Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 1, pp. 23-26, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(94)00342-4

Reversal of Chirality Induced by *m*-Methyl Substitution of DIOP in the Rhodium(I)-Catalyzed Asymmetric Hydrogenation of α-Phenyl-Substituted Enamides[1)]

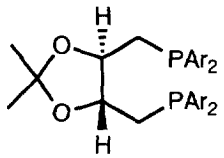
Toshiaki Morimoto, Noriya Nakajima, and Kazuo Achiwa*

School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka-shi 422, Japan

Abstract: Remarkable effects of the substituted diphenylphosphino groups of modified DIOPs on the enantioselectivity were observed in the asymmetric hydrogenation of α-phenyl-substituted enamides using their rhodium(I) complexes as catalysts. MOD-DIOP bearing *p*-methoxy and *m*,*m*'-dimethyl groups was found to show reversal of chirality in the hydrogenation of *N*-phenyl-*N*-(1-phenylvinyl)acetamides in comparison with DIOP and its other analogs.

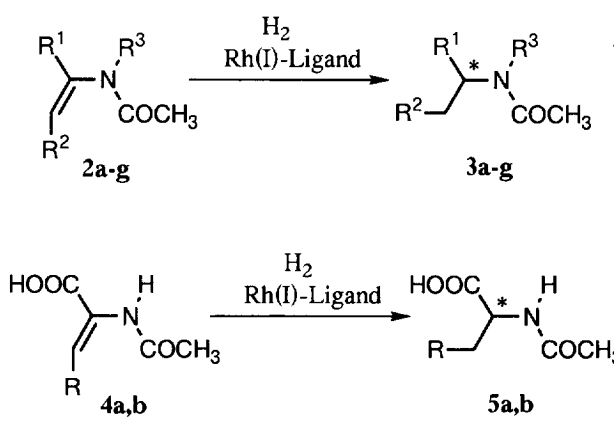
In our previous studies on the development of efficient chiral bisphosphine ligands for asymmetric hydrogenations, we proposed a design idea, "respective control concept" and prepared several efficient ligands such as BCPMs, DIOCP, modified DIOPs, and modified BPPMs.[2)] Among them, a modified DIOP ((*R*,*R*)-MOD-DIOP (**1e**)) bearing both *p*-methoxy and *m*,*m*'-dimethyl groups was found to be an efficient ligand in the rhodium(I)-catalyzed asymmetric hydrogenation of itaconic acid and its derivatives, affording (*S*)-products in high ee.[3)] Recently, we reported the asymmetric hydrogenations of enamides, (*Z*)-*N*-(1-phenylpropenyl)-acetamide (**2a**) and (*Z*)-α-(acetamido)cinnamic acid (**4a**) catalyzed by rhodium(I) complexes of DIOP (**1a**) and modified DIOPs (**1b-e**).[4)] Contrary to the results on the asymmetric hydrogenation of itaconic acids, *m*-methyl groups or *p*-dimethylamino groups of modified DIOPs (**1b,d**) were less effective for the enantioselection of **2a** (Entries 2, 4 in Table 1); in particular, the enantioselectivity of **1e** was very low (Entry 5). On the other hand, in the rhodium(I)-catalyzed asymmetric hydrogenation of **4a**, all (*R*,*R*)-DIOP (**1a**) and its analogs (**1b-e**) gave (*R*)-product (**5a**) in good enantiomeric excess; modified DIOPs bearing *m*-methyl groups showed somewhat better enantioselectivity. The hydrogenation of **4b** using **1a** or **1e** as the ligand also gave similar results. These results prompted us to investigate the effects of *m*-methyl groups of modified DIOPs on the enantioselectivity in the asymmetric hydrogenations of other enamides bearing α-phenyl groups.

This communication describes the remarkable effects of the substituents of DIOPs (**1b-e**) on the enantioselectivity in the asymmetric hydrogenation of α-phenyl-substituted enamides (**2a-f**).



(4*R*,5*R*)-DIOPs

1a: Ar=C_6H_5
1b: Ar=*p*-$Me_2NC_6H_4$
1c: Ar=*p*-$MeOC_6H_4$
1d: Ar=*m*-MeC_6H_4
1e: Ar=*p*-MeO-*m*,*m*'-$Me_2C_6H_2$



	R^1	R^2	R^3
a	Ph	Me	H
b	Ph	H	Ph
c	*p*-$MeOC_6H_4$	H	Ph
d	*p*-$O_2NC_6H_4$	H	Ph
e	*o*-MeC_6H_4	H	Ph
f	*m*-MeC_6H_4	H	Ph
g	*t*-Bu	H	Ph

	R
a	Ph
b	H

Scheme 1

We first carried out the asymmetric hydrogenation of an enamide, *N*-phenyl-*N*-(phenylvinyl)acetamide (**2b**), using rhodium(I) complexes of (*R,R*)-DIOP (**1a**) and modified (*R,R*)-DIOPs (**1b-e**) (subst./Rh = 200, 1 atm). The results are summarized in Table 1. The rhodium(I) complexes of DIOP (**1a**) and *p*-MeO-DIOP (**1c**) showed similar selectivities giving (*S*)-product (**3b**) in moderate ee's (Entries 6, 9), but the enantioselectivies of *p*-Me_2N-DIOP (**1b**) and *m*-Me-DIOP (**1d**) were quite low (Entries 8, 10). Surprisingly, the rhodium(I) complex of (*R,R*)-MOD-DIOP (**1e**) showed reversal of chirality affording (*R*)-product (**3b**) in high ee in comparison with the complexes of **1a** and **1c** giving (*S*)-product (**3b**) (Entries 6, 9, 11). The asymmetric hydrogenations of other enamides (**2c,d,f**) bearing a group of *p*-MeO, *p*-O_2N, or *m*-Me gave similar results; the rhodium(I) complexes of **1a** and **1c** affording (*S*)-products, and that of **1e** giving (*R*)-products (Entries 15-19, 22, 23). Very few examples showing reversal of chirality caused by substituents on the diphenylphosphino groups of bisphosphine ligands are known; *o*-methoxy-substituted DIOP was shown to have reversal of chirality in the rhodium(I)-catalyzed asymmetric hydrogenations of α-(*N*-acylamino)acrylic acids and their esters compared with the original DIOP (**1a**).[5] The enantioselectivity using **1e** was dramatically reduced by changing the substrate structure, **2b** (R=Ph) with **2e** (R=*o*-MeC_6H_4) (Entry 21). In case of the enamide (**2g**) bearing an α-*t*-Bu group instead of Ph, both **1c** and **1e** showed the same chirality although the enantioselectivity was low (Entries 24, 25). The effects of changing the hydrogen pressure and the temperature on the enantioselectivity were investigated; a higher pressure (20 atm) or a lower temperature (0 °C) effected somewhat lower enantioselectivity (Entries 7, 12, 13). These effects may be explained by the Halpern's mechanism;[6] the major enantiomer of the product arises from the less stable diastereomer of the substrate-catalyst adduct intermediate.

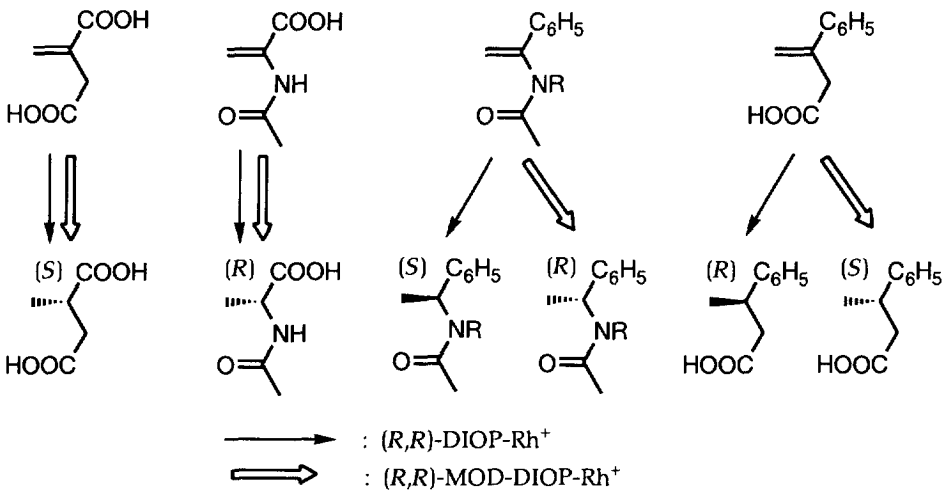
We next carried out the asymmetric hydrogenation of 3-phenyl-3-butenoic acid with rhodium(I) complexes of (*R,R*)-DIOP (**1a**) and (*R,R*)-MOD-DIOP (**1e**) in order to investigate the effect of the phenyl group of the substrate on the enantioselectivity. The results are depicted in Scheme 2 along with the results on the hydrogenations of itaconic acid, *N*-acyldehydroamino acid, and α-phenylenamide. MOD-DIOP (**1e**) possesses the same chiral recognition property for all these functionalized olefins, but **1a** and **1c** show a different property to these phenyl substituted olefins in comparison with **1e**. In other words, the enantioselectivity of enamides (**2**) with **1e** is the same with those of *N*-acyldehydroamino acid, itaconic acid, and its derivatives with **1a,c,e**. Although the quite opposite enantioselectivity of MOD-DIOP (**1e**) in comparison with the other DIOPs (**1a,c**) is not clearly understood, a possible mechanism for the reversal of chirality may be explained as follows.

Table 1. Asymmetric Hydrogenation of Enamides (**2a-g**) Catalyzed by Rh(I) Complexes of DIOPs (**1a-e**)[a]

Entry	Enamide				Ligand	Rh[b]	S/C	atm	°C	h	Convn[c] (%)	ee[d] (%)
	R^1	R^2	R^3									
1	Ph	Me	H	**2a**	**1a**	Rh^+	1000	5	50	4	30	60 (*S*)[e]
2					**1b**	Rh^+	1000	5	50	4	100	24 (*S*)[e]
3					**1c**	Rh^+	1000	5	50	4	100	71 (*S*)[e]
4					**1d**	Rh^+	1000	5	50	4	83	49 (*S*)[e]
5					**1e**	Rh^+	1000	5	50	4	90	9 (*R*)[e]
6	Ph	H	Ph	**2b**	**1a**	Rh^+	200	1	50	20	100	59.5 (*S*)[f]
7					**1a**	Rh^+	500	20	50	10	100	52.7 (*S*)[f]
8					**1b**	Rh^+	200	1	50	20	100	4.4 (*R*)[f]
9					**1c**	Rh^+	200	1	50	20	100	42.4 (*S*)[f]
10					**1d**	Rh^+	200	1	50	20	100	0.8 (*S*)[f]
11					**1e**	Rh^+	200	1	50	20	100	76.7 (*R*)[f]
12					**1e**	Rh^+	500	20	50	10	100	53.4 (*R*)[f]
13					**1e**	Rh^+	200	1	0	20	100	69.2 (*R*)[f]
14					**1e**	Rh^N	200	1	50	20	100	68.8 (*R*)[f]
15	*p*-$MeOC_6H_4$	H	Ph	**2c**	**1a**	Rh^+	200	1	50	20	100	60.7 (*S*)
16					**1c**	Rh^+	200	1	50	20	100	51.2 (*S*)
17					**1e**	Rh^+	200	1	50	20	100	53.5 (*R*)
18	*p*-$O_2NC_6H_4$	H	Ph	**2d**	**1c**	Rh^+	200	1	50	20	100	28.4 (*S*)
19					**1e**	Rh^+	200	1	50	20	100	74.7 (*R*)
20	*o*-MeC_6H_4	H	Ph	**2e**	**1c**	Rh^+	200	1	50	20	100	60.0 (*S*)
21					**1e**	Rh^+	200	1	50	20	100	7.2 (*S*)
22	*m*-MeC_6H_4	H	Ph	**2f**	**1c**	Rh^+	200	1	50	20	100	43.9 (*S*)
23					**1e**	Rh^+	200	1	50	20	100	71.3 (*R*)
24	*t*-Bu	H	Ph	**2g**	**1c**	Rh^+	200	1	50	20	68	20.7 (*R*)[g]
25					**1e**	Rh^+	200	1	50	20	94	14.5 (*R*)[g]

a) All hydrogenations were carried out in EtOH ([Subst.]=0.2M). b) Rh^+=[ligand $Rh^+(COD)]BF_4^-$. Rh^N: A neutral rhodium(I) complex was prepared just prior to use by mixing $[Rh(COD)Cl]_2$ and each ligand in a molar ratio of 1:2.4 under argon. c) Determined by ^1H NMR, HPLC, or GLC analysis. d) Determined by HPLC analysis with a chiral column of Chiralcel OJ or OD (hexane: isopropyl alcohol=400:1–5:1). The configurations of the products (**3c-f**) obtained from **2c-f** are estimated ones. Two enantiomers of **3d** or **3e** were eluted on Chiralcel OJ in reverse order in comparison with the others. e) According to the sign of optical rotation, the absolute configuration was determined in comparison with a reported value, -134.8° (*c* 2.4, MeOH) for (*S*)-*N*-(α-ethylbenzyl)acetamide.[7] f) The absolute configutration was determined by comparison of its retention time on HPLC with that of an authentic specimen.[8] g) The absolute configutration was determined by comparison of its retention time on HPLC with that of an authentic specimen.[9]

Interaction between the phenyl group (R^1) of the enamides and the phenyl group of DIOP (**1a**) may change the conformation of the diphenylphosphino group situated near the prochiral vinyl group, resulting in faster addition of a hydrogen molecule to a minor pro-*S* complex intermediate. On the other hand, *m,m'*-dimethyl groups of MOD-DIOP (**1e**) inhibit the phenyl-phenyl (π-π) interaction owing to their steric hindrance, resulting in the *R*-selectivity.



Scheme 2

Thus remarkable influence of the substituents of diarylphosphino groups on the enantioselectivity has been observed in the asymmetric hydrogenation of enamides; especially *m*-methyl groups of MOD-DIOP (**1e**) were regarded as having dramatic effects on the enantioselection in the asymmetric hydrogenation of α-phenyl-substituted enamides (**2b-f**). In addition it is worth noting that both DIOP (**1a**) and *p*-MeO-DIOP (**1c**) gave opposite stereochemical products in the asymmetric hydrogenation of α-phenyl-substituted enamides in contrast to the products obtained from α-(*N*-acylamino)acrylic acids or itaconic acid and its derivatives.

Further investigations on the mechanism of the reversal of chirality are in progress.

References and Notes

1) Asymmetric Reaction Catalyzed by Chiral Metal Complexes. LXIII.
2) For reviews, see; Takahashi, H.; Morimoto, T.; Achiwa, K. *J. Synth. Org. Chem., Jpn.*, **1990**, *48*, 29. Inoguchi, K.; Achiwa, K. *Synlett*, **1992**, 169.
3) Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.*, **1989**, *30*, 735. Morimoto, T.; Chiba, M.; Achiwa, K. *Chem. Pharm. Bull.*, **1993**, *41*, 1149.
4) Morimoto, T.; Chiba, M.; Achiwa, K. *Chem. Pharm. Bull.*, **1992**, *40*, 2894.
5) Brown, J. M.; Murrer, B. A. *Tetrahedron Lett.*, **1980**, *21*, 581.
6) Landis, R.; Halpern, J. *J. Am. Chem. Soc.*, **1987**, *109*, 1746.
7) Manna, A. L.; Ghislandi, V.; Hulbert, O. B.; Scope, O. M. *Farmaco Ed. Sci.*, **1967**, *22*, 1037.
8) An optically pure authentic specimen (**3b**, 99% ee (*S*): $[\alpha]_D^{25}$+9.8 (*c* 1.53, MeOH)) was prepared by heating a mixture of (*S*)-1-phenylethylamine, iodobenzene, and CuI-Cu powder in sulfolane (affording (*S*)-*N*-phenyl-1-phenylethylamine: $[\alpha]_D^{24}$ +17.4 (*c* 1.36, MeOH)), followed by *N*-acylation with acetic anhydride.
9) An optically active authentic specimen (**3g**, 95% ee (*R*): $[\alpha]_D^{25}$ +71.3 (*c* 0.59, MeOH)) was prepared *via* condensation of pinacolone with (*R*)-1-phenylethylamine, catalytic hydrogenation with Raney Ni, hydrogenolysis with ammonium formate/Pd on carbon, and *N*-acetylation.

(*Received in Japan* 25 *August* 1994; *accepted* 3 *October* 1994)