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Chiral C_2-Symmetric 2,5-Disubstituted Pyrrolidine Derivatives as Chiral Catalyst Ligands in the Reaction of Diethylzinc with Arylaldehydes

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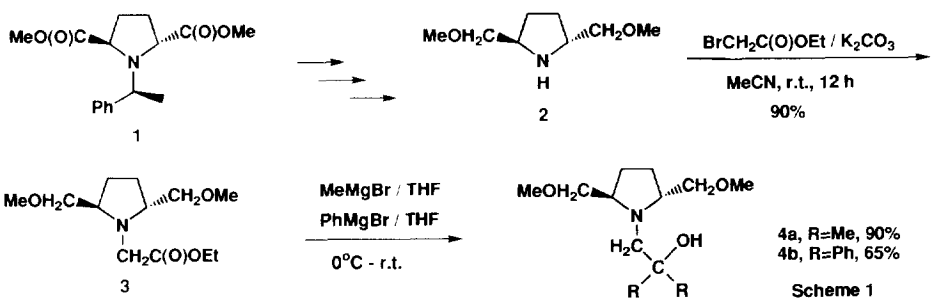
Summary: Two kinds of chiral C_2-symmetric 2,5-disubstituted pyrrolidine derivatives having a β-aminoalcohol moiety were successfully synthesized and their catalytic abilities of asymmetric induction were examined in the reaction of diethylzinc with arylaldehydes. The production of *sec*-alcohols in high yields and high enantiomeric excesses having the R-configuration could be achieved when N-(2',2'-diphenyl-2'-hydroxyethyl)-(2R, 5R)-bis(methoxymethyl)pyrrolidine was used as a chiral ligand. On the other hand, when N-methyl-(2R, 5R)-bis(diarylhydroxymethyl)pyrrolidine was used as a catalyst, the enantiomeric excesses of the *sec*-alcohols went down and the inversion of the enantioselectivity was observed in the reaction of m-chloro-, p-chloro-, and m-fluorobenzaldehyde with diethylzinc.

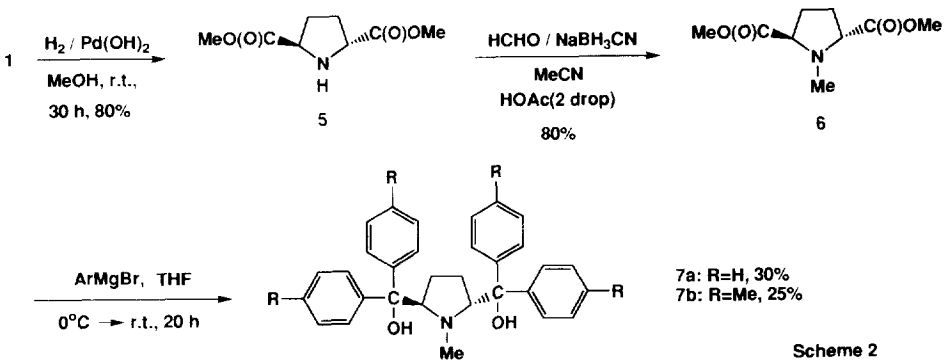
High efficiencies of C_2-symmetric chiral reagents including auxiliaries and catalyst ligands in the chiral inductions have attracted much attention in asymmetric synthesis.[1] Previously, we reported a short synthesis of homochiral C_2-symmetric 2,3,4,5-tetrasubstituted pyrrolidines from D-mannitol and their use as chiral ligands in the reaction of diethylzinc with benzaldehyde.[2] A dramatic change of enantioselectivity was observed between the bis(benzylideneacetal) ligands which favoured the (S)-alcohol and the methoxylated ones which afforded the (R)-alcohol. These results imply that the flexibility of the substituents on the pyrrolidine ring may play an important role in enantioselectivity. In this paper we wish to report the catalytic asymmetric induction abilities of chiral C_2-symmetric 2,5-disubstituted N-β-hydroxyethylpyrrolidine derivatives in the reaction of diethylzinc with arylaldehydes in order to elucidate the effect of the substituents at the 3-, and 4-position of pyrrolidine ring on the enantioselectivity. We also disclose the catalytic abilities of chiral C_2-symmetric N-methyl-2,5-bis(diarylhydroxymethyl)pyrrolidine in this addition reaction.

Chiral C_2-symmetric 2,5-disubstituted pyrrolidines have been well recognized as useful chiral auxiliaries for asymmetric synthesis.[3] These compounds have been prepared first by resolution of *trans*-1-benzyl-2,5-pyrrolidinedicarboxylic acid,[4] and then synthesized from homochiral starting materials: D-mannitol,[5] (S)-O-benzylglycidol,[6] and L-proline[7] by way of relatively long reaction sequences. Recently, Yamamoto reported a

convenient synthesis of each enantiomer of the 2,5-disubstituted pyrrolidines by reaction of dimethyl 2,5-dibromoadipate with (S)-(-)-1-phenylethylamine and chromatographic separation.[8] According to this method 1-[(S)-1'-phenylethyl]-(2R, 5R)-bis(methoxycarbonyl)pyrrolidine (**1**) and a N-unsubstituted pyrrolidine (**2**) were obtained. The compound (**2**) was treated with ethyl α-bromoacetate to give the N-ethoxycarbonylmethyl derivative (**3**). The N-β-hydroxypyrrolidines (**4a**) and (**4b**) were then obtained from the reaction of **3** with methylmagnesium bromide and phenylmagnesium bromide, respectively (Scheme 1). On the other hand, the synthesis of chiral C_2-symmetric N-methyl-(2R,5R)-bis(diarylhydroxymethyl)pyrrolidines (**7a**) and (**7b**) were carried out starting from **1** through a N-unsubstituted pyrrolidine (**5**) and a N-methyl derivative (**6**) by removal of the N-1-phenylethyl group and N-methylation using formaldehyde, followed by treatment with the corresponding arylmagnesium bromide as shown in Scheme 2.

It is well known that the reaction of aldehydes with diethylzinc giving sec-alcohols (**8**) takes place in the presence of a β-aminoalcohol.[9] Excellent chiral inductions including asymmetric amplifications[10] by use of chiral β-aminoalcohols in this reaction have been reported.[10] Thus we also examined this reaction using the





two kinds of chiral C_2-symmetric pyrrolidine derivatives (**4**) and (**7**) having a β-aminoalcohol moiety mentioned above. The enantiomeric excess of the product (**8**) was determined by HPLC analysis using chiral stationary phase column (CHIRALCEL OD) or ^{1}H NMR analysis of the corresponding (+)-MTPA ester, and the absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation.[10,11] Their results are summarized in Table 1 and 2, respectively. As shown in Table 1, high yields (85-95%) and high enantiomeric excesses (75-95%) of the corresponding *sec*-alcohols (**8**) were obtained by using 5 mol% of **4b** as a chiral catalyst ligand. The product configuration (R), chemical yield, and enantiomeric excess in the reaction of diethylzinc with benzaldehyde are almost same as those reported previously in which the corresponding chiral C_2-symmetric 2,3,4,5-tetrasubstituted pyrrolidine derivative was used as a chiral catalyst ligand.[2] Thus the chiral ligand characters for the C_2-symmetric 2,5-disubstituted and 2,3,4,5-tetrasubstituted pyrrolidines appear to be very similar in the reaction of diethylzinc with benzaldehyde and the substituents at the 3- and 4-positions of pyrrolidine ring have no effect on the enantioselectivity of this addition reaction. On the other hand, when **7a** or **7b** was used as a catalyst, the enantiomeric excesses of **8**

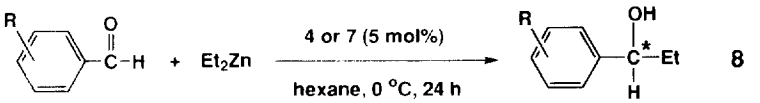


Table 1. Asymmetric addition reaction of diethylzinc to arylaldehyde in the presence of chiral pyrrolidines (4).

R	Cat.	Yield / %[a]	ee / %	configuration
H	4a	90	61[b]	R
H	4b	99	91[b]	R
p-Me	4b	99	96[b]	R
o-OMe	4b	85	83[b]	R
p-OMe	4b	85	73[b]	R
p-F	4b	96	70[c]	R
m-F	4b	88	85[d]	R
p-Cl	4b	92	76[b]	R
m-Cl	4b	96	90[b]	R
o-Cl	4b	86	92[d]	R

[a] Isolated yields; [b] Determined by chiral HPLC; [c] Determined by comparison of the optical rotation value with the literature value; [d] Determined by ^{1}H NMR analysis of the corresponding (+)-MTPA ester.

Table 2. Asymmetric addition reaction of diethylzinc to arylaldehyde in the presence of chiral pyrrolidines (7a and 7b).

R	Cat.	Yield / %[a]	ee / %	configuration
H	7a	82	16[b]	R
H	7b	82	15[b]	R
p-Me	7a	70	53[b]	R
p-Me	7b	70	52[b]	R
o-OMe	7a	73	42[b]	R
p-OMe	7a	72	43[b]	R
p-F	7b	50	16[c]	R
m-F	7b	45	15[d]	S
p-Cl	7a	71	13[b]	S
m-Cl	7a	90	40[b]	S
m-Cl	7b	90	38[b]	S
o-Cl	7a	76	10[d]	R

[a] Isolated yields; [b] Determined by chiral HPLC; [c] Determined by comparison of the optical rotation value with the literature value; [d] Determined by ^{1}H NMR analysis of the corresponding (+)-MTPA ester.

went down and the inversion of the enantioselectivity affording the S-configuration preferentially was observed in the reaction of m-chloro, p-chloro, and m-fluorobenzaldehyde with diethylzinc (Table 2). This result is particularly interesting in view of the fact that no inversion phenomenon of the enantioselectivity by changing the substitution mode of the substrate arylaldehydes from o-chloro- to m-chloro- and p-chlorobenzaldehyde could be observed when N-methyl-(2S)-diphenylhydroxymethylpyrrolidine reported by Soai[12] and C_2-symmetric ones (**4**) described here were used as a chiral ligand. At present the reason of this inversion phenomenon has remained obscure and the work along these lines is in progress.

Typical procedure: To a saspension of β-aminoalcohol (**4b**) (18.0 mg, 0.050 mmol) in hexane (2.0 ml), diethylzinc (2.2 mmol, 2.2 ml of 1 M hexane solution) was added at 0 °C. After stirring for 0.5 h, benzaldehyde (106.0 mg, 1.0 mmol) was added and the reaction mixture was stirred for 24 h at 0 °C. The reaction was quenched by 3% HCl aqueous solution and the product was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by silica gel TLC to give optically active 1-phenylpropanol (**8**) (134.2 mg, 99%).

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