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First application of amino-TADDOL derivatives in enantioselective addition of diethylzinc to aryl aldehydes: effect of substituents on the nitrogen atom

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Abstract

Five amino-TADDOL derivatives have been used as catalysts for the enantioselective addition of diethylzinc to aromatic aldehydes. Moderate to good enantioselectivities were obtained (up to 88% ee). The substituents on the nitrogen atom play an important role in the stereochemistry, even reversing the enantioselectivity. The effects of Li salts of aminoalcohols on the reaction were explored.

1. Introduction

In recent years, a variety of aminoalcohols, namely exclusively 1,2-aminoalcohols, have been used as catalysts in the enantioselective addition of diethylzinc to aldehydes.[1] Applications of 1,3[2]- and 1,4[3]-aminoalcohols have been occasionally reported. There are also a few examples of 1,2-substituted ferrocenyl aminoalcohols[4] and 2-amino-2′-hydroxy-1,1′-binaphtyl (NOBIN).[5] However, inspection of the impressively long lists of these ligands revealed an almost total absence of the representatives of the amino-TADDOL series.

It has been known that, in metal complexes, (*P*)-BINOL and (*R*,*R*)-TADDOL provide similar ligand spheres with λ-shape of axially disposed aromatic groups.[6] Therefore, we thought that amino-TADDOLs could also be applicable to the enantioselective reaction. We first used amino-TADDOL derivatives **1**, **2**, **3**, **4** and **5** (Fig. 1) as catalysts for the addition of Et_2Zn to aromatic aldehydes.

We found that the substituents on the nitrogen atom strongly affected both the chemical yield and the enantioselectivity, and in some cases showed a reverse stereochemistry.[10b] The lithium

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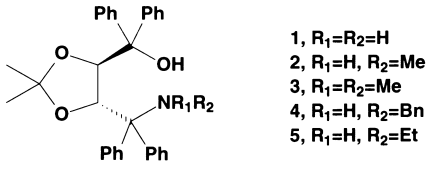


Figure 1.

salts of ligands were also studied which showed different effects compared to their parent ligands. Herein we wish to report the results of this study.

2. Results and discussion

Compounds **1**–**4** were directly prepared according to the literature.[8a] Compound **5** was prepared by direct ethylation instead of by the literature method.[8b] Attempts to modify the amino group with *n*-Bu and *i*-Pr all failed by direct alkylation, reductive alkylation with aldehyde or reduction of ketoamide derivative.

Since benzaldehyde has been most extensively studied in other systems, we focused our efforts on the diethylzinc addition to benzaldehyde in our initial study so that the results could be easily compared with those from previous studies. It was reacted for 24 h at 0°C in hexane and 5% mol ligand was used as a catalyst. The results from these experiments are tabulated in Table 1.

An interesting trend emerges with changing the substituent on the nitrogen atom (entries 1–4, Table 1). The primary aminoalcohol **1** without additive was inefficient in terms of both chemical yield and enantioselectivity (entry 1, Table 1). In addition, it gave a condensation by-product **6** (Fig. 2), which was identified by NMR, MS, IR and X-ray diffraction analysis.[7] The molecular structure of **6** is shown in Fig. 3.

Compound **6** was also tested as a catalyst for the addition reaction according to standard procedures; it turned out to be an inefficient catalyst with 38% yield and 0% ee.

Substituting one hydrogen atom with a methyl on the nitrogen in **2** led to a much improved enantioselectivity with 80% ee (*R*) as well as chemical yield (99%). The benzyl derivative **4** gave the same effect with 81% ee (*S*). However, the sense of stereoinduction is opposite between **2** and **4** (cf. entries 2 and 4, Table 1). Using **3**, where another methyl is introduced onto the nitrogen in **2**, again caused the reversal of the configuration with 85% ee (*S*) (entry 3, Table 1).

Some other representative aldehydes have been investigated under the same reaction conditions (entries 5–28, Table 1)

Ligand **2** always gave products of (*R*)-configuration while **3** and **4** favored the opposite configuration. In all cases, **4** afforded excellent yields (85–100% yield) and good enantioselectivity (79–88% ee), which shows that **4** is not sensitive to steric or electronic effects of aldehydes. Ligand **2** is strongly affected by the steric hindrance. When the 2-MeO substitutent was changed to a 4-MeO, the enantiomeric excess rose from 57 to 71% and the yield decreased from 100 to 60% (cf. entries 5 and 8, Table 1). On the other hand, the electronic effect had a great influence on **3**; substitution of 4-CF_3 with 4-MeO led to an increase in ee and yield from 43 to 88% and from 70 to 94%, respectively. It is very interesting to note that such a small change in the substituent on the nitrogen atom can lead to such a big difference. Extensive studies have been made previously concerning the enantioselective addition of diethylzinc to aldehydes by experimental and theoretical methods. In general, it is thought bulky alkyl groups on the nitrogen atom tend to increase

Table 1
Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by amino-TADDOL[a]

Entry	Substrate	Catalyst	%yield[b]	%ee	Configuration[f]
1	C_6H_5CHO	**1**	38	40[c]	R
2		**2**	99	80[c]	R
3		**3**	61	85[c]	S
4		**4**	88	81[d]	S
5	4-MeO-C_6H_4CHO	**2**	60	71[d]	R
6		**3**	94	88[d]	S
7		**4**	100	87[d]	S
8	2-MeO-C_6H_4CHO	**2**	100	57[d]	R
9		**3**	95	69[d]	S
10		**4**	100	83[d]	S
11	4-Me-C_6H_4CHO	**2**	82	70[c]	R
12		**3**	47	79[c]	S
13		**4**	93	78[c]	S
14	4-F-C_6H_4CHO	**2**	87	70[e]	R
15		**3**	33	72[e]	S
16		**4**	85	82[e]	S
17	4-Cl-C_6H_4CHO	**2**	100	70[c]	R
18		**3**	89	68[c]	S
19		**4**	99	80[c]	S
20	4-Br-C_6H_4CHO	**2**	100	67[c]	R
21		**3**	100	72[c]	S
22		**4**	100	81[c]	S
23	4-CF_3-C_6H_4CHO	**2**	95	70[c]	R
24		**3**	70	43[c]	S
25		**4**	87	79[c]	S
26	1-$C_{10}H_7CHO$	**2**	100	67[d]	R
27		**3**	86	86[d]	S
28		**4**	100	88[d]	S

a. Aldehyde: Cat: Et_2Zn=1.0:0.05:2.1, (molar ratio); at 0°C and 24 hours;

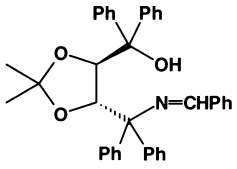
b. Isolated yield;

c. e.e determined by HPLC with a chiraicel OJ column;

d. e.e determined by HPLC with a chiraicel OD column;

e. e.e determined by HPLC with a chiraicel AS column;

f. Determined by comparison of specific rotation with literature data or known compounds. (See ref 12c)



6

Figure 2.

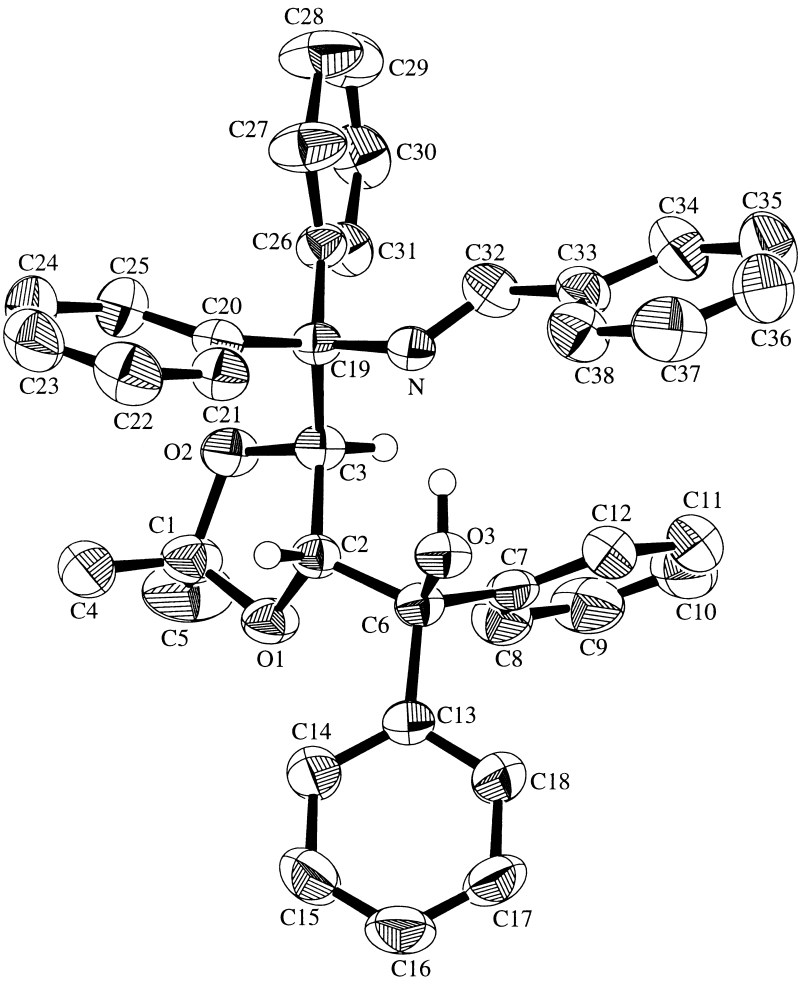


Figure 3. The molecular structure of **6**

the enantioselectivity for 1,2-aminoalcohols.[9] However, sometimes a simple change of the backbone substituents in ligands leads to reversal of stereochemistry.[10] In this case, we assume that the crowded fabric of the 1,4-aminoalcohol has caused our experiment results.

We postulate the reactive intermediates like **7** and **8** (Fig. 4). The *syn* tricyclic structures are less favored because of the electrostatic repulsion between the two non-reacting Zn–Et groups in the

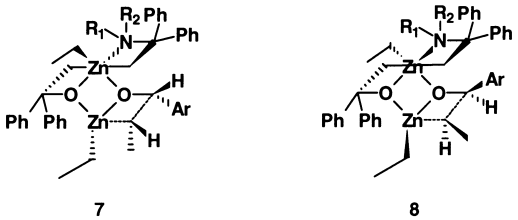


Figure 4.

central four-membered ring,[11a] so alkylation of benzaldehyde occurs from the mixed-ligand complexes **7** and **8** mainly via *anti*-configured 7/4/4 tricyclic transition states.[11]

When $R_1 = R_2 = H$ or $R_1 = Me$, $R_2 = H$, it reacts via **7** and gives *R*-enriched products. When $R_1 = R_2 = Me$, the repulsion between R_1 and adjacent Ph reinforces that between R_2 and the ethyl on the bridged zinc atom, and the transition state is forced to reverse to avoid the repulsion. It gives *S*-enriched products. In the case of **4**, it also gives *S*-enriched ones for the same reason as with **3**, because of the repulsion between Bn on the nitrogen and the ethyl on the bridged zinc atom. The results from **5** (shown in Table 2) supported this assumption. In the case of $R_1 = Et$ and $R_2 = H$, since ethyl is larger than methyl and smaller than benzyl, the energy difference between **7** and **8** was so small that there must be a rapid equilibrium between them and the reaction can take place via both **7** and **8** equally. Therefore, in all cases, **5** gave low ee values (entries 1–4, Table 2).

Table 2
Enantioselective addition of diethylzinc to aldehydes catalyzed by **5**[a]

Entry	Substrate	Catalyst	%yield[b]	%ee	Configuration[e]
1	C_6H_5CHO	**5**	91	9[c]	R
2	4-MeO-C_6H_4CHO	**5**	83	16[d]	R
3	4-CF_3-C_6H_4CHO	**5**	98	2.4[c]	S
4	1-$C_{10}H_7CHO$	**5**	100	10[d]	R

a. Aldehyde: Cat: Et_2Zn=1.0:0.05:2.1, (molar ratio); at 0°C and 24 hours;

b. Isolated yield;

c. e.e determined by HPLC with a chiraicel OJ column;

d. e.e determined by HPLC with a chiraicel OD column;

e. Determined by comparison of specific rotation with literature data or known compounds. (See ref 12c)

It has been noted previously that use of the lithium salt of a ligand usually leads to enhancement in selectivity,[12] and decrease in enantiomeric excess or reverse of the sense of chirality compared to the parent alcohol.[13] Under our conditions, when the lithium salts of the ligands were used as catalysts, there was a sharp decrease in enantioselectivity for **2** and **3** (cf. entries 2, 3, 6 and 7, Table 3). For ligand **4**, it also led to a slight decrease (cf. entries 10 and 11, Table 3). On the contrary, for **1** the selectivity and yield increased from 40 to 56% and from 38 to 72%, respectively, and no by-product was detected when the lithium salt was used. We propose that the presence of an additional labile hydrogen on the nitrogen may cause the reaction to proceed through a different intermediate. For **5**, it did not matter much. Obviously, Li^+ plays an important role in reaction mechanism. We could elucidate these effects by following 7/4/4 tricylic complexes **9** and **10** (Fig. 5). Because the Li atom takes the place of Zn–Et in the seven-membered ring, the loss of electrostatic repulsion between the two non-reacting Zn–Et groups in central four-membered ring caused the decrease of ee values (entries 1–4 and 6–8, Table 3) or reversal of the configuration (entry 7, Table 3).

In order to probe the assumed model **9** and **10**, we changed the order of addition of BuLi. After 2.1 equiv. of diethylzinc was first added to a solution of the ligand in hexane and stirred for 30 min, 1 equiv. of BuLi was added. After 10 min, 1 equiv. of aromatic aldehyde was syringed into the reaction mixture at 0°C and stirred for 24 h. The results turned out to be completely different (shown in Table 4); it just caused relatively lower decrease of ee values than Li salts. We assumed it was due to metal exchange between Zn and Li.

Experiments are underway to apply the present ligands to other asymmetric reactions.

Table 3
Effect of lithium salts of **1**, **2**, **3**, **4** and **5** on the yield and enantioselectivity[a]

Entry	Substrate	Catalyst	%yield[b]	%ee	Configuration[e]
1	C_6H_5CHO	Li-**1**	72	56[c]	R
2		Li-**2**	99	0	\
3		Li-**3**	99	0	\
4		Li-**4**	92	78[c]	S
5		Li-**5**	95	14[c]	R
6	4-MeO-C_6H_4CHO	Li-**2**	64	7[d]	R
7		Li-**3**	98	3[d]	R
8		Li-**4**	91	65[d]	S
9		Li-**5**	77	19[d]	R

a. Aldehyde: Cat: Et_2Zn: n-BuLi=1.0:0.05:2.1:0.05, (molar ratio); at 0°C and 24 hours;

b. Isolated yield;

c. e.e determined by HPLC with a chiraicel OJ column;

d. e.e determined by HPLC with a chiraicel OD column;

e. Determined by comparison of specific rotation with literature data or known compounds.(see ref 12c)

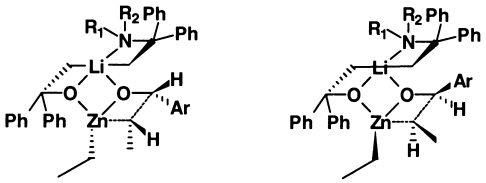


Figure 5.

Table 4
Effect of addition order of *n*-BuLi on the reaction[a]

Entry	Substrate	Catalyst	%yield[b]	%ee	Configuration[e]
1	C_6H_5CHO	**2**	95	59[c]	R
2		**3**	74	39[c]	S
3	4-MeO-C_6H_4CHO	**2**	91	69[d]	R
4		**3**	63	62[d]	S

a. Aldehyde: Cat: Et_2Zn: n-BuLi=1.0:0.05:2.1:0.05, (molar ratio); at 0°C and 24 hours;

b. Isolated yield;

c. e.e determined by HPLC with a chiraicel OJ column;

d. e.e determined by HPLC with a chiraicel OD column;

e. Determined by comparison of specific rotation with literature data or known compounds. (See ref 12c)

3. Experimental

All experiments were carried out under an Ar atmosphere. Aromatic aldehydes were distilled with calcium hydride and hexane was dried using standard methods and was distilled before use. Et_2Zn (1 M in hexane solution) was purchased from Fluka.

3.1. General procedure for the enantioselective addition of Et_2Zn to aromatic aldehydes using **1–5** as catalyst

To a suspension of **3** (27 mg, 0.05 mmol) in hexane (2.0 ml) was added diethylzinc (2.1 ml, 2.1 mmol) at 0°C. After stirring the mixture for 30 min, 4-methoxybenzaldehyde (136.0 mg, 1.0 mmol) was added and the reaction mixture was stirred for 24 h at 0°C. The reaction was quenched by 10% HCl and the product was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and then evaporated under reduced pressure. The residue was purified by flash chromatography (pentane:AcOEt 5:1) to give 100% yield and 87% ee of alcohol.

3.2. General procedure for the enantioselective addition of Et_2Zn to aromatic aldehydes using lithium salt of **1–5** as catalyst

To a suspension of **3** (27 mg, 0.05 mmol) in hexane (2.0 ml) was added equivalent of *n*-BuLi, stirred for 20 min, and diethylzinc (2.1 ml, 2.1 mmol) was then added at 0°C. After stirring of the mixture for 30 min, 4-methoxybenzaldehyde (136.0 mg, 1.0 mmol) was added and the reaction mixture was stirred for 24 h at 0°C. The reaction was quenched by 10% HCl and the product was extracted with ethyl acetate. The extract was dried over $MgSO_4$, and then evaporated under reduced pressure. The residue was purified by flash chromatography (pentane:AcOEt 5:1) to give 91% yield and 65% ee of alcohol.

3.3. Preparation of **5**

The mixture of **1** (0.98 g, 2.1 mmol), K_2CO_3 (500 mg, 25 mmol), 18-crown-6 (70 mg, 0.2 mmol) and EtI (2.5 ml, 25 mmol) was dissolved in 20 ml CH_3CN, then refluxed for 5 days. Et_2O (50 ml) was added to the solution, then filtered and directly evaporated. The residue was purified by flash chromatography (pentane:AcOEt 8:1) to give 1.02 g (2.0 mmol, 98% yield) of **5**. The spectral data are in accord with those reported.[8]

3.4. Preparation of **6**

In the general procedure of **1** as catalyst, it gave **6** as a by-product (25 mg, 0.045 mmol). Yield 90%. $[\alpha]_D^{20} = -39.0$ ($c = 1.10$, $CHCl_3$). Mp 230–232°C. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 8.51 (s, 1H, OH), 7.81–7.78 (m, 2H, arom. H), 7.65–7.63 (m, 2H, arom. H), 7.52–7.02 (m, 22H, arom. H), 4.47 (d, J = 8.33, 1H, CH), 4.27 (d, J = 8.34, 1H, CH), 1.17 (s, 6H, CH_3). MS (EI): m/z 554 (M^+, 14), 271 (100), 105 (38), 165 (19), 77(15). Anal. calcd for $C_{38}H_{35}NO_3$: C, 82.42; H, 6.37; N, 2.53. Found: C, 81.97; H, 6.33; N, 2.41. IR (KBr, cm^{-1}): $\nu = 3430$, 3057, 1636, 1599, 1491, 1446, 1371, 1172, 1080, 1054, 943, 886, 704.

Crystal structure analysis of **6**: X-ray diffraction data were collected on a Rigaku AFC7R diffractometer with graphite monochromated Mo-Kα radiation, $\lambda = 0.71069$ Å, and a 12 Kw rotating anode generator, at room temperature using the ω–2θ scan technique to a maximum 2θ value of 55.0°. Compound **6**, colorless cube, $C_{38}H_{35}NO_3$, $Mr = 553.69$, crystal size $0.2 \times 0.2 \times 0.3$ mm, orthorhombic, space group $P2_12_12$ (#19), $a = 16.792(4)$ Å, $b = 18.484(2)$ Å, $c = 9.874(2)$ Å, $V = 3064.7(10)$ Å^3, $Z = 4$, $\mu = 0.75$ cm^{-1}, $F_{000} = 1176.00$, $\rho_{calc} = 1.20$ g cm^{-1}, $R = 0.040$, $Rw = 0.046$. The intensities of representative reflections were measured after every 200; of 3967 collected reflections, 3013 were independent. A linear correction factor was applied to account for this. The

data were corrected for Lorentzian-polarization effects. The structure were solved by heavy atom Patterson methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. All calculations were performed using Texsan.[14]

Acknowledgements

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