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Highly Enantioselective Hydrogenation of α-Dehydroamino Acids by Rhodium Complexes with New Unsymmetric P–Chirogenic Bisphosphine Ligands

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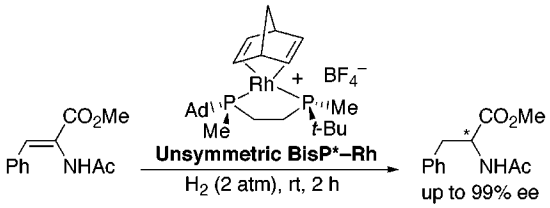
ABSTRACT



New rhodium catalysts with unsymmetric P–chirogenic bis(phosphino)ethanes, BisP*–Rh, exhibited very high enantioselectivity (98–99%) in the hydrogenation of α-dehydroamino acid derivatives. Such high enantioselectivity should result from the asymmetric environment around the Rh atom, as was shown in the molecular structure of the catalyst analyzed by X-rays. The asymmetry can be controlled by the combination of the alkyl groups on the two phosphorus atoms.

Optically active phosphine−transition metal complexes have played an important role in catalytic asymmetric synthesis.[1] Since a C_2 symmetric bisphosphine ligand, DIOP, showed high enantioselectivity, it has been considered that C_2 symmetric bisphosphine ligands are endowed with superior catalytic properties.[2] The C_2 symmetric ligands such as DIPAMP,[3] BINAP,[4] DuPHOS,[5] BIPNOR,[6] and PennPHOS[7] have exhibited high enantioselectivity over a broad range. On the other hand, it has been shown that unsymmetric bisphosphine ligands,[8] which have different groups on the two phosphorus atoms, have also been shown to be effective in some cases of asymmetric hydrogenation. However, an unsymmetric bis(trialkylphosphine) ligand has not yet been reported. We also reported previously that (*S*,*S*)-1,2-bis-(alkylmethylphosphino)ethane (alkyl = 1-adamantyl, *tert*-butyl, cyclohexyl, cyclopentyl, 1,1-diethylpropyl; abbreviated as BisP*) effected highly enantioselective hydrogenation of α-dehydroamino acids.[9]

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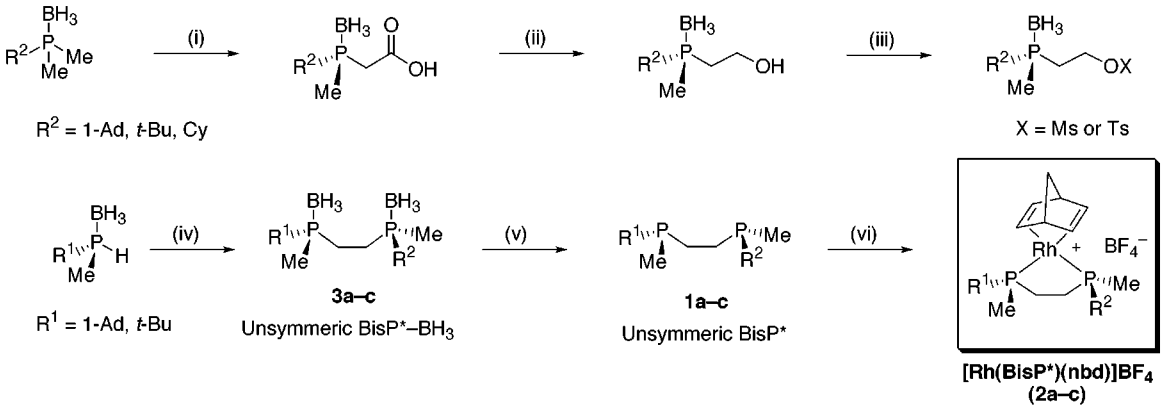
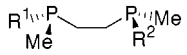
Scheme 1



i) a) *s*-BuLi/(−)-sparteine, ether, −78 °C, 3 h, b) CO_2. ii) BH_3–THF, THF, 0 °C, 1 h. iii) MsCl, CH_2Cl_2, −15 °C, 1 h or *p*-TsCl, Py, rt, 5 h. iv) a) *n*-BuLi, THF, 0 °C, 20 min, b) the tosylates or the mesylates, 55 °C, 2 h. v) a) TfOH, toluene, rt, 20 min, b) KOH/ EtOH, 55 °C, 2 h. vi) $[Rh(nbd)_2]BF_4$, THF.

Recently, we prepared rhodium complexes coordinated with new unsymmetric BisP* ligands (**1a**−**c**) which have



1a–c

Unsymmetric BisP*

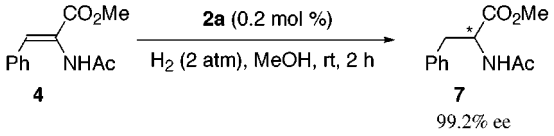
1a : R^1 = 1-Ad, R^2 = *t*-Bu
1b : R^1 = 1-Ad, R^2 = Cy
1c : R^1 = *t*-Bu, R^2 = Cy

different alkyl groups on the two P* atoms in order to introduce an asymmetric environment around the Rh atom more effectively.[10] This Letter reports a series of enantioselective hydrogenations of α-dehydroamino acid derivatives using the newly designed unsymmetric BisP*−Rh catalysts and proposes a design concept to obtain high enantioselectivity.

The synthetic route to obtain the unsymmetric BisP*−Rh is shown in Scheme 1. The bisphosphine−borane precursors, (*R*)-1-boranato[alkyl(methyl)phosphino]ethanol 2-tosylates or (*R*)-1-boranato[alkyl(methyl)phosphino]ethanol 2-mesylates, were synthesized from alkyl(dimethyl)phosphine−boranes in three steps. The tosylates and mesylates were coupled with lithiated (*S*)-alkylmethylphosphine−boranes[11] to provide (*S*,*S*)-unsymmetric BisP*−BH_3, which were converted into the corresponding cationic rhodium complexes according to the reported procedure.[12]

The preliminary hydrogenation with dehydro-*N*-acetylphenylalanine methyl ester **4** in the presence of rhodium complex **2a** provided a quantitative yield of *N*-acetylphenylalanine methyl ester **7** with 99.2% ee (*R*) (Scheme 2).

Scheme 2



Encouraged by this result, various α-dehydroamino acid derivatives were applied as reagents (Table 1). Asymmetric hydrogenation of di- or trisubstituted dehydroamino acid derivatives **4** and **5** with **1a** showed very high enantioselectivity (entries 3 and 8), although **1b** and **1c** provided **4** and **5** with considerably lower enantioselectivity (entries 4, 5, 9, and 10).

It has been considered difficult to achieve high enantioselectivity in the hydrogenation of tetrasubstituted α-dehydroamino acid derivatives.[13] The symmetric BisP*−Rh's also gave low enantiomeric excesses (entries 11, 12, 16, and 17), although they showed somewhat higher values for **6c** (entries 21 and 22). However, **1b** and **1c** showed very high enantioselectivity for the valine derivative **6a** (entries 14 and 15), although **1a** gave a low value for **6a** (entry 13). A similar tendency of enantioselectivity was observed for **6b** (entries 18−20) and **6c** (entries 23−25), although remarkable difference was observed between **1b** and **1c** in the hydrogenation of **6c**.

To examine the asymmetric environment around the rhodium atom, crystallizations of **2a**−**c** were performed. After many trials, only **2a** gave crystals suitable for X-ray work.

The molecular structure of **2a** is depicted in Figure 1.[14] The bond distances, bond angles, and torsion angles around

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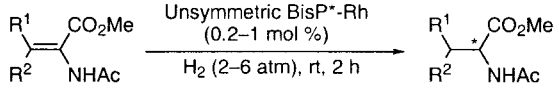
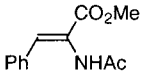
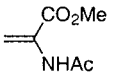
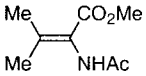
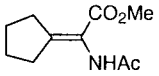
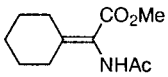
(11) Nagata, K.; Matsukawa, S.; Imamoto, T. *J. Org. Chem.* **2000**, *65*, 4185.
(12) (a) McKinstry, L.; Livinghouse, T. *Tetrahedron Lett.* **1994**, *35*, 9319. (b) Mckinstry, L.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145.
(13) (a) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (b) Sawamura, M.; Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9602.
(14) Complex **2a**: monoclinic $P2_1$ (No. 4); a = 11.045(6) Å, b = 13.512(9) Å, c = 17.94(2) Å, β = 91.98(3)°, V = 2031 Å^3, Z = 2, R = 0.055; Rw = 0.075; GOF = 1.75; bond lengths Rh1−P1 2.315(3) Å, Rh1−P2 2.316(3) Å, Rh1−nbd ca. 2.2 Å, bond angles P1−Rh1−P2 82.9(1)°, 1-Ad−P1−Me 106.3(6)°, *t*-Bu−P2−Me 104.8°, torsion angle P1−C−C−P2 48.2(9)°.

Table 1. Rh-Catalyzed Enantioselective Hydrogenation of α-Dehydroamino Acid Derivatives[a]



entry	substrate	ligand	% ee[b] (confign)[c]
1		1-Ad-BisP*	99.9 (*R*)[d]
2		*t*-Bu-BisP*	99.9 (*R*)[d]
3	**4**	Ad^{t}Bu-BisP* (**1a**)	99.2 (*R*)
4		AdCy-BisP* (**1b**)	77.7 (*R*)
5		^{t}BuCy-BisP* (**1c**)	68.7 (*R*)
6		1-Ad-BisP*	99.6 (*R*)[d]
7		*t*-Bu-BisP*	98.1 (*R*)[d]
8	**5**	Ad^{t}Bu-BisP* (**1a**)	96.2 (*R*)
9		AdCy-BisP* (**1b**)	67.9 (*R*)
10		^{t}BuCy-BisP* (**1c**)	60.0 (*R*)
11		1-Ad-BisP*	12.4 (*R*)
12		*t*-Bu-BisP*	35.9 (*R*)[d]
13		Ad^{t}Bu-BisP* (**1a**)	21.3 (*R*)
14	**6a**	AdCy-BisP* (**1b**)	94.0 (*R*)
15		^{t}BuCy-BisP* (**1c**)	93.5 (*R*)
16		1-Ad-BisP*	9.5 (*R*)
17		*t*-Bu-BisP*	14.4 (*R*)
18	**6b**	Ad^{t}Bu-BisP* (**1a**)	16.3 (*R*)
19		AdCy-BisP* (**1b**)	87.6 (*R*)
20		^{t}BuCy-BisP* (**1c**)	82.8 (*R*)
21		1-Ad-BisP*	82.4 (*R*)[d]
22		*t*-Bu-BisP*	83.6 (*R*)[d]
23		Ad^{t}Bu-BisP* (**1a**)	79.5 (*R*)
24	**6c**	AdCy-BisP* (**1b**)	98.2 (*R*)
25		^{t}BuCy-BisP* (**1c**)	85.8 (*R*)

[a]Reactions were conducted at rt and an initial H_2 pressure of 2 or 6 atm using 0.8 M MeOH solution of substrate and the catalyst precursors [(*S*,*S*)-BisP*-Rh(nbd)]$^+BF_4^-$ (0.2 or 1 mol %). Reaction time was 1–2 h, and complete conversion was observed in all cases. [b]Enatiomeric excesses were determined by chiral capillary GC using Chrompack's Chiral–L–Val column (25 m) (di- and tetrasubstituted) or HPLC using a Daicel Chiral OJ column (trisubstituted). [c]Absolute configurations were confirmed by comparison of the signs of optical rotation and chiral HPLC or GC elution order, with configurationally defined examples. [d]See Ref. 5.

the Rh and two phosphorus atoms are approximately the same as the corresponding ones of the symmetric BisP*−Rh. However, the conformation of the five-membered chelation ring is strongly distorted compared with that of the symmetric BisP*−Rh since steric repulsion of the 1-adamanyl group on P1 with the neighboring atoms is different from that of the *tert*-butyl group. The distortion is well explained by the dihedral angles between the planes of P1−Rh−P2 and Rh−P1−C1, and between the planes of P1−Rh−P2 and Rh−P2−C2. The former dihedral angle of the 1-adamantyl group is 46.9° whereas the latter one of the *tert*-butyl group is 26.7°. These values are nearly the same for the symmetric BisP*−Rh complex. Such a difference should cause a further asymmetric environment around the Rh atom. The asymmetry should be introduced when the substrate molecule comes close to the Rh atom at the transition state.

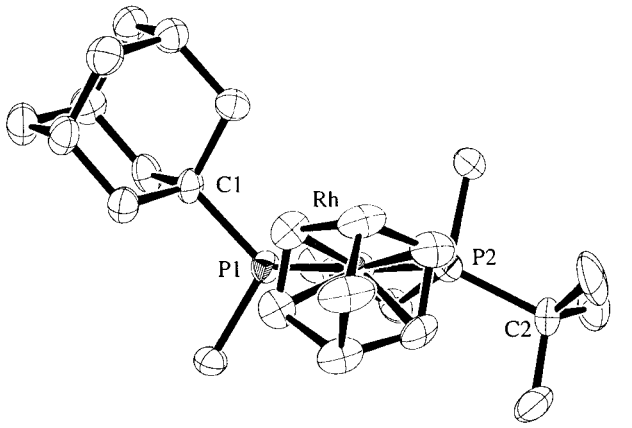


Figure 1. ORTEP drawing of rhodium complex (30% probability) [Rh((*S*,*S*)-Ad^{t}Bu-BisP*)(nbd)]BF_4 (**2a**): the hydrogen atoms and the BF_4 anion are omitted for clarity. Dihedral angles C1−P1−Rh−P2 46.9°, C2−P2−Rh−P1 26.7°.

In summary, catalytic asymmetric hydrogenation of di-, tri-, or tetrasubstituted α-dehydroamino acid derivatives by the unsymmetric BisP*−Rh **2a**−**c** gave high reactivity and enantioselectivity. X-ray crystallographic analysis of **2a** exhibited a distorted chelation ring structure compared with the corresponding ones of the symmetric BisP*−Rh complexes. This suggests that the asymmetric environment is effectively controlled by choosing the alkyl groups on the phosphorus atoms.

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Supporting Information Available: Experimental procedures for the preparation of unsymmetric BisP*−BH_3 (**3a**−**c**), a general experimental procedure for the enantioselective hydrogenation, and characterization data for compounds **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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