Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5819–5822
Tetrahedron Letters

A highly enantioselective allyl-transfer through suppression of epimerization ☆

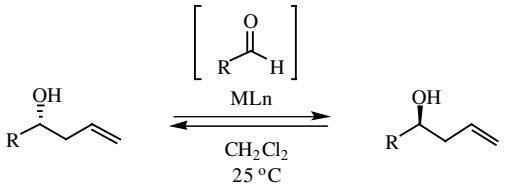
Cheng-Hsia Angeline Lee and Teck-Peng Loh*

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore

Received 19 April 2004; revised 27 May 2004; accepted 3 June 2004

Abstract—A highly enantioselective allyl transfer method was successfully developed, producing terminal homoallylic alcohols in moderate to high yields. In all cases, reactions were carried out under mild acid conditions; reducing the reaction temperature suppressed racemization.

The preparation of highly enantiomerically enriched homoallylic alcohols is gaining widespread attention, especially in the area of pharmaceuticals and agrochemicals. As important synthetic routes to many biologically active molecules,[1] immense efforts have been committed to the exploration of chiral reagents[2] and chiral catalysts[3] for the carbonyl-allylation and carbonyl–ene reactions. Recently, the enantioselective crotyl transfer reaction developed by Nokami et al.[2f,4] has also been shown to be useful for the synthesis of this class of compounds. While crotyl transfer has been shown to proceed with good stereochemical fidelity, Lewis acid-catalyzed enantioselective allyl transfer has been found to afford products with much lower selectivities.[4,5] Our group and others have shown that the low selectivity observed for allyl transfers is due to racemization of the enantiomerically enriched homoallylic alcohols mediated by the reverse reaction with or without the presence of aldehyde during the course of the reaction[5,6] (Eq. 1).

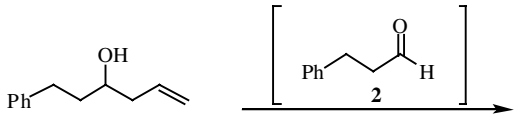


(1)

We were encouraged to carry out further investigations aimed at suppressing this racemization, hoping to develop a highly enantioselective allyl transfer reaction in order to obtain terminal homoallylic alcohols.

Conceptually, we envisaged that if the racemization step could be suppressed, highly enantioselective allyl

Table 1. Screening acids with or without aldehyde[a]



1 (89% *ee*)

Entry	Acid	Ee[b] (%)	
		Without aldehyde **2**	With aldehyde **2**
1	$In(OTf)_3$	51	0
2	$InCl_3$	88	50
3	$InBr_3$	82	10
4	$Sn(OTf)_2$	89	70
5	$Cu(OTf)_2$	89	29
6	$Zn(OTf)_2$	88	78
7	$Sc(OTf)_3$	89	73
8	$La(OTf)_3$	88	76
9	CSA	89	80
10	pTSA·H_2O	89	75

[a] Reactions were performed with linear homoallylic alcohol **1** (89% ee), hydrocinnamaldehyde **2** and acid in CH_2Cl_2 unless otherwise stated. (1*R*)-(−)-10-Camphorsulfonic acid (CSA), *p*-toluenesulfonic acid monohydrate (pTSA·H_2O).

[b] Determined by HPLC analysis employing a chiral stationary phase Daicel Chiralcel OD column.

Keywords: Allyl transfer; Camphor; Chiral auxiliaries; Homoallylic alcohols; Enantioselectivities.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.06.014

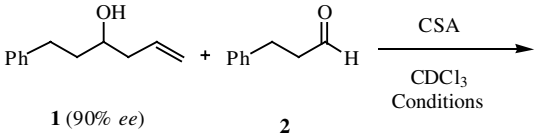
* Corresponding author. Tel.: +65-68747851; fax: +65-67791691; e-mail: chmlohtp@nus.edu.sg

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.06.014

transfer might be possible. First, we systematically measured the epimerization rate of terminal homoallylic alcohol **1** using a wide variety of Lewis acids and Brönsted acids in dichloromethane at ambient temperature (Table 1). In most cases, no racemization was observed except when indium complexes were used as Lewis acids (entries 1–3). This is consistent with our previous report on the involvement of a retro-cleavage,[5a] which gradually resulted in the reduction of the enantioselectivity. More racemization was observed when performed in the presence of the parent aldehyde.

Next, we investigated the effect of reaction temperature on the rate of racemization using CSA as catalyst. As expected, the enantiometric excess of **1** remained unaffected at 0, 15, 25 °C and at reflux. However, the addition of 1 equiv of hydrocinnamaldehyde (Table 2) was found to speed up the racemization process. It was found that racemization occurred at 25 °C and at reflux after 120 min, giving rise to 64% ee and 17% ee, respectively. Thus, it seemed that epimerization could be suppressed by reducing the reaction temperature.

Table 2. Monitoring ee at various temperatures[a]



1 (90% *ee*) **2**

Entry	Conditions	Time duration[b] (min)	Remarks
1	0 °C	120	No change
2	15 °C	120	No change
3	25 °C	120	64% ee
4	Reflux	120	17% ee

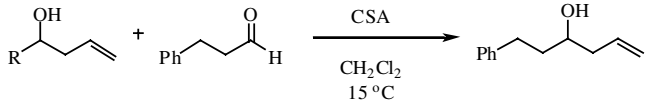
[a] Reactions were performed with linear homoallylic alcohol **1**, hydrocinnamaldehyde **2** and CSA in $CDCl_3$ unless otherwise stated.
[b] After the stated time a reaction aliquot was worked up, purified and analyzed using HPLC.

A few chiral reagents were tested for the allyl transfer with hydrocinnamaldehyde at 15 °C (Table 3). Among them, (+)-camphor was found to give the best yield and ee. As shown in Table 3, the homoallylic alcohol can be obtained in 70% yield with 90% ee. It is important to note that carrying out the reaction at −78 °C gave the product in good ee (92%) but lower yield (13%). Another point to note is that good yields and excellent enantioselectivities were achieved when the molarity was increased from 3 to 6 M. The optimized conditions for this allyl transfer are 15 °C, with 3 equiv of camphor-derived homoallylic alcohol at 6 M concentration.

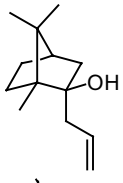
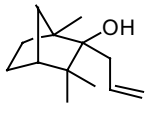
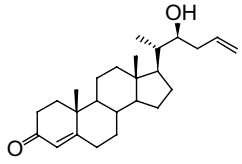
With the above modifications and optimization, we proceeded to investigate the asymmetric allyl transfer from **3** to different aldehydes (Table 4). Various terminal homoallylic alcohols were successfully obtained in moderate to good yields and excellent ee. In a few cases, reducing the temperature to 0 °C furnished the products with better enantioselectivities (entries 3–4). Furthermore, excess chiral reagent and camphor can be recovered and reused. To illustrate, the excess camphor-derived homoallylic alcohol **3** and the camphor from the reaction in entry 3 (Table 4) were recovered in 93% and 72% yields, respectively.

In conclusion, we have found that homoallylic alcohols containing a terminal double bond racemize in the pres-

Table 3. Allyl-transfer using various chiral reagents[a]

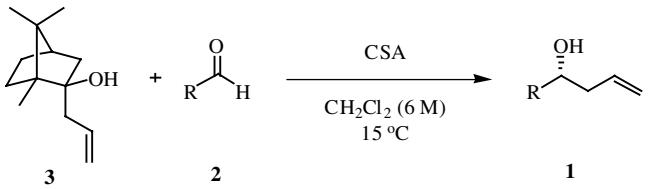


3 **2** **1**

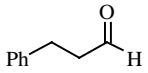
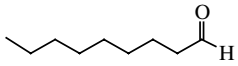
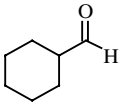
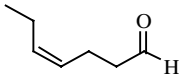
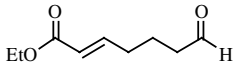
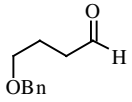
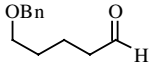
Entry	**3**	Time (h)	Yield (%)[b]	ee (%)
1		145	70	90
2		142	10	60
3		144	51	71

[a] Reactions were performed using homoallylic alcohol **3**, hydrocinnamaldehyde **2** and CSA in CH_2Cl_2 (3 M) unless otherwise stated.
[b] Isolated yield.

Table 4. Allyl-transfer with various aldehydes[a,b]



3 **2** **1**

Entry	R	Time (h)	Recovery of **3** (%)[c]	Yield (%)[d]	%ee[e]
1		145	80	70	90[g]
2		164	108	12	90
3[f]		136	93	78	96[h]
4[f]		144	96	54	90[i]
5		146	83	81	92
6		146	92	65	92
7		136	101	62	92
8		163	84	50	94

[a] Reaction was performed at 15 °C with homoallylic alcohol **3**, aldehyde **2** and CSA in CH_2Cl_2 (6 M) unless otherwise stated.
[b] Yields of Prins cyclized product were found to be less than 5%.
[c] Determined with respect to 2 equiv.
[d] Isolated yield.
[e] Determined by HPLC analysis using Chiralcel columns or ^1H NMR analysis of Mosher acid derivatives. Please refer to supporting information.
[f] Performed at 0 °C.
[g] 86% ee (76% yield) was obtained when performed at 25 °C.
[h] 86% ee (66% yield) was obtained when performed at 15 °C.
[i] 78% ee (62% yield) was obtained when performed at 15 °C.

ence of strong Lewis acids and at high temperature with or without the addition of aldehyde. Our studies have shown that carrying the reaction out at low temperature using a mild acid such as CSA prevents this racemization process. We have successfully developed a highly enantioselective allyl transfer method to obtain terminal homoallylic alcohols in moderate to high yields with excellent enantioselectivities. Excess chiral camphor-derived homoallylic alcohol and the camphor generated from the reaction can be recovered and reused, thus making this method attractive for the large scale preparation of homoallylic alcohols with high enantioselectivities.

Supporting information available. Experimental details, characterization data and stereochemical proofs.

Acknowledgements

We are grateful to the National University of Singapore for its generous financial support. We thank Prof. Li S. F. Y. for assistance extended to this project.

References and notes

1. (a) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701–3704; (b) Felpin, F. X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192–9199.
2. (a) Roush, W. R.; Grover, P. T. *J. Org. Chem.* **1995**, *60*, 3806–3813; (b) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946–948; (c) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem.*

Soc. **2002**, *124*, 7920–7921; (d) Loh, T. P.; Lee, C. L. K.; Tan, K. T. *Org. Lett.* **2002**, *4*, 2985–2987; (e) Lee, C. L. K.; Lee, C. H. A.; Tan, K. T.; Loh, T. P. *Org. Lett.* **2004**, *6*, 1281–1283; (f) Nokami, J.; Nomiyama, K.; Shafi, S. M.; Kataoka, K. *Org. Lett.* **2004**, *6*, 1261–1264.

3. Denmark, S. E.; Fu, J. J. *Chem. Rev.* **2003**, *103*, 2763–2794, and references cited therein.
4. (a) Nokami, J.; Anthony, L.; Sumida, S. *Chem. Eur. J.* **2000**, *6*, 2909–2913; (b) Nokami, J.; Nomiyama, K.; Matsuda, S.; Imai, N.; Kataoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1273–1276; (c) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168–9169.
5. (a) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2921–2922; (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577–580; (c) Cavallo, A. S.; Sedy, O.; Salisova, M.; Schmitt, M. *Eur. J. Org. Chem.* **2002**, 3042–3049; (d) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919–3922.
6. Loh, T. P.; Hu, Q. Y.; Chok, Y. K.; Tan, K. T. *Tetrahedron Lett.* **2001**, *42*, 9277–9280.