Enantioselective Addition of Diethylzinc to Aldehydes Using 1,1'-Bi-2-naphthol-3,3'-dicarboxamide as a Chiral Auxiliary

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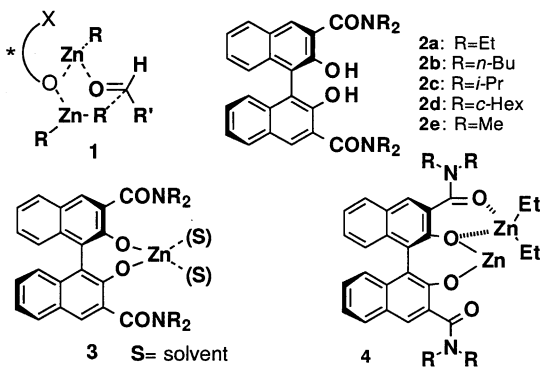
A highly enantioselective addition of diethylzinc to a wide range of aldehydes was achieved by using *N,N,N',N'*-tetraalkyl-1,1'-bi-2-naphthol-3,3'-dicarboxamides as chiral auxiliaries.

Enantioselective addition of dialkylzinc to aldehydes is one of the most reliable method to prepare optically active *sec*-alcohols.[1] To date, various types of optically active β-amino alcohols and titanium alkoxides have been used as chiral sources for this type of reactions.[1] Furthermore, a camphor-derived β-hydroxy-carboxamide has been found to serve as a chiral auxiliary.[2] By the introduction of these chiral sources, excellent level of enantioselectivity has been realized in most addition reactions but the reaction of some substrates such as alkynylaldehydes and *o*-fluorobenzaldehyde still shows moderate enantioselectivity.[3-5] With the mechanism of asymmetric induction of these reactions, amino alcohol-assisted enantioselective addition has been extensively studied and the transition state structure (**1**, X: NR_2) wherein the chirality of the amino alcohol moiety regulates the chirality of the asymmetric oxygen atom formed by the coordination of dialkylzinc and in turn discriminates the enantioface of aldehydes, has been proposed to rationalize the stereochemistry of the addition reaction.[1b,6] Addition reaction using β-hydroxy carboxamide has been considered to proceed through a similar transition state [**1**, X: O=C(NR_2)-].[2] Recently, we found that optically active *N,N,N',N'*-tetraethyl-1,1'-bi-2-naphthol-3,3'-dicarboxamide (**2a**) could be used as an efficient chiral auxiliary for enantioselective Simmons-Smith cyclopropanation.[7] Although the mechanism of asymmetric induction of this reaction is still unclear at present, the NMR analysis in CD_2Cl_2 indicated that compound **2** formed seven-membered zinc chelate **3** upon the addition of 1 equiv. of Et_2Zn and the additional diethylzinc made a chelate **4** in which the zinc ion was coordinated by phenolic and amide carbonyl oxygen atoms.[8] The chelate **4** seemed to provide the reaction site appropriate for enantioselective alkyl group transfer from dialkylzinc to aldehydes: Coordination of the amide carbonyl fixes one of ethyl groups to direct toward the *re*-face of the aldehyde in conformer **A** which is more favorable than the conformer **B** suffering from steric repulsion between the aldehyde and the amide *N*-alkyl group (Figure 1). This consideration prompted us to examine the addition of diethylzinc to aldehydes in the presence of *N,N,N',N'*-tetraalkyl-1,1'-bi-2-naphthol-3,3'-dicarboxamide.



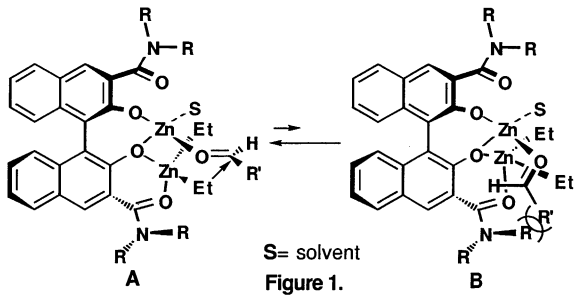


Figure 1.

We first examined the alkylation of phenylpropargylaldehyde as a test substrate with 10 mol% of chiral auxiliary under various reaction conditions. Interestingly, the reaction using (*R*)-**2a** in a polar solvent gave higher enantioselectivity than that in a nonpolar solvent such as toluene (Table 1, entry 1-4) and tetrahydrofuran was found to be the solvent of choice (entry 4). We next examined the effect of the amide alkyl group on enantioselectivity (entries 5-11) and found that the isopropyl amide (*R*)-**2c** showed the best enantioselectivity (entry 8). Finally, the reaction with (*R*)-**2c** at -23 °C afforded (*R*)-1-phenyl-1-pentyn-3-ol of 92% ee in 90 % yield (entry 9). Enantiomeric excess was determined by HPLC

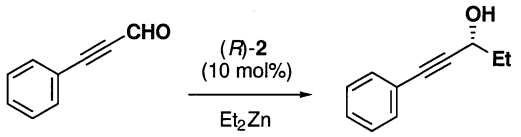
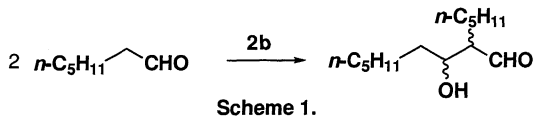


Table 1. Enantioselective ethylation of phenylpropargylaldehyde using **2a-d** as chiral auxiliaries

Entry	Auxiliary	Solvent	Et_2Zn /eq	Temp. /°C	Time /h	Yield /%	% Ee
1	**2a**	toluene	1.3	0	6	69	56
2	"	CH_2Cl_2	1.3	0	15	74	62
3	"	Et_2O	1.3	0	6	88	66
4	"	THF	1.3	0	6	92	78
5	**2b**	toluene	1.3	0	15	79	59
6	"	THF	1.3	0	15	68	84
7	**2c**	THF	1.3	0	6	77	88
8	"	THF	1.3	-23	24	56	92
9	"	THF	2.0	-23	24	90	92
10	**2d**	THF	1.3	0	6	56	80
11	**2e**	THF	1.3	0	15	82	79

analysis and the absolute configuration was assigned by comparison of specific rotation.[4b)]

Ethylation of other aldehydes was also examined under the above reaction conditions. Although there is no reasonable explanation at present, the best chiral auxiliary [(*R*)-**2b** or (*R*)-**2c**)] to be used was dependent upon the substrates examined. The results are summarized in Table 2. All the substrates including *o*-fluorobenzaldehyde gave (*R*)-*sec*-alcohols of high enantioselectivity greater than 90% ee. The stereochemistry is consonant to the transition state model described in Figure 1. Reaction with reduced amount (2 mol %) of **2** also showed high enantioselectivity equal to that with 10 mol % of **2** but the reaction rate became slow (entry 2). Despite of the above description, only heptanal underwent the undesired and poor stereoselective aldol reaction (Scheme 1). No addition product was detected by TLC analysis.



Scheme 1.

Table 2. Enantioselective ethylation of aldehydes using **2b** or **2d** as a chiral auxiliary

Entry	Aldehyde	Auxiliary	Temp./°C	Time /h	Yield /%	%Ee (Confign)
1	C_6H_5CHO	**2b**	0	24	88	99[a)] (*R*)[b)]
2	"	**2b**[c)]	0	72	63	98 (*R*)
3	"	**2c**	0	24	82	97 (*R*)
4	*p*-ClC_6H_5CHO	**2b**	0	24	88	97[d)] (*R*)[b)]
5	*p*-$CH_3OC_6H_5CHO$	**2b**	0	24	85	94[e)] (*R*)[b)]
6	*o*-FC_6H_5CHO	**2b**	0	24	86	95[f)] (*R*)[g)]
7	*c*-$C_6H_{11}CHO$	**2c**	0	24	51	98[h] (*R*)[i)]
8	4-*t*-Bu-$C_6H_{10}CHO$[j)]	**2c**	0	48	51	98[k)] (-)[l)]
9	(*E*)-C_6H_5CH=$CHCHO$	**2b**	-23	24	53	91[m)] (*R*)[b)]

[a]Determined by HPLC analysis using DAICEL Chiralcel OJ (hexane/*i*-PrOH 15:1) after benzoylation. [b]Assigned by chiroptical comparison with the literature values (reference 9). c) Two mol% of **2b** was used. [d]Determined by HPLC analysis using DAICEL Chiralcel OB-H (hexane/*i*-PrOH 30:1). [e]Determined by HPLC analysis using DAICEL Chiralcel OD (hexane/*i*-PrOH 30:1). [f]Determined by HPLC analysis using DAICEL Chiralpak AD (hexane/*i*-PrOH 50:1) after 3,5-dinitrobenzoylation. [g]Assigned by chiroptical comparison with the literature values (reference 5a). [h]Determined by HPLC analysis using DAICEL Chiralpak AD (hexane/*i*-PrOH 200:1) after benzoylation. [i]Assigned by chiroptical comparison with the literature values (reference 10). [j]*trans*-isomer. [k]Determined by HPLC analysis using DAICEL Chiralpak AD (hexane/*i*-PrOH 200:1) after 3,5-dinitrobenzoylation. [l]Not determined. [m]Determined by HPLC analysis using DAICEL Chiralcel OD (hexane/*i*-PrOH 9:1)

Typical experimental procedure is as follows: A hexane solution of diethylzinc (1.0 M, 0.67 ml) was added to a solution of (a*R*)-**2c** (18 mg, 0.033 mmol) in anhydrous tetrahydrofuran (1.5 ml) at -23 °C and stirred for 15 min. To this solution was added a solution of phenylpropargylaldehyde (44 mg, 0.33 mmol) in tetrahydrofuran (0.5 ml) and the mixture was stirred for 24 h at the temperature. Usual work-up and chromatography on silica gel (hexane-ethyl acetate= 4:1) afforded (*R*)-1-phenyl-1-pentyn-3-ol (48.0 mg, 90%) as a colorless oil. $[\alpha]_D^{23}$ = +19.8° (c=1.96, Et_2O) [lit[4b] $[\alpha]_D^{23}$ = -13.7° (c=2.00, Et_2O) for (*S*)-form of 70% ee]. Enantiomeric excess was determined to be 92% ee by HPLC analysis using optically active column (Daicel Chiralcel, OJ; Hexane/*i*-PrOH 9:1).

In conclusion, *N*,*N*,*N'*,*N'*-tetralkyl-1,1'-bi-2-naphthol-3,3'-dicarboxamides which could control both the conformation of diethylzinc and an aldehyde in the transition state, were demonstrated to be efficient chiral auxiliaries for addition of dialkylzinc to a wide variety of substrates including aromatic, α,β-unsaturated, and α-branched aliphatic aldehydes.

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References and Notes

Research Fellow of the Japan Society for the Promotion of Science.

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3 For example, the addition of diethylzinc to phenylpropargylaldehyde in the presence of (*S*)-(+)-diphenyl(*N*-methylpyrrolidin-2-yl)methanol shows moderate 70% ee (reference 4), while chiral titanium catalysts shows high enantioselectivity (reference 5). The addition of diethylzinc to *o*-fuluorobenzaldehyde in the presence of titanium-TADDOLate catalyst also shows moderate 62% ee (reference 5a). However, reactions of other substrates using these chiral auxiliary or catalyst show excellent enantioselectivity.

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8 Treatment of amide (**2a** or **2e**) with equimolar amount of diethylzinc in CD_2Cl_2 evolved twice molar amount of ethane to give a chelate **3** having a seven-membered ring structure of C2-symmetry. ^{13}C NMR of **3** (R= Et or Me) showed fifteen and thirteen signals, respectively. Further addition of diethylzinc provided a new species, ^1H NMR of which showed two new signals corresponding to *N*-alkyl groups at lower field (*e.g.*, 3.43 and 3.51 ppm, when R= Me), suggesting the formation of the chelate **4**. The complex **3** (R= Et) crystallized out in the form of a trimer from the 1:1 solution of **2a** and diethylzinc. The structure of the trimer was determined unambiguously by X-ray analysis, the data of which will be published elsewhere. ^1H NMR of **3** in THF-d_8 suggested that the complex existed as an equilibrium mixture of three species; monomer, dimer, and trimer.

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