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Reversal of enantioselectivity by adding $Ti(O^iPr)_4$: novel sulfamide-amine alcohol ligands for the catalytic asymmetric addition of diethylzinc to aldehydes

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Abstract

Novel sulfamide-amine alcohol ligands (**6**) derived from (−)-ephedrine (**4a**) and (+)-pseudoephedrine (**4b**) with multiple stereogenic centers were applied to the catalytic asymmetric addition of diethylzinc to aldehydes, providing (*S*)-products in high yields and good enantioselectivities. These sulfamide-amine alcohols together with $Ti(O^iPr)_4$ were shown to obtain the (*R*)-products in significant enantiomeric excesses (e.e.) and high yields. In addition, sulfamide-amine alcohols were superior to the original chiral sources **4a** and **4b**, which afforded no enantioselectivity in the $Ti(O^iPr)_4$-mediated reaction.

Keywords: Sulfamide-amine alcohol; Catalytic asymmetric addition; Diethylzinc; Reversal of enantioselectivity; Aldehyde

1. Introduction

The design and synthesis of new chiral ligands is the key in the development of highly asymmetric catalysis [1]. In the past decade, although many highly effective ligands for catalytic asymmetric reactions have been developed [1,2], efficient ligands with short synthetic routes, especially from commercially available chiral sources, are still desirable.

Very recently, many novel small organic molecules containing arranged muticenters have been developed in the catalytic asymmetric reactions. For examples, ligand **1** derived from L-proline was synthesized and efficiently catalyzed the direct aldol reactions of aromatic and aliphatic aldehydes with high enantioselectivities [3]. Ligand **2** derived from chiral phenylglycinol showed excellent results in the asymmetric ruthenium-catalyzed reduction of ketones [4]. Ligand **3** derived from *trans*-4-hydroxy-L-proline have been used to the catalytic enantioselective nucleophilic alkylation of α-ketoesters and got good results [5]. We are interested in developing new muticenter chiral ligands based on (−)-ephedrine (**4a**), (+)-pseudoephedrine (**4b**) and sulfonamide ligands (**5**). In this way, the novel sulfamide-amine alcohol ligands (**6**) derived from **4a** and **4b**, which are both cheap commercially available chiral sources were designed. Owing to the highly electron-withdrawing nature of the sulfonyl group, the N–H group of sulfonamides is acidic and the sulfonamide nitrogen atom is a poor electron donor [6]. It therefore serve as another weakly coordinative site and the ligand possibly binds zinc in a tridentate fashion. Thus, they can reduce the number of possible diastereomeric intermediates or transition states, strongly increasing the probability of an efficient chirality transfer. Herein we report the application of the sulfamide-amine alcohols for

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the catalytic asymmetric addition of diethylzinc to aldehydes [7].

2. Experimental

All reactions were carried out under an argon atmosphere condition and monitored by thin layer chromatography (TLC). Column chromatography purifications were performed using silica gel. All solvents were dried and degassed by standard methods and all aldehydes and diethylzinc were purchased from Aldrich. Melting points were measured on a Yazawa micro melting point apparatus (uncorrected). NMR spectra were measured in $CDCl_3$ on a Bruker DRX-400 NMR spectrometer (400 MHz) with TMS as an internal reference. Optical rotations were measured with a HORIBA SEPA-200 high sensitive polarimeter. High resolution mass spectra (HRMS) were recorded on a Mariner-TOF 5303 (Applied Biosystems, USA). Enantiomeric excess (e.e.) determination was carried out using GC with a chiral cyclodex β-2, -3, 6-M, 30 m × 0.32 mm capillary column on an Agilent HP-4890 GC instrument with FID detector.

2.1. Synthesis of ligand (*6a*)

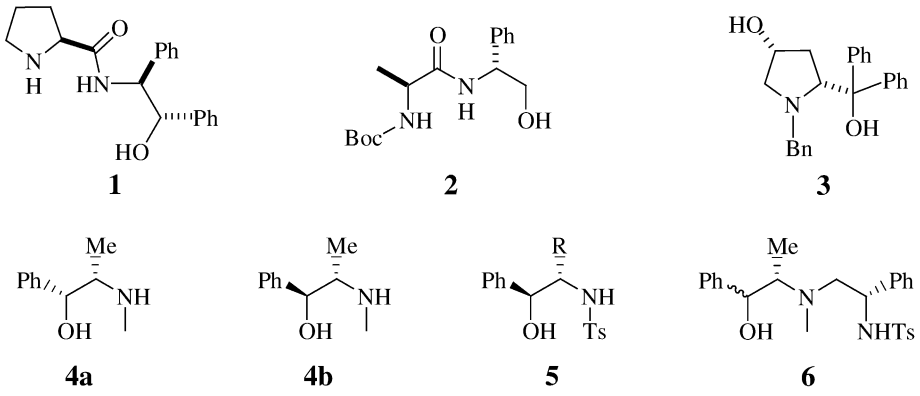
(*S*)-2-Phenyl-1-tosylaziridine (1.0 g, 3.66 mmol) and (−)-ephedrine (0.76 g, 4.57 mmol) were dissolved in dry acetonitrile (30 mL) and the mixture was stirred under refluxing for 40 h. The solvent was evaporated under reduced pressure, leaving a sticky oil. The residue was dissolved into a little of dichloromethane and substantial petroleum ether was added. Subsequently, a white precipitate was obtained and followed by recrystallization to give the pure ligand **6a** as white solid (1.12 g), 70% yield. m.p. 36–38 °C; $[\alpha]_D^{20} = -38.21$ (*c* 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$): ð 0.74 (d, *J* = 6.8 Hz, 3H), 1.85 (s, 3H), 2.41 (s, 3H), 2.86–2.91 (m, 1H), 3.04 (t, *J* = 6.8 Hz, 1H), 3.24 (t, *J* = 11.4 Hz, 1H), 3.54–3.57 (m, 1H), 4.52 (d, *J* = 6.8 Hz, 1H), 7.01–7.03 (m, 2H), 7.25–7.27 (m, 5H), 7.32–7.37 (m, 3H), 7.40–7.44 (m, 2H), 7.59 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): ð 12.7, 22.2, 29.5, 43.9, 64.4, 67.8, 77.0, 126.9, 127.7, 128.6, 128.8, 129.0, 129.2, 130.2, 137.4, 137.9, and 143.8; HRMS (APCI) calculated for $C_{25}H_{30}N_2O_3S$ ($M - H^+$): 437.1904, found: 437.1887.

2.2. Synthesis of ligand (*6b*)

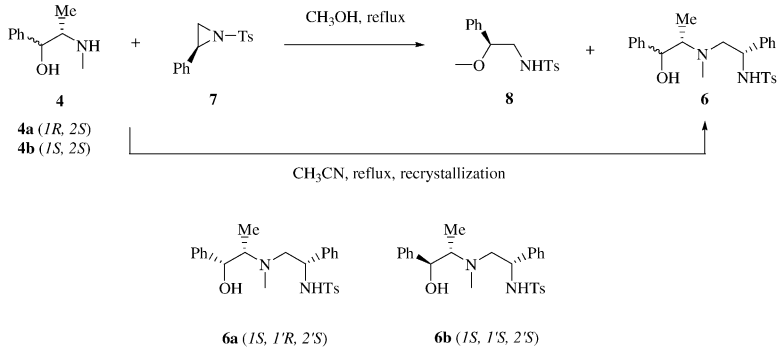
Compound **6b** was prepared in the same way as **6a** from (*S*)-2-phenyl-1-tosylaziridine (1.0 g, 3.66 mmol) and (+)-pseudoephedrine (0.76 g, 4.57 mmol) to give the pure ligand **6b** with 75% yield (1.20 g). m.p. 188–189 °C; $[\alpha]_D^{20} = +30.23$ (*c* 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$): ð 0.52 (d, *J* = 4.0 Hz, 3H), 2.04 (s, 3H), 2.44 (s, 3H), 2.85–2.89 (m, 1H), 3.16–3.21 (m, 1H), 3.54 (s, 1H), 3.71 (t, *J* = 6 Hz, 1H), 4.23 (d, *J* = 8.0 Hz, 1H), 4.48 (br, 1H), 5.05 (br, 1H), 7.13 (t, *J* = 4.0 Hz, 2H), 7.26–7.35 (m, 10H), 7.72 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): ð 10.8, 22.2, 30.1, 45.4, 64.5, 68.1, 75.8, 127.8, 128.0, 128.5, 129.0, 129.4, 130.4, 137.6, 138.6, 142.5, and 144.1; HRMS (APCI) calculated for $C_{25}H_{30}N_2O_3S$ ($M - H^+$): 437.1904, found: 437.1876.

2.3. General procedures for the addition of Et_2Zn to aldehydes

Under a dry argon atmosphere, chiral ligand (10 mol%, 0.05 mmol) in dry toluene (4 mL) was cooled to 0 °C and a solution of Et_2Zn (1.0 M in hexane, 1.1 mmol) was added slowly. After stirring for 30 min at 0 °C, freshly distilled aldehyde (0.5 mmol) was added and the reaction was stirred for 24 h at 10 °C. The reaction mixture was quenched with 1N aqueous HCl at 0 °C. The aqueous phase was extracted with ethyl acetate (3 mL × 5 mL). The combined organic phase was washed with little brine, dried with anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 12:1) to give the carbinol. The enantiomeric purity of the product was determined by HPLC. The absolute configurations of the products were assigned by comparison to literature values.



Scheme 1.



Scheme 2. Synthesis of the novel sulfamide-amine alcohol ligands.

2.4. General procedures for the Ti-mediated addition of Et_2Zn to aldehydes

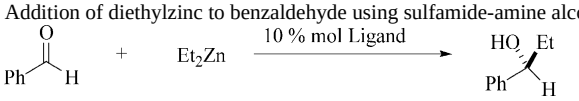
Under a dry argon atmosphere, to a solution of chiral ligand (10 mol%, 0.05 mmol) in dry dichloromethane (4 mL) was added $Ti(O^iPr)_4$ (1.2 equiv. 0.06 mmol) at room temperature. After stirring the mixture for 15 min, a solution of Et_2Zn (1.0 M in hexane, 1.5 mmol) was added at 0 °C. The mixture was stirred for 0.5 h and the resulting solution cooled to 0 °C and treated with the aldehyde (0.5 mmol). The mixture was allowed to react at 10 °C for 24 h and quenched with 1N aqueous HCl at 0 °C. The aqueous phase was extracted with ethyl acetate (3 mL × 5 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 12:1) to give the carbinol. The enantiomeric purity of the product was determined by HPLC. The absolute configurations of the products were assigned by comparison to literature values (Scheme 1).

3. Results and discussion

Sulfamide-amine alcohols (**6**) were prepared from **4** and (*S*)-2-phenyl-1-tosylaziridine (**7**), which was conveniently synthesized from commercially available (*S*)-phenylglycinol in one step (Scheme 2) [8]. The experiment was firstly conducted in methanol and provided substantial byproduct (**8**), which was generated from ring opening of aziridine with methanol [9,10]. When the reaction was carried out in refluxing acetonitrile, the desired products were obtained in high yields of 70% **6a** and 75% **6b**, respectively. Fortunately, after the reaction was complete checked by TLC, the solvent was removed. The residue was dissolved into a little of dichloromethane (DCM) and substantial petroleum ether was added. Subsequently, a white precipitate was generated and followed by recrystallization to give the pure ligands. This allowed us to avoid complex column chromatography.

The sulfamide-amine alcohols were applied into the asymmetric addition of diethylzinc to benzaldehyde in 10 mol%

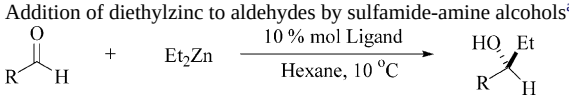
Table 1
Addition of diethylzinc to benzaldehyde using sulfamide-amine alcohols[a]



Entry	Ligand	Solvent	Temperature (°C)	Yield (%)[b]	e.e. (%)[c]
1	**6a**	Toluene	10	96	78 (*S*)
2	**6b**	Toluene	10	13	13 (*S*)
3	**6a**	DCM	10	21	44 (*S*)
4	**6a**	THF	10	16	41 (*S*)
5	**6a**	Ether	10	14	9 (*S*)
6	**6a**	Hexane	10	99	81 (*S*)
7	**6a**	Hexane	0	49	82 (*S*)
8	**6a**	Hexane	20	88	81 (*S*)
9	**6a**	Hexane	−10	41	79 (*S*)

[a] Et_2Zn/aldehyde/ligand = 2.2:1:0.1; 24 h.
[b] Isolated yield.
[c] The e.e. values were determined by GC; the absolute configuration assigned by comparison to literature values.

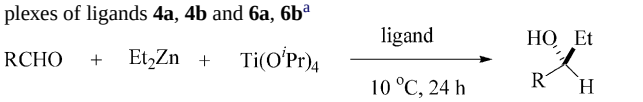
Table 2
Addition of diethylzinc to aldehydes by sulfamide-amine alcohols[a]



Entry	Ligand	Aldehyde	Yield (%)[b]	e.e. (%)[c]
1	**6a**	4-Chlorobenzaldehyde	61	80 (*S*)
2	**6a**	4-Anisaldehyde	30	79 (*S*)
3	**6a**	4-Tolualdehyde	57	77 (*S*)
4	**6a**	4-Fluorobenzaldehyde	73	83 (*S*)
5	**6a**	4-Bromobenzaldehyde	87	80 (*S*)
6	**6a**	2-Chlorobenzaldehyde	94	77 (*S*)
7	**6a**	2-Anisaldehyde	99	82 (*S*)
8	**6a**	Benzaldehyde	99	81 (*S*)
9	**4a**	Benzaldehyde	86	72 (*R*)
10	**4b**	Benzaldehyde	29	35 (*S*)

[a] Et_2Zn/aldehyde/ligand = 2.2:1:0.1; Hexane, 10 °C, 24 h.
[b] Isolated yield.
[c] The e.e. values were determined by GC; the absolute configuration assigned by comparison to literature values.

Table 3
Addition of diethylzinc to aldehydes using in situ-formed titanium(IV) complexes of ligands **4a**, **4b** and **6a**, **6b**[a]



Entry	Ligand	Solvent	Aldehyde	Yield (%)[b]	e.e. (%)[c]
1	**6a**	DCM	Benzaldehyde	73	16 (*R*)
2	**6b**	DCM	Benzaldehyde	69	34 (*R*)
3	**6b**	Toluene	Benzaldehyde	99	16 (*R*)
4	**6b**	Hexane	Benzaldehyde	99	13 (*R*)
5[d]	**6b**	DCM	Benzaldehyde	95	34 (*R*)
6[e]	**6b**	DCM	Benzaldehyde	96	47 (*R*)
7[d]	**4a**	DCM	Benzaldehyde	78	0
8[d]	**4b**	DCM	Benzaldehyde	74	0
9[d]	**6b**	DCM	4-Chlorobenzaldehyde	99	25 (*R*)
10[d]	**6b**	DCM	4-Fluorobenzaldehyde	99	28 (*R*)
11[d]	**6b**	DCM	2-Anisaldehyde	94	17 (*R*)

[a] $Ti(O^iPr)_4/Et_2Zn$/aldehyde/ligand = 1.2:1.5:1:0.1, 10 °C for 24 h.
[b] Isolated yield.
[c] The e.e. values were determined by GC; the absolute configuration assigned by comparison to literature values.
[d] Et_2Zn (3 equiv.).
[e] Et_2Zn (3 equiv.), 70 h.

loading (Table 1). With toluene as the solvent, **6a** afforded (*S*)-1-phenyl-1-propanol in 96% yield and 78% e.e. (Table 1, entry 1), while **6b** gave low e.e. and poor yield (Table 1, entry 2). Obviously, the results showed that **6a** was better than **6b**. Thus, **6a** was chosen as destined ligand and tested in other solvents (Table 1, entries 3–6). As expected, the reaction was strongly influenced by the solvent. Reaction temperature only exhibited very slight effect on the enantioselectivity although higher temperature gave higher yield (Table 1, entries 7–9). The best result of 99% yield and 81% e.e. was observed in hexane at 10 °C (entry 6).

With conditions optimized for benzaldehyde, ligand **6a** was extended to the asymmetric addition of diethylzinc to other aromatic aldehydes (Table 2). Good yields and enantioselectivities for the substituted benzaldehydes with (*S*)-products were obtained. In contrast, the chiral sources **4a** and **4b** only provided 86% yield with 72% e.e., 29% yield with 35% e.e., respectively (Table 2, entries 9 and 10). Therefore, the novel sulfamide-amine alcohol ligand **6a** was indeed superior to the original chiral sources **4a** and **4b** in yield and enantioselectivity.

Based on the consideration of the ligand feature, the sulfamide-amine alcohol ligands were used to the $Ti(O^iPr)_4$-mediated addition of diethylzinc to aldehydes (Table 3). Firstly, by changing the solvent from toluene or hexane to DCM, **6b** was used as desired ligand and DCM was employed as solvent in the followed experiments (Table 3, entries 1–6). Noteworthily, the two original chiral sources **4a** and **4b** gave moderate yields but no enantioselectivity (Table 3, entries 7 and 8). Differently, the sulfonamide-amine alcohol ligands derived from **4a** and **4b** provided the opposite (*R*)-products in significant enantiomeric excess for the tested substrates (Table 3, entries 1–6 and 9–11).

Previous work described that *N*,*N*-dimethylation or *N*-methylation of some ligands can lead to reversal of enantioselectivity in the asymmetric addition of diethylzinc to aldehydes [11], and that a change in the backbone substituent in ligands can also get product with opposite configuration [12]. Very recently, Zheng and co-workers reported that all ligands derived from D-fructose gave (*R*)-products and by changing of backbone from six-membered pyranose-ring to five-membered furanose-ring afforded (*S*)-products [13]. Unlike the above examples that the product of opposite configuration was obtained by changing the backbone itself of the ligand, in this paper in the same reaction only adding of $Ti(O^iPr)_4$ could change the absolute configuration of products. In that way, ligands induced (*S*)-enriched products and ligands with $Ti(O^iPr)_4$ induced (*R*)-enriched products. Mechanistically, although the actual active species are unclear, the possible binding models of the two catalyst systems shown in Fig. 1 are suggested. The former is formed in situ as ethylzinc aminoalkoxide by the reaction of sulfamide-amine alcohol with Et_2Zn and the nitrogen of sulfamide coordinated to Zn weakly (model A) [14–16], while the latter is formed in situ by the reaction of the ligand with $Ti(O^iPr)_4$ and both the sulfonyl oxygen and the sulfonamide nitrogen participated in the coordinations (model B) [17]. The reversal of the enantioselectivies of the product should be probably ascribed to the difference between the coordination forms of the two catalyst systems.

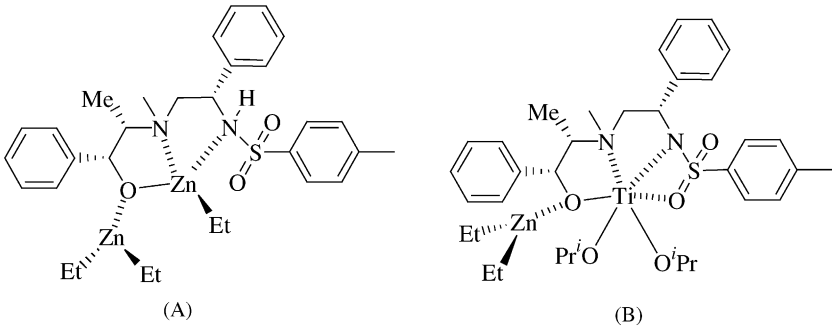


Fig. 1. Possible trivalent binding modes of zinc to the ligands and multivalent binding mode of titanium to the ligands.

4. Conclusion

We have conveniently synthesized novel sulfamide-amine alcohol ligands from (−)-ephedrine (**4a**) and (+)-pseudoephedrine (**4b**) in one step and applied them to the catalytic asymmetric addition of diethylzinc to aldehydes. The sulfamide-amine alcohol ligands provides excellent yield and good enantioselectivities in the absence of $Ti(O^iPr)_4$. However, these ligands together with $Ti(O^iPr)_4$ are shown to provide the product of the opposite absolute configuration in significant enantiomeric excess and high yield. Delightedly, sulfamide-amine alcohols were superior to the original chiral sources **4a** and **4b**, which afforded no enantioselectivity in the $Ti(O^iPr)_4$-mediated reaction. Further work is in progress in our laboratory with the aim of expanding the use of these inexpensive chiral compounds to other enantioselective processes. The mechanistic works for explaining the reversal of the stereochemistry in the asymmetric addition of diethylzinc to aldehydes are underway.

Acknowledgements

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