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Reversal of Chirality Induced by *m*-Methyl Substitution of DIOP in the Rhodium(I)-Catalyzed Asymmetric Hydrogenation of α -Phenyl-Substituted Enamides¹)

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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).





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-O₂N, 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-MeC₆H₄) (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.

| Entry | Enamide | | | | Licond | ուհ) | 5/0 | | °C | L | Convn ^{c)} | ee ^{d)} |
|----------|---|----------------|----------------|-----|------------|-----------------|------------|--------|----------|----------|---------------------|---|
| | R1 | R ² | R ³ | | Liganu | Kn ^o | 3/0 | aun | | n | (%) | (%) |
| 1 | Ph | Me | Н | 2a | 1a | Rh+ | 1000 | 5 | 50 | 4 | 30 | 60 (S) ^{e)} |
| 2 | | | | | 1 b | Rh+ | 1000 | 5 | 50 | 4 | 100 | 24 (S) ^{e)} |
| 3 | | | | | 1 c | Rh+ | 1000 | 5 | 50 | 4 | 100 | 71 (S) ^{e)} |
| 4 | | | | | 1 d | Rh+ | 1000 | 5 | 50 | 4 | 83 | 49 (S) ^{e)} |
| 5 | | | | | 1 e | Rh+ | 1000 | 5 | 50 | 4 | 90 | <u>9 (R)</u> e) |
| 6 | Ph | Н | Ph | 2 b | la | Rh+ | 200 | 1 | 50 | 20 | 100 | 59.5 (S) ^{f)} |
| 7 | | | | | 1a | Rh+ | 500 | 20 | 50 | 10 | 100 | 52.7 (S)f) |
| 8 | | | | | 1 b | Rh+ | 200 | 1 | 50 | 20 | 100 | $4.4 (R)^{f}$ |
| 9 | | | | | 1 c | Rh+ | 200 | 1 | 50 | 20 | 100 | 42.4 (S) ^{f)} |
| 10 | | | | | 1 d | Rh+ | 200 | 1 | 50 | 20 | 100 | 0.8 (S)f) |
| 11 | | | | | 1 e | Rh+ | 200 | 1 | 50 | 20 | 100 | <u>76.7 (R)</u> f) |
| 12 | | | | | 1 e | Rh+ | 500 | 20 | 50 | 10 | 100 | <u>53.4 (R)</u> f) |
| 13 | | | | | 1 e | Rh+ | 200 | 1 | 0 | 20 | 100 | <u>69.2 (R)</u> f) |
| 14 | | | | | 1 e | Rh ^N | 200 | 1 | 50 | 20 | 100 | <u>68.8 (R)</u> f) |
| 15 | p-MeOC ₆ H ₄ | н | Ph | 2 c | 1 a | Rh+ | 200 | 1 | 50 | 20 | 100 | 60.7 (S) |
| 16 | | | | | 1 c | Rh+ | 200 | 1 | 50 | 20 | 100 | 51.2 (S) |
| 17 | | | | | 1 e | Rh+ | 200 | 1 | 50 | 20 | 100 | <u>53.5 (R)</u> |
| 18 | p-O ₂ NC ₆ H ₄ | Н | Ph | 2 d | 1 c | Rh+ | 200 | 1 | 50 | 20 | 100 | 28.4 (S) |
| 19 | | | | | 1 e | Rh+ | 200 | 1 | 50 | 20 | 100 | <u>74.7 (R)</u> |
| 20 | o-MeC ₆ H ₄ | H | Ph | 2 e | 1 c | Rh+ | 200 | 1 | 50 | 20 | 100 | 60.0 (S) |
| 21 | | | | | 1 e | Rh+ | 200 | 1 | 50 | 20 | 100 | <u>7.2 (S)</u> |
| 22 | m-MeC ₆ H ₄ | Н | Ph | 2 f | 1 c | Rh+ | 200 | 1 | 50 | 20 | 100 | 43.9 (S) |
| 23 | | | | | 1 e | Rh+ | 200 | 1 | 50 | 20 | 100 | <u>71.3 (R)</u> |
| 24 25 | <i>t</i> -Bu | Н | Ph | 2 g | 1 c 1 e | Rh+ Rh+ | 200 200 | 1 1 | 50 50 | 20 20 | 68 94 | 20.7 (R)8 ⁾ <u>14.5 (R)</u> 8 ⁾ |

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

a) All hydrogenations were carried out in EtOH ([Subst.]=0.2M). b) Rh⁺=[ligand Rh⁺(COD)]BF₄⁻. 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-(\alpha-ethylbenzyl)acetamide.⁷ f) The absolute configuration was determined by comparison of its retention time on HPLC with that of an authentic specimen.⁸ g) The absolute configuration was determined by comparison of its retention time on HPLC with that of an authentic specimen.⁹

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Interaction between the phenyl group (\mathbb{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.



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.
- For reviews, see; Takahashi, H.; Morimoto, T.; Achiwa, K. J. Synth. Org. Chem., Jpn., 1990, 48, 29. Inoguchi, K.; Achiwa, K. Synlett, 1992, 169.
- 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): [α]_D²⁵+9.8 (c 1.53, MeOH)) was prepared by heating a mixture of (S)-1-phenylethylamine, iodobenzene, and Cul-Cu powder in sulfolane (affording (S)-N-phenyl-1-phenylethylamine: [α]_D²⁴+17.4 (c 1.36, MeOH)), followed by N-acylation with acetic anhydride.
- 9) An optically active authentic specimen (3g, 95% ee (R): [α]_D²⁵ +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.

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