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L-Proline-derived tertiary amino alcohol as a new chiral ligand for enantioselective alkynylation of aldehydes

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ABSTRACT

The easily prepared chiral tertiary amino alcohol **1a** was found to catalyze the reaction of alkynylzinc reagents with various aldehydes to generate chiral propargylic alcohols with moderate-to-good enantioselectivities. The mechanism of the reaction is also discussed in this Letter. A novel theoretical computation of those evaluated ligands was introduced which may supply valuable experience to help designing new chiral ligands.

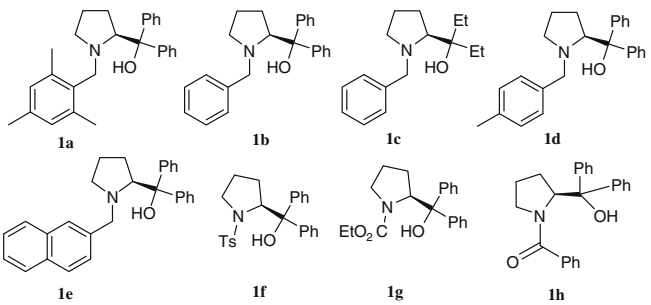
The catalytic enantioselective addition of terminal alkynes to aldehydes has generated great amount of interest in recent years. The resulting propargylic alcohols are versatile building blocks for many chiral compounds.[1–4] Although some impressive results have been obtained with several effective asymmetric catalysts,[5] most of these ligands are derived from chiral binol or (−)-*N*-methyl ephedrine. Thus, it is still desirable to develop new types of chiral catalysts which are greatly needed to probe how the chiral catalysts act on the reaction and how to develop new types of chiral ligands. L-Proline and its derivatives have shown powerful utilities in many asymmetric reactions, especially as chiral ligands or chiral resources.[6] Herein, we report an L-proline-derived tertiary amino alcohol **1a**, as a new chiral ligand for the catalytic asymmetric alkynylation of aldehydes, as our continuing interest.[7] Several papers have reported the utilization of tertiary amino alcohols as ligands to catalyze the asymmetric alkynylation of aldehydes,[8–12] but few of them have discussed the mechanism of this reaction. In this Letter, the mechanism of the reaction will be discussed, and theoretical explanation based on calculations will be introduced to help us understand how to design new types of chiral ligands more successfully.

Initially, we synthesized **1b** as a ligand for the alkynylation of benzaldehyde which resulted in the formation of an adduct of 65% ee in toluene. This was a promising result. In order to screen more effective ligands and study the relationships between ligand structure and the enantioselectivity, we prepared ligands **1a–h** (Scheme 1). Ligands **1a**, **1b**, **1c**, **1d**, **1e,** and **1g** were prepared according to the procedure described by Kanth;[13] ligand **1f** was obtained from the diphenyl prolinol by N-tosylation;[14] and ligand **1h** was prepared following the literature procedure.[15]

Screening of ligands in the reaction between benzaldehyde and phenylacetylene in toluene, we found that ligand **1a**[16] gave the best result with 77% ee (Fig. 1). Interestingly, although these ligands were derived from the same starting material, different configurations of the products were observed (Fig. 1). This will be discussed in this Letter later.

Encouraged by the results shown in Figure 1, we chose ligand **1a** to further our study. Then the effects of the reaction conditions, such as the choice of solvents, the reaction temperature, and the amount of ligand **1a** were investigated.

At room temperature, the best ee was obtained in toluene (Table 1, entry 3). Lower reaction temperatures did not improve the enantioselectivities (Table 1, entries 10 and 11). Increasing the amount of ligand **1a** to 30 mol % improved the selectivity (80% ee) slightly (Table 1, entry 8), while further increasing the amount of the ligand does not increase the ee anymore (Table 1, entry 9). Decreasing the amount of **1a** to 10 mol % gave the chiral product with 69% ee (Table 1, entry 7). Additives (1.0 mol %) were also investigated. Unfortunately, they did not show any beneficial effects on this reaction.



Scheme 1. Evaluated ligands in this Letter.

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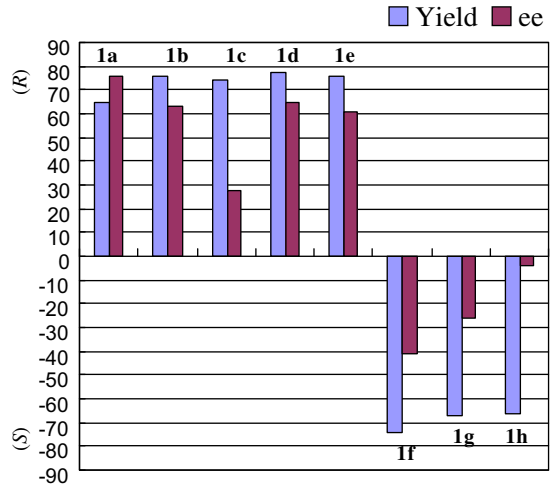


Figure 1. Yields and ees of the product catalyzed by the evaluated ligands in this Letter.

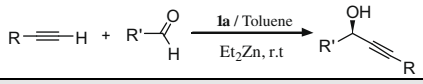
Having optimized the alkynylation of benzaldehyde with phenylacetylene in the presence of chiral ligand **1a**, we decided to screen a series of aldehydes and acetylenes to evaluate the scope of this reaction. As shown by the results summarized in Table 2, good enantioselectivities were achieved for most of the substrates. Aromatic aldehydes bearing electron-withdrawing group at the *ortho*-position gave better results than that at the *meta*- or *para*-positions (Table 2, entries 2–9). For other acetylenes, good results could also be obtained for the reaction. For example, 78% ee was obtained for the addition of 4-methylphenylacetylene to 2-chlorobenzaldehyde (Table 2, entry 12). The reaction of phenylacetylene addition to the aliphatic aldehydes was also observed, but only 46% ee was obtained.

As we know the suitable match between the ligand and the center metal is very important for the asymmetric catalytic reactions. Interestingly, the configuration of the product seems to be correlated to the substituent at *N* atom in the ligand. Ligands with electron-donating group at the *N* atom give the (*R*)-form product, while ligands with electron-withdrawing group give the inverted configuration (Fig. 1). These attracted us to find out the relationships between the ligand structure and the enantioselectivity/the configuration of the product. If we know these well, it may help us to design new chiral ligands.

In order to explain the correlation between the electronic similarity of the coordinated atoms (*N* and *O*) and the ee of the product more convincingly, we calculated the *NBO* charge of the coordinated atoms using the GAUSSIAN 03 programs.[19] The results are listed in Table 3.

Comparing ligands **1a–e**, the *NBO* charge of the *N* atom and *O* atom in each ligand was correlated to the enantioselectivity of

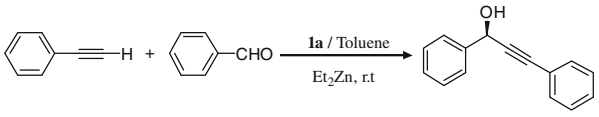
Table 2
Enantioselective alkynylation of various aldehydes with **1a**[a]



Entry	Aldehyde	R	Yield[b] (%)	ee[c] (%)
1	Benzaldehyde	Ph	76	80
2	2-Anisaldehyde	Ph	70	77
3	2-Bromobenzaldehyde	Ph	61	83
4	3-Bromobenzaldehyde	Ph	87	74
5	2-Chlorobenzaldehyde	Ph	71	83
6	3-Chlorobenzaldehyde	Ph	83	82
7	4-Chlorobenzaldehyde	Ph	78	72
8	α-Naphthaldehyde	Ph	82	75
9	β-Naphthaldehyde	Ph	87	75
10	2-Thiophenaldehyde	Ph	80	79
11	2-Fluorobenzaldehyde	Ph	85	73
12	2-Chlorobenzaldehyde	4-CH_3Ph	63	78
13	Benzaldehyde	Me_3Si	60	71

[a] All the reactions were processed under argon at room temperature for 24 h, phenylacetylene/Et_2Zn/benzaldehyde/ligand = 2:2:1:0.3.[17]
[b] Isolated yield.
[c] The enantiomeric excess was determined by chiral HPLC analysis of the corresponding products on a Chiralcel OD-H column. The configuration of the product is *R* assigned by comparing the retention time to the literature.[18]

Table 1
Optimization of the reaction conditions[a]



Entry	Solvent	*T*	Additive	Yield[b]	ee[c] (%)
1	THF	rt	—	54	59
2	Et_2O	rt	—	67	61
3	Toluene	rt	—	65	77
4	Hexane	rt	—	59	71
5	DCM	rt	—	64	53
6	DME	rt	—	72	73
7[d]	Toluene	rt	—	65	69
8[e]	Toluene	rt	—	70	80
9[f]	Toluene	rt	—	69	79
10	Toluene	0 °C	—	61	65
11	Toluene	−25 °C	—	59	78
12	Toluene	rt	Et_3N	71	77
13	Toluene	rt	DMAP	69	77
14	Toluene	rt	DiMPEG	71	77

[a] All the reactions were processed under argon at room temperature for 24 h, phenylacetylene/Et_2Zn/benzaldehyde/ligand = 1:1:0.5:0.1.
[b] Isolated yield.
[c] The enantiomeric excess was determined by chiral HPLC analysis of the corresponding products on a Chiralcel OD-H column.
[d] 10 mol % ligand was used.
[e] 30 mol % ligand was used.
[f] 40 mol % ligand was used.

Table 3
The calculated *NBO* charge of *N* and *O* atoms in ligands **1a–f**[a]

Ligand	*NBO* charge		
	N	*O*	Δ[b]
1a	−0.517	−0.762	0.245
1b	−0.516	−0.765	0.249
1c	−0.521	−0.782	0.261
1d	−0.517	−0.764	0.247
1e	−0.516	−0.765	0.249
1f	−0.778	−0.758	−0.020

[a] The results were calculated by using a GAUSSIAN 03 program.
[b] $\Delta = N–O$.

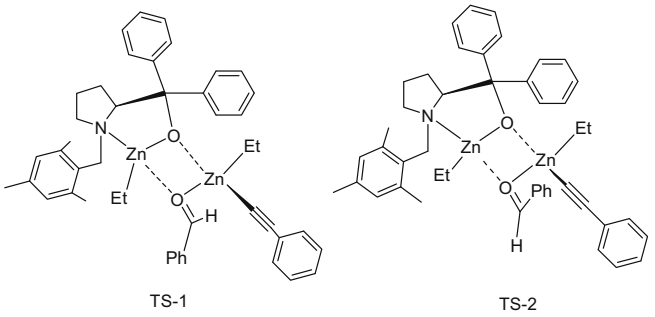


Figure 2. The proposed transition states of the reaction.

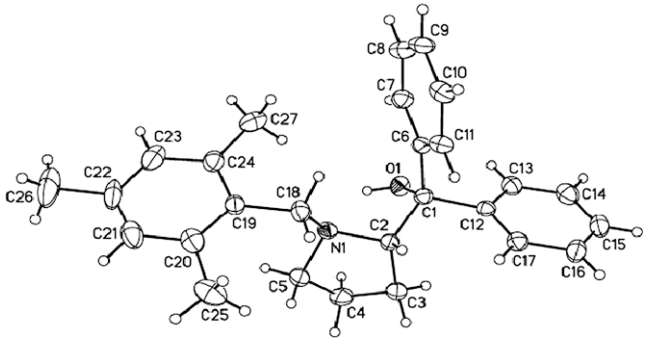


Figure 3. X-ray structure of ligand **1a**.

the product. Those with large margin gave the product with lower ee, while ligand **1a** with the smallest margin gave the product with the best ee which indicates that the smallest Δ ($N–O$) of the ligand may form the most selective catalyst with Et_2Zn. Interestingly, the calculated Δ value for ligand **1f** is <0. This is in accordance with the observed inverted configuration. Unfortunately, calculation on ligand **1g** and **1h** did not give similar results, although both of them gave configuration-inverted product. This is probably because of the presence of another coordinative oxygen atom in C=O, which may result in complicated coordination.

The proposed transition states are shown in Figure 2. The proposed TS-1 which may give the lower energy was the favorable way to give the *R* configuration product, while TS-2 which was the unfavorable transition state gave the product with the inverted configuration (Fig. 3).

In conclusion, we have successfully developed an efficient catalyst system for the enantioselective synthesis of propargylic alcohols via alkynylzinc addition to various aldehydes. The study has shown that the chiral ligand **1a** in the absence of Lewis acids can form an active catalyst with Et_2Zn which could afford products with up to 83% ee. The mechanism of the reaction was proposed and the theoretical calculations about those evaluated ligands with a GAUSSIAN 03 program have also been performed, the results of which may supply us useful guidance in designing new chiral ligands.

Acknowledgments

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16. *Character data of ligand* **1a**: Careful evaporation of a solution of **1a** in methanol gave a single crystal which is suitable for crystallographic analysis. Mp 108–110 °C; $[\alpha]_D^{25}$ +71.0 (*c* 1.01, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.30–7.27 (m, 4H), 7.16–7.09 (m, 2H), 6.80 (s, 2H), 4.87 (s, 1H), 3.99 (dd, J = 9.4, 5.3 Hz, 1H), 3.43–3.32 (m, 1H), 3.13 (d, J = 12.2 Hz, 1H), 2.63 (td, J = 9.2, 4.5, 4.5 Hz, 1H), 2.48–2.34 (m, 1H), 2.21 (s, 3H), 2.17 (s, 6H), 1.93 (ddd, J = 17.8, 11.1, 6.5 Hz, 1H), 1.68 (ddd, J = 12.8, 8.4, 4.1 Hz, 1H), 1.60–1.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 147.6, 137.8, 136.7, 133.1, 129.4, 128.5, 126.8, 126.5, 125.5, 78.1, 72.6, 54.6, 54.0, 40.7, 30.5, 24.3, 21.4, 21.2; IR (cm^{-1}): 3401, 3051, 2968, 2937, 2888, 2842, 1448; HRMS (EI) calcd for $[C_{27}H_{31}NO–H_2O]^+$ requires m/z 367.2300, found 367.2282. Selective crystal structure data: $C_{27}H_{31}NO$, triclinic, space group $P1$, a = 6.0379(10) Å, b = 12.783(2) Å, c = 15.101(2) Å, α = 96.757(17)°, β = 98.206 (16)°, γ = 103.14(2)°, V = 1109.7(3) Å^3, Z = 2, T = 293(2) K. For the detailed information of the crystal data, please see CCDC 695642.
17. *General experimental procedure for the addition of alkyne to aldehyde*: To a solution of ligand **1a** (0.0579 g, 0.15 mmol) in dry toluene (2.0 ml) at room temperature was added a solution of $ZnEt_2$ (15% in hexane, 1.1 ml). After the mixture was stirred at room temperature for 2.0 h, phenylacetylene (110 μl, 1.0 mmol) was added and the stirring continued for another 2.0 h. The white solution was treated with benzaldehyde (50 μl, 0.5 mmol) at 0 °C and stirred at room temperature for 24 h. After the reaction was completed, it was cooled to 0 °C and quenched by 5% aqueous HCl (2.0 ml). The mixture was extracted with ethyl acetate (EtOAc) (3 × 10 ml). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel H, EtOAc/petroleum ether = 1:8) to give the pure product. 76% yield. 80% ee determined by HPLC analysis (Chiralcel OD-H column, IPA/hexane = 20:80). Retention time: t_{major} = 7.57 min, t_{minor} = 10.51 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.2 Hz, 2H), 7.48–7.25 (m, 8H), 5.69 (s, 1H), 2.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 132.2, 129.2, 129.1, 128.9, 128.8, 127.2, 122.9, 89.1, 87.2, 65.6.
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