 TON) for rhodium-catalyzed hydrogenation of a wide range of functionalized olefin derivatives. Compared to TangPhos and DuanPhos, better or comparable enantioselectivities were achieved with ZhangPhos, which suggests that the chiral cyclohexane rings on its backbone make the ligand more conformational rigid. Especially, better enantioselectivities obtained at high temperature makes ZhangPhos a promising ligand for high temperature asymmetric catalysis. Further studies to optimize the synthesis of ZhangPhos and explore its application in diverse asymmetric catalytic reactions will be reported in due course.

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[15] CCDC 776144 (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] These are not optimal reaction condition. To compare with the results of TangPhos, the same reaction conditions were used.

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