EFFICIENT ASYMMETRIC HYDROGENATION OF (Z)-2-ACETAMIDOCINNAMIC ACID CATALYZED BY THE RHODIUM COMPLEX OF MODIFIED N-BENZYL-(3R,4R)-3,4-BIS(DIPHENYLPHOSPHINO)PYRROLIDINE (DEGPHOS)[1]

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Modified Degphoses ((R,R)-MOD-, XYL-Degphos) have been prepared and catalytic asymmetric hydrogenetion of (Z)-2-acetamidocinnamic acid was carried out with their rhodium(I) cationic complexes. The catalytic activities of the modified Degphoses were enhanced.

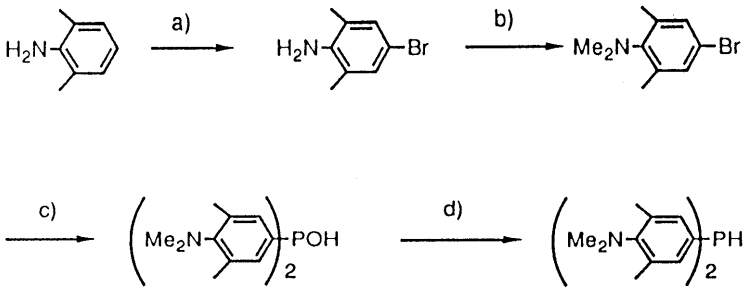
KEYWORDS catalytic asymmetric hydrogenation; bisphosphine-rhodium(I) complex; modified Degphos; amino acid precursor

Our recent studies to develop highly efficient chiral bisphosphine ligands for catalytic asymmetric hydrogenation have led to the proposal of a new designing concept, named the "Respective Control Concept."[2] On the basis of this concept, we have developed BCPMs,[3] DIOCP,[4] modified BPPMs[5] and DIOPs.[6] The rhodium complexes of these ligand had higher catalytic activity and enantioselectivity than those of the original ligands bearing the diphenylphosphino group on the asymmetric hydrogenation of not only α-amino acid precursors, itaconic acid derivatives and α-keto esters but also on the newly prepared prochiral intermediates of optically active medicines and natural compounds. From these finding, this concept have clarified the role of electron-rich phosphino groups in enhancing the catalytic activities and enantioselectivities.

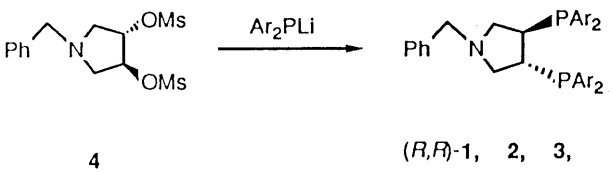
Thus this designing concept has already been successfully applied to the ligands such as BPPM (C_2-unsymmetric type) and DIOP (C_2-symmetric type) which form a seven-member chelate ring with rhodium. So it became important to apply this concept to the 1,2-substituted bisphosphine ligands forming five-member chelate rings. Here we report that our concept is also applicable to the 1,2-substituted bisphosphine ligand.

Among 1,2-substituted bisphosphine ligands, N-benzyl-Degphos (N-benzyl-(3R,4R)-bis(diphenylphosphino)pyrrolidine, 1) was recently developed as a ligand for the asymmetric hydrogenation of α-amino acid precursors, and its cationic rhodium complex had both a high enantioselectivity and a catalytic activity.[7] On the basis of our concept, we developed modified Degphoses to achieve more efficient asymmetric hydrogenation of α-amino acid precurcors. Modified BPPM and DIOP bearing bis(4-methoxy-3,5-dimethyl-phenyl)phosphino groups (MOD-BPPM,[5a] MOD-DIOP[6b]) were already reported and (R,R)-MOD-Degphos (N-benzyl-(3R,4R)-(+)-3,4-bis[bis(4′-methoxy-3′,5′-dimethyl-phenyl)phosphino]-pyrrolidine, 2) was similarly prepared from N-benzyl-(3S,4S)-(+)-di(methylsulfonyl)pyrrolidine (4). Degphos (1) was also synthesized in this manner as shown in Chart 1.

Further, we selected, as a newly modified phosphino group, bis(3,5-dimethyl-4-dimethylamino-phenyl)phosphine which was expected to have not only the stereo-controlling effect of the meta-dimethyl group but also the electron-donating effect of the para-dimethylamino and meta-dimethyl groups, similar to the MOD-group. Bis(3,5-dimethyl-4-dimethylamino-phenyl)phosphine was synthesized,

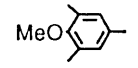


a) HBr, DMSO b) H_2CO, HCOOH c) Mg, $(EtO)_2POH$, THF d) $CeCl_3$, $LiAlH_4$, THF

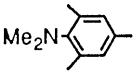


4 (*R,R*)-**1**, **2**, **3**,

Ar= Ph-, **1** **Degphos**
$[\alpha]_D^{22}$ +77.2° (*c* 1.62, toluene)
(lit., $[\alpha]_D^{22}$ +76.5° (*c* 1.7, toluene)[7]

Ar= 

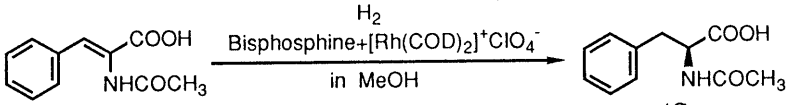
, **2** **MOD-Degphos**
$[\alpha]_D^{22}$ +54.7° (*c* 0.72, toluene)

Ar= 

, **3** **XYL-Degphos**
$[\alpha]_D^{22}$ -7.8° (*c* 0.75, toluene)

Chart 1

Table I. **Asymmetric Hydrogenation of (Z)-2-Acetamidocinnamic Acid Catalyzed by Modified Degphos-Cationic Rhodium Complex** [a]



Bisphosphine	Condn.(atm/°C/h)	[Subst.]/[Rh]	Convn.(%) [b]	e.e.% [c]
(3*R*,4*R*) - Degphos	5/50/20	10^3	100	92
1	20/50/20	10^4	100	78
	5/50/20	10^4	44	83
	20/50/20	$2x10^4$	24	81
(3*R*,4*R*) - MOD - Degphos	5/50/20	10^3	100	96
	20/50/20	10^4	100	94
2	5/50/20	10^4	100	94
	20/50/20	$2x10^4$	100	93
(3*R*,4*R*) - XYL - Degphos	5/50/20	10^3	100	94
	20/50/20	10^4	100	94
3	5/50/20	10^4	100	92
	20/50/20	$2x10^4$	100	93

a) All hydrogenation was carried out with [Subst.] = 0.5 M in methanol.
b) Determined by ^{1}H-NMR spectroscopy. c) Calcurated using the reported value $[\alpha]_D^{26}$ +46.0° (*c* 1.0, EtOH) for pure (*S*)-(+)-*N*-acethyl-phenylalanine.[8] All products were of the *S*-configration.

and from that (R,R)-XYL-Degphos (N-benzyl-(3R,4R)-(-)-3,4-bis[bis(3′,5′-dimethyl-4′-dimethylaminophenyl)phosphino]pyrrolidine, 3) was prepared as indicated in Chart 1.

Using the rhodium(I) cationic complexes of these ligands ([Rh(COD)·ligand]$^+ClO_4^-$) prepared in situ by mixing the ligand with rhodium biscyclooctadiene perchlorate (molar ratio; $[Rh(COD)_2]^+ClO_4^-$: ligand = 1 : 1.2) in methanol, asymmetric hydrogenation of (Z)-2-acetamidocinnamic acid was carried out as summarized in Table I. The hydrogenation using the Degphos-rhodium cationic complex showed very high enantioselectivities for almost all the reactions under high hydrogen pressure.[7] In this work, we carried out all hydrogenation under milder hydrogen pressure (5 or 20 atm) than described above to elucidate the effects of the electron-rich phosphino groups. These results show that the rhodium complexes of 2 and 3 have higher catalytic activities and enantioselectivities than that of 1 even when the amount of the catalyst is decreased. When the new catalysts were used, even at a ratio of 20,000 molar substrate to the rhodium and an initial hydrogen pressure of 20 atm at 50°C for 20 h, the hydrogenation was completed and it gave high optical yields of 93%ee. These facts clearly indicated that the electron-rich phosphino groups (not so hindered as the dicyclohexylphosphino group[9]) play an important role in enhancing the catalytic activities and enantioselectivities. So our concept is also potentially useful for developing the efficient 1,2-substituted bisphosphine ligands.

The efficient asymmetric hydrogenation of other prochiral substrates using new catalysts and the further application of our concept to other types of ligands is in progress in our laboratory.

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9) N-benzyl-(3R,4R)-(-)-3,4-bis(dicyclohexylphosphino)pyrrolidine ($[\alpha]_D^{22}$ -6.5°(c 0.8, toluene) was also synthesized from N-benzyl-Degphos. But the hydrogenation did not proceed completely under the same conditions.

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