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Synthesis of a New Chiral Bisphosphine Ligand, MOCBP, and Its Use in Rhodium(I)-Catalyzed Asymmetric Hydrogenation of a Cyclic Enamide¹

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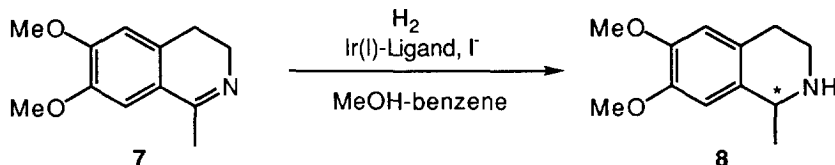
Abstract: A new chiral bisphosphine ligand (**6**) bearing a cyclobutane framework was readily prepared by using diastereoselective [2+2] cycloaddition. Its rhodium(I) complex was found to be an efficient catalyst for the asymmetric hydrogenation of a cyclic enamide, *N*-acetyl-1-methylene-1,2,3,4-tetrahydroisoquinoline (**9**), affording (*R*)-(-)-*N*-acetylsalsolidine (**10**) in up to 80.6% ee.

Much progress has been made in the enantioselective synthesis of various amines including biologically active alkaloids. Although numerous methods for the synthesis of optically active amines and their derivatives have been developed employing enantioselective or diastereoselective reactions with a stoichiometric amount of chiral reagents or auxiliaries,² only a few methods using chiral catalysts have been reported; such as chiral bisphosphine-rhodium(I),³ -iridium(I)⁴ or ruthenium(II) complexes,⁵ a chiral titanium complex,⁶ chiral aminoalcohol-borane complexes,⁷ and a chiral aminoether.⁸ Therefore, it is still a major target of research to develop new efficient catalysts for the enantioselective conversion of prochiral imines or their synthons to the corresponding chiral amines or their derivatives.

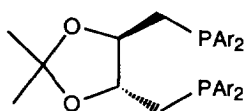
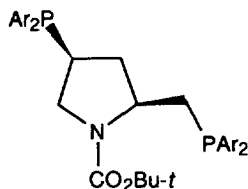
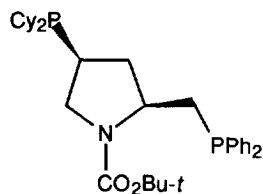
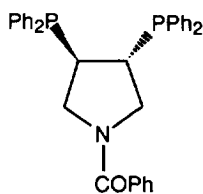
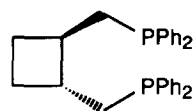
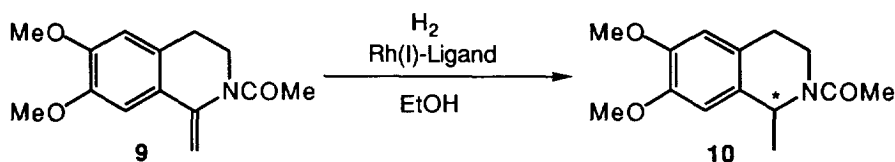
Recently, we reported that modified DIOPs (**1b,c**) showed excellent enantioselectivities in the rhodium(I)- or iridium(I)-catalyzed asymmetric hydrogenations of α -phenyl-substituted enamides (substrate/catalyst (S/C)=200~1000, ~76.7% ee)⁹ and a cyclic imine, 2,3,3-trimethylindolenine (S/C=100, 81.4% ee).¹⁰ As a part of our continued effort to synthesize optically active amines and their derivatives using chiral catalysts, our attention has been focused on the development of efficient methods for the construction of naturally occurring cyclic amines or their derivatives as optically active forms.

This communication describes the synthesis of a new efficient chiral bisphosphine ligand (**6**) and its use in the rhodium(I)-catalyzed asymmetric hydrogenation of a cyclic enamide (**9**) leading to an optically active *N*-acetyl-1,2,3,4-tetrahydroisoquinoline, *N*-acetylsalsolidine (**10**).

We first carried out the asymmetric hydrogenation of a six-membered cyclic imine (**7**) with a neutral iridium(I) complex of a modified DIOP, (*R,R*)-MOD-DIOP (**1c**),¹¹ (S/C=100) in the presence of tetrabutyl-



ammonium iodide under a hydrogen pressure of 100 atm. The conversion was 91%, but the ee of **8** was low (27.5% (*R*)). Other bisphosphine ligands, BPPM (**2a**) and BCPM (**3**), also showed very low enantioselectivity, although the latter and its analogs had been revealed by our group to have excellent enantioselectivity in the rhodium(I)-catalyzed asymmetric hydrogenation of several functionalized ketones.¹²

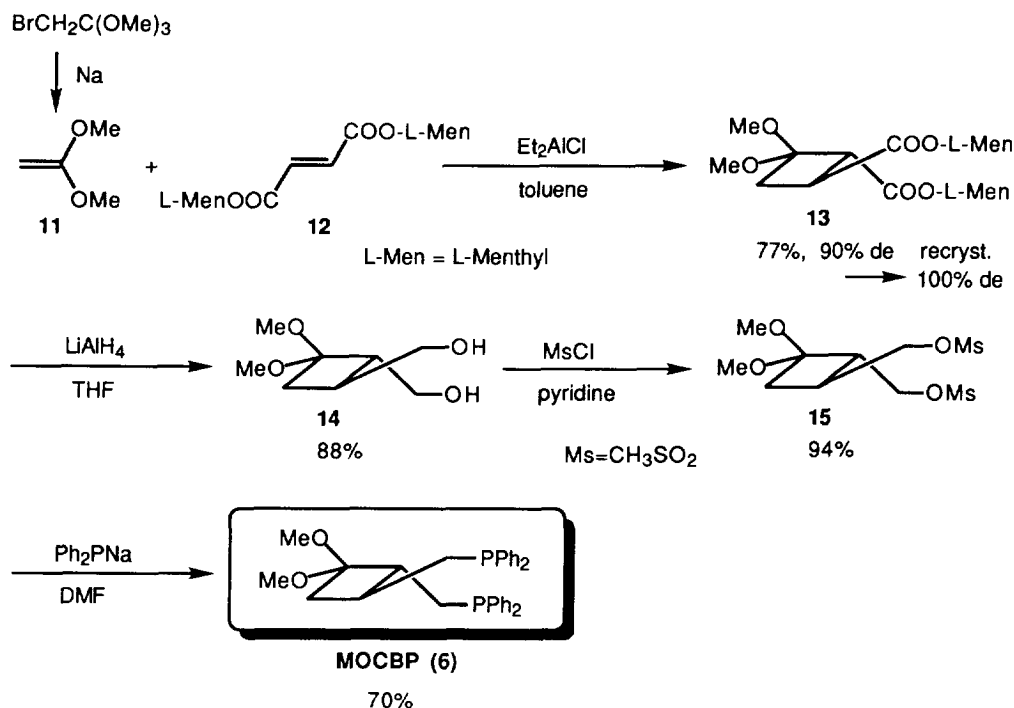
(4*R*,5*R*)-DIOP (**1a**): Ar = C₆H₅(4*R*,5*R*)-*p*-MeO-DIOP (**1b**): Ar = C₆H₄OMe-*p*(4*R*,5*R*)-MOD-DIOP (**1c**): Ar = C₆H₂Me₂-*m,m'*-OMe-*p*(2*S*,4*S*)-BPPM (**2a**): Ar = C₆H₅(2*S*,4*S*)-*p*-MeO-BPPM (**2b**): Ar = C₆H₄OMe-*p*(2*S*,4*S*)-BCPM (**3**)(3*R*,4*R*)-Degphos(*N*-Benzoyl) (**4**)(1*R*,2*R*)-C4DIOP (**5**)Table 1. Asymmetric Hydrogenation^{a)} of *N*-Acetyl-1-methylene-1,2,3,4-tetrahydroisoquinoline (**9**) Catalyzed by Bisphosphine-Rh(I) Complexes

Entry	Ligand	Rh	Subst./Cat.	atm	Convsn. ^{b)} (%)	ee ^{c)} (%)
1	(<i>R,R</i>)-DIOP (1a)	Rh ⁺ (COD)BF ₄ ⁻	1000	5	72	40.5 (<i>S</i>)
2	(<i>R,R</i>)- <i>p</i> -MeO-DIOP (1b)	Rh ⁺ (COD)BF ₄ ⁻	1000	5	100	51.6 (<i>S</i>)
3	(<i>R,R</i>)-MOD-DIOP (1c)	Rh ⁺ (COD)BF ₄ ⁻	200	1	100	62.4 (<i>S</i>)
4	(<i>S,S</i>)- <i>p</i> -MeO-BPPM (2b)	[Rh(COD)Cl] ₂	200	1	100	48.4 (<i>S</i>)
5	Degphos (<i>N</i> -Benzoyl) (4)	Rh ⁺ (COD)BF ₄ ⁻	200	1	100	29.1 (<i>S</i>)
6	MOCBP (6)	Rh ⁺ (NBD)ClO ₄ ⁻	200	1	100	25.6 (<i>S</i>)
7		Rh ⁺ (NBD)ClO ₄ ⁻	200	1	98	46.2 (<i>R</i>)
8		Rh ⁺ (COD)BF ₄ ⁻	200	1	100	80.6 (<i>R</i>) ^{d)}
9		Rh ⁺ (COD)BF ₄ ⁻	500	1	100	80.6 (<i>R</i>)
10		Rh ⁺ (COD)BF ₄ ⁻	200	5	100	76.6 (<i>R</i>)

a) All hydrogenations were carried out with 1.0 mmol of substrate (**9**) and 1×10^{-3} – 5×10^{-3} mmol of rhodium(I) complex of ligand in 5 ml of ethanol at 50°C for 20 h (except entry 9 (40 h)) under a hydrogen pressure of 1–5 atm. b) Determined by HPLC. c) Determined by HPLC with a chiral column, CHIRALCEL AS (Daicel Chemical Industries) employing hexane/isopropyl alcohol (20:1) as the solvent system. The absolute configuration was determined on the basis of the sign of optical rotation.^{5b, 13} The maximum optical rotation value of pure (*R*)-**10** was estimated to be $[\alpha]_D^{23}$ -192.5 (CHCl₃) on the basis of d). d) $[\alpha]_D^{23}$ -155.2 (*c* 1.85, CHCl₃).

Then, we tried the asymmetric hydrogenation of an enamide (**9**) derived from **7** by using several bisphosphine-rhodium(I) complexes. The results are summarized in Table 1. The rhodium(I) complex of *p*-MeO-DIOP (**1b**) showed higher catalytic activity and better enantioselectivity than that of DIOP (**1a**) (Entries 1 and 2), and the cationic rhodium(I) complex exhibited better enantioselectivity than the neutral one (Entry 4). In the previous communication,^{9a} we have revealed that MOD-DIOP (**1c**) exhibits peculiar reversal of chirality (*R*-selectivity) in the rhodium(I)-catalyzed hydrogenation of *N*-phenyl-*N*-(1-phenylvinyl)acetamides in comparison with DIOP (**1a**) (*S*-selectivity). However, in the present case (Entry 5), MOD-DIOP (**1c**) showed the same *S*-selectivity as DIOP (**1a**) and *p*-MeO-DIOP (**1b**) did, and the enantioselectivity with **1c** was worse than that with **1a** or **1b**. A modified BPPM, *p*-MeO-BPPM (**2b**),¹⁴ and Degphos (**4**),¹⁵ which are known to have high enantioselectivity in the rhodium(I)-catalyzed hydrogenation of *N*-acyldehydroamino acids, also did not show high enantioselectivity (Entries 6 and 7).

Previously, it was demonstrated that the torsional angle of bisphosphine ligands, DIOP analogs containing carbocyclic frameworks, has effect on the enantioselectivity in the hydrogenation of *N*-acyldehydroamino acids.¹⁶ Among them, C4DIOP (**5**) was shown to possess the highest selectivity, but for the synthesis of C4DIOP (**5**) troublesome optical resolution was needed to employ. Therefore, we planned to synthesize a new chiral bisphosphine ligand (**6**) bearing a four-membered ring by using diastereoselective [2+2] cycloaddition as a key reaction. The new ligand, (2*R*,3*S*)-2,3-bis[(diphenylphosphino)methyl]-1,1-dimethoxycyclobutane (**6**)¹⁷ (abbreviated to MOCBP), was synthesized in good overall yield by a sequence of reactions starting with the cycloaddition of di-*L*-menthyl fumarate (**12**) and ketene dimethylacetal (**11**),¹⁸ followed by LiAlH₄ reduction,¹⁸ mesylation, and diphenylphosphination¹⁹ as shown in Scheme 1.



Scheme 1

The asymmetric hydrogenation of **9** using **6** as a ligand was carried out under the conditions described in Table 1. A high enantioselectivity with 80.6% ee was achieved (Entry 8). Even in a larger S/C ratio (500), the

reaction proceeded completely to give the product (**10**) with the same ee (Entry 9). The effect of changing the hydrogen pressure on the enantioselectivity was observed (Entry 10).

Thus, we synthesized a new chiral bisphosphine ligand, MOCBP (**6**), by using diastereoselective [2+2] cycloaddition, and found that its rhodium(I) complex was an efficient catalyst for the asymmetric hydrogenation of a cyclic enamide, *N*-acyl-1-methylene-1,2,3,4-tetrahydroisoquinoline (**9**), affording (*R*)-(-)-*N*-acetylsalsolidine (**10**) in up to 80.6% ee.

Further application and modification of the ligand, MOCBP (**6**), are in progress.

References and Notes

- Asymmetric Reactions Catalyzed by Chiral Metal Complexes. LXIV.
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- 6**: a colorless viscous oil, $[\alpha]_D^{23} +17.8$ (*c* 2.2, CHCl₃); ³¹P{¹H} NMR (202 MHz, CDCl₃) δ /ppm: -20.6, -20.3.
- Optically pure **13** and **14** were prepared essentially according to the reported procedure [Ahmad, S. *Tetrahedron Lett.* **1991**, *32*, 6997.].
- Diphenylphosphination with lithium diphenylphosphide in THF was far less effective than that with sodium diphenylphosphide in DMF.