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Boc-L-proline as a new chiral ligand for enantioselective phenylacetylene addition to aromatic aldehydes

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Abstract—The N-terminal protected amino acid (Boc-L-proline) is a chiral ligand for the enantioselective phenylacetylene addition to aromatic aldehydes, thus expanding the utility of the simplest enzyme, proline, in asymmetric catalysis. Good yields and enantioselectivities (up to 77% ee) were achieved.

Enantioselective formation of C–C bonds is an area of intense research.[1,2] The asymmetric addition of alkynylzinc to aldehydes is an important method of synthesizing chiral propargyl alcohols, which are important precursors to many chiral organic compounds. Recently, many significant chiral ligands in this area have been disclosed including ephedrine,[3] BINOL–Ti complex[4,5] and sulfonamido alcohols.[6] Though many significant results have been achieved, large efforts to develop new types of efficient chiral catalysts for this important asymmetric reaction are greatly needed to probe how the chiral catalysts act on the reaction and how to develop ligands, which can be prepared and derived from cheap chiral pool, especially from natural optically active molecules and their simple derivatives. It is very interesting and challenging.

L-Proline and its derivatives have become a series of important molecules in asymmetric catalysis due to its rigid structure, easy availability, and cheapness. They have shown powerful utilities in asymmetric aldol, Mannich, Michael reactions, and so on. Corey and Hetal,[7] and List[8] and other chemists have reported many important and significant examples using them as chiral ligands or chiral resources.

Based on the results of L-proline and its derivatives in catalytic asymmetric reactions and our recent report on catalytic asymmetric addition of alkynylzinc to aromatic aldehydes, we supposed that natural L-proline or its derivatives can also catalyze the asymmetric addition of alkynylzinc to aldehydes. To the best of our knowledge, no results of N-terminal protected amino acids as chiral ligands in this reaction has been disclosed to date.[9] Herein, we report the initial results of Boc-L-proline,[10] which has been used directly as a chiral ligand in this reaction.

Initially, we tried to use (*S*)-proline itself to catalyze the asymmetric reaction, but it is hard to dissolve the natural amino acid in general organic solvents. Therefore we used DMF or DMSO as the solvent, but we obtained a racemic product. Then we used the readily commercial available Boc-L-proline to promote the reaction. The results showed that this change resulted in a surprising jump in the enantioselectivity.

Interestingly, when the salt of Boc-L-proline treated with BuLi was used as the chiral ligand, the product had a low ee (<5% ee). So we supposed that under acidic condition, the carboxyl group of the amino acid could easily bind with $Ti(O^iPr)_4$ and the carbonyl group of the *t*-butoxycarbonyl might chelate with $Ti(O^iPr)_4$.[11] This complex behaved as a Lewis acid so we supposed that the coordinated complex might catalyze the asymmetric addition of alkynylzinc to aldehydes. When the BuLi was added, the carboxyl group of the amino acid could

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not bind with $Ti(O^iPr)_4$ and the coordinated complex was not steady (Fig. 1). So the product had a low ee.

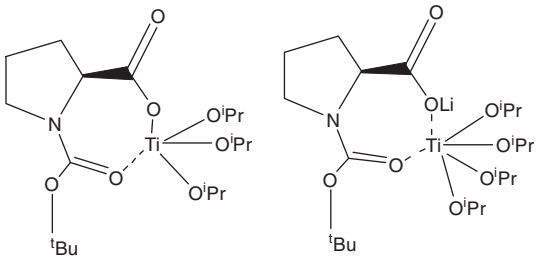
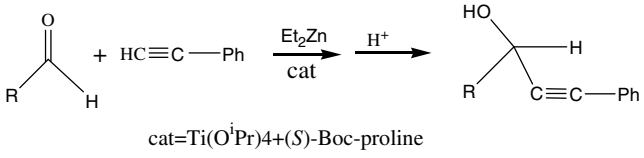


Figure 1.

We conducted the asymmetric alkynylzinc addition to aldehydes in these steps[13] (Scheme 1). The conditions influencing the reaction were summarized in Table 1.



Scheme 1.

We found that this reaction was strongly influenced by the solvents and the amount of $Ti(O^iPr)_4$. Low enantioselectivities were afforded in CH_2Cl_2 (entry 11) and THF (entry 12), or when the amount of $Ti(O^iPr)_4$ was decreased (entry 4). The amount of the ligand was increased from 10% to 30%, but the ee's only increased a little (entries 1, 2, 5, and 14). The temperature of the reaction was decreased from room temperature to 0 °C, and no significant change in ee was observed (entry 10).

The chiral propargyl alcohols generated from other aromatic aldehydes were obtained with 62–77% ee at room temperature when using the above procedure, and the results were summarized in Table 2. The reactions of phenylacetylene with fluoro-, chloro-, bromo-substituted benzaldehydes containing electron-withdrawing substituents showed higher ee's than those bearing electron-donating substituents. The reactions of the phenylacetylene addition to aliphatic aldehydes such as *n*-butyl aldehyde and isobutyl aldehyde were also observed, but only 35% ee was obtained.

Table 2. Asymmetric addition of phenylacetylene to aromatic aldehydes promoted by the ligand Boc-L-pro[a–d]

Entry	Aldehyde	Time (h)	Yield (%)	Ee (%)
1	Benzaldehyde	12	81	66
2	3-Tolualdehyde	12	75	67
3	4-Tolualdehyde	12	80	67
4	3-Anisaldehyde	12	78	62
5	4-Anisaldehyde	12	83	70
6	4-Chlorobenzaldehyde	12	68	75
7	4-Fluorobenzaldehyde	12	80	77
8	α-Naphthaldehyde	18	84	70
9	β-Naphthaldehyde	18	73	73
10	4-Bromobenzaldehyde	12	58	74
11	3-Bromobenzaldehyde	12	81	67

[a] In all of the entries: Et_2Zn/phenylacetylene/aldehyde/$Ti(O^iPr)_4$/Boc-L-pro = 3:3:1:0.6:0.2.
[b] All the reactions were processed under argon and at room temperature.
[c] $Ti(O^iPr)_4$ was freshly distilled before use.
[d] The ee values were determined by HPLC with Chiracel OD column.

In conclusion, we have successfully demonstrated the use of (*S*)-Boc-proline as an effective chiral ligand for the catalytic asymmetric addition of phenylacetylene to aromatic aldehydes under very mild condition. Many important features such as cheapness and readily commercial availability in both enantiometric forms make it

Table 1. Asymmetric addition of phenylacetylene to benzaldehyde using Boc-L-pro as the ligand[a]

Entry	Ligand (%)	$Ti(O^iPr)_4$[b]/ligand	Solvent[c]	Temperature	Ee[d](%)/configuration[e]
1	10	3/1	Ether/Tol.	rt	53
2	15	3/1	Ether/Tol.	rt	61
3	20	None	Tol./Tol.	0 °C	3
4	20	1/1	Ether/Tol.	0 °C	3
5	20	2/1	Ether/Tol.	rt	64
6	20	3/1	Tol./Tol.	rt	55
7	20	4/1	Ether/Tol.	rt	66
8	20	6/1	Ether/Tol.	0 °C	55
9	20	3/1	Ether/Tol.	rt	66/*R*
10	20	3/1	Ether/Tol.	0 °C	66/*R*
11	20	3/1	DCM/DCM	rt	30/*R*
12	20	3/1	THF/Tol.	rt	54/*R*
13	20	3/1	Ether/Ether	rt	60/*R*
14	30	3/1	Ether/Tol.	rt	67/*R*
15	40	3/1	Ether/Tol.	rt	61/*R*

[a] Phenylacetylene/Et_2Zn/benzaldehyde = 3:3:1.
[b] $Ti(O^iPr)_4$ was freshly distilled.
[c] The former solvent dissolved the ligand, and the latter solvent in Et_2Zn. The ratio is 2:0.75.
[d] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD column.
[e] The absolute configurations were based on determination of the specific rotation and in comparison with the relevant literature values.[12]

possible to develop a new efficient chiral catalyst in this asymmetric reaction.

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13. General addition procedure: Under argon, the ligand Boc-L-pro (10.8 mg, 0.05 mmol) and $Ti(O^iPr)_4$ (45 μL, 0.15 mmol) were mixed in dry ether (2.0 mL) at room temperature and stirred for 1 h. The solution of Et_2Zn (1.0 M in toluene, 0.75 mL) was then added. After the mixture was stirred at room temperature for 2 h, phenylacetylene (82.4 μL, 0.75 mmol) was added and the stirring continued for 1 h. The orange solution was cooled to 0 °C and treated with aldehydes (0.25 mmol). The resulting mixture was allowed to warm to room temperature and to be stirred for 12–18 h. After the reaction was complete (monitoring with TLC), it was cooled to 0 °C and quenched with aqueous HCl (5%). Then the mixture was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 20%EtOAc in hexane) to give the product.