A Chiral 1,2-Bisphospholane Ligand with a Novel Structural Motif: Applications in Highly Enantioselective Rh-Catalyzed Hydrogenations**

Wenjun Tang and Xumu Zhang*

The design and synthesis of chiral phosphane ligands have played a significant role in the development of efficient transition metal catalyzed reactions. Catalytic asymmetric hydrogenation, as one of the most practical and efficient methods for the synthesis of chiral building blocks, has attracted much attention in both academia and industry.[1] Although excellent enantioselectivities have been obtained by using chiral bisphosphane ligands such as DIPAMP,[2] DIOP,[3] Chiraphos,[4] Norphos,[5] BPPM,[6] DEGphos,[7] BINAP,[8] DuPhos,[9] BPE,[9] BICP,[10] SpirOP,[11] PennPhos,[12] BisP*,[13] MiniPhOS,[14] Binaphane,[15] and PHANEPHOS,[16] the search for more practical and efficient ligands in terms of ease of preparation, high enantioselectivity, and high turnover number (TON) remains an important goal in asymmetric hydrogenation. Herein we report the synthesis and application of a new chiral 1,2-bisphospholane ligand, (*1S*,1*S*′,2*R*,2*R*′)-1,1′-di-*tert*-butyl-[2,2′]-diphospholanyl (**1**; abbreviated (1*S*,1*S*′,2*R*,2*R*′)-TangPhos, Figure 1) in highly efficient rhodium-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids, α-(acylamino)acrylic esters, and α-arylenamides. The ligand contains four stereogenic centers: two carbon and two phosphorus centers. This structural motif is different from axially dissymmetric BINAP, bisphosphanes with two stereogenic carbon centers (e.g. Chiralphos), and bisphosphanes with two stereogenic phosphorus centers (e.g. DIPAMP and BisP*). We hypothesized that the two five-membered phospholane rings in the backbone of **1** restrict its conformational flexibility, which could lead to high enantioselectivity in asymmetric reaction.

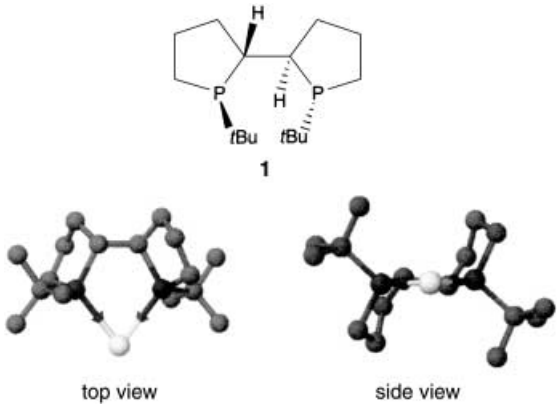
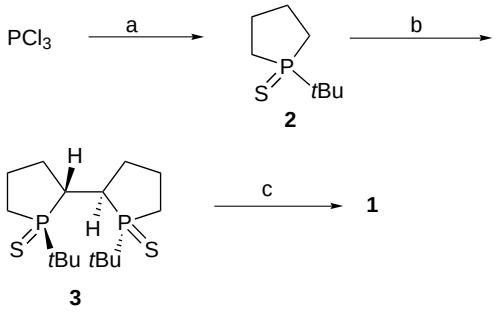


Figure 1. MM2 Calculations of the Rh–TangPhos complex based on the CAChe program.

The importance of the conformational properties of a Rh-ligand complex in determining enantioselectivity has been well recognized. In general, ligands with rigid backbones are preferred for achieving high enantioselectivities. Imamoto's BisP* is a good ligand for asymmetric hydrogenation.[13] However, BisP* contains two methylene groups in the backbone and its five-membered ring metal ligand complex is conformationally flexible. We reasoned that the Rh–TangPhos complex should have a well-defined rigid conformation through two additional five-membered rings on the backbone. Molecular modeling (Figure 1) showed that the Rh–TangPhos complex exhibits a similar but more rigid chiral environment than the Rh–BisP* complex.

Ligand **1** was prepared in three steps from readily accessible materials by using phosphane sulfides as intermediates (Scheme 1).[17] Phosphane sulfide **2** was directly prepared from phosphorus chloride in one step with three operations.



Scheme 1. Synthesis of **1**. Reagents and conditions: a) *t*BuMgCl, $BrMg(CH_2)_4MgBr$, S, 45%; b) *n*BuLi, (−)-sparteine, $CuCl_2$, recrystallization, 20%; c) hexachlorodisilane, benzene, 88%.

Selective deprotonation of **2** by an *n*BuLi–(−)-sparteine complex followed by a Cu-mediated oxidative coupling afforded the C_2-symmetric bisphosphane sulfide **3** with 95% *ee*, along with the formation of the *meso* compound (C_2:*meso* 83:17). Recrystallization afforded optically pure **3** in 20% yield. The configuration at the P atom of **3** was assigned by comparison with the structure of BisP*,[18] the relative stereochemistry of the carbon and phosphorus centers was assigned based on a known compound.[19] Desulfuration of **3** by hexachlorodisilane[20] afforded white air-sensitive crystalline solid **1** ((1*S*,1*S*′,2*R*,2*R*′)-TangPhos) in 88% yield.

α-(Acylamino)acrylic acids and esters were hydrogenated in methanol at room temperature under hydrogen (20 psi). The catalyst was formed in situ from $[Rh(nbd)_2]SbF_6$ (nbd = 3,5-norbornadiene) and bisphosphane **1** (1:1.1). As shown in Table 1, a wide array of ring-substituted phenylalanine derivatives were formed with extremely high enantioselectivities. It is noted that almost 100% *ee* values were obtained in the hydrogenation of both α-(acylamino)acrylic acids and their esters. The catalyst can tolerate thio- and halogen groups. The 2-naphthyl (Table 1, entries 13 and 14) as well as the *N*-benzoyl derivatives (Table 1, entries 15 and 16) were also hydrogenated with high enantioselectivities (>99% *ee*).

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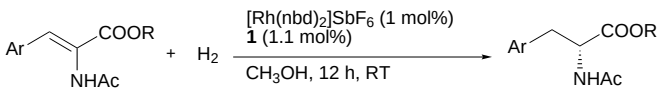
Table 1. Rh-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acid derivatives.[a]



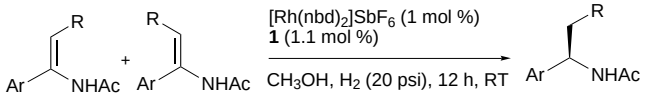
4a–p **5a–p**

Entry	**4**	Ar	R	*ee* [%][b]
1	**a**	Ph	H	> 99
2	**b**	Ph	CH_3	99
3	**c**	*p*-FPh	H	> 99
4	**d**	*p*-FPh	CH_3	> 99
5	**e**	*p*-MeOPh	H	> 99
6	**f**	*p*-MeOPh	CH_3	> 99
7	**g**	*m*-BrPh	H	> 99
8	**h**	*m*-BrPh	CH_3	> 99
9	**i**	*o*-ClPh	H	> 99
10	**j**	*o*-ClPh	CH_3	> 99
11	**k**	2-thienyl	H	> 99
12	**l**	2-thienyl	CH_3	> 99
13	**m**	2-naphthyl	H	> 99
14	**n**	2-naphthyl	CH_3	> 99
15	**o**	Ph	H, *N*-Bz	> 99
16	**p**	Ph	CH_3, *N*-Bz	> 99

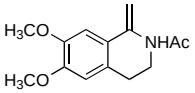
[a] See Experimental Section for details. [b] The *R* absolute configuration was assigned by comparison of the optical rotation with reported data. Enantiomeric excesses were determined by chiral GC (Chiralsil-VAL III FSOT) or Chiral HPLC (Chiralcel OJ). The *ee* values of the acids were determined on the corresponding methyl ester.

α-Arylenamides were also hydrogenated with the Rh–TangPhos catalyst. As shown in Table 2, a variety of α-arylenamides were hydrogenated to form chiral amides with excellent enantioselectivities. Enantiomeric excesses of more than 99% were observed in the hydrogenation of α-phenyl-enamides, regardless of the substituents on the phenyl ring (Table 2, entries 1–5). Hydrogenation of a 2-naphthyl derivative also gave an excellent *ee* value (Table 2, entry 6). For β-substituted isomeric enamide mixtures (*Z*/*E*) and β-methyl-substituted enamides with various substituents on the 1-aryl group, high *ee* values were also obtained, regardless of the various β-substituents or the electronic properties of the 1-aryl group (Table 2, entries 7–12). Asymmetric hydrogenation of *N*-acetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroquinoline proceeded smoothly, yielding (*R*)-(−)-*N*-acetylsalsolidine in quantitative yield and with 97% *ee*. The enantioselectivities of the hydrogenation of enamides with the Rh–TangPhos system are comparable or higher than those observed with the Rh–DuPhos system.[21]

Table 2. Rh-catalyzed asymmetric hydrogenation of α-arylenamides.[a]



6a–m **7a–m**

Entry	**6**	Ar	R	*ee* [%][b]
1	**a**	Ph	H	> 99
2	**b**	*m*-MePh	H	> 99
3	**c**	*p*-CF_3Ph	H	> 99
4	**d**	*p*-CyPh	H	> 99
5	**e**	*p*-PhPh	H	99
6	**f**	2-naphthyl	H	> 99
7	**g**	Ph	CH_3	98
8	**h**	*p*-CF_3Ph	CH_3	98
9	**i**	*p*-MeOPh	CH_3	98
10	**j**	2-naphthyl	CH_3	99
11	**k**	Ph	$CH(CH_3)_2$	98
12	**l**	Ph	CH_2Ph	99
13	**m**			97

[a] See Experimental Section for details. Enamides **6** were prepared according to the literature method. For the *E*/*Z* ratio of **6g–l**, see references [10b, 21]. [b] The *R* absolute configuration was assigned by comparison of the optical rotation with reported data. Enantiomeric excesses were determined by chiral GC on a Supelco Chiral Select 1000 column or by chiral HPLC on a (*R*,*R*)-Poly Whelk-01 column.

To evaluate further the catalytic efficiency of Rh–TangPhos system in asymmetric hydrogenations, the catalyst precursor [Rh(nbd)(**1**)]SbF_6 was prepared. Hydrogenation of methyl α-(acetylamino)-2-phenylacrylate in the presence of [Rh(nbd)(**1**)]SbF_6 (0.01 mol%, 10000 TON) afforded (*R*)-methyl 2-acetylamino-3-phenylpropionate in 100% yield and with 99.8% *ee*. High turnovers (10000) were also observed in the hydrogenation of *N*-acetyl-1-phenylethenamine, yielding *N*-acetyl-1-phenylethylamine in 100% yield and with 99.3% *ee*.

In conclusion, we have designed and synthesized a new chiral 1,2-bisphospholane ligand TangPhos (**1**) in a three-step synthetic route. This readily accessible ligand is potentially practical for the Rh-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids and α-arylenamides. Further applications of the ligand in asymmetric catalysis are in progress.

Experimental Section

1: Hexachlorodisilane (3.25 mL, 5.08 g, 18.9 mmol) was added dropwise to a solution of **3**[22] (440 mg, 1.26 mmol) in benzene (25 mL). The mixture was stirred at reflux for 4 h. After the solution was cooled to room temperature, degassed NaOH solution (50 mL, 30% *w*/*w*) was slowly added to the reaction mixture in an ice-water bath. The resulting mixture was then stirred at 60 °C until the aqueous layer became clear. The two phases were separated. The water phase was washed twice with degassed benzene (2 × 30 mL). The combined benzene layers were dried over Na_2SO_4 and concentrated. The solid residue was redissolved in a minimum amount of degassed dichloromethane, which was subsequently passed through a basic Al_2O_3 plug (eluent: Et_2O:Hexane 1:10) to give pure crystalline **1** (320 mg, 88%): ^{1}H NMR (360 MHz, CD_2Cl_2): $\delta = 1.01$ (d, $^3J_{HP} = 11.5$ Hz, 18H), 1.64 (m, 8H), 1.87 (m, 2H), 2.00 (m, 2H), 2.25 ppm (m, 2H); ^{13}C NMR (90 MHz, CD_2Cl_2): $\delta = 23.6$ (t, $^2J_{CP} = 6.6$ Hz), 28.5 (dd, $^2J_{CP} = 7.0$, 7.5 Hz), 28.8, 28.9, 34.6 (t, $^2J_{CP} = 5.1$ Hz), 42.9 ppm (m); ^{31}P NMR (145 MHz, CD_2Cl_2): $\delta = 14.5$ ppm; APCI MS: 287 [M^++H]; HRMS calcd for $C_{16}H_{33}P_2$: 287.2058, found: 287.2035.

[Rh(nbd)(**1**)]SbF_6: A solution of (1*S*,1*S*′,2*R*,2*R*′)-TangPhos (**1**, 57 mg, 0.2 mmol) in THF (1 mL) was added dropwise to a solution of [Rh(nbd)$_2$]SbF_6 (104 mg, 0.2 mmol) in degassed THF (1 mL) at −10 °C. The resulting mixture was stirred at ambient temperature for 15 min. Degassed diethyl ether (12 mL) was then added to the vigorously stirred solution. The resulting dark brown precipitate was filtered, further washed with diethyl ether (3 × 10 mL), and dried under vacuum. Yield: 80 mg, 56%. ^{1}H NMR (360 MHz, CD_2Cl_2): $\delta = 1.05$ (d, $^3J_{HP} = 7.2$ Hz, 18H), 1.56 (m, 2H), 1.73 (m, 2H), 1.86 (s, 2H), 1.99 (m, 2H), 2.21 (m, 4H), 2.38 (m, 4H), 4.15 (s, 2H), 5.56 (s, 2H), 5.70 ppm (s, 2H); ^{31}P NMR (145 MHz, CD_2Cl_2): $\delta = 101.1$ ppm (d, $^2J_{RhP} = 151.6$ Hz); ESI MS: 481 [$M - SbF_6^-$]; HRMS calcd for $C_{23}H_{40}P_2Rh$: 481.1660, found 481.1627.

General hydrogenation procedure: (1*S*,1*S*′,2*R*,2*R*′)-TangPhos (**1**, 0.10 mL, 0.05 M solution in methanol, 0.005 mmol) was added to a solution of

$[Rh(nbd)_2]SbF_6$ (2.3 mg, 0.0045 mmol) in methanol (3 mL) in a glovebox. After the mixture was stirred for 10 min, the substrate (0.5 mmol) was added. The hydrogenation was performed at room temperature under H_2 (20 psi) for 12–48 h. After carefully releasing the hydrogen, the reaction mixture was passed through a short silica-gel plug to remove the catalyst. The resulting solution was used directly for chiral GC or HPLC to measure the enantiomeric excess. For the hydrogenation of dehydroamino acids, the enantiomeric excesses were measured after conversion into their corresponding methyl esters by treatment with $TMSCHN_2$ (TMS = trimethylsilyl).

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Helical Chiral Polymers without Additional Stereogenic Units: A New Class of Ligands in Asymmetric Catalysis**

Michael Reggelin,* Melanie Schultz, and Michael Holbach

Soluble polymers may be promising ligands in transition metal catalysis for a number of reasons. The reisolation of the chiral catalyst by precipitation or ultrafiltration should be easy, and all the analytical and kinetic advantages of a reaction in homogenous phase should be maintained. If the polymer is chiral and nonracemic, asymmetric induction can be expected, and finally, a number of beneficial effects related to the macromolecular state of the system may allow for the synthesis of novel ligands with properties not achievable with micromolecules. These effects include, for example, cooperativity and chiral amplification as observed in polyisocyanates.[1]

The most obvious way to prepare a polymeric chiral soluble ligand is to attach only one metal binding site per polymer chain. This was rather successful in the asymmetric dihydroxylations described by Bolm et al.[2] and Janda et al.[3] The major disadvantage of this approach is the very low density of reactive centers per unit mass. To improve this situation it is necessary to prepare multiple-site polymeric catalysts with uniform microenvironments. The polybinaphthols prepared by Pu et al. appear to be successful examples of this strategy.[4] The remaining problems with these ligands include the necessity to prepare the enantiomerically pure monomers and the question of contraproductive interactions of the different sources of chirality (planar chirality of the monomers and helical chirality of the polymer). Indeed, we think that for the phosphane-modified helical chiral dodecapeptides developed by Gilbertson et al.[5] the major reason for the failure to achieve good enantioselectivities in asymmetric hydrogenation reactions is such a contraproductive interaction between the centrochirality of the constituting amino acids and the helical secondary structure. Facing this situation we felt it would be best to erase all sources of chirality except the helicity of a stereoregular and configurationally stable polymer containing donor atoms such as nitrogen or phosphorus.

We followed the work of Okamoto et al.[6, 7] and prepared two chiral polymers by helix-sense selective anionic polymerization of sterically congested methacrylates by using a chiral nonracemic base mixture as initiator (Scheme 1, Table 1). The chiral initiator was prepared by mixing either (+)- or (−)-1-(2-pyrrolidinomethyl)pyrrolidine ((*S*)- or (*R*)-**4**) and the diamine **3** with one equivalent of *n*BuLi at room temperature in toluene. This mixture was added to solutions of the monomers **1** and **2** so that the monomer/initiator ratio was

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