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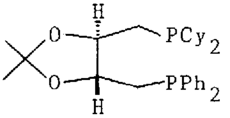
HIGHLY EFFICIENT ASYMMETRIC HYDROGENATION OF ITACONIC ACID DERIVATIVES CATALYZED BY A MODIFIED DIOP-RHODIUM COMPLEX1)

Toshiaki Morimoto, Mitsuo Chiba, and Kazuo Achiwa*
School of Pharmaceutical Sciences, University of Shizuoka,
2-2-1 Oshika, Shizuoka 422, Japan

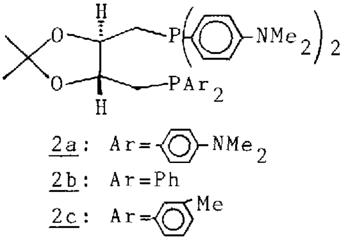
Abstract: A modified DIOP analogue bearing 4-methoxy and 3,5-dimethyl groups on each phenyl group has been synthesized. The rhodium complex of the ligand has been found to give very high optical yields in the asymmetric hydrogenation of itaconic acid and its derivatives bearing β-aryl groups, the products of which are the key-intermediates for optically active lignan derivatives.

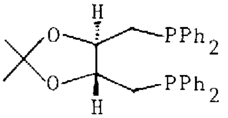
Although there are many examples of asymmetric hydrogenations of N-acyldehydroamino acids in high enantioselectivities(>90% ee),2) only a few chiral ligands have been reported to be effective for asymmetric hydrogenation of itaconic acid and its derivatives.3)

In our previous communications,4,5) we disclosed that DIOCP (1) bearing a dicyclohexylphosphino group and DIOP analogues (2) bearing *para*-dimethylamino groups enhanced the catalytic activity and enantioselectivity of their rhodium complex catalysts compared with DIOP (3) in the asymmetric hydrogenations of ketopantolactone (in the cases of 1 and 2), itaconic acid ,and its ester (in the case of 2).



(-)-DIOCP (1)

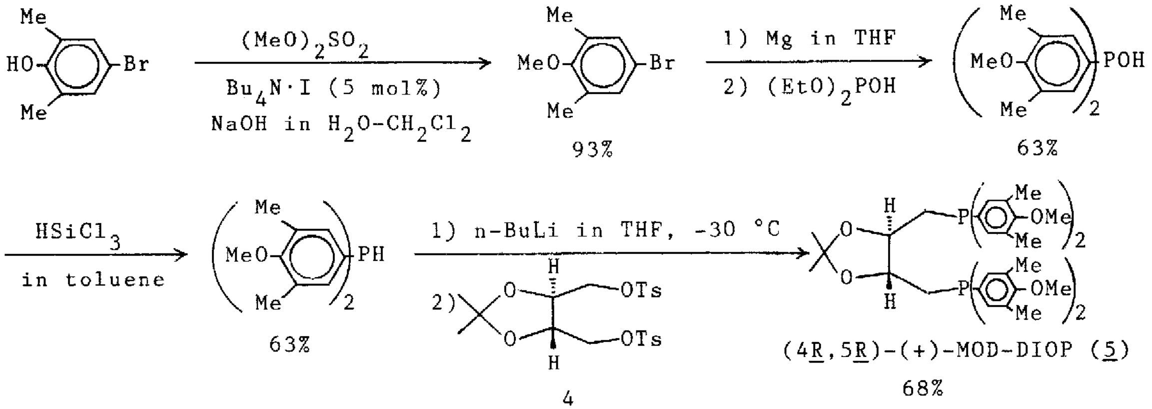




(4R, 5R)-(-)-DIOP (3)

In order to develop highly efficient catalysts for the asymmetric hydrogenation of itaconic acid and its derivatives, we designed and synthesized on the basis of our concept5) a new bisphosphine ligand (5) named MOD-DIOP, a modified symmetrical DIOP bearing both 4-methoxy and 3,5-dimethyl groups on each phenyl group. These substituents were expected to enhance the activitiy and the enantioselectivity of the rhodium complex catalyst by their electron-donating effects, and in addition, *meta*-methyl groups to be sterically effective for higher enantioselection.

Bisphosphine ligand (5) was prepared in the following manner (Scheme 1). Bis(4-methoxy-3,5-dimethylphenyl)phosphine was accessible from commercially



Scheme 1

available 4-bromo-2,6-dimethylphenol. Under an argon atmosphere the phosphine obtained was converted to a lithium phosphide, which was allowed to react with ditosylate (4) in THF at -30 °C yielding the bisphosphine, (4R,5R)-(+)-MOD-DIOP (5).[6]

A preliminary asymmetric hydrogenation was carried out with itaconic acid and dimethyl itaconate in the presence of 0.1 mol% of the rhodium complex of 5 in methanol under the conditions shown in Table 1. The cationic rhodium (Rh^+) complex of 5 was found to show very high enantioselectivity and catalytic activity, while the rhodium complexes of DIOP (3) were much less effective.[5]

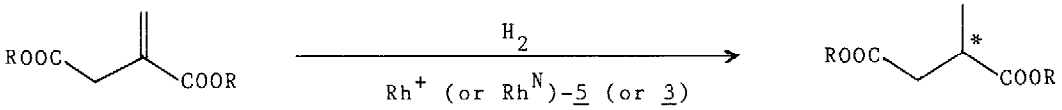


Table 1. Asymmetric Hydrogenations[a] of Itaconic Acid and Dimethyl Itaconate

ligand	Rh	substrate			
		itaconic acid[b]		dimethyl itaconate[c]	
		convn.[d] (%)	ee[e] (%)	convn.[f] (%)	ee[g] (%)
5	Rh^N	100	86 (S)	100.0	41 (46) (S)
5	Rh^+	100[h]	91 (S)	100.0	79 (88) (S)
3	Rh^N	7	--	30	7 (8) (S)
3	Rh^+	88	62 (S)	44	9 (10) (S)

a) All hydrogenations were carried out in the presence of 0.1 mol% of Rh^N (= $[\text{Rh(COD)Cl}]_2$) - or Rh^+ (=$\text{Rh}^+(\text{COD})\cdot\text{BF}_4^-$)-complex catalysts. b) $[\text{NEt}_3]/[\text{Subst.}]$ = 1.0; 1 atm, 30 °C, 20 h (Rh^N) or 1 h (Rh^+); MeOH (0.5 M). c) 1 atm, 30 °C, 4 h; MeOH (0.5 M). d) Determined by ^{1}H NMR analysis. e) Calculated on the basis of the reported value $[\alpha]_D^{20}$ +16.88° (c 2.16, EtOH) for pure (R)-(+)-methylsuccinic acid.[7] f) Determined by GLC analysis. g) Calculated on the basis of the maximum optical rotation $[\alpha]_D^{20}$ +6.86° (neat) determined by HPLC analysis. The values in parentheses are those estimated by using the reported value $[\alpha]_D^{25}$ +6.11° (neat).[8] h) 1 atm, 30 °C, 2 h.

The analogues of itaconic acid and its half-ester bearing β-aryl groups were also hydrogenated in similar manners as shown in Table 2. The rhodium complex of 5 showed very high enantioselectivity, giving rise to optically active arylmethyl-substituted succinic acids and half-esters (~96% ee). The itaconic acid half-esters were hydrogenated more smoothly than the dicarboxylic acids. Considerable influence of hydrogen pressure on the enantioselectivity was observed; an increase in the pressure caused a decrease of the optical yield. This is probably because of the formation of the hydride complex of the catalyst in competition with the complex formation between the catalyst and the substrate. The obtained optically active half-esters (S-form) are useful intermediates for the synthesis of the "non-natural" antipode of lignans. Since the antipode of 5 is easily obtainable, the present method can provide a simple, efficient, and large scale preparation of the key-inter-

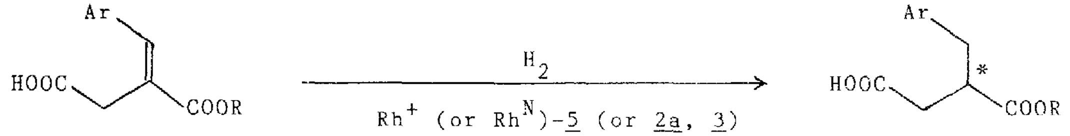
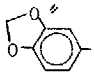
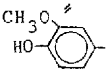
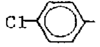


Table 2. Asymmetric Hydrogenations[a] of β-Aryl-substituted Analogues of Itaconic Acid and Half-ester

substrate					
Ar	R	ligand	Rh	convn.[b] (%)	ee[c] (%)
	H	5	Rh^{+}[d]	79	96 (S)
〃	H	5	Rh^{N}[d] [e]	64	(70)[f] (S)
〃	H	2a	Rh^{+}[d]	83	(73)[f] (S)
	H	5	Rh^{+}	72	90 (S)
〃	CH_3	5	Rh^{+}	100	90 (86)[g] (S)
〃	CH_3	5	Rh^{N}	100	94 (90)[g] (S)
〃	CH_3	3	Rh^{+}	100	58 (56)[g] (S)
	CH_3	5	Rh^{+}	100	91 (90)[h] (S)
	CH_3	5	Rh^{+}	100	94 (S)[i]

a) [Rh] / [Subst.] ≈2x10^{-3}, [NEt_3] / [Subst.] =1.0, MeOH (0.5 M); 1 atm, 30 °C, 30-40 h. b) Determined by ^{1}H NMR analysis. c) Determined by HPLC analysis of its morpholino derivative, O NCOCH$_2$CH(CH$_2$Ar)COOMe on Chiralcel OC (Daicel). The values in parentheses are those estimated by using the optical rotation values reported previously. d) [Rh] / [Subst.] =10^{-3}. e) 5 atm, 30 °C, 20 h. f) Calculated on the basis of the maximum optical rotation $[\alpha]_D$ +27° (c 2.0, AcOEt) for the pure R-enantiomer.[8] g) Calculated on the basis of the maximum optical rotation $[\alpha]_D^{20}$ -30.5° (c 1.35, MeOH) for the pure S-enantiomer.[10a] h) Calculated on the basis of the maximum optical rotation $[\alpha]_D$ -29° (c 1.1, MeOH) for the pure S-enantiomer.[10b] i) The absolute configuration was considered as S by comparing the optical rotation (-) with that of the other analogues.

mediates for various naturally occurring, optically active lignan derivatives.[10]

Thus, we modified DIOP for developing highly efficient asymmetric catalysts on the basis of our design concept, and found the DIOP analogue bearing both a para-electron-donating group and meta-methyl groups to be a very efficient ligand for the asymmetric hydrogenation of electron-deficient olefins such as itaconic acids. The methodology may be useful for developing highly efficient chiral bisphosphine ligands other than ones bearing diphenylphosphino groups so far reported . Further studies on the development of new efficient ligands and application of the present method to natural lignan synthesis are in progress.

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References and Notes

1) Asymmetric Reactions Catalyzed by Chiral Metal Complexes XXX.
2) For reviews: M. Nógràdi, "Stereoselective Synthesis", VHC, Weinheim, 1987, pp 55-103; K. E. Koenig, "Asymmetric Synthesis", J. D. Morrison, Ed., Academic Press, Orlando, 1985, Vol. 5, pp 71-101.
3) K. Achiwa, Tetrahedron Lett., 1475 (1978); I. Ojima, T. Kogure, and K. Achiwa, Chem. Lett., 567 (1978); K. Achiwa, Heterocycles, 12, 515 (1979); H. Takahashi and K. Achiwa, Chem. Lett., 1921 (1987); W. C. Christopfel and B. D. Vineyard, J. Am. Chem. Soc., 101, 4406 (1979); H. Kawano, Y. Ishii, T. Ikariya, M. Saburi, S. Yoshikawa, Y. Uchida, and H. Kumobayashi, Tetrahedron Lett., 28, 1905 (1987).
4) M. Chiba, H. Takahashi, H. Takahashi, T. Morimoto, and K. Achiwa, Tetrahedron Lett., 28, 3675 (1987).
5) T. Morimoto, M. Chiba, and K. Achiwa, Tetrahedron Lett., 29, 4755 (1988).
6) Physical data for 5: mp 128-129 °C (EtOH); $[\alpha]_D^{21}$ +14.4° (c 1.08, benzene); IR (KBr) ν_{max} cm^{-1}: 1480, 1218, 1118, 1035, 1010; ^1H NMR ($CDCl_3$) δ: 1.36 (6H, s, $(CH_3)_2C\langle$), 2.24 (24H, s, 8xm-CH_3), 1.90-2.58 (4H, m, 2x$CH_2P\langle$), 3.70 (12H, s, 4xCH_3O), 3.48-3.96 (2H, m, 2x-$OCH\langle$), 7.10 (8H, dd, J=3.4, 7.6 Hz, arom.).
7) E. Berner and R. Leonardsen, Ann. Chem., 538, 1 (1939).
8) R. Rossi, P. Diversi, and Ingrosso, Gazz. Chim. Ital., 98, 1391 (1968).
9) S. G. Cohen and A. Milovanović, J. Am. Chem. Soc., 90, 3495 (1968).
10) a) E. Brown and A. Daugan, Tetrahedron Lett., 26, 3997 (1985) and the references cited therein; b) E. Brown and A. Daugan, ibid., 27, 3719 (1986); c) E. Brown and A. Daugan, Heterocycles, 26, 1169 (1987); d) For a review: R. S. Ward, Chem. Soc. Rev., 11, 75 (1982).

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