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Catalytic Asymmetric Hydrogenation of Dimethyl Itaconate with Trans-Chelating Chiral Diphosphine Ligands TRAP–Rhodium Complexes

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Abstract: Asymmetric hydrogenation of dimethyl itaconate catalyzed by the transchelating chiral diphosphine (R,R)-(S,S)-EtTRAP-rhodium complex gave (S)-dimethyl 2-methylsuccinate with 96% ee. Dimethyl 2-isopropylidenesuccinate, a tetrasubstituted olefin substrate, was also hydrogenated with (R,R)-(S,S)-BuTRAP-rhodium complex in high enantioselectivity (78% ee), but with opposite enantioselection.

INTRODUCTION

Catalytic asymmetric hydrogenation of olefins has been intensively studied with chiral phosphinerhodium complexes.² Most of the chiral phosphine ligands so far used have been cis-chelating bidentate diphosphines. The use of trans-chelating chiral diphosphines in the asymmetric hydrogenation has been scarcely studied,^{3,4} although it seems to be interesting not only from synthetic chemistry standpoint but also for organometallic chemistry. Recently, we have developed a series of chiral diphosphines TRAPs (Figure 1),⁵⁻⁷ which were designed to coordinate to transition metals in the trans-chelating manner. We have already reported the application of TRAPs to the asymmetric hydrogenation of α -acetamidoacrylates including β , β -disubstituted α -acetamidoacrylates, tetrasubstituted olefins.^{3,8} Herein, we wish to report the asymmetric hydrogenation of dimethyl itaconate 1⁹ and dimethyl 2-isopropylidenesuccinate 12 in the presence of rhodium complexes coordinated with TRAPs.



Dedicated to the memory of Professor Hidemasa Takaya, deceased on 5 October 1995

RESULTS AND DISCUSSION

The asymmetric hydrogenation of 1 was performed with 0.5 mol% cationic (R,R)-(S,S)-TRAPrhodium catalyst prepared in situ from $[Rh(COD)_2]BF_4$ and (R,R)-(S,S)-TRAP in CH₂Cl₂ (Scheme 1). The results were shown in Table 1. (R,R)-(S,S)-EtTRAP, which bears the flexible and least bulky *P*-substituents, was found to be most effective for the enantioselective hydrogenation. The hydrogenation of 1 with EtTRAPrhodium complex proceeded smoothly, producing (S)-dimethyl 2-methylsuccinate 2 with 96% ee in a quantitative yield (entry 1). Decrease in the catalyst amount (0.05 mol%) did not cause a decrease of the enantioselectivity (entry 2). Of note is that the *P*-substituents of TRAP have a remarkable effect on the enantioselectivity. Slight increase in length of the *P*-alkyl chains (e.g., BuTRAP: 86% ee) resulted in a significant decrease of the enantioselectivity (entry 3). The primary alkyl substituents branched at the β -position on the phosphorus brought about very low selectivity (entry 4). The hydrogenation with *i*-PrTRAP gave 2 only in 25% yield and 30% ee together with a trace of 3, which arose from isomerization of olefin 1 (entry 5). The sterically congested *iso*-propyl groups on phosphorus atoms would encumber the coordination of 1 on the rhodium atom. Ph- and FurTRAP, which have rigid *P*-aromatic substituents, were less effective for the asymmetric hydrogenation than Et- and BuTRAP (entry 6,7).

Scheme 1



Table 1. Asymmetric Hydrogenation of 1 Catalyzed by (R,R)-(S,S)-TRAP-rhodium complexes.^a

entry	Ligand	time, h	conversion, % ^b	2:3	ee, % ^c	configd
1	EtTRAP	6	100	100:0	96	s
2 ^e	EtTRAP	72	100	99:1	95f	S
3	BuTRAP	6	100	100 : 0	86	S
4	i-BuTRAP	6	100	100:0	17	S
5	i-PrTRAP	6	25	99 :1	30	S
6	PhTRAP	3	100	100 : 0	26	R
7	FurTRAP	6	100	100:0	7	R

^a The ratio of 1 (1 mmol, 0.5 M):[Rh(COD)₂]BF₄:TRAP was 200:1:1.1 unless otherwise noted. ^b Determined by ¹H NMR analysis of crude product. ^c Determined by HPLC analysis of 2 with a chiral stationary phase column Chiralcel OD-H. ^d Assigned by specific rotation. ^e The ratio of 1 (10 mmol, 2 M):[Rh(COD)₂]BF₄:TRAP was 2000:1:1.1. $f[\alpha]^D_{25}$ -5.70 (neat), lit. $[\alpha]^D_{25}$ +6.11 (neat) for (R)-2 in ref 10.

Deuteriation of 1 with EtTRAP-rhodium complex gave some insight into the present asymmetric hydrogenation with respect to the formation of 3 (Scheme 2).¹¹ The deuteriation proceeded under reflux in CH₂Cl₂ for 6 hrs to afford a mixture of deuteriation product 4 (90% ee) and 3 (92:8) in 41% conversion, and was completed in 24 hrs to give only 4 (90% ee) in 98% yield. Any other products (3 and 5 etc.) were not

detected at all. The findings indicate that the isomerization of 1 may not occur through β -hydride elimination of 9, but takes place via reversible formation of olefin rhodium complexes 7 and 11 through π -allyl hydride rhodium intermediate 10 (Scheme 3).¹² It is to be noted that the coordination of 1 to rhodium atom precedes an oxidative addition of hydrogen onto rhodium atom. Subsequent insertion of the olefin coordinated to the hydride rhodium bond of 8 followed by reductive elimination gave the optically active 4 and 6.

Scheme 2



Scheme 3



Next, the asymmetric hydrogenation of dimethyl 2-isopropylidenesuccinate 12, a tetrasubstituted olefin, was attempted with TRAP-rhodium complexes (Scheme 4). As shown in Table 2, (R,R)-(S,S)-EtTRAP-rhodium complex did not provide with sufficient catalytic activity and high enantioselectivity in the asymmetric hydrogenation of 12 in CH₂Cl₂ (entry 1). However, the hydrogenation of 12 in *i*-PrOH with EtTRAP-rhodium catalyst proceeded smoothly at 20 °C to give (S)-dimethyl 2-isopropylsuccinate with moderate enantoselectivity in high yield (entry 2). No olefinic isomerization of 12 was detected. It is remarkable that the sense of enantioselection induced was opposite to that for the asymmetric hydrogenation of dimethyl itaconate 1. Of interest is that such inversion of enantiofaceselection was also observed in the asymmetric hydrogenation of β -unsubstituted α -acetamidoacrylate vs. β , β -disubstituted α -acetamidoacrylates.³ Use of BuTRAP improved the enantioselectivity in the asymmetric hydrogenation of 12 in a 2 M CH₂Cl₂ solution at 0 °C for 26 hrs with atmospheric pressure of H₂ in the presence of 0.5 mol% of BuTRAP-rhodium complex, (S)-dimethyl 2-isopropylsuccinate 13 was produced with 78% ee in 96% conversion. On the other

hand, the rhodium complex coordinated with *i*-BuTRAP, which has primary but β -branched alkyl substituent on the phosphorus, had little catalytic activity (entry 5). The hydrogenation of **12** did not work well with ligands, bearing secondary alkyl (entry 6) or rigid bulky aromatic substituents (entry 7, 8).

Scheme 4



entry	Ligand	solvent	temp, °C	conv, % ^b	ee, % ^c	configd
1	EtTRAP	CH ₂ Cl ₂	30	55	58	S
2	EtTRAP	i-PrOH	20	96	68	S
3	BuTRAP	i-PrOH	20	98	71 ^e	S
4f	BuTRAP	i-PrOH	0	96	78	S
5	i-BuTRAP	i-PrOH	20	5		_
6	<i>i</i> -PrTRAP	i-PrOH	20	5	_	
7	PhTRAP	i-PrOH	20	trace	_	_
8	FurTRAP	<i>i</i> -PrOH	20	13	6	R

Table 2. Asymmetric Hydrogenation of 12 Catalyzed by (R,R)-(S,S)-TRAP-rhodium complexes.^a

^a The ratio of 12 (1 mmol, 0.5 M) : $[Rh(COD)_2]BF_4$: TRAP was 200 : 1 : 1.1 unless otherwise noted. No byproduct was observed. ^b Determined by ¹H NMR analysis of crude product. ^c Determined by HPLC analysis of 12 with a chiral stationary phase column Chiralcel OB-H. ^d Assigned by specific rotation. ^e $[\alpha]^{D}_{20}$ +13.93 (c 1.148, CHCl₃), lit. $[\alpha]^{D}_{20}$ +17 (c 1, CHCl₃) for (S)-13 in ref 13. ^f The reaction was performed in 2 M solution of 12.

The inversion of the enantiofaceselection in the asymmetric hydrogenation of 12 coupled with the lack of olefin isomerization of 12 might suggest any different reaction mechanism for the hydrogenation of 1 and 12. We present a possible mechanism for the hydrogenation of 12, which involves an oxidative addition of hydrogen to rhodium prior to olefin coordination (Scheme 5),¹⁴ as proposed for the asymmetric hydrogenation of β_{β} -disubstituted α -acetamidoacrylates catalyzed by EtTRAP-rhodium complex.

Scheme 5



EXPERIMENTAL

General: Optical rotation was measured with a Perkin Elmer 243 polarimeter. ¹H NMR spectra were obtained with a Varian VXR-200 spectrometer. Dimethyl itaconate was commercially available and purified by distillation before use. Dimethyl 2-isopropylidenesuccinate¹⁵ and [Rh(COD)₂]BF4¹⁶ was prepared by literature method. CH₂Cl₂ and *i*-PrOH was distilled under nitrogen over CaH₂.

Asymmetric Hydrogenation of Dimethyl Itaconate (1) with EtTRAP-Rhodium Catalyst: A mixture of $[Rh(COD)_2]BF_4$ (1.0 mg, 2.5 µmol) and (R,R)-(S,S)-EtTRAP (1.7 mg, 2.8 µmol) in dry degassed CH₂Cl₂ (0.5 ml) was stirred at room temperature for 10 min in argon atmosphere, and then a degassed solution of 1 (790 mg, 5.0 mmol) in CH₂Cl₂ (4.5 ml) was added via cannula. Immediately, the mixture was further degassed by two freeze-thaw cycles, before hydrogen was introduced into the reaction vessel. Then, the reaction mixture was vigorously stirred under reflux for 72 hrs. After the solvent was evaporated, the residue was subjected to bulb-to-bulb distillation giving 789 mg (99 %) of (S)-2: Colorless oil; bp 100 °C (bath temp)/18 mmHg; ¹H NMR (200 MHz, CDCl₃, TMS) δ 1.23 (d, J = 7.1 Hz, 3H), 2.41 (dd, J = 16.4 and 6.0 Hz, 1H), 2.75 (dd, J = 16.4 and 8.0 Hz, 1H), 2.83-3.02 (m, 1H), 3.68 (s, 3H), 3.70 (s, 3H).

Asymmetric Hydrogenation of Dimethyl 2-Isopropylidenesuccinate (12) with BuTRAP-Rhodium Catalyst: A mixture of $[Rh(COD)_2]BF_4$ (2.0 mg, 5.0 µmol) and (R,R)-(S,S)-BuTRAP (3.9 mg, 5.5 µmol) in dry *i*-PrOH (0.5 ml) was stirred at room temperature for 10 min in argon atmosphere, and 12 (186 mg, 1.0 mmol) was added. Immediately, the flask was cooled at -78 °C, and evacuated and filled with hydrogen. Then, the reaction mixture was stirred at 0 °C for 24 h. After the solvent was evaporated, the residue was purified by bulb-to-bulb distillation giving 179 mg (96 %) of (S)-13: Oil; bp 125 °C (bath temp)/18 mmHg; ¹H NMR (200 MHz, CDCl₃, TMS) δ 0.93 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 1.90-2.09 (m, 1H), 2.42 (dt, J = 12.5 and 8.8 Hz, 1H), 2.66-2.82 (m, 2H), 3.67 (s, 3H), 3.70 (s, 3H).

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