## Communications to the Editor

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# DESIGN OF METHOXY-SUBSTITUTED BPPM ANALOGUES AND THEIR APPLICATION TO THE ASYMMETRIC SYNTHESIS OF N-ACETYLPHENYLALANINE[1)]

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We describe the preparation of methoxy-substituted BPPM ((2S,4S)-N-(tert-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)-methyl]pyrrolidine) analogues for highly effective asymmetric hydrogenation of (Z)-2-acetamidocinnamic acid. o-Methoxy-BPPM-$Rh^+$ gave a very high optical yield (98% enantiomeric excess (ee), (R)) and p-methoxy-BPPM-$Rh^+$ was very actively catalytic ([Subst.]/[Rh]=$10^4$). On the bases of these results and our "respective control concept," we developed a highly effective chiral ligand (5) for asymmetric synthesis of N-acetylphenylalanine.

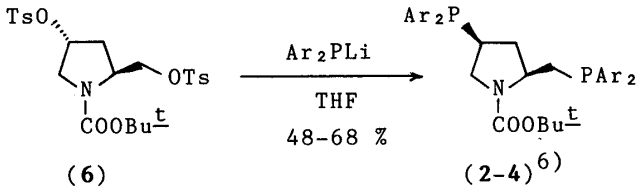
KEYWORDS —— chiral bisphosphine ligand; methoxy-substituted BPPM analogue; highly effective asymmetric hydrogenation; N-acetylphenylalanine; respective control concept

Various types of chiral bisphosphine ligands have been developed for asymmetric hydrogenation catalyzed by their rhodium complexes. Almost all of these chiral bisphosphines have two phenyl rings on each phosphorous atom. Among several example of the interesting chiral ligands, DIPAMP ((R,R)-(1,2-ethanediylbis[(o-methoxyphenyl)phenylphosphine]) bearing an o-methoxyphenyl group gave high optical yields in excess of 95% in the reduction of dehydroamino acid.[2)] Methoxy-substituted DIOP ((2R,3R)-2,3-O-isopropylidene-2,3-dihyroxy-1,4-bis(diphenylphosphino)-butane) analogues also had an interesting enantioselectivity in the asymmetric hydrogenation of enamides.[3,4)]

Now we have prepared the methoxy-substituted BPPM ((2S,4S)-N-(tert-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine) (1) analogues (o-methoxy-BPPM (2), m-methoxy-BPPM (3) and p-methoxy-BPPM (4)) and examined their effects on the asymmetric hydrogenation of (Z)-2-acetamidocinnamic acid. The methoxy-substituted BPPM analogues (2, 3, 4) were prepared from ditosylate[5)] (6) with lithium diarylphosphide in tetrahydrofuran (Chart 1).

The initial results of the asymmetric hydrogenation catalyzed by methoxy-substituted BPPM-rhodium complexes are summarized in Table I (entries 1-8). All hydrogenations were carried out in the presence of 0.1-0.01 mol% a cationic rhodium catalyst prepared *in situ* by mixing $[Rh(NBD)_2]ClO_4$ and a chiral ligand in a ratio of 1 : 1.2 and triethylamine ($[NEt_3]$/[Rh]=50) at 50 °C for 20 h in ethanol under the initial hydrogen pressure of 20 atm.

Table I shows that o-methoxy-BPPM (2) gave a much higher optical yield (98% enantiomeric excess (ee), (R)) than the other ligands. But when p-methoxy-BPPM

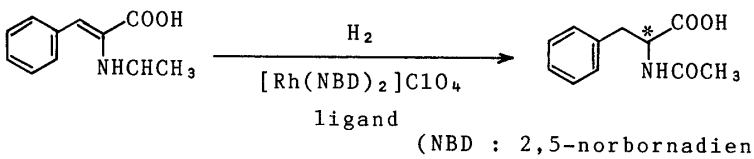


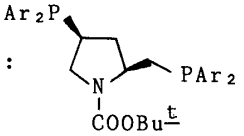

(6) (2-4)[6]

(2) : Ar= 2-$CH_3O$-$C_6H_4$-
(3) : Ar= 3-$CH_3O$-$C_6H_4$-
(4) : Ar= 4-$CH_3O$-$C_6H_4$-

Chart 1

Table I. Asymmetric Hydrogenation of (Z)-2-Acetamidocinnamic Acid[a]

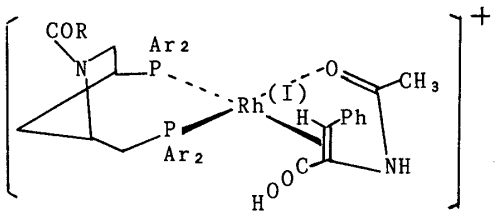



ligand : 


(1)-(5)

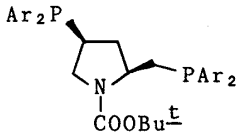
| Ligand (Ar=, Ar=) | Entry | [Subst.]/[Rh] | Convn. (%)[b] | Opt. yield (%)[c] (Confign.) |
|---|---|---|---|---|
| BPPM (1) | 1 | $10^3$ | 100 | 78.0 (R) |
| (Ar=Ar= $C_6H_5$-) | 2 | $10^4$ | 11 | 79.7 (R) |
| o-methoxy-BPPM (2) | 3 | $10^3$ | 100 | 98.0 (R) |
| (Ar=Ar= 2-$CH_3O$-$C_6H_4$-) | 4 | $10^4$ | 64 | 98.9 (R) |
| m-methoxy-BPPM (3) | 5 | $10^3$ | 100 | 84.8 (R) |
| (Ar=Ar= 3-$CH_3O$-$C_6H_4$-) | 6 | $10^4$ | 7 | — |
| p-methoxy-BPPM (4) | 7 | $10^3$ | 100 | 90.4 (R) |
| (Ar=Ar= 4-$CH_3O$-$C_6H_4$-) | 8 | $10^4$ | 100 | 89.8 (R) |
| (5) (Ar= 2-$CH_3O$-$C_6H_4$-, | 9 | $10^3$ | 100 | 98.1 (R) |
| Ar= 4-$CH_3O$-$C_6H_4$-) | 10 | $10^4$ | 84 | 98.0 (R) |

a) All hydrogenations were carried out with [Subst.]=0.5 M in EtOH. b) Determined by $^1$H-NMR analysis. c) Calculated on the basis of the optical rotation of pure enantiomer: N-acetyl-(S)-(+)-phenylalanine; $[\alpha]_D^{20}$ +40.1° (c1.00, MeOH).




[$PAr_2$] → rate-accelerating function (p-methoxy)

[$PAr_2$] → enantioselecting function (o-methoxy)




(5)

Ar= 2-$CH_3O$-$C_6H_4$-
Ar= 4-$CH_3O$-$C_6H_4$-

Chart 2

(**4**) was used as a ligand, the hydrogenation proceeded smoothly with a very high substrate-to-catalyst ratio ($10^4$ : 1). The steric factor of the o-methoxy group plays an important role in high enantioselectivity and p-methoxy group, as it is a better electron donor group than the other groups, and accelerates the reaction rate.[7] Therefore, the o-methoxy and p-methoxy groups in the chiral ligands appeared to be more suitable for the enantioselectivity of asymmetric hydrogenation and its reaction rate (Chart 2).

Recently, we have proposed the "respective control concept"[8] which states that one phosphino group of the bisphosphine ligands oriented cis to the prochiral group of the substrate controls the enantioselectivity of asymmetric hydrogenation, and another group oriented trans to the prochiral group accelerates its reaction rate. This further develops a highly effcient chiral ligand in the asymmetric syntheses of catalyzed by chiral bisphosphine-rhodium complexes. On the basis of our new concept, we have developed chiral pyrrolidinebisphosphine, BCPM ((2S, 4S)-N-(tert-butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl] pyrrolidine).[9] This compound has the (diphenylphosphino)methyl group on the $C_2$ position of the pyrrolidine ring which gives the high enantioselectivity, and the dicyclohexylphosphino group on the $C_4$ position which accelerates the reaction rate.[10,11]

From these and the present asymmetric hydrogenation findings, we prepared new chiral pyrrolidinebisphosphine (**5**) bearing the [di(2-methoxy)phenylphosphino]-methyl group on the $C_2$ position of the pyrrolidine ring and the di(4-methoxy)-phenylphosphino group at the $C_4$ position for highly effective asymmetric hydrogenation of (Z)-2-acetamidocinnamic acid. The new chiral pyrrolidinebisphosphine (**5**) was synthesized from 4-hydroxy-L-proline ethyl ester hydrochloride (**7**), as shown in Chart 3.

The results of the asymmetric hydrogenation of (Z)-2-acetamidocinnamic acid catalyzed by chiral ligand (**5**)-rhodium complex are summarized in Table I (entries

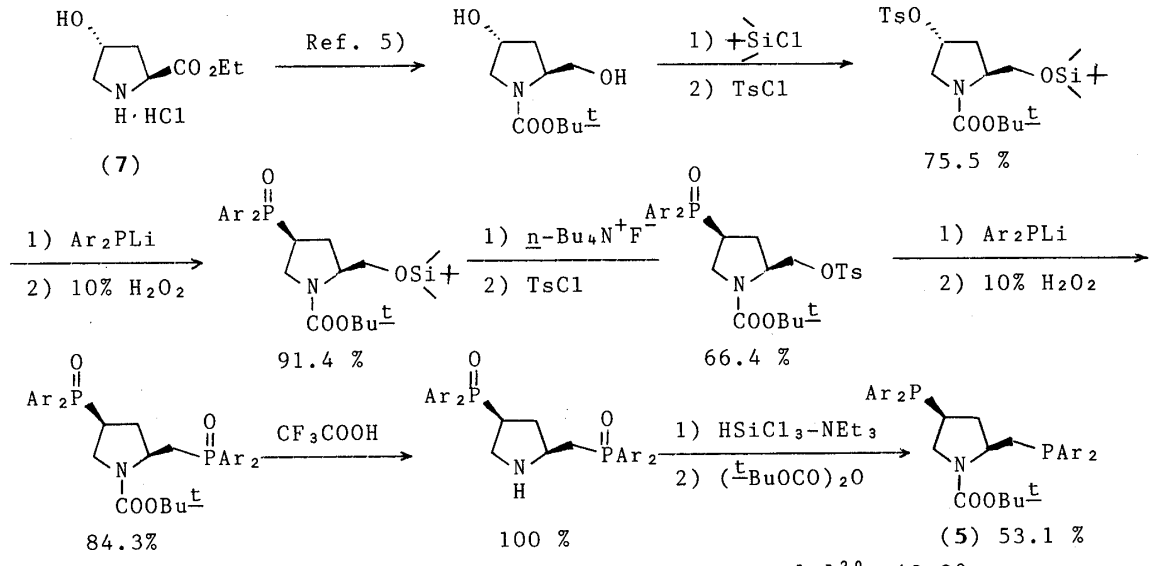



Chart 3

9-10). The newly synthesized chiral ligand (**5**) gave N-acetyl-(R)-phenylalanine with a very high optical yield (98% ee) comparable to that when o-methoxy-BPPM (**2**) was used as a ligand. And **5** accelerated the reaction rate of hydrogenation ([Subst.]/[Rh]=$10^4$): convn; 84%) slightly more than o-methoxy-BPPM (**2**) (convn; 64%), but less than p-methoxy-BPPM (**4**) (convn; 100%). This result may be rationalized under the assumption that the steric factor of o-methoxy group affects the rate of the oxidative addition of molecular hydrogen to the rhodium.

Our "respective control concept" was also useful for asymmetric hydrogenation of the prochiral enamide-acid group.

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6) **2**: $[\alpha]_D^{20}$ -85.5° (c1.02, benzene), **3**: $[\alpha]_D^{20}$ -40.6° (c1.02, benzene), **4**: $[\alpha]_D^{23}$ -39.1° (c1.00, benzene).
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