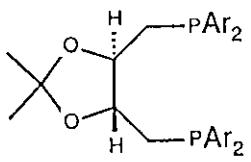
PREPARATION OF NEWLY MODIFIED DIOP BEARING BIS(4-DIMETHYLAMINO-3,5-DIMETHYLPHENYL)PHOSPHINO GROUPS AND ITS APPLICATION TO EFFICIENT ASYMMETRIC HYDROGENATION OF ITACONIC ACID DERIVATIVES[1]

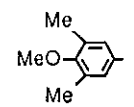
Kiyoshi Yoshikawa, Kiyoshi Inoguchi, Toshiaki Morimoto, and Kazuo Achiwa*
School of Pharmaceutical Sciences ,University of Shizuoka , 395 Yada Shizuoka 422, Japan

Abstract—We prepared a modified DIOP analogue bearing bis(4-dimethylamino-3,5-dimethylphenyl)phosphino groups. Its rhodium complex was found to be a useful catalyst for asymmetric hydrogenation of dimethyl itaconate and itaconic acid derivatives bearing β-aryl groups.

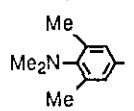
In our previous papers, we described the net role of the electronic effects of the phosphino groups on the activities and enantioselectivities of the rhodium complex catalysts in the asymmetric hydrogenation.[2] Moreover we developed MOD-DIOP (2)[3] and MOD-BPPM[4] bearing bis(4-methoxy-3,5-dimethylphenyl)phosphino groups on the basis of our designing concept, and the 3,5-dimethyl groups were found to play important roles in enhancing the enantioselectivities. From these findings, we have prepared a newly modified DIOP analogue ((*R,R*)-XYL-DIOP, 3) bearing bis(4-dimethylamino-3,5-dimethylphenyl)phosphino groups. Its rhodium complex was found to be more efficient for asymmetric hydrogenation of dimethyl itaconate and an itaconic acid derivative bearing a β-naphthyl group than MOD-DIOP rhodium complex. The latter hydrogenation product was recently proposed as a key intermediate for the synthesis of new human renin inhibitors.[5]
XYL-DIOP (3) was prepared in the manner shown in Scheme 1. *Bis(4-dimethylamino-3,5-dimethylphenyl)*-phosphine (4) was prepared by the reduction of the corresponding phosphine oxide with $LiAlH_4$-$CeCl_3$ in THF in reasonable yield.[6] Phosphination of ditosylate (5) with the lithiated 4 was carried out in THF at -30°C yielding 3.[7]



Ar = Ph- , DIOP (1)



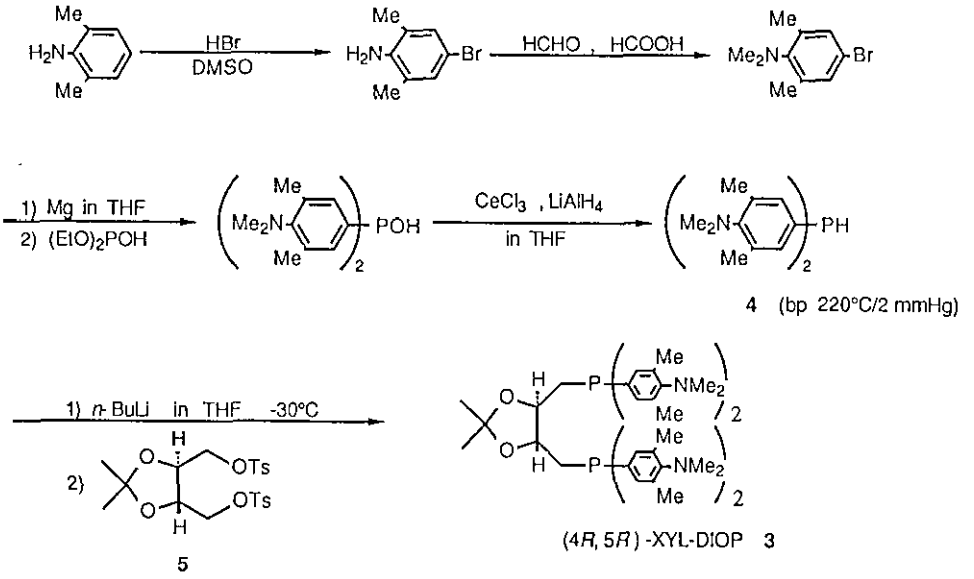
, MOD-DIOP (2)



, XYL-DIOP (3)

Asymmetric hydrogenations of dimethyl itaconate, itaconic acid, and its derivatives bearing β-aryl groups (6,7) catalyzed by DIOP analogues-rhodium complexes were carried out and the results were summarized in Table 1. In the case of using dimethyl itaconate as a substrate, the rhodium complex of **3** was found to have higher catalytic activity and enantioselectivity than that of DIOP (**1**) and to have higher enantioselectivity than that of MOD-DIOP (**2**). Moreover, in comparison with DIOP analogues bearing only 4-dimethylamino groups (under the same conditions, convn. 100%, 53%ee [2a]), the 3,5-dimethyl groups of **3** were proved to have some influences on enhancing the enantioselectivity. Thus it has become apparent that our designing concept was useful for not only enhancing the catalytic activities and enantioselectivities by the electron-donating effects of the electron-rich phosphino groups but also increasing the enantioselectivities by the steric effects of 3,5-dimethyl groups of aromatic rings.

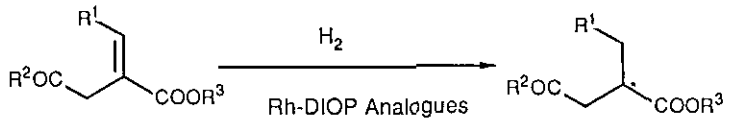
The hydrogenation product of **6** was a key intermediate for the synthesis of biologically active lignans.[3] As Table 1 shows, the rhodium complex of **3** was comparable to that of **2** on the catalytic activity and enantioselectivity in the asymmetric hydrogenation of **6**. However, when itaconic acid was used as a substrate in the presence of equimolar amount of triethylamine, the hydrogenation catalyzed by the rhodium complex of **3** did not proceed to completion under the conditions described in Table 1. We already described that this deactivation of the catalyst was probably due to the partial protonation of dimethylamino groups but the hydrogenation could proceed smoothly under a minimum applied hydrogen pressure to give somewhat lower optical yield.[2b]

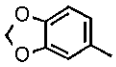
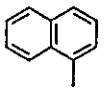


Scheme 1

Asymmetric hydrogenation of **7** was carried out under a hydrogen pressure of 5 atm and the other conditions were described in Table 1. The hydrogenation product of *R*-enantiomer was recently proposed as a key intermediate of new human renin inhibitors. The rhodium complex of **3** had higher catalytic activity and enantioselectivity than that of **2**. As the antipode of **3** ((*S*,*S*)-**3**) can be synthesized from (*S*,*S*)-**5** in the same

Table 1. Asymmetric Hydrogenation of Itaconic Acid Derivatives



Substrate R¹	R²	R³	Ligand	[Subst.]/[Rh]	Rh[a]	Convn. / %[b]	e.e. /%
H	OH	H	DIOP[c]	1000	Rh^N	7	------
(itaconic acid)[d]					Rh^+	20	70 (*S*)
			MOD-DIOP[c]		Rh^N	100	86 (*S*)
					Rh^+	100	91 (*S*)
			XYL-DIOP		Rh^N	92	78[e] (*S*)
					Rh^+	95	84 (*S*)
H	OMe	Me	DIOP[c]	1000	Rh^N	30	7 (*S*)
(dimethyl itaconate)[f]					Rh^+	44	9 (*S*)
			MOD-DIOP[c]		Rh^N	100	41 (*S*)
					Rh^+	100	79 (*S*)
			XYL-DIOP		Rh^N	100	80[g] (*S*)
					Rh^+	100	84 (*S*)
	OH	OMe	DIOP[h]	500	Rh^N	------	------
	(6)[i]				Rh^+	100	58 (*S*)
			MOD-DIOP[h]		Rh^N	100	94 (*S*)
					Rh^+	100	90 (*S*)
			XYL-DIOP		Rh^N	100	94[j] (*S*)
					Rh^+	100	90 (*S*)
		H	DIOP	1000	Rh^N	100	26[k] (*S*)
	(7)[i]				Rh^+	94	23 (*S*)
			MOD-DIOP		Rh^N	85	74 (*S*)
					Rh^+	96	60 (*S*)
			XYL-DIOP		Rh^N	100	81 (*S*)
					Rh^+	100	80 (*S*)

a) Rh^N: $[Rh(COD)Cl]_2$ + Ligand ([Ligand]/[Rh]= 1.2), Rh^+: $[Rh(COD)Ligand]^+BF_4^-$.
b) Determined by ^1H nmr analysis, or by glc analysis in the case of the hydrogenation product of dimethyl itaconate. c) Reported data in ref. 2a. d) H_2 1 atm, 30 °C, 20 h; $[Et_3N]$/[Subst.] =1.0; MeOH (0.5 M). e) Calculated on the basis of reported value $[\alpha]_D^{20}$ +16.88° (*c* 2.16, EtOH) for pure (*R*)-(+)-methylsuccinic acid.[8] f) H_2 1 atm, 30 °C, 4 h; MeOH (0.5 M). g) Calculated on the basis of the maximum optical rotation $[\alpha]_D^{20}$ +6.86° (neat) determined by hplc analysis.[2b] h) Reported data in ref. 3. i) H_2 1 atm, 30 °C, 40 h; $[Et_3N]$/[Subst.] =1.0; MeOH (0.5 M). j) Determined by hplc analysis of the corresponding morpholino derivative on Chiralcel OC (Daicel). k) Determined by hplc analysis of the corresponding methyl ester on Chiralcel OC (Daicel). l) H_2 5 atm, 50 °C, 20 h; $[Et_3N]$/[Subst.]= 1.0; MeOH (0.25 M).

manner shown in Scheme 1, the enantiomer of the hydrogenation compounds of **6** and **7** will be prepared readily. Thus XYL-DIOP (**3**) was found to be one of the most useful analogues of DIOP for asymmetric hydrogenation of itaconic acid derivatives. This means that on our designing concept,[9] "Respective Control Concept," not only the electronic effects but also the steric effects of 3,5-dimethyl groups must be considered to achieve high enantioselectivities.

Further investigation along this line is in progress in our laboratory.

ACKNOWLEDGEMENT

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7 Physical data for **3**: $[\alpha]_D^{22}$ +25.7° (*c* 0.80, benzene); ^{1}H nmr ($CDCl_3$) δ: 1.35 (6H, s, $(CH_3)_2C=$), 2.22-2.43 (4H, m, 2x-$CH_2P=$), 2.24 (24H, d, J=3.0 Hz, 8x*m*-CH_3-), 2.79 (24H, d, J=1.5 Hz, 4x$(CH_3)_2N$-), 3.76-3.86 (2H, m, 2x-CH=), 7.09 (8H, dd, J=7.7, 8.6 Hz, arom.)

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