Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 10, pp. 2521-2526, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00330-4

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

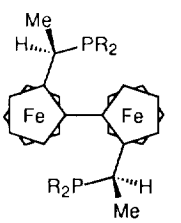
Ryoichi Kuwano, Masaya Sawamura[1] and Yoshihiko Ito*

Department of Synthetic Chemistry and Biological Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606-01, Japan

Abstract: Asymmetric hydrogenation of dimethyl itaconate catalyzed by the trans-chelating 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 phosphine-rhodium 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 **1**[9] and dimethyl 2-isopropylidenesuccinate **12** in the presence of rhodium complexes coordinated with TRAPs.



(*R*,*R*)-(*S*,*S*)-TRAP

R = Et : EtTRAP
R = Bu : BuTRAP
R = *i*-Bu : *i*-BuTRAP
R = *i*-Pr : *i*-PrTRAP
R = Ph : PhTRAP
R = 2-Fur : FurTRAP

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*)-TRAP–rhodium catalyst prepared in situ from $[Rh(COD)_2]BF_4$ and (*R,R*)-(*S,S*)-TRAP in CH_2Cl_2 (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 EtTRAP–rhodium 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

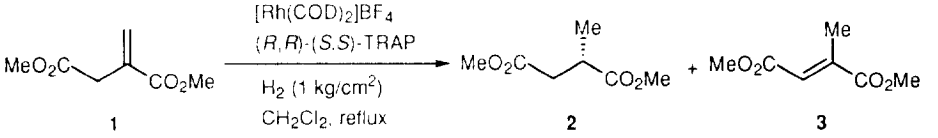


Table 1. Asymmetric Hydrogenation of **1** Catalyzed by (*R,R*)-(*S,S*)-TRAP–rhodium complexes.[a]

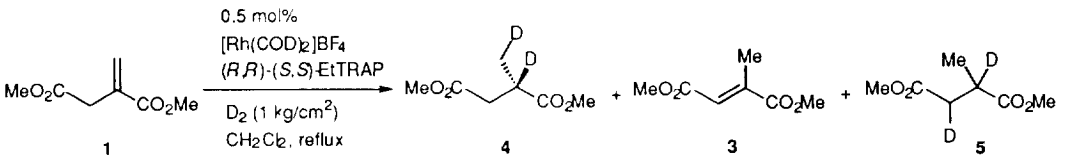
entry	Ligand	time, h	conversion, %[b]	**2** : **3**	ee, %[c]	config[d]
1	EtTRAP	6	100	100 : 0	96	*S*
2[e]	EtTRAP	72	100	99 : 1	95[f]	*S*
3	BuTRAP	6	100	100 : 0	86	*S*
4	*i*-BuTRAP	6	100	100 : 0	17	*S*
5	*i*-PrTRAP	6	25	99 : 1	30	*S*
6	PhTRAP	3	100	100 : 0	26	*R*
7	FurTRAP	6	100	100 : 0	7	*R*

[a] The ratio of **1** (1 mmol, 0.5 M):$[Rh(COD)_2]BF_4$: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):$[Rh(COD)_2]BF_4$: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.

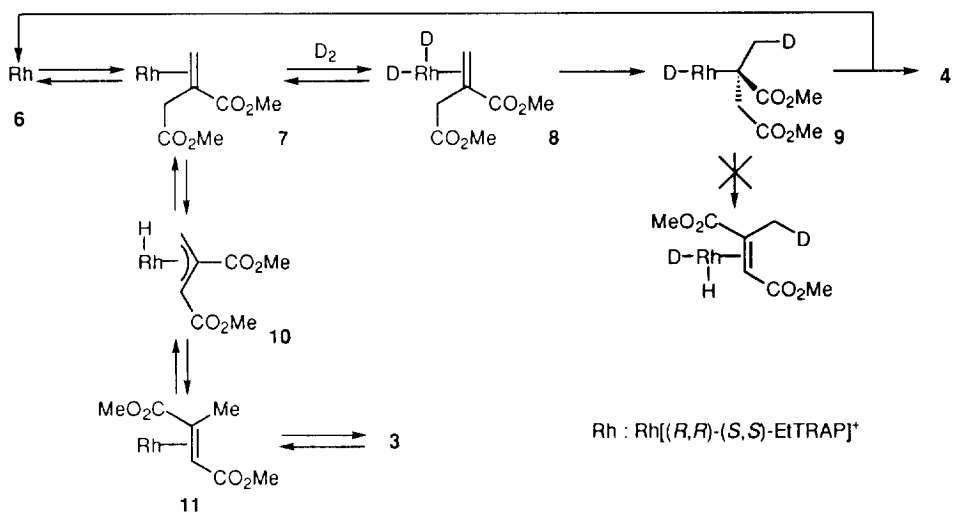
Deuteriation of **1** with EtTRAP–rhodium complex gave some insight into the present asymmetric hydrogenation with respect to the formation of **3** (Scheme 2).[11] The deuteriation proceeded under reflux in CH_2Cl_2 for 6 hrs to afford a mixture of deuteriation product **4** (90% ee) and **3** (92:8) 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



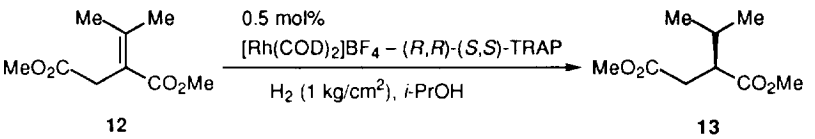
Scheme 3



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 CH_2Cl_2 (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** (entry 3, 4). On treatment of **12** in a 2 M CH_2Cl_2 solution at 0 °C for 26 hrs with atmospheric pressure of H_2 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



12 **13**

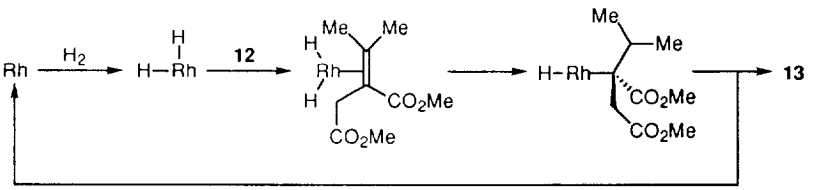
Table 2. Asymmetric Hydrogenation of **12** Catalyzed by (*R*,*R*)-(*S*,*S*)-TRAP–rhodium complexes.[a]

entry	Ligand	solvent	temp, °C	conv, %[b]	ee, %[c]	config[d]
1	EtTRAP	CH_2Cl_2	30	55	58	*S*
2	EtTRAP	*i*-PrOH	20	96	68	*S*
3	BuTRAP	*i*-PrOH	20	98	71[e]	*S*
4[f]	BuTRAP	*i*-PrOH	0	96	78	*S*
5	*i*-BuTRAP	*i*-PrOH	20	5	—	—
6	*i*-PrTRAP	*i*-PrOH	20	5	—	—
7	PhTRAP	*i*-PrOH	20	trace	—	—
8	FurTRAP	*i*-PrOH	20	13	6	*R*

[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, $CHCl_3$), lit. $[\alpha]^D_{20}$ +17 (*c* 1, $CHCl_3$) 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. ^{1}H NMR spectra were obtained with a Varian VXR-200 spectrometer. Dimethyl itaconate was commercially available and purified by distillation before use. Dimethyl 2-isopropylidenesuccinate[15] and $[Rh(COD)_2]BF_4$[16] was prepared by literature method. CH_2Cl_2 and *i*-PrOH was distilled under nitrogen over CaH_2.

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 CH_2Cl_2 (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 CH_2Cl_2 (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; ^{1}H NMR (200 MHz, $CDCl_3$, 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; ^{1}H NMR (200 MHz, $CDCl_3$, 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).

Acknowledgment. This work was supported by Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists.

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(*Received in UK* 4 *September* 1995)