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Reversal of stereochemistry by adding $Ti(O^iPr)_4$ in the enantioselective phenylacetylene addition to aldehydes using L-prolinol-backbone ligand

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Abstract

Chiral ligands **1**–**2** with L-prolinol backbone have been applied to the enantioselective phenylacetylene addition to aldehydes, providing chiral propargylic alcohols in high yields and moderate enantioselectivities. Only the ligand **1** in combination with $Ti(O^iPr)_4$ afforded the products with opposite absolute configuration in significant enantiomeric excesses and high yields. The ratio of $Ti(O^iPr)_4$ to the ligand had great influence on the enantiomeric excess of the product.

Keywords: Reversal of stereochemistry; Enantioselective alkynylzinc addition; L-Prolinol-backbone; Propargylic alcohol; Aldehyde

1. Introduction

The asymmetric alkynylzinc addition to aldehydes can simultaneously form a new C–C bond and a stereogenic center in one step, which has become the preferred way of synthesizing the useful chiral propargylic alcohols [1]. Thus, the development of various chiral ligands as catalysts for the enantioselective alkynylation has gained considerable significance during the past years [2]. We believe that a good catalyst system should not only induce the asymmetric reaction in high yields and excellent enantioselectivities, but afford the products with either absolute configuration. However, obtaining the chiral sources with opposite absolute configuration becomes difficult, for many good chiral ligands derive from natural chiral sources mostly existing in single enantiomer. To solve this problem, seeking a new way of leading to the reversal of the stereochemistry in the asymmetric alkynylzinc addition reaction shows necessary.

In the asymmetric addition of diethylzinc to aldehydes, the usual way to get the product with opposite configuration is to change the backbone itself of the chiral ligand [3], while our group has reported that only adding $Ti(O^iPr)_4$ could lead to the reversal of the product configuration in the system catalyzed by sulfamide-amine alcohol ligands [4,5]. To the best of our knowledge, there is no report on the reversal of the product configuration in the asymmetric alkynylzinc addition reaction. As part of further extending the application of our methodology, in this paper, we report our finding of another readily available chiral ligand **1** for asymmetric alkynylzinc addition to aldehydes and reversal of product configuration by adding $Ti(O^iPr)_4$ in the reaction (Scheme 1).

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. All aldehydes, diethylzinc, dimethylzinc and phenylacetylene were commercially available. NMR

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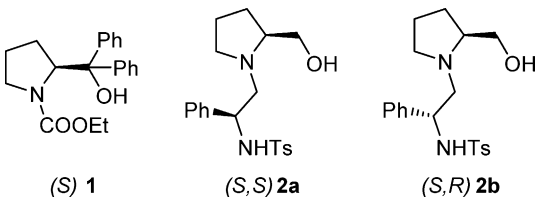


Scheme 1. Evaluated ligands.

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. Enantiomeric excess (ee) determination was carried out using HPLC with a Daicel Chiralcel OD-H column on an Agilent HP-1100 HPLC instrument; Solvent, 90:10 hexane/isopropanol; Flow rate 1 mL min^{-1}; 219 nm UV detection.

2.1. Synthesis of ligand (*1*)

Ligand **1** was synthesized according to literature procedure [6] (Scheme 2). Characterization of ligand **1**: 36% yield; mp: 115–116 °C; $[\alpha]_D^{20} = -44$ (c 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.81 (s, 1H), 1.23 (s, 3H), 1.49 (d, J = 3.6 Hz, 1H), 1.95 (d, J = 4.8 Hz, 1H), 2.05–2.12 (m, 1H), 2.96 (s, 1H), 3.41 (d, J = 7.6 Hz, 1H), 4.14 (s, 2H), 4.92–4.95 (m, 1H), 7.27–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 14.72, 23.03, 29.73, 47.81, 61.96, 66.02, 81.67, 127.21, 127.51, 127.69, 127.92, 128.22, 143.79, 146.45, 158.39.

2.2. General procedures for asymmetric alkynylation reactions

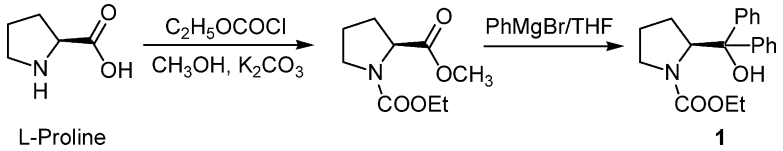
Phenylacetylene (0.75 mmol) was added into a 10 mL two-neck round bottom flask containing 2 mL dry diethyl ether at room temperature under dry argon atmosphere. The stirred mixture was then cooled to 0 °C for 5 min, followed by the addition of a 1.0 M solution of diethylzinc in hexane (0.75 mmol). The resulting solution was brought to rt and stirred for 2 h, and then ligand (0.025 mmol, 10 mol%) was added. The homogenous solution was stirred at rt for 30 min and then aldehyde (0.25 mmol) was added via syringe. The resulting mixture was stirred at rt for 18–20 h. When the reaction was complete, it was quenched by adding sat. NH_4Cl (2 mL) at 0 °C. The aqueous phase was extracted with diethyl ether (3 × 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 afford pure product. The enantiomeric excess was determined by HPLC analysis using a Chiralcel column. The configuration was assigned by comparison with the sign of specific rotation of the known compounds. The racemic propargylic alcohols were obtained by addition of PhC ≡ CLi to aldehydes [7].

2.3. General procedures for the Ti-mediated asymmetric alkynylation reactions

Under a dry argon atmosphere, to a solution of the chiral ligand (10 mol%, 0.025 mmol) in dry toluene (2 mL) was added $Ti(O^iPr)_4$ (0.1 mmol) at room temperature. The stirred mixture was then cooled to 0 °C for 5 min, followed by the addition of a 1.0 M solution of diethylzinc in hexane (0.75 mmol). The resulting solution was brought to rt and stirred for 2 h, and then phenylacetylene (0.75 mmol) was added. The homogenous solution was stirred at rt for 1 h and then aldehyde (0.25 mmol) was added via syringe. The resulting mixture was stirred at rt for 18–20 h. When the reaction was complete, it was quenched by adding sat. NH_4Cl (2 mL) at 0 °C. The aqueous phase was extracted with diethyl ether (3 × 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 afford pure product.

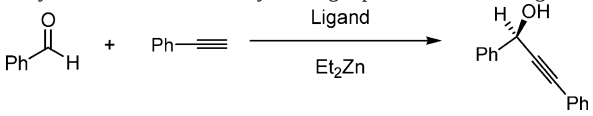
3. Results and discussion

L-Prolinol-derived sulfamide-amine alcohols **2** have proved to be excellent catalysts for asymmetric addition of diethylzinc to aldehydes [5]. Unexpectedly, when ligands **2** were employed as catalysts for asymmetric alkynylation reaction, modest results were obtained (Table 1, entries 1–2). Notably, the configurations of the propargylic products from the system catalyzed by ligands **2** were constantly *S* as determined by comparing with the literature [8]. This showed that the absolute configurations of the addition products were dependent on the absolute configuration of the L-prolinol backbone. Ligand **1**, another type of ligand with L-prolinol backbone, had also been used as catalyst for this reaction and induced (*S*)-product with 16% ee (entry 3). After screening the different solvents, we chose toluene as the optimal solvent (entries 4–6). Increasing the loading of the ligand and the amount of phenylacetylene versus diethylzinc led to the



Scheme 2. Synthesis of chiral ligand **1**.

Table 1
Alkyne addition to benzaldehyde using L-prolinol-backbone ligands[a]



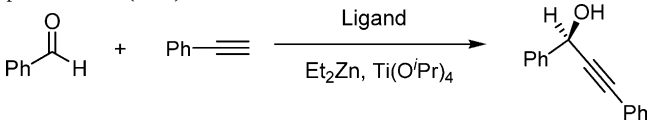
Entry	Ligand (mol%)	Solvent	Yield (%)[b]	ee (%)[c]
1	**2a** (10)	Toluene	99	23 (*S*)
2	**2b** (10)	Toluene	96	27 (*S*)
3	**1** (10)	Toluene	99	16 (*S*)
4	**1** (10)	Hexane	99	5 (*S*)
5	**1** (10)	DCM	44	0
6	**1** (10)	Et_2O	76	2 (*S*)
7	**1** (20)	Toluene	99	25 (*S*)
8[d]	**1** (10)	Toluene	99	19 (*S*)
9[d]	**1** (30)	Toluene	99	24 (*S*)
10[d]	**1** (40)	Toluene	99	1 (*S*)
11[d,e]	**1** (22)	Toluene	99	36 (*S*)
12[d,f]	**1** (22)	Toluene	82	29 (*S*)

[a] Phenylacetylene/Et_2Zn/aldehyde/ligand = 2.4:2.2:1:0.1; toluene, rt, 20 h.
[b] Isolated yield.
[c] The ee values were determined by HPLC. The absolute configuration was assigned by comparison to literature value.
[d] Phenylacetylene/Et_2Zn/aldehyde/ligand = 3.0:3.0:1:0.1; toluene, rt, 20 h.
[e] Temperature = 0 °C.
[f] Temperature = −20 °C.

rise of the enantioselectivity (entries 7–10). Low temperature afforded the best result of 99% yield and 36% ee (entry 11).

Based on the consideration of the ligand feature, ligands **1**–**2** were used to Ti(O^iPr)$_4$-mediated asymmetric alkynylation reaction (Table 2, entries 1–2). The results catalyzed by **2** showed reduced enantioselectivities and unchanged absolute

Table 2
Alkyne addition to benzaldehyde using L-prolinol-backbone ligands in the presence of Ti(O^iPr)$_4$[a]



Entry	Ligand (mol%)	Solvent	Yield (%)[b]	ee (%)[c]
1	**2a** (10)	Toluene	99	7 (*S*)
2	**2b** (10)	Toluene	99	6 (*S*)
3	**1** (10)	Toluene	99	37 (*R*)
4	**1** (10)	Hexane	99	15 (*R*)
5	**1** (10)	DCM	70	32 (*R*)
6	**1** (10)	Et_2O	89	27 (*R*)
7[d]	**1** (22)	Toluene	99	44 (*R*)
8[e]	**1** (22)	Toluene	96	43 (*R*)

[a] Phenylacetylene/Et_2Zn/aldehyde/Ti(O^iPr)$_4$/ligand = 3.0:3.0:1:0.4:0.1; rt, 20 h.
[b] Isolated yield.
[c] The ee values were determined by HPLC. The absolute configuration was assigned by comparison to literature value.
[d] Temperature = 0 °C.
[e] Temperature = −20 °C.

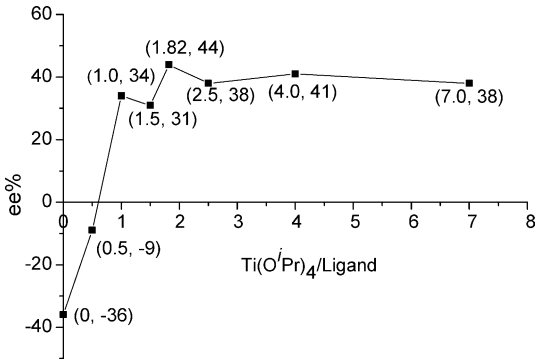


Fig. 1. Relationship between the ratio of Ti(O^iPr)$_4$/ligand and the enantiomeric excess.

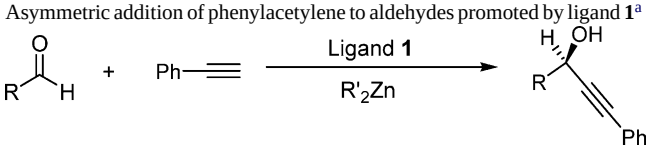
configurations of products. Differently, ligand **1** induced the (*R*)-product and got enhanced result in Ti-mediated reactions (entry 3). After investigating the solvent effect, toluene was the best (entries 4–6). In addition, lower temperature gave better result of 99% yield and 44% ee (entries 7–8).

From the above results, it can be seen that in the asymmetric alkynylation reaction catalyzed by ligand **1** only adding Ti(O^iPr)$_4$ can lead to the reversal of the absolute configuration of the product. As the Lewis acidity of the complex differs with the proportions of Ti(O^iPr)$_4$ to the ligand [9], the influence of the proportions on the enantioselectivity of the alkynylation reaction was investigated (Fig. 1). In the absence of Ti(O^iPr)$_4$ the configuration of the product was *S* and increasing the amount of Ti(O^iPr)$_4$ led to the drop of the enantioselectivity, which made the configuration reverse finally. With the further increase of the ratio of Ti(O^iPr)$_4$ to the ligand, the enantioselectivities were almost constant. We considered that the complex (ligand/Ti(O^iPr)$_4$ = 1.82) was acidic enough to catalyze the opposite stereocontrolled reaction.

It is known that the presence of polyethers could lead to a significant increase in enantioselectivity at many asymmetric reactions [2c,10]. In this paper, we employed DIMPEG (*M* = 2000) as the additive in this reaction. The results showed that the additive was beneficial to the asymmetric alkynylation reaction using ligand **1**, but unfavorable to the same reaction in the presence of Ti(O^iPr)$_4$ (Table 3, entries 1–2). In the same system, Me_2Zn instead of Et_2Zn gave depressed enantioselectivities (entries 3–4). Subsequently, *o*-methylbenzaldehyde and 1-naphthylaldehyde were employed to study the configuration-reversed alkynylation in the presence of ligand **2** under the optimal conditions (entries 5–8). The best results of 56% ee and 61% ee were obtained, respectively (entries 7–8).

Mechanistically, although the actual active species are unclear, the possible binding models of the two catalyst systems shown in Fig. 2 were suggested. In the absence of Ti(O^iPr)$_4$, the sulfamide–amine alcohol ligand bound with Zn in a bidentate fashion (model **A**). Differently, in the Ti(O^iPr)$_4$-mediated reaction, the carbonyl oxygen of the ligand **2** possibly served as a weak coordination site in the cycle and the ligand **1**

Table 3
Asymmetric addition of phenylacetylene to aldehydes promoted by ligand **1**[a]



Entry	$Ti(O^iPr)_4$[b]	R'	DIMPEG[c]	R	Yield (%)[d]	ee (%)[e]
1	–	Et	+	Ph	99	46 (*S*)
2	+	Et	+	Ph	99	40 (*R*)
3	–	Me	+	Ph	61	24 (*S*)
4	+	Me	–	Ph	69	37 (*R*)
5	–	Et	+	*o*-Me-Ph	80	52 (*S*)
6	+	Et	–	*o*-Me-Ph	84	52 (*R*)
7	–	Et	+	1-Naphthyl	80	56 (*S*)
8	+	Et	–	1-Naphthyl	99	61 (*R*)

[a] Phenylacetylene/R'_2Zn/aldehyde/ligand = 3.0:3.0:1:0.22; toluene; 0 °C; 20 h.
[b] "+" stands for "adding"; "–" stands for "not adding"; ligand/$Ti(O^iPr)_4$ = 1.82.
[c] DIMPEG (2.5 mol%).
[d] Isolated yields.
[e] The ee values were determined by HPLC. The absolute configuration was assigned by comparison to literature value.

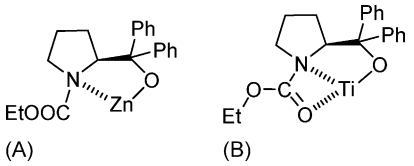


Fig. 2. Possible binding modes of metal (Zn or Ti) to the ligand **1**.

bound with Ti in a tridentate fashion (model **B**). The reversal of the enantioselectivities of the product should be probably ascribed to the difference between the coordination forms of the two catalyst systems.

4. Conclusion

In conclusion, we have successfully applied chiral ligands **1**–**2** with L-prolinol backbone to the enantioselective phenylacetylene addition to aldehydes, providing chiral propargylic alcohols in high yields and moderate enantioselectivities. Only the ligand **1** in combination with $Ti(O^iPr)_4$ afforded the products with opposite absolute configuration in significant enantiomeric excesses and high yields. The ratio of $Ti(O^iPr)_4$ to the ligand had great influence on the enantiomeric excess of the product. This provides a simple way to prepare enantiomeric products in the asymmetric alkynylation reaction and it is potentially applicable to other stereocontrolled catalytic processes.

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