C_2-SYMMETRIC *N*-(β-MERCAPTOETHYL)PYRROLIDINE AS A CHIRAL CATALYST LIGAND IN THE ADDITION REACTION OF ALDEHYDES AND DIETHYLZINC

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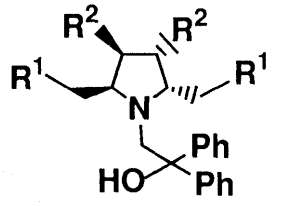
A chiral C_2-symmetric *N*-(β-mercaptoethyl)pyrrolidine bearing 6-membered benzylidene acetal functionalities fused at the 2,3- and 4,5-positions was found to exhibit high efficiency in the asymmetric addition reaction of aldehydes with diethylzinc.

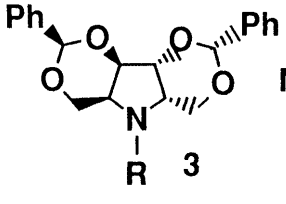
KEY WORDS C_2-symmetric *N*-(β-mercaptoethyl)pyrrolidine; chiral catalyst; addition reaction; aldehyde; diethylzinc

In the past decade there has been an enormous progress in research in the field of catalyst ligands in the asymmetric reactions of organometallics.[1] In particular, asymmetric addition reactions of aldehydes and organozinc reagents have been widely exploited in the search for chiral catalyst ligands of high efficiency.[2] Whereas much of the activity has been confined mainly to chiral-substituted β-aminoalcohol,[3] ethylenediamine,[4] and 1,2-glycol derivatives,[5] very recently, it has been found that the sulfur-containing compounds such as substituted β-aminothiols derived from optically active ephedrine and norephedrine,[6] o-aminomethyl-thiophenols prepared from chiral α-methylbenzylamine,[7] a β-hydroxysulfoxide derived from chiral α-ketosulfoxide,[8] and β-hydroxysulfides prepared from D-camphor[9] have potential as a chiral catalyst ligand for the enantioselective addition reactions of aldehydes and reduction of imides.[6b] In the course of our investigation of catalytic abilities of chiral C_2-symmetric pyrrolidines in the asymmetric addition reaction of aldehydes and diethylzinc, we found 2,3,4,5-tetra- and 2,5-disubstituted *N*-(β,β-diphenyl-β-hydroxyethyl)pyrrolidines (**1** and **2**) to be efficient catalyst ligands.[10] Here we wish to disclose an examination of catalytic abilities of C_2-symmetric chiral *N*-(β-mercaptoethyl)pyrrolidines in the asymmetric addition reaction of diethylzinc and a variety of aldehydes, and report a pyrrolidine derivative (**3a**) bearing 6-membered benzylidene acetal functionalities to be an excellent catalyst ligand in both chemical and optical yields.



1 $R^1 = R^2 = OMe$

2 $R^1 = OMe$, $R^2 = H$



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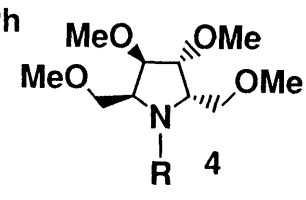

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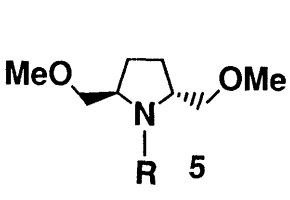

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a : R = CH_2CH_2SH **b** : R = CH_2CH_2OH **c** : R = H

The homochiral C_2-symmetric *N*-(β-mercaptoethyl)pyrrolidines (**3a**, **4a**, and **5a**)[11] were prepared in 65, 72, and 69% yields from the corresponding 2,3,4,5-tetra- and 2,5-disubstituted pyrrolidines (**3c**,[10] **4c**,[10] and **5c**[12]), respectively, by treatment with excess of ethylenesulfide in acetonitrile at room temperature for 24 h. First, efficiency of the catalyst ligands (**3a**, **4a**, and **5a**) including chemical yield

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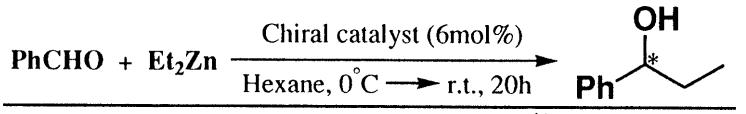
and enantioselectivity in the reaction of diethylzinc and benzaldehyde was examined and compared with that of the corresponding *N*-(β-hydroxyethyl)pyrrolidines (**3b**,[10] **4b**,[10] and **5b**[11])under the standard conditions using 6 mol% of a catalyst ligand with benzaldehyde (1 eq) and diethylzinc (2 eq) in hexane at temperatures ranging from 0 °C to room temperature for 20 h. The results summarized in Table 1 show that the catalyst (**3a**) exhibited excellent functions both in chemical yield and in enantioselectivity, although *N*-(β-mercaptoethyl)pyrrolidines (**4a** and **5a**) of other substitution mode gave poor optical yields. Inversion of the enantioselectivity of the product 1-phenylpropanol from (S) to (R) was observed by changing the catalysts from **3a**, which has rigid 2,3;4,5-bisbenzylideneacetal moiety in pyrrolidine skeleton, to **4a** and **5a**, which bear methoxyl groups enabling flexible rotation at the 2,3,4,5-positions, and this phenomenon was the same as those observed by the corresponding *N*-(β-hydroxyethyl)pyrrolidines (**3b**, **4b**, and **5b**) and those reported previously.[10]

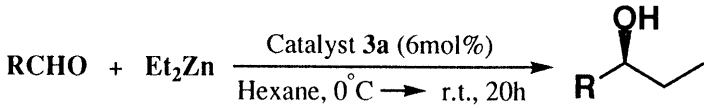
Table 1. Asymmetric Addition of Diethylzinc to Benzaldehyde with Chiral Catalysts



Entry	Catalyst	Yield (%)	%ee[b]	Config.
1	**3a**	94	96	*S*
2[a]	**3b**	48	42	*S*
3	**4a**	78	5	*R*
4[a]	**4b**	70	27	*R*
5	**5a**	81	11	*R*
6	**5b**	75	29	*R*

a) Data reported in the literature (ref.10).
b) Determined by HPLC analysis using DAICEL CHIRALCEL OD.

Table 2. Asymmetric Addition of Diethylzinc to Aldehydes with the Chiral Catalyst (**3a**)



Entry	R	Yield (%)	%ee	Config.
1	*p*-$CH_3C_6H_4$	96	99[a]	*S*
2	*o*-BrC_6H_4	89	99[a]	*S*
3	*p*-ClC_6H_4	70	81[b]	*S*
4	*p*-$CH_3OC_6H_4$	88	82[a]	*S*
5	*o*-$CH_3OC_6H_4$	93	86[a]	*S*
6	1-Naphthyl	85	86[a]	*S*
7	*trans*-PhCH=CH	94	77[a]	*S*
8	$PhCH_2CH_2$	90	85[b]	*S*
9	$CH_3(CH_2)_7$	91	88[c]	*S*

a) Determined by HPLC analysis using DAICEL CHIRALCEL OD.
b) Determined by ^{1}H-NMR analysis of the corresponding (-)-MTPA ester.
c) Determined by ^{19}F-NMR analysis of the corresponding (-)-MTPA ester.

Next, we have focused our attention on the catalyst (**3a**) for investigation of enantioselective addition reaction of various types of aldehydes including aromatic, α,β-unsaturated, and saturated ones

with diethylzinc, and the results are shown in Table 2. High efficiency in chemical yields and the (S)-enantioselectivity[13] of the catalyst (**3a**) was demonstrated in the reaction of saturated aldehydes as well as arylaldehydes, among which excellent chemical and optical yields (99%) were attained for *p*-tolylaldehyde and *o*-bromobenzaldehyde (entries 1 and 2).

In conclusion, we have shown an easily accessible β-aminomercaptane (**3a**) to be a highly effective and widely applicable chiral catalyst ligand for the asymmetric addition reaction of aldehydes with dialkylzinc. It should be noted that **3a** is the first efficient catalyst ligand which contains primary thiol functionality associated with C_2-symmetric framework as a chiral element, while Noyori and Oguni have claimed that, concerning β-aminoalcohol catalysts, the primary alcoholic function does not act efficiently in the asymmetric addition reaction of aldehydes and dialkylzinc reagents.[2a]

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11) N-(β-Mercaptoethyl)pyrrolidines **3a**, **4a**, and **5a** were obtained as oil of $[\alpha]_D^{20}$+54.77° (c 1.27, $CHCl_3$), -18.90° (c 3.77, $CHCl_3$), and +65.56° (c 2.56, $CHCl_3$), respectively. The alcohol **5b** (oil, $[\alpha]_D^{20}$+46.60° (c 1.62, $CHCl_3$)) was synthesized analogously as the corresponding 2,3,4,5-tetrasubstituted pyrrolidines from **5c** by reaction with ethyl bromoacetate (K_2CO_3/CH_3CN/rt/12 h) followed by reduction with $LiAlH_4$ (THF/0 °C /2 h).
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13) The absolute configuration of the products was assigned by comparison of the sign of specific optical rotations for the secondary alcohols obtained with those reported in the literatures except for the product (S)-1-*o*-bromophenylpropanol (entry 2 in Table II), which was assigned by transformation to (S)-1-phenylpropanol through debromination (n-BuLi/THF, then H_2O).

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