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A novel approach for investigating enantioselectivity in asymmetric hydrogenation

Hideo Shimizu, Takero Ishizaki, Takahiro Fujiwara and Takao Saito*

Takasago International Corporation, Central Research Laboratory, Nishi-Yawata, Hiratsuka, Kanagawa 254-0073, Japan

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Abstract—A new and convenient method for investigating the relationship between the position of the enantiodetermining sites in chiral phosphine ligands and enantioselectivity in asymmetric hydrogenation is proposed. We have also synthesized four new diphosphine ligands, some of which give high enantioselectivity in the asymmetric hydrogenation of an enamide.

Asymmetric hydrogenation is one of the most powerful tools in organic synthesis.[1] As enantioselectivities are highly affected by chiral ligands in catalysis, various ligands have been fine-tuned for ultimate selectivity. Some of these perform with sufficient enantioselectivity for use in applications to industrial needs.[2] Enantioselectivity is the result of various factors associated with a ligand, including steric effects, rigidity of the framework, electronic properties, etc. Of these, we focused on the location of the carbon atoms, which can impact enantioselectivity. In many papers, the origin of enantioselectivity has been explained using a two-dimensional model, which is divided into four quandrants, as illustrated in Figure 1.[3] This explanation puts an emphasis on which quandrants of the four should be shielded by the ligand. Although this model can account for the enantiomer observed, it cannot predict the extent of enantioselectivity. To the best of our knowledge, there is little guidance in the literature as to where in any quadrant the enantiodetermining groups should be during a hydrogenation so as to maximize enantioselectivity.[4] Moreover there is no one ligand that gives high enantioselectivity for any substrate, that is, each substrate has its own ligand of choice. We reasoned that a substrate must have its best location (or 'sweet spot'), at which maximum shielding in the quandrant occurs leading to high selectivity. A study on the relationship between the locations of enantiodetermining groups within several related ligands and enantioselectivity in asymmetric hydrogenations of various substrates might ultimately provide a prediction as to the ligand of choice for future substrates. Described herein is a new approach for a better understanding of the positioning of enantiodetermining groups in C_2 symmetric diphosphine ligands. The use of a template serves to position carbon atoms in ligands at various coordinates during an asymmetric hydrogenation of an enamide in search of the reaction's 'sweet spot' (Fig. 2).

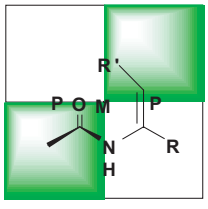

Figure 1. Quandrants.

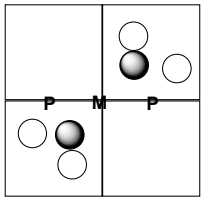

Figure 2. Where is the 'sweet spot'?

For convenience, in order to identify the location of enantiodetermining groups, we adopted a mapping approach based on MM2 calculations.[5] The enantiodetermining groups can be easily found by

* Corresponding author. Tel.: +81-463-25-2189; fax: +81-463-25-2084; e-mail: takao_saito@takasago.com

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conformational analysis by MM2 calculations. Taking DuPHOS[6] as an example, a side view of its Rh complex indicates that two methyl groups (C and C′) out of four on the phospholane rings are the key enantiodetermining residues (Fig. 3).

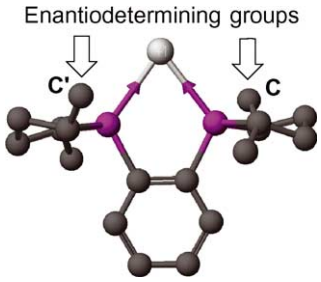


Figure 3. Enantiodetermining groups.

Conformational analysis of metal complexes gives us information about bond distances, angles, etc. As for C_2 symmetric ligands, three kinds of data allow us to establish the positions of the enantiodetermining groups in three dimensions: (1) the bond distance between two enantiodetermining carbon atoms (C and C′) (d), (2) the bond distance between a central metal atom M and C (r) and (3) the torsion angle of the line formed by C and M with the plane containing two phosphine atoms and M (θ). The complex was oriented within the coordinates as described in Figure 4. First, the location of M was set to the origin, the plane containing two phosphine atoms and M being situated in the x–y plane. Among lines containing M, one which is parallel to the line formed by two phosphine atoms was defined as the x-axis, one on the x–y plane, which is vertical to the x axis to be the y axis, and one which is vertical to the x–y plane to be the z axis. Setting the location of the enantiodetermining carbon atom C to be value (x, y, z) affords three equations (Fig. 5). By solving these equations, the value of C can be determined.

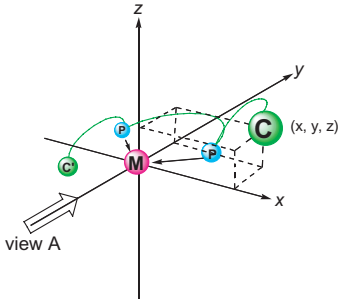
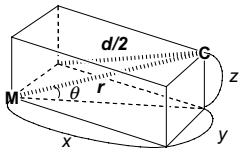


Figure 4. Fixing a metal complex into a coordinate.

Next, we designed and synthesized C_2 symmetric ligands, illustrated in Figure 6, so that their enantiodetermining groups occur at different locations within the coordination picture above. When discussing a relationship between the locations and enantioselectivities, it would be desirable to eliminate electronic effects to the extent possible as they may also impact enantioselectivity. Therefore, all of the ligands were designed to have similar electronic conditions, with bisbenzodioxole as their framework[7] and two alkyl groups on each phosphorus atom.



$$z = r\sin\theta$$

$$x^2 + z^2 = (d/2)^2$$

$$x^2 + y^2 + z^2 = r^2$$

Figure 5. Equations.

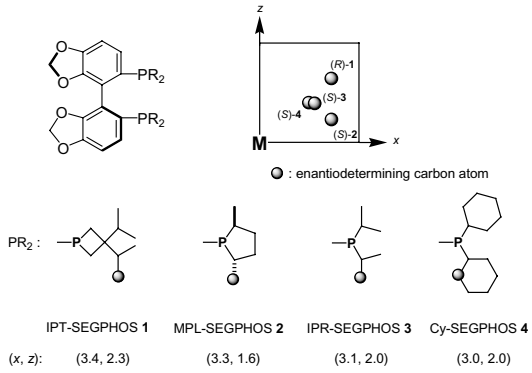
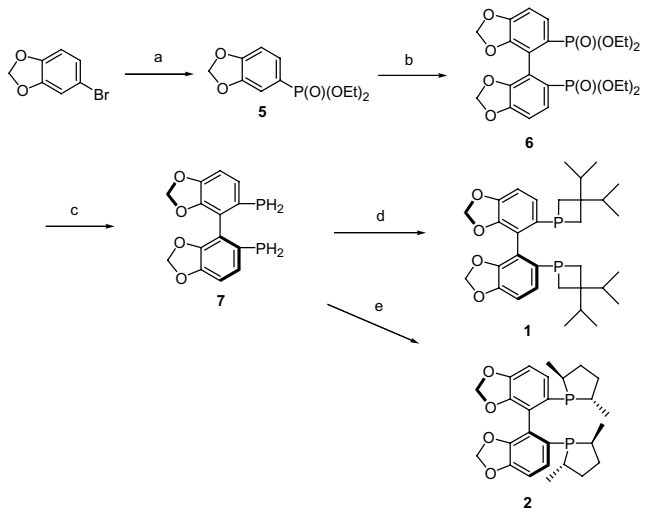


Figure 6. Designed ligands and their calculated location of their enantiodetermining carbon atoms.

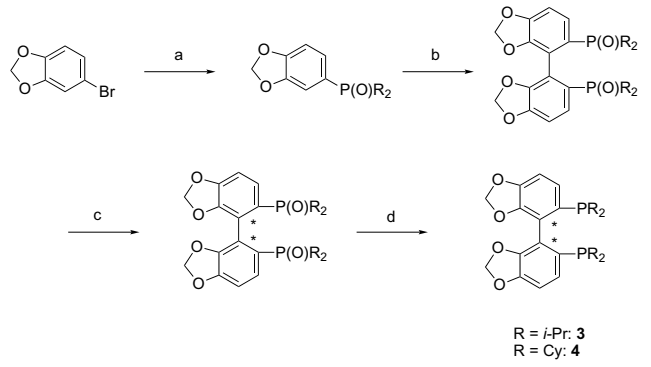
According to the calculation,[8] (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(3,3-di-isopropylphosphetane) **1** (IPT-SEGPHOS)[9] should be located at the grid point of (3.4, 0.1, 2.3), whereas (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(2,5-dimethylphospholane) **2** (MPL-SEGPHOS)[10,11] (3.3, 0.3, 1.6), (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(di-isopropylphosphine) **3** (IPR-SEGPHOS)[12] (3.1, 0.4, 2.0) and (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(dicyclohexylphosphine) **4** (Cy-SEGPHOS)[13] (3.0, 0.4, 2.0). As differences in y values are negligible, only values in the x–z planes (from viewpoint A) were considered.

Preparations of the (*S*)-**1** and (*aS*,*S*,*S*)-**2** are shown in Scheme 1. The Grignard reagent derived from 3,4-methylenedioxybromobenzene was treated with diethyl chlorophosphate to afford phosphonate **5**. Lithiation of **5** followed by coupling with $FeCl_3$ gave diphosphonate **6**. Resolution of **6** and reduction with lithium aluminium hydride gave diphosphine **7**. Finally, phosphetane rings of **1** and phospholane rings of **2** were formed by exposing **7** with the corresponding cyclic sulfates in the presence of LDA.

Synthesis of (+)-**3** is described in Scheme 2. Treatment of the Grignard reagent derived from 1-bromo-3,4-methylenedioxybenzene with chlorodiisopropylphosphine followed by oxidation gave the phosphine oxide. After coupling of the phosphine oxide, resolution was performed with (+)-dibenzoyltartaric acid [(+)-DBT]. Reduction of the diphosphine oxide gave (+)-**3**, where (+)-**4** was prepared following the literature.[13]



Scheme 1. Synthesis of **1** and **2**. Reagents and conditions: (a) (i) Mg, (ii) $ClP(O)(OEt)_2$; (b) (i) LDA, (ii) $FeCl_3$; (c) (i) (+)-di-p-toluoyltartaric acid ((+)-DTT), (ii) NaOH, (iii) $LiAlH_4$, Me_3SiCl; (d) (i) cyclic sulfate of 2,2-diisopropyl-1,3-propane-diol, LDA, (ii) H_2O_2, (iii) $HSiCl_3$, $PhNMe_2$; (e) cyclic sulfate of (2*R*,5*R*)-2,5-hexanediol, LDA.

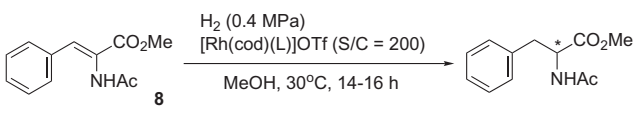


Scheme 2. Synthesis of **3** and **4**. Reagents and conditions: (a) (i) Mg, (ii) $ClP(i\text{-}Pr)_2$, (iii) H_2O_2 or (i) Mg, (ii) $ClP(O)Cy_2$; (b) (i) LDA, (ii) $FeCl_3$; (c) (i) DBT, (ii) NaOH; (d) $HSiCl_3$, $(i\text{-}Pr)_2NEt$ (for **3**) or $PhNMe_2$ (for **4**).

Cationic Rh catalysts bearing these ligands were used in the asymmetric hydrogenation of the commonly studied substrate, methyl α-acetamidocinnamate, **8**. Results are shown in Table 1. A complex bearing **1** gave a comparatively moderate ee, whereas that bearing **2** gave a somewhat higher enantioselectivity. Curiously, (*S*)-**1** gave the same configuration of the product derived from **8** with (*aS*,*S*,*S*)-**2**, although (*S*)-**1** should shield complementary quandrants relative to that of (*aS*,*S*,*S*)-**2**. On the other hand, Rh complexes ligated by (+)-**3** or (+)-**4** gave excellent ees. Further optimization revealed that reduced hydrogen pressure (0.1 MPa) and using THF as solvent improved the ee up to 98%.

Our interpretation of these results is as follows:
(i) enantiodetermining carbon atoms of IPT-SEGPHOS **1** are too far from each other (ca 8.4 Å) and thus cannot sufficiently interact with substrate **8**, the length of which is estimated to be 8.8 Å.
(ii) MPL-SEGPHOS **2**, IPR-SEGPHOS **3** and Cy-SEGPHOS **4** have similar bond distances between their two enantiodetermining groups (7.3–7.4 Å). In this case, IPR-SEGPHOS **3** and Cy-SEGPHOS **4** have more 'gaps' in steric repulsion between the two transition states. Ligands **3** and **4** appear to shield the sweet spot in these asymmetric hydrogenations, that is, the grid point around (3.0, 2.0) is the sweet spot for the asymmetric hydrogenation of **8**.

Table 1. Asymmetric hydrogenation of methyl α-acetamidocinnamate



Entry	Ligand	Conversion (%)[a]	Ee[a] (config.)
1	(*S*)-**1**	>99	63 (*S*)
2	(*aS*,*S*,*S*)-**2**	>99	75 (*S*)
3	(+)-**3**	>99	97 (*R*)
4	(+)-**4**	>99	95 (*R*)
5[b,c]	(+)-**3**	>99	98 (*R*)
6[b]	(+)-**4**	>99	98 (*R*)

[a] Conversions and ees were determined by HPLC with Daicel Chiralcel OJ column.
[b] Hydrogen pressure (0.1 MPa) and THF as solvent was adopted.
[c] Reaction time was 4 h.

Moreover, Me-DuPHOS is known to give 98% ee in hydrogenation of **8**.[6] When we convert its enantiodetermining groups to the coordinate scheme in Figure 4, it locates its methyl groups at the point (3.0, 2.1), very close to that of **3** and **4**, supporting our working hypothesis that shielding the sweetest spot should give high ees.

In conclusion, a new approach for investigating the impact of the location of the enantiodetermining groups on a ligand on enantioselectivity has been developed. Although more data is necessary to ensure accuracy, mapping the location of the key enantiodetermining residue on a ligand is effective in finding the sweet spot to be shielded for high enantioselection in asymmetric hydrogenations. Accumulation of the data with more ligands should reveal the location of sweet spots. Making a library of sweet spots may make it possible to select a ligand of choice out of a huge number of diphosphine ligands. Moreover, it will also enable the design of new ligands for a particular substrate based on the position of its sweet spot. That is, ligand design will be performed so that the ligand should effectively shield a targeted sweet spot.

It should be noted that in this study, only (*x*, *z*) values are discussed. The effects of protrusion of enantiodetermining groups over a metal atom (*y* values) and electronic properties are currently under investigation, which may explain the inversion of configuration observed with **1** and **2**. The absolute configurations of **3** and **4** are also yet to be determined. Efforts to synthesize more ligands, which shield other locations within the coordinate are also in progress.

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8. Our calculation afforded values below; **1**: $d = 8.36$ Å, $r = 4.18$ Å, $\theta = 33.4°$; **2**: $d = 7.44$ Å, $r = 3.73$ Å, $\theta = 26.0°$; **3**: $d = 7.32$ Å, $r = 3.68$ Å, $\theta = 33.0°$; **4**: $d = 7.30$ Å, $r = 3.68$ Å, $\theta = 33.2°$.
9. (*S*)-(*4,4′-Bi-1,3-benzodioxole*)-*5,5′-diylbis*(*3,3-di-isopropyl-phosphetane*) (*S*)-**1**: Mp 68–70 °C; ^{1}H NMR (CD_2Cl_2): δ 6.98–6.94 (m, 2H), 6.87 (d, $J = 7.7$ Hz, 2H), 5.97 (d, $J = 1.1$ Hz, 2H), 5.84 (d, $J = 1.1$ Hz, 2H), 2.13–2.07 (m, 2H), 1.92–1.87 (m, 2H), 1.70 (dd, $J = 12.6$, 23.1 Hz, 2H), 1.66 (dd, $J = 6.6$, 6.6 Hz, 2H), 1.47 (dd, $J = 6.6$, 6.6 Hz, 2H), 1.28 (dd, $J = 12.6$, 23.1 Hz, 2H), 0.89 (d, $J = 6.6$ Hz, 6H), 0.88 (d, $J = 6.6$ Hz, 6H), 0.71 (d, $J = 6.6$ Hz, 6H), 0.68 (d, $J = 6.6$ Hz, 6H); ^{31}P NMR (CD_2Cl_2) δ −27.0; EI-MS m/z 554 $(M)^+$; $[\alpha]_D = -226.5$ (c 1.0, $CHCl_3$ 98.8% ee).
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11. (*aS,S,S*)-(*4,4′-Bi-1,3-benzodioxole*)-*5,5′-diylbis*(*2,5-di-methylphospholane*) (*aS,S,S*)-**2**: Mp 163–165 °C; ^{1}H NMR ($CDCl_3$): δ 7.19 (dd, $J = 3.3$, 8.2 Hz, 2H), 6.95 (d, $J = 8.2$ Hz, 2H), 6.03 (m, 2H), 5.98 (d, $J = 1.1$ Hz, 2H), 2.65–2.50 (m, 2H), 2.42–2.26 (m, 2H), 2.23–2.05 (m, 4H), 1.64 (dddd, $J = 2.2$, 4.9, 13.2, 24.2 Hz, 2H), 1.50–1.37 (m, 2H), 1.33 (dd, $J = 7.1$, 18.1 Hz, 6H), 0.90 (dd, $J = 7.1$, 10.4, 6H); ^{31}P NMR ($CDCl_3$): δ −2.3; EI-MS m/z 469 $(M-H)^+$; $[\alpha]_D = +255.4$ (c 1.0, $CHCl_3$).
12. (+)-(*4,4′-Bi-1,3-benzodioxole*)-*5,5′-diylbis*(*diisopropyl-phosphine*) (+)-**3**: Mp 84–86 °C; ^{1}H NMR ($CDCl_3$): δ 7.03 (d, $J = 7.9$ Hz, 2H), 6.88 (d, $J = 7.9$ Hz, 2H), 5.95 (2H, $J = 1.5$ Hz, 2H), 5.80 (d, $J = 1.5$ Hz, 2H), 2.19–2.06 (m, 2H), 1.84–1.72 (m, 2H), 1.10 (dd, $J = 7.1$, 14.2 Hz, 6H), 1.07 (dd, $J = 7.1$, 14.2 Hz, 6H), 0.93 (dd, $J = 7.1$, 13.1 Hz, 6H), 0.90 (dd, $J = 7.1$, 11.0 Hz, 6H); ^{31}P NMR ($CDCl_3$): δ − 3.0; CI-MS: m/z 475 $(M)^+$; $[\alpha]_D = +6.5$ (c 1.0, $CHCl_3$).
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