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Preliminary communication

Asymmetric reactions catalyzed by chiral metal complexes

XXXII. Efficient asymmetric hydrogenation of itaconic acid derivatives catalyzed by rhodium complexes of improved (2*S*,4*S*)-*N*-(t-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (BPPM) analogues

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Abstract

We have prepared analogues of (2*S*,4*S*)-*N*-(t-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphsphino)methyl]pyrrolidine (BPPM), bearing *para*-dimethylamino groups to prove the utility of our designing concept with regard to electronic effects of the phosphino groups on the enantioselectivity and the activity of the rhodium complex catalysts. Their rhodium complexes are much more effective than those of BPPM and (2*S*,4*S*)-*N*-(t-butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (BCPM) for the asymmetric hydrogenation of dimethyl itaconate. The hydrogenation has also been used successfully in an efficient asymmetric synthesis of the key intermediate of new human renin inhibitors.

We have previously prepared the chiral pyrrolidinebisphosphine ligand, (2*S*,4*S*)-*N*-(t-butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (BCPM) [1], as an improved BPPM on the basis of our new concept for the design of efficient chiral catalysts. Our "Respective control concept" states that one phosphino group of the bisphosphine ligands oriented *cis* to the prochiral group of substrates controls the enantioselectivity, and the *trans*-oriented phosphine accelerates the reaction rate. Although we have carried out efficient asymmetric hydrogenations of several prochiral carbonyl and olefinic compounds by using BCPM-Rh complexes, effective hydrogenations could not be achieved in some cases, such as, when *N*-acyldehydroamino acid or dimethyl itaconate was used as the substrate. In these cases, the steric effect of the dicyclohexylphosphino group was considered to be responsible for lowering the enantioselectivity and the activity of the catalyst,

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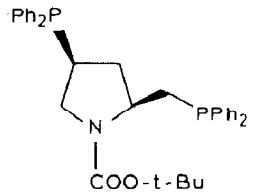
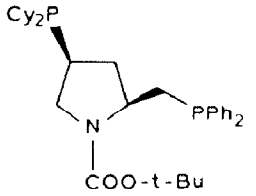
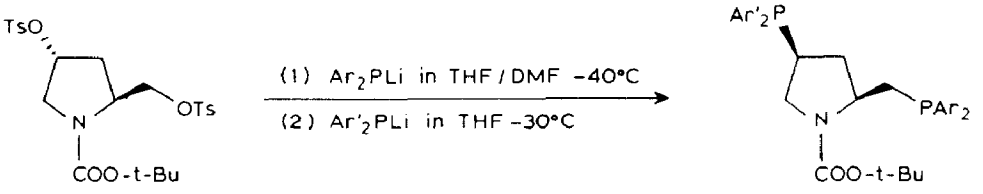


BPPM



BCPM



(1, 2, 3)

Scheme 1. **1**: Ar = Ar′ = *p*-$Me_2NC_6H_4$, $[\alpha]_D^{20} - 56.6°$ (*c* 0.7, benzene); **2**: Ar = Ph, Ar′ = *p*-$Me_2NC_6H_4$, $[\alpha]_D^{20} - 40.7°$ (*c* 0.7, benzene); **3**: Ar = *p*-$Me_2NC_6H_4$, Ar′ = Ph, $[\alpha]_D^{20} - 45.0°$ (*c* 0.8, benzene).

while the electron-rich phosphino groups are known to increase the activity of the rhodium complex catalysts [2].

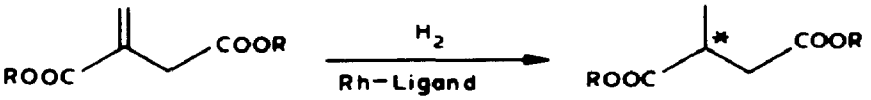
We wish to report here (1) the net role of the electronic effects of the phosphino groups on the enantioselectivity and the activity of the BPPM-rhodium complex catalysts and (2) the efficient asymmetric hydrogenations of an ester and a half-amide derivative of itaconic acid, catalyzed by improved BPPM-rhodium complexes. We prepared BPPM analogues **1**, **2**, and **3** bearing *para*-dimethylamino groups in the manner shown in Scheme 1. Electronic effects of the *para*-substituted diarylphosphino groups on the enantioselectivities were expected to be elucidated with less regard to the steric effects than in the cases of dicyclohexylphosphino group and *ortho*- or *meta*-substituted diarylphosphino groups [3].

Asymmetric hydrogenation of dimethyl itaconate * was carried out using the rhodium complexes of BPPM analogues **1**, **2**, and **3**, BPPM and BCPM under the conditions shown in Table 1. The results show that the rhodium complexes of **1** and **2** have higher catalytic activities ([Substrate]/[Rh] = 10^3, 1 atm, 25 °C, 2 h, conversion 100%) and enantioselectivities (89% e.e. and 93% e.e.) than the other complexes. These results imply that the electron-rich phosphino group on the C(4) of the pyrrolidine ring plays an important role in increasing not only the catalytic activity but also the enantioselectivity. The rhodium complexes of **1** and **2** probably form a rigid five-membered ring chelation of the substrate with the rhodium by a back-donation (d-π^*) from the rhodium to the electron-deficient olefin, providing the high enantioselectivity. Table 1 also shows that the electron-rich phosphino group on C(2) (in the cases of **1** and **3**) has only slightly enhanced the catalytic activity and the enantioselectivity. Although we have demonstrated [6] that electron-rich phosphino groups of improved DIOPs (sterically more C(2)-symmetrical) control the

* There were few reports presenting effective asymmetric hydrogenation of dimethyl itaconate [4], where the reported value $[\alpha]_D^{25} + 6.11°$ (neat) [5] was used for pure (*R*)-methylsuccinic acid dimethyl ester.

Table 1

Asymmetric hydrogenation of dimethyl itaconate and itaconic acid



Ligand	Substrates			
	Dimethyl itaconate [a]		Itaconic acid	
	Conversion (%) [b]	Optical yield (%) [c]	Conversion (%) [f]	Optical yield (%) [g]
BPPM	36	5 (*S*)	16	83 (*S*) [d]
			(100)	(82 (*S*)) [e]
BCPM	21	16 (*S*)	100	92 (*S*) [h]
			(100)	(79 (*S*)) [h]
1	100	89 (*S*)	21	90 (*S*) [d]
			(100)	(88 (*S*)) [e]
2	100	93 (*S*)	19	94 (*S*) [d]
			(100)	(91 (*S*)) [e]
3	55	68 (*S*)	27	74 (*S*) [d]
			(100)	(82 (*S*)) [e]

[a] Hydrogenations of dimethyl itaconate were carried out in the presence of neutral rhodium catalyst prepared immediately before use by mixing $[Rh(COD)Cl]_2$ and the ligand in a molar ratio of 1/2.4 under Ar. [Subst.]/[Rh] = 10^3 (MeOH 0.5 *M*), 1 atm, 25 °C, 2 h. [b] Determined by GLC analysis. [c] Determined by HPLC analysis on Chiralcel OB (Daicel). We estimated the maximum optical rotation of (*S*)-methylsuccinic acid dimethyl ester to be $[\alpha]_D^{25}$ −6.86° (neat) on the basis of the observed value, $[\alpha]_D^{25}$ −6.38°, for the product of 93% ee. [d] Under conditions similar to those described in [a] except for 20 h [Subst.]/[NEt_3] = 1. [e] 5 atm, 50 °C, 20 h. [f] Determined by ^1H NMR spectroscopy. [g] Calculated by using the reported value $[\alpha]_D^{20}$ +16.88° (*c* 2.16, EtOH) for pure (*R*)-(+)-methylsuccinic acid [8]. [h] The value reported in ref. 9 using the cationic complex.

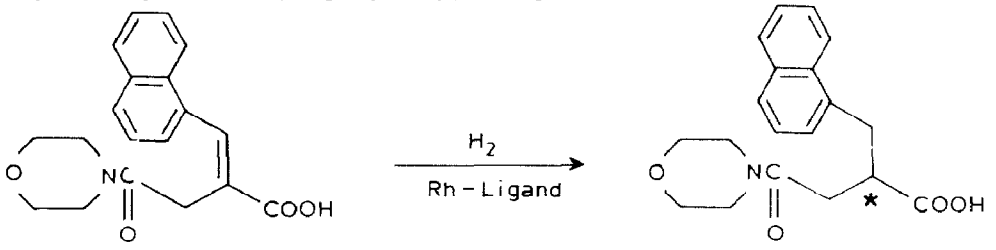
chelation site of an electron-deficient prochiral group to the rhodium at the *trans*-position, in the present cases the electron-rich phosphino group on C(2) position is regarded as being *cis*-oriented to the prochiral group, owing to the steric effect of the pyrrolidine ring [7]. It is noteworthy that (1) the steric effects of the bisphosphine ligands are more significant than the electronic effects for determining the chelation site of the substrate and (2) the electron-rich phosphino group oriented *trans* to the electron-deficient prochiral group plays an important role in increasing the catalytic activity and the enantioselectivity.

Asymmetric hydrogenation of itaconic acid has also been carried out. The hydrogenations did not proceed to completion under the conditions described above, but under a hydrogen pressure of 5 atm the hydrogenations proceeded smoothly to give somewhat lower optical yields. This deactivation is probably due to the partial protonation of the *para*-dimethylamino groups resulting in a decrease of the electron-donating effect and lowering the catalytic activity.

In order to test the usefulness of the hydrogenations, we carried out the asymmetric synthesis of 2-(1-naphthylmethyl)-3-(morpholinocarbonyl)propionic acid (**5**), the *R*-enantiomer of which was recently proposed as a key intermediate of new human renin inhibitors [10]. The asymmetric hydrogenation of half-amide **4** was carried out under the conditions shown in Table 2, to give the *S*-enantiomer of **5**. Among these ligands, **1** and **2** gave quantitative chemical yields and high optical yields (90% e.e. and 81% e.e.). Since the synthesis of the antipode of BPPM has been

Table 2

Asymmetric synthesis of 2-(1-naphthylmethyl)-3-(morpholinocarbonyl)propionic acid [a]



(4) (5)

Ligand	Conversion (%) [b]	Optical yield (%) [c]
BPPM	98	19 (*S*)
BCPM	trace	–
1	100	90 (*S*)
2	100	81 (*S*)
3	100	63 (*S*)

[a] All hydrogenations were carried out in the presence of 0.1 mol% of the neutral rhodium complexes at 50 °C for 20 h in MeOH (0.25 *M*) under an initial hydrogen pressure of 5 atm. $[NEt_3]/[Rh] = 50$. [b] Determined by ^1H NMR spectroscopy. [c] Determined by HPLC of the corresponding methyl ester on Chiralcel OC (Daicel).

reported [11], our asymmetric hydrogenation is an efficient route to the key intermediate of human renin inhibitors.

Thus, improved BPPM (**1** and **2**) bearing a bis(*para*-dimethylaminophenyl)phosphino group at C(4) position were found to be effective in the asymmetric hydrogenation of electron-deficient olefins. We have outlined the net role of the electronic effects of the phosphino groups on the enantioselectivities and the activities of the rhodium complex catalysts.

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