doi:10.1246/cl.2010.1013
Published on the web August 21, 2010

Asymmetric Allylation of Aldehydes Catalyzed by Simple Dual Small Organic Molecules: L-Proline and L-Prolinol

Guo-hong Chen, Ling-yan Liu,* Xiao-ning Wei, Wei-xing Chang, and Jing Li*
The State Key Laboratory Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

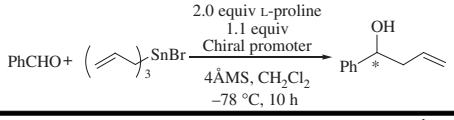
(Received June 2, 2010; CL-100521; E-mail: lijing@nankai.edu.cn, liulingyan@nankai.edu.cn)

A novel and simple methodology for the asymmetric allylation of aldehydes was reported. Double small organic molecules such as L-proline and L-prolinol were first employed for providing a chiral environment so as to afford chiral homoallylic alcohols in high yields and moderate enantioselectivities in our protocol.

The asymmetric allylation of aldehydes is an important process to obtain chiral homoallylic alcohols, which are important building blocks in modern organic synthesis and widely applied to the synthesis of natural products and pharmaceuticals. To date, numerous methodologies have already been developed for the synthesis of chiral homoallylic alcohols.[1] Among these approaches, allylsilanes[2] and allylstannanes[3] are widely used as allylation reagents for the asymmetric allylation of aldehydes. In contrast, there are few reports of the asymmetric allylation of aldehydes using allyltin halide.[4] On the other hand, asymmetric organocatalysis based either on Lewis acid or base interactions has been recognized as an efficient method for obtaining chiral compounds with high enantioselectivity. The application of enantiomerically pure "small" organic molecules represents a promising alternative catalytic concept in addition to other frequently used syntheses based on metal containing catalysts.[5] Yanagisawa reported the asymmetric allylation of aldehydes with tetraallyltin catalyzed by L-aspartic acid in 2004, but the best enantiomeric-excess value was only 40%.[6] In addition, Tsogoeva et al. published allylation of imine catalyzed by chiral formamide derivatives with the participation of 2 equiv of L-proline in 2006.[7] Obviously, there was a double-molecule-chiral catalysis in this reaction. On the basis of these concepts, and as continuation of our ongoing program on asymmetric allylation of carbonyl compounds catalyzed by small organic molecules,[4a] we herein reported an asymmetric allylation of aldehydes using triallyltin monobromide catalyzed by double small organic molecules such as natural L-proline and L-prolinol, which are widely used owing to availability, stability, and low cost.

At the beginning, various natural amino acids which are commercially available and their derivatives were examined. A mixture of benzaldehyde and L-proline (2 equiv) was stirred in dichloromethane at room temperature in the presence of active 4 Å molecular sieves (MS). After that, triallyltin bromide was added followed by another chiral promoter (1.1 equiv) at −78 °C. The product was obtained by aqueous work-up and column chromatography after stirring at room temperature for 10 h. The results are shown in Table 1. It was found that this reaction could give high yield up to 80% and 20% ee in the absence of additional chiral promoter (Table 1, Entry 1). Unfortunately, lower enantioselectivities were obtained when adding additional natural amino acids than that of no additive, although all reactions proceed smoothly and afford the corresponding homoallylic alcohol in high or excellent yields (Table 1, Entries 2–8). It was surmised to be caused by these two promoters' chiral mismatch. Thus, D-proline was chosen to combine with other L-amino acids as co-promoters in the asymmetric allylation under the same conditions. However, the same ee value was obtained when D-proline was used instead of L-proline (Table 1, Entries 9, 10, and 18). The mismatch of the two promoters can be excluded. In order to get higher ee values, we turned our attention to amino alcohols directly derived from natural amino acids. The enantioselectivity was actually increased as expectated (Table 1, Entries 11–15) and L-prolinol rendered the best catalytic activity in enantioselectivity with 56% ee. In addition, we also investigated other chiral promoters, such as L-tartaric acid, *R*-BINOL, and cinchonidine. As a result, very high yields could be produced but with lower enantioselectivity (Table 1, Entries 16–19).

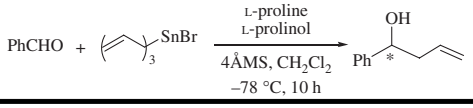
Table 1. A survey of various chiral promoters



Entry	Promoter	Yield/%[a]	ee/%[b]	Config.[c]
1	—	80	20	*R*
2	5-Methyl-L-norleucine	80	13	*R*
3	L-β-Homophenylalanine	87	9	*R*
4	L-Tyrosine	80	10	*R*
5	L-Threonine	83	11	*R*
6	L-Arginine	93	8.5	*R*
7	L-Methionine	78	8.5	*R*
8	L-Alanine	80	8.6	*R*
9[d]	L-Tyrosine	80	11	*S*
10[d]	L-Threonine	72	10	*S*
11	**L-Valinol**	**80**	**44**	***R***
12	**L-Prolinol**	**86**	**56**	***R***
13	**L-Phenylalaninol**	**72**	**53**	***R***
14	L-Methioninol	83	37	*R*
15	L-Threoninol	93	20	*R*
16	L-Tartaric acid	83	11.6	*R*
17	*R*-BINOL	95	9.5	*R*
18	*S*-BINOL	75	11	*R*
19	Cinchonidine	86	8.4	*R*

[a]Isolated yield. [b]Chiral GC (γ-cyclodextrin column). [c]The absolute configuration of the product was determined by comparison of the optical rotation with the literatures. [d]Using D-proline as another promoter.

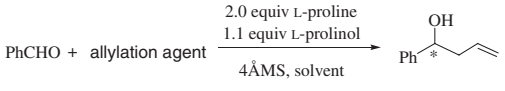
Table 2. Screening the loading of promoters in the asymmetric allylation



Entry	L-Proline /equiv	L-Prolinol /equiv	Yield/%[a]	ee/%[b]
1	**2**	**1.1**	**86**	**56**
2	1	1.1	80	26
3	0.5	1.1	81	18
4	2	0.2	67	20
5	2	0.5	73	21
6	2	2	88	57

[a]Isolated yield. [b]Chiral GC (γ-cyclodextrin column).

Table 3. The asymmetric allylation of benzaldehyde with various allylation reagents



Entry	Allylation agent	Solvent	Yield/%[a]	ee/%[b]
1	$(CH_2=CHCH_2)_3SnBr$	**CH_2Cl_2**	**86**	**56**
2	$(CH_2=CHCH_2)_3SnBr$	THF	67	0
3	$(CH_2=CHCH_2)_3SnBr$	DMF	44	6
4	$(CH_2=CHCH_2)_3SnBr$	CH_3CN	67	18
5	$(CH_2=CHCH_2)_2SnBr_2$	CH_2Cl_2	56	18
6	$CH_2=CHCH_2SnBr_3$	CH_2Cl_2	72	5
7	$(CH_2=CHCH_2)_4Sn$	CH_2Cl_2	52	10
8	$CH_2=CHCH_2SiCl_3$	CH_2Cl_2	—	—
9	$CH_2=CHCH_2SiMe_3$	CH_2Cl_2	—	—

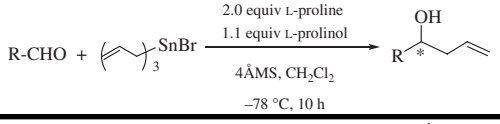
[a]Isolated yield. [b]Chiral GC (γ-cyclodextrin column).

The effect of promoter loading on the allylation of benzaldehyde with triallyltin bromide was then studied (Table 2). However, a decrease in the promoter loading of L-proline or L-prolinol resulted in a similar yield but lower enantioselectivity (Table 2, Entries 2–5). Even increasing the loading of L-prolinol, we could only achieve a similar ee value (57%) (Table 2, Entry 6).

Next, we investigated the effect of solvents and allytin reagents in the presence of 2.0 equiv of L-proline and 1.1 equiv of L-prolinol (Table 3). However, no improvement was observed. Furthermore, in the case of allylsilane, the reaction did not proceed at all under these reaction conditions (Table 3, Entry 8 and 9).[2]

To understand the scope and the generality of the double small-organic-molecule-catalyzed asymmetric allylation of aldehydes, we chose a variety of aldehydes for our study and the results are summarized in Table 4.[8] Among the various aldehydes tested, all aromatic aldehydes could be smoothly allylated

Table 4. The asymmetric allylation of triallyltin monobromide with various aldehydes



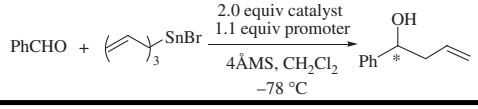
Entry	R	Yield/%[a]	ee/%[b]	Config.[c]
1	Ph	86	56	*R*
2	*p*-ClC_6H_4	89	62	*R*
3	*p*-BrC_6H_4	87	64	*R*
4	*p*-$CF_3C_6H_4$	83	59	*R*
5	*p*-$NO_2C_6H_4$	—	—	—
6	*p*-MeC_6H_4	72	57	*R*
7	*p*-$MeOC_6H_4$	78	59	*R*
8	*o*-FC_6H_4	82	42	*R*
9	*o*-BrC_6H_4	88	40	*R*
10	*o*-$NO_2C_6H_4$	86	46	*R*
11	*o*-$CF_3C_6H_4$	85	35	*R*
12	*m*-BrC_6H_4	90	47	*R*
13	*m*-$NO_2C_6H_4$	74	50	*R*
14	*m*-$CF_3C_6H_4$	89	46	*R*
15	2,4-DichloroC_6H_3	84	32	*R*
16	Ph–CH=CH–	61	54	*R*
17	CH_3–CH=CH–	14	4	*R*
18	Heptanal	<10	—	—

[a]Isolated yield. [b]Chiral GC (γ-cyclodextrin column). [c]The absolute configuration of the product was determined by comparison of the optical rotation with literatures.

to give the corresponding optically active homoallylic alcohols in high yields and moderate enantioselectivities except for 4-nitrobenzaldehyde. Upon closer inspection of the data in Table 4, we noticed that aldehydes with a strong electron-withdrawing group at the *para*-position (Table 4, Entries 2–4) gave higher enantiomeric excess values than those with an electron-donating group in the *para*-position (Table 4, Entries 6 and 7). With regards to the aromatic aldehydes bearing substituents at the *ortho*-position, they gave higher yields but lower enantioselectivities than those with the corresponding substituent at the *para*-position (Table 4, Entries 9 to 3, 11 to 4). It's rather strange that 2-nitrobenzaldehyde could smoothly react with triallyltin bromide under standard conditions and gave the corresponding product in high yield and moderate enantioselelctivity, whereas in the case of 4-nitrobenzaldehyde, no product was obtained. Asymmetric allylation could proceed with various *m*-substituted benzaldehyde and afford the corresponding products in high yields and moderate enantioselectivities (Table 4, Entries 12–14). Furthermore, homoallylic alcohol in considerable yield and moderate enantioselectivity was obtained in the allylation of 2,4-dichlorobenzaldehyde with triallyltin bromide (Table 4, Entry 15). As for α,β-unsaturated aldehydes, cinnamaldehyde gave better yield and enantioselectivity than that of crotonaldehyde (Table 4, Entries 16 and 17). Nevertheless, this reaction did not occur in the case of aliphatic aldehydes such as heptanal (Table 4, Entry 18).

With the aim of understanding the mechanism of the reaction, we performed several experiments as shown in Table 5 and Table 1. From Entries 1–3 in Table 5, we could conclude

Table 5. The asymmetric allylation of triallyltin monobromide with benzaldehyde catalyzed by various promoters



Entry	Cat.	Promoter	Yield/%[a]	ee/%[b]	Config.[c]
1	L-Proline	—	80	20	*R*
2	—	L-Prolinol	70	7	*R*
3	L-Proline	L-Prolinol	86	56	*R*
4	D-Proline	L-Prolinol	84	54	*S*

[a]Isolated yield. [b]Chiral GC (γ-cyclodextrin column). [c]The absolute configuration of the product was determined by comparison of the optical rotation with literatures.

that the combination of the two promoters is quite essential for improving the ee value. Moreover, it is noteworthy that the product's absolute configuration changed when D-proline was used instead of L-proline (Table 5, Entries 3 and 4; Table 1, Entries 4, 5, 9, 10, 17, and 18). This implies that the absolute configuration of the product was mainly determined by proline instead of the other co-promoter. Furthermore ^{1}H NMR was used to trace the reaction of L-proline and benzaldehyde in an NMR tube or the whole reaction system, but no valuable information was observed. We then attempted to adopt another method to trace the reaction of triallyltin monobromide and L-prolinol or L-proline by ^{119}Sn NMR or FT-IR. However unfortunately, we still have not obtained any valid results. Therefore, ongoing studies are currently in progress on this asymmetric allylation with a detailed reaction mechanism.

In conclusion, a novel protocol was first developed for the asymmetric allylation of aldehydes using simple double small organic molecules such as readily available L-proline and L-prolinol. In this methodology, all aromatic aldehydes reacted smoothly in high yields and moderate or modest enantioselectivities. A mechanism was also studied. But the detailed reaction transition state still remained unclear presently. Nevertheless this may establish the groundwork for the Barbier-type asymmetric allylation of aldehydes with organotin reagents. Work on this line is in progress in our research group.

This work was supported by the NSFC (Nos. 20421202 and 20372033) and the Nankai University.

References and Notes

1 a) T. D. Haddad, L. C. Hirayama, B. Singaram, *J. Org. Chem.* **2010**, *75*, 642. b) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207. c) H. Ito, T. Okura, K. Matsuura, M. Sawamura, *Angew. Chem., Int. Ed.* **2010**, *49*, 560. d) M. Tokuda, M. Uchida, Y. Katoh, H. Suginome, *Chem. Lett.* **1990**, 461. e) M. Yasuda, N. Kitahara, T. Fujibayashi, A. Baba, *Chem. Lett.* **1998**, 743.

2 For selected examples of the catalytic asymmetric allylation of aldehydes using allylsilane, see: a) J. Bode, D. Gauthier, E. Carreira, *Chem. Commun.* **2001**, 2560. b) A. Yanagisawa, H. Kageyama, Y. Nakatsuka, K. Asakawa, Y. Matsumoto, H. Yamamoto, *Angew. Chem., Int. Ed.* **1999**, *38*, 3701. c) M. Wadamoto, N. Ozasa, A. Yanagisawa, H. Yamamoto, *J. Org. Chem.* **2003**, *68*, 5593. d) A. Kadlčíková, R. Hrdina, I. Valterová, M. Kotora, *Adv. Synth. Catal.* **2009**, *351*, 1279. e) P. Wang, J. Chen, L. Cun, J. Deng, J. Zhu, J. Liao, *Org. Biomol. Chem.* **2009**, *7*, 3741. f) P. Kwiatkowski, P. Mucha, G. Mlostoń, J. Jurczak, *Synlett* **2009**, 1757.

3 For selected examples of the asymmetric allylation of aldehydes using allyltributylstannane, see: a) R. Qiu, X. Xu, Y. Li, G. Zhang, L. Shao, D. An, S. Yin, *Chem. Commun.* **2009**, 1679. b) G. S. S. Reddy, B. Sammaiah, L. N. Sharada, *Synth. Commun.* **2009**, *39*, 3905. c) E. S. Schmidtmann, M. Oestreich, *Angew. Chem., Int. Ed.* **2009**, *48*, 4634. d) M. Yasuda, T. Azuma, K. Tsuruwa, S. A. Babu, A. Baba, *Tetrahedron Lett.* **2009**, *50*, 3209. e) X. Zhang, *Synlett* **2008**, 65. f) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763.

4 a) L. Liu, J. Sun, N. Liu, W. Chang, J. Li, *Tetrahedron: Asymmetry* **2007**, *18*, 710. b) S. Kobayashi, K. Nishio, *Tetrahedron Lett.* **1995**, *36*, 6729.

5 a) H. Gröger, J. Wilken, *Angew. Chem., Int. Ed.* **2001**, *40*, 529. b) B. List, *Synlett* **2001**, 1675. c) E. Jarvo, S. Miller, *Tetrahedron* **2002**, *58*, 2481. d) B. List, *Tetrahedron* **2002**, *58*, 5573.

6 A. Yanagisawa, Y. Nakamura, T. Arai, *Tetrahedron: Asymmetry* **2004**, *15*, 1909.

7 S. Jagtap, S. Tsogoeva, *Chem. Commun.* **2006**, 4747.

8 Standard experimental procedures: L-proline (1 mmol, 2 equiv), freshly distilled dichloromethane (3 mL), 4 Å MS (20 mg), and benzaldehyde (53 mg, 0.5 mmol) were successively added to a Schlenk flask under nitrogen at room temperature. L-Prolinol (0.55 mmol, 1.1 equiv) and triallyltin bromide (161 mg, 0.5 mmol) were then added at −78 °C and then warmed to room temperature stirring for 10 h. After the reaction completed, it was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane, dried with anhydrous magnesium sulfate, filtered, concentrated, then separated and purified by column chromatography. The product gave satisfactory NMR spectra. Enantiomeric excess was determined by chiral GC analysis with N_2/air as vector gas. Chiral GC conditions: γ-cyclodextrin column, initial temperature 100 °C, for 5 min, then rate 1 °C min^{-1}. until 200 °C. $t_R = 28.385$ min (major), 29.788 min (minor), 56% ee.

