ORGANIC LETTERS

2004
Vol. 6, No. 8
1281−1283

An Unusual Approach to the Synthesis of Enantiomerically Cis Linear Homoallylic Alcohols Based on the Steric Interaction Mechanism of Camphor Scaffold

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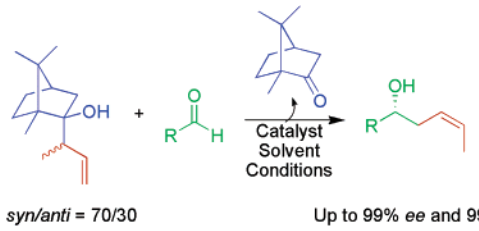
Received February 29, 2004

ABSTRACT



Camphor is used as the chiral auxiliary for the enantioselective synthesis of cis linear homoallylic alcohols. A range of catalysts, aldehydes, and solvents were investigated to obtain the optimum yield, enantioselectivity, and cis olefinic geometry.

Over the last few decades, homoallylic alcohols have become indispensable moieties for the construction of complex organic molecules, securing their widespread involvement in the synthesis of both natural products and medicinal agents.[1] Even though extensive efforts have been devoted to the exploration of chiral reagents and catalysts for the carbonyl-allylation and carbonyl-ene reactions to produce homoallylic alcohols, almost all current methods produce branched homoallylic alcohols **1** exclusively,[2] except a few special cases, hence limiting access to the linear homoallylic alcohols ***E*-2** and ***Z*-2**[3] (Figure 1).

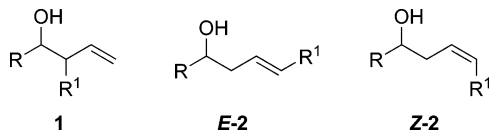


Figure 1. Various regioisomers of homoallylic alcohols.

While the enantioselective crotyl transfer reactions developed by Nokami[3a,4] and our group[5] have been shown to be useful for the synthesis of trans linear homoallylic alcohols ***E*-2**, there are no reported examples for a one-pot synthesis

(1) (a) Nicolaou, K. C.; Kim, D. W.; Baati. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701. (b) Hornberger, K. R.; Hamblet, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894. (c) Felpin, F. X.; Lebreton. J. *J. Org. Chem.* **2002**, *67*, 9192.

(2) For reviews, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Helmchen, G., Hoffmann, R., Mulzer, J., Schaumann, E., Eds. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*, 21st ed.; Thieme Stuttgart: New York, 1996; Vol. 3, pp 1357−1602. (c) Denmark, S. E.; Fu, J. P. *Chem. Rev.* **2003**, *103*, 2763.

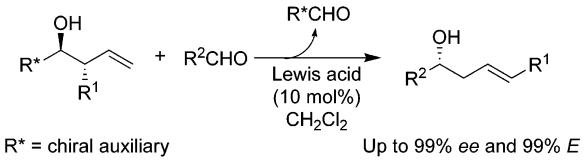
(3) For some examples, see: (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Tan, K. T.; Cheng, H. S.; Chng, S. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 2958. (c) Loh, T. P.; Lee, C. L. K.; Tan, K. T. *Org. Lett.* **2002**. *17*, 2985. (d) Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 4990. (e) Hirashita, T.; Yamamura, H.; Kawai, M.; Araki, A. *Chem. Commun.* **2001**, 387. (f) Okuma, K.; Tanaka, Y.; Ohta, H.; Matsuyama, H. *Heterocycles*, **1993**, *1*, 37.

(4) Nokami, J.; Nomiyana, K.; Matsuda, S.; Imai, N.; Kataoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1273.

(5) Loh, T. P.; Hu, Q. Y.; Chok, Y. K.; Tan, K. T. *Tetrahedron Lett.* **2001**, *42*, 9277.

10.1021/ol049633z CCC: $27.50
Published on Web 03/19/2004

Scheme 1. Crotyl Transfer Reactions Furnishing Trans Linear Homoallylic Alcohol



of enantiomerically cis linear homoallylic alcohols ***Z*-2** (Scheme 1).

We recognized that if another chiral auxiliary[6] can be judiciously chosen to effectively present a steric environment, in which the formation of the branched homoallylic alcohols precursor is highly diastereometrically selective, stereoselective access to the linear homoallylic alcohols would be achieved. It is hence predictable that this crotyl transfer reaction can provide a valuable platform for the development of a new highly stereoselective homoallylic alcohol protocol.

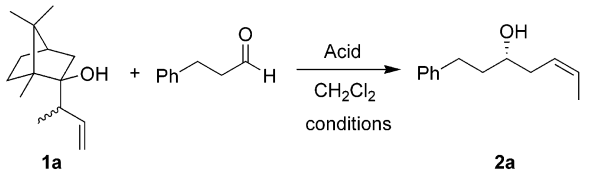
This plan was probed by allowing the diastereomic mixture (syn/anti = 70/30) of camphor[7] branched homoallylic alcohol, prepared from the addition of crotylmagnesium bromide to (1*R*)-(+)-camphor,[8] to react with 3-phenylpropanal under the catalysis of a series of Brönsted and Lewis acids. In accordance with the recent surge in interest in metal triflates, indium(III) triflate has emerged as a promising choice particularly in our research group.[9] However, no desired product was obtained for this crotyl transfer reaction when $In(OTf)_3$ was employed as the acid catalyst (Table 1, entry 1).

Optimal results were obtained when the reaction was carried out at ambient temperature and at a higher concentration level (6.0 M solution), with 3 equiv of the branched homoallylic alcohol **1a** being added slowly to a stirred solution of 1 equiv of 3-phenylpropanal and 0.1 equiv of CSA for 120 h (Table 1, entry 8). This superior catalytic efficiency exhibited by CSA prompted us to select this Brönsted acid for further explorations.

With these optimized conditions, we carried out crotyl transfer reactions on various aldehydes. While the slightly bulkier substrate[3c] (Table 2, entry 4) gave a moderate yield, the linear ones offered excellent yields (Table 2, entries 2 and 3). Reactions of the dioxygenated substrates (Table 2, entries 5−7) afforded the desired products with ee up to 99% displaying the cis olefinic geometries almost predominantly.

This reaction can also be tolerated on other functional groups. Using *cis*-hept-4-enal afforded fine yields with comparable ee and cis olefinic geometry (>99% ee, 84% *Z*) (Table 2, entry 8), while the α,β-unsaturated ethyl ester-type aldehyde needed a longer time to be depleted before moderate yields were achieved with admirable ee and cis olefinic geometry (>99% ee, 97% *Z*) (Table 2, entry 9). On

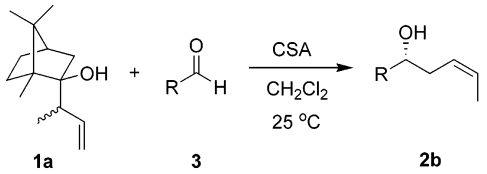
Table 1. Allyl Transfer[a] from **1a**[b] to 3-Phenylpropanal with Various Acids



entry	acid	*T* (°C)	time (h)	yield (%)	% ee (Z:E)
1[c]	$In(OTf)_3$	25	18		
2	pTSA	25	18	<7	96 (95:5)
3	TFA	25	18	<7	94 (94:6)
4	CSA	25	18	25	93 (94:6)
5	CSA	0	18	20	93 (97:3)
6	CSA	−78	10	15	93 (97:3)
7	Br−CSA	25	120	77	95 (99:1)
8[d]	CSA	25	120	88	94 (99:1)

[a] Reactions were performed with branched homoallylic alcohol **1a** (0.5 mmol), aldehyde (0.75 mmol), and acid (0.05 mmol) in CH_2Cl_2 (2 mL), unless otherwise stated. [b] Branched homoallylic alcohol is synthesized by Grignard reaction with a yield of 87% (syn:anti = 70:30). [c] Desired product not formed. [d] Reactions were performed with branched homoallylic alcohol **1a** (0.913 mmol), aldehyde (0.304 mmol), and acid (0.03 mmol) in CH_2Cl_2 (0.1 mL).

Table 2. Catalyzed Allyl Transfer Reaction from **1a** to Various Aldehydes **3**[a,b]



entry	**3**	time (h)	yield[c] (%)	% ee (% *Z*)
1	$PhCH_2CH_2CHO$	120	88	94 (99)[d,g,h]
2	*n*-$C_5H_{11}CHO$	144	68	97 (>99)[f]
3	*n*-$C_8H_{17}CHO$	144	95	90 (94)[f]
4	*c*-$C_6H_{11}CHO$	144	40	92 (96)[e]
5	$BnO(CH_2)_2CHO$	120	74	97 (>99)[d]
6	$BnO(CH_2)_3CHO$	96	94	99 (>99)[d]
7	$BnO(CH_2)_4CHO$	96	80	98 (98)[d]
8	$CH_3CH_2CH{=}CH(CH_2)_2CHO$	96	83	>99 (84)[f]
9	$EtO_2CCH{=}CH(CH_2)_3CHO$	240	66	98 (99)[f]
10	PhCHO	240	trace	
11	2-NO_2PhCHO	240	trace	

[a] Reactions were performed with branched homoallylic alcohol **1a** (0.913 mmol), **2** (0.304 mmol), and CSA (0.03 mmol) in CH_2Cl_2 (0.1 mL), unless otherwise stated. [b] Branched homoallylic alcohol used has a syn/anti ratio of 70/30. [c] Combined yield based on **2**. [d] Determined by chiral HPLC. [e] Determined by HPLC of the 2,4-dinitrobenzoyl derivative. [f] Determined by HPLC of the Mosher derivative. [g] Absolute stereochemistry was determined by comparison with literature values. [h] Reactions of the (1*S*)-(−)-camphor branched homoallylic alcohol with **2** furnished the other enantiomer (60% yield; 93% ee; 99% *Z*).

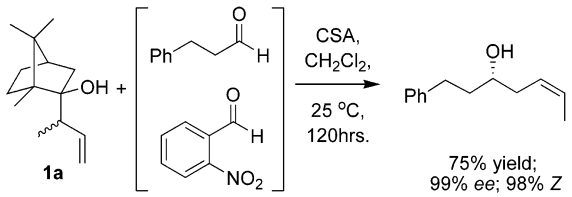
(6) For an extensive list of chiral auxiliaries, see: (a) Rahmen, A. U.; Shah, A. *Stereoselective Synthesis in Organic Cheimstry*; Springer: Berlin, 1993. (b) Seyden-Penne, I. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995. (c) Ager, D. J.; Prakash, J.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

(7) For a review on camphor-based chiral auxiliaries, see: Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.

(8) Dimitrov, V.; Simova, S.; Kostova, K. *Tetrahedron* **1996**, *52*, 1699.

the basis of the sluggish reactivity of aromatic aldehydes (Table 2, entries 10 and 11), a chemoselective study revealed that the transfer selectively will go to the aliphatic substrate even in the presence of a more reactive aldehyde (Scheme 2).

Scheme 2. Chemoselective Study

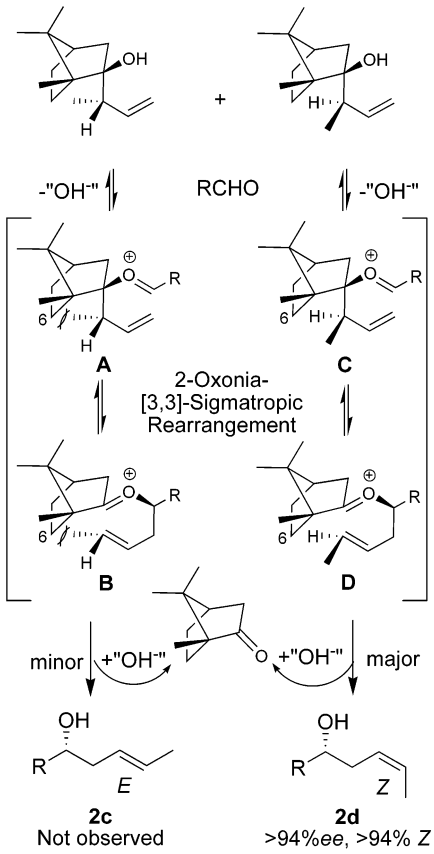


Of mechanistic interest is the recovery of the excess chiral camphor homoallylic alcohol **1a**, which is enriched with the anti isomer (syn/anti = 40/60) from a diastereomeric ratio of syn/anti = 70/30. From the molecular model for the transition state of the corresponding camphor branched homoallylic alcohol depicted in Scheme 3, we realized that only one isomer, the syn branched homoallylic alcohol, was allowed to transfer using this camphor auxiliary.[10]

The branched homoallylic alcohol **1a** probably formed oxonium-type ions with the aldehyde catalyzed by an acid catalyst, revealing two possible transition states. The anti branched homoallylic alcohol would most likely adopt a transition state similar to that of **A**. On the basis of a six-membered transition state,[11] it is evident that this anti isomer of the branched homoallylic alcohols will have a severe steric repulsion with the C-6 of the camphor scaffold, which explained why the trans linear isomer **2c** was not observed at all. On the contrary, the transition state **C** shows that the syn isomer's methyl groups are fixed in a manner that avoids any close contacts with the camphor's methylene protons before undergoing the rearrangement to furnish the thermodynamically preferred linear regioisomer **2d**.

With that, a conceptually different strategy to access to cis linear homoallylic alcohols, with moderate to high yields, has been demonstrated. To the best of our knowledge, this is the first efficient method that controls, in situ, both the enantioselectivity (up to 99% ee) and the olefinic geometry (up to 99% *Z*) of cis linear homoallylic alcohols. Our

Scheme 3. Proposed Transition State of Crotyl Transfer Using the Camphor Scaffold



investigations have also shown that this chemoselective crotyl transfer is highly feasible for aliphatic substrates. Moreover, excess chiral camphor-derived branched homoallylic alcohol (89%) and the camphor (83%) generated from the reaction can be recovered and reused, thus, making this method attractive for scale-up preparation of cis linear homoallylic alcohols with high enantioselectivities. We anticipate that this new Brönsted acid-catalyzed allyl transfer reaction will be an indispensable tool in the synthesis of complex natural products, thereby allowing this methodology to undergo an exciting renaissance as a synthetic method.

Acknowledgment. We thank the National University of Singapore and Biomedical Research Council (BMRC) for generous financial support. Chi-Lik Ken Lee is grateful to Agency for Science Technology and Research (ASTAR) for a doctorate scholarship.

Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049633Z

(9) (a) Loh, T. P.; Hu, Q. Y.; Ma, L. T. *J. Am Chem. Soc.* **2001**, *123*, 2450. (b) Loh, T. P.; Hu, Q. Y.; Tan, K. T.; Cheng, H. S. *Org. Lett.* **2001**, *3*, 2669. (c) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2921.

(10) Another reaction, performed with *only* the pure syn branched homoallylic alcohol **1a** (0.36 mmol; 1.2 equiv), 3-phenylpropanal (0.3 mmol; 1 equiv), and CSA (0.03 mmol; 0.1 equiv) in CH_2Cl_2 (0.1 mL.; 3.0 M), furnished the desired linear homoallylic alcohol (*81% yield*, *98% ee*, and *99% Z*).

(11) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.