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2-Amino-1-phenyl-1,3-propanediol Derivatives. New Ligands for Asymmetric 1,4-Addition of Organozinc Reagents to Enones

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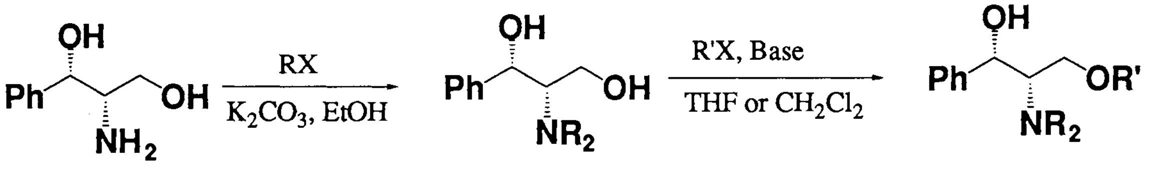
In the presence of (1*S*,2*S*)-3-benzyloxy-2-morpholino-1-phenylpropanol derived readily from (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol and nickel acetylacetonate, diethylzinc added to α,β-unsaturated ketones to give alkylated product in high optical purity (up to 95%ee). The effects of solvents and additives and the use of such ligands as a chiral catalyst were also investigated.

Enantioselective addition of an alkyl group to α,β-unsaturated ketones constitutes one of the most straightforward ways to chiral β-substituted carbonyl compounds.[1)] To this end dialkylzinc has received considerable attention as a convenient reagent when a suitable chiral ligand mostly derived from amino alcohol is present.[2)] For example, complexes prepared in situ from nickel acetylacetonate and dimethylaminoisoborneol,[3)] proline,[4)] norephedrin,[5)] chiral pyridine,[6)] and other derivatives[7)] effected conjugate addition to give the product with moderate to good enantioselectivity. While such a strategy enabled dialkylzinc to be employed as a reagent for the conjugate addition, the addition to aldehyde was also promoted in the presence of an amino alcohol, which has a similar structure to that used for the conjugate addition.[2)] As to the accessibility of such chiral ligands possessing an amino alcohol structure, many of the reported examples did not use readily available substrates, and sometimes involved rather tedious preparations. Reported herein is the use of chiral 2-amino-1,3-diols derived from readily available and inexpensive (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol, possessing a same framework of natural compound chrolamphenical,[8)] as an efficient chiral auxiliary for asymmetric conjugate addition to α,β-unsaturated ketones. The present substrate has the following characteristic features



1 2 3

a: R_2 = n-Bu_2, R' = Bn
b: R_2 = n-Bu_2, R' = Me
c: R_2 = n-Bu_2, R' = TBDMS
d: R_2 = n-Bu_2, R' = CPh_3

e: R_2 = -$(CH_2)_4$-, R' = Bn
d: R_2 = -$(CH_2)_5$-, R' = Bn
g: R_2 = -$CH_2CH_2OCH_2CH_2$-, R' = Bn

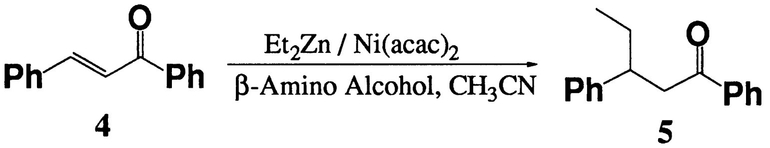


Table 1. Addition of Diethylzinc to Chalcone **4** in the Presence of Amino Alcohol **3**

Entry	**3** /mol%	Ni(acac)$_2$/mol%	Yield of **5**/%	ee/%a)	Config.b)
1	**3a** (100)	5	49	84	*R*
2	**3b** (100)	5	31	58	*R*
3	**3c** (100)	5	83	72	*R*
4	**3d** (100)	5	44	81	*R*
5	**3e** (100)	5	86	82	*R*
6	**3f** (100)	5	91	91	*R*
7	**3f** (100)c)	5	85	91	*R*
8	**3g** (100)	5	90	91	*R*
9	**3g** (100)c)	5	82	94	*R*
10	**3g** (120)c)	5	85	95	*R*
11	**3g** (50)c)	5	81	89	*R*
12	**3g** (30)c)	5	79	87	*R*
13	**3g** (20)c)	5	64	85	*R*
14	**3g** (20)c)	1	64	88	*R*

a) Determined by HPLC analysis using chiral column (Daicel OB). b) Determined by comparison with the reported sign of the optical rotation.11) c) In the presence of molecular sieves 3A.

as a chiral auxiliary: three different functional groups capable of being transformed into various derivatives in a highly selective manner, which enables the creation of a proper environment for the asymmetric induction, and adjusting a subtle balance of the three functional groups on steric and electronic effects is readily carried out by choosing suitable protecting groups on the amino and hydroxyl functionalities.

The chiral amino alcohols **3a-g** were prepared starting from **1** in two steps in good to excellent overall yields: *N*-alkylation of **1** with 2 equivalents of alkyl halide followed by etherification with alkyl halide-NaH or chlorosilane-Et$_3$N. The efficiency of these amino alcohols as a chiral auxiliary for conjugate addition of diethylzinc was investigated by using chalcone as substrate, and the results are shown in Table 1.

All the reactions were carried out according to the following typical procedure: under an argon atmosphere a mixture of nickel acetylacetonate (2.6 mg, 0.01 mmol), (1*S*,2*S*)-3-benzyloxy-2-morpholino-1-phenylpropanol **3g**8) (65.5 mg, 0.2 mmol), and molecular sieves 3A (1.0 g) in acetonitrile (3.0 mL) was heated at 80 °C for 1 h. To the resulting mixture was added a solution of chalcone (41 mg, 0.2 mmol) in acetonitrile (1.0 mL) at room temperature, and it was stirred for 30 min at room temperature. A solution of diethylzinc (2.0 M in hexane, 0.3 ml, 0.6 mmol) was added to the mixture at -40 °C, and the entire mixture was stirred at -40– -35 °C for 2.75 h. The normal workup followed by purification on TLC gave (*R*)-1,3-diphenyl-1-pentanone (38.7 mg, 82%) as a colorless oil.10) The optical purity of the product was determined to be 94%ee by HPLC using a chiral column

(Daicel OB) (eluent: Hexane/*i*-PrOH = 500/1), and the absolute configuration was assigned to be *R* by comparison of the sign of the optical rotation with the reported value.[11)]

As shown in Table 1, the degree of the asymmetric induction was dependent on the structure of the chiral ligand. A relatively larger and in particular aromatic substituent at the primary hydroxyl group was needed for higher enantiomeric excess. As to the substituents at the nitrogen, alicyclic derivatives recorded good results. Among the alicyclic derivatives, morpholino derivative **3g** gave the best result, where the alkylated product was obtained in 91%ee (entry 8). A slightly better enantiofacial discrimination was attained when the reaction was conducted in the presence of molecular sieves 3A (entry 9). The catalytic use of **3g** met with 88%ee when the reaction was carried out in the presence of 1 mol% of $Ni(acac)_2$, indicating that the present auxiliary was capable of working as a catalyst when a suitable quantity of an additive was present (entry 14).

Table 2. Addition of Diethylzinc to Chalcone **4** in the Presence of Amino Alcohol **3g**[a)]

Entry	Solvent	Additive/mol%	Yield of **5**/%	ee/%[b)]
1	DMF	$Ni(acac)_2$ (5)	14	5
2	Toluene	$Ni(acac)_2$ (5)	32	40
3	THF	$Ni(acac)_2$ (5)	11	44
4	EtCN	$Ni(acac)_2$ (5)	40	89
5	CH_3CN	$Ni(acac)_2$ (5)	82	94
6	CH_3CN	$NiCl_2$ (5)	44	89
7	CH_3CN	$NiBr_2$ (5)	9	85
8	CH_3CN	NiI_2 (5)	4	72
9	CH_3CN	None	16	0

a) The reaction was carried out according to the general procedure at -40--30 °C (see text). b) Determined by HPLC analysis using chiral column OB.

Next, the effects of additives and solvents were also examined using the same addition reaction to chalcone in the presence of amino alcohol **3g**, and the results are summarized in Table 2. As shown, this reaction was sensitive to the reaction solvents and the additives; DMF gave the product of only a few per cent ee, whereas moderate selectivity was recorded in THF and toluene, and cyanoalkanes promoted the addition reaction most efficiently,[5c)] giving the addition product with high ee. As an additive, nickel halides effected the enantiofacial discrimination most effectively, and among them nickel acetylacetonate was found to be the additive of choice. Other enones besides chalcone were subjected to the present ethylation reaction conditions, and the aliphatic and alicyclic enones did not seem to be suitable for the present enantiofacial discrimination, whereas those possessing an aromatic ring next to the carbonyl recorded good selectivity.[12)]

The asymmetric alkylation with diethylzinc promoted by chiral amino diols derived from (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol provides an easy access to β-alkylated ketones in high optical purity. In particular, the derivatives possessing a protecting group bearing a benzyl unit at the primary hydroxyl group and an alicyclic derivative at the nitrogen gave the best result, in which the present chiral auxiliary recorded comparable efficiency to the ephedrin derivatives reported by Soai.[5)] Since the chiral auxiliary is readily prepared from an inexpensive commercially available starting material,[13)] where the modification is quite flexible due to three different functional groups, the reaction is conducted under mild conditions, and the use of a catalytic amount of the chiral auxiliary met with good to high level of chiral induction, the present methodology offers a useful addition to the existing procedures.

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9) The following spectral properties were obtained for **3g**: $[\alpha]_D^{23}$ +3.62 (c 0.28, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.39-7.22 (m, 10H), 4.51 (d, J = 9.9 Hz), 4.33 (dd, J = 11.9 and 14.8 Hz, 1H), 3.83-3.70 (m, 4H), 3.43-3.45 (m, 2H), and 3.04-2.70 (m, 5H); IR (neat) 3020, 2840, 1130, and 710 cm^{-1}.
10) $[\alpha]_D^{23}$ -8.53 (c 0.77, EtOH); ^1H NMR ($CDCl_3$) δ 7.92-7.14 (m, 10H), 3.21-3.31 (m, 3H), 1.75-1.83 (m, 2H), and 0.80 (t, J = 7.3 Hz, 3H); IR (neat) 3050, 1700, 1460, 760, and 710 cm^{-1}.
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12) The following results were obtained from the reaction of other enones with diethylzinc under the conditions described in this paper: (*E*)-4-phenyl-3-buten-2-one (31%, 35%ee), (*E*)-1-phenyl-2-buten-1-one (77%, 86%ee), 2-cyclopenten-1-one (58%, 24%ee), and 2-cyclohexen-1-one (41%, 18%ee).
13) (1*S*,2*S*)-2-Amino-1-phenyl-1,3-propanediol is commercially available from Aldrich, Merck, Fluka, and Tokyo Kasei Co.

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