ORGANIC LETTERS

2002
Vol. 4, No. 22
3777−3779

Novel Catalytic Kinetic Resolution of Racemic Epoxides to Allylic Alcohols

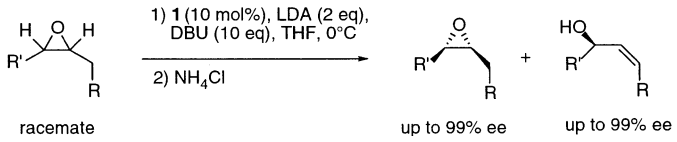
Arnaud Gayet, Sophie Bertilsson, and Pher G. Andersson*

Department of Organic Chemistry, Institute of Chemistry, Uppsala University, Box 531, S-751 21 Uppsala, Sweden

phera@kemi.uu.se

Received April 8, 2002 *(Revised Manuscript Received July 17, 2002)*

ABSTRACT

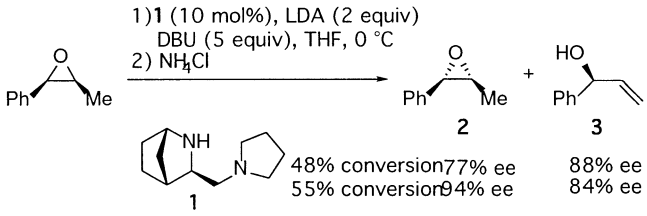


The kinetic resolution of racemic epoxides via catalytic enantioselective rearrangement to allylic alcohols was investigated. Using the Li-salt of (1*S*,3*R*,4*R*)-3-(pyrrolidinyl)methyl-2-azabicyclo [2.2.1] heptane 1 as catalyst allowed both epoxides and allylic alcohols to be obtained in an enantioenriched form.

Kinetic resolution involves a chiral reagent that promotes the selective reaction of one enantiomer over the other to give both the starting material and product in an enantiomerically enriched form.[1] This methodology is a well-established approach to the generation of optically active compounds.[2]

We have investigated the asymmetric β-elimination of racemic epoxides as a route to produce the optically active epoxides and allylic alcohols.[3] The epoxide deprotonation reaction has been widely employed for the synthesis of enantioenriched allylic alcohols from *meso*-epoxides. A number of chiral, nonracemic bases have been developed and used in the reaction.[4,5] However, only two of the bases reported have proven to be useful in the catalytic version of the reaction.[6,7] With regards to kinetic resolution, Asami[8] and co-workers used a chiral lithium amide base, lithium (*S*)-2-(pyrrolidin-1-yl)methylpyrrolidide, employing two different *cis*-3-alkylcyclohexene oxides as substrates. However a stoichiometric amount of this lithium base was needed in order to produce allylic alcohol in an enantiomeric excess over 60%. Lithium amide Li-**1** (Scheme 1) was introduced by our research group in 1998 and has proven to be an excellent catalyst for a large group of meso substrates.[6] However, the use of **1** in the kinetic resolution of racemic

Scheme 1. Kinetic Resolution of *cis*-ss-Methylstyrene Oxide Promoted by Li-**1**



(1) (a) Kagan, H. B.; Fiaud, J. C. *Topics in Stereochemistry*; Eliel, E. L., Fiaud, J. C., Eds.; Wiley: New York, 1988; Vol. 18, pp 249−330. (b) Kagan, H. B. *Tetrahedron* **2001**, *57*, 2449−2468.

(2) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5−26, and references therein.

(3) For earlier studies in this field, see: (a) Mori, K.; Hazra, B. G.; Pfeiffer, R. J.; Gupta, A. K.; Lindgren, B. S. *Tetrahedron* **1987**, *43*, 2249−2254. (b) Asami, M.; Kanemaki, N. *Tetrahedron Lett.* **1989**, *30*, 2125−2128. (c) Bigi, A.; Mordini, A.; Thurner, A.; Faigl, F.; Poli, G.; Tõke, L. *Tetrahedron: Asymmetry* **1998**, *9*, 2293−2299.

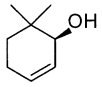
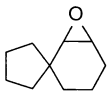
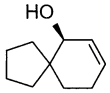
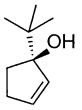
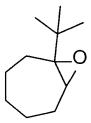
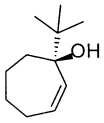
(4) For reviews, see: (a) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439−1457. (b) Asami, M. *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 188−199. (c) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361−14384. (d) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1−26.

(5) For the first reports on the different groups of lithium amide bases, see: (a) Asami, M. *Chem. Lett.* **1984**, 829−832. (b) Bhuniya, D.; Singh, V. K. *Synth. Commun.* **1994**, *24*, 1475−1481. (c) Milne, D.; Murphy, P. J. *J. Chem. Soc., Chem. Commun.* **1993**, 884−886. (d) Tierney, J. P.; Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1019−1022.

(6) (a) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760−10761. (b) Södergren, M. J.; Bertilsson, S. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 6610−6618.

10.1021/ol025983e CCC: $22.00
Published on Web 10/05/2002

Table 1. Kinetic Resolution of Racemic Epoxides Using Li-**1**

entry	epoxide		%conv.[a]	%ee[b] (epoxide)	yield[c] (epoxide)	Allylic alcohol[d]		%ee[b] (alcohol)	Yield[c] (alcohol)
1		R= Me	**4**	43	78	45	 R= Me	**5(*R*)**	96	30
2				52	87	38			94	40
3		R=Et	**6**	40	30	53	R=Et	**7(*R*)**	90	31
4				63	70	32			90	47
5		R=i-Pr	**8**	46	73	48	R=i-Pr	**9(*S*)**	nd[e]	41
6				52	92	41			nd[e]	45
7		R= tBu	**10**	44	64	51	R= tBu	**11(*R*)**	99	36
8				58	99	36			99	40
9			**12**	52	99	47		**13(*S*)**	94	43
10			**14**	56	93	40		**15(*S*)**	90	45
11			**16**	63	nd[e]	32		**17(*R*)**	60	52
12				42		50			79	34
13			**18**	47	nd[e]	48		**19(*R*)**	90	40
14				41		51			94	34

[a] All reactions were set up using the conditions described in Scheme 1. Conversions were determined by CSP (chiral stationary phase, chirasil Dex-CB) on the basis of epoxide consumption relative to an internal standard (*n*-dodecane). [b] Determined by CSP. [c] Isolated yields. [d] Absolute configuration tentatively assigned on the basis of the stereochemical model published earlier.[6b]

epoxides has only been briefly investigated.[6b] In this initial study, *cis*-*β*-methylstyrene oxide was resolved to produce both the epoxide and the allylic alcohol in enantioselectivities of 77−94% (Scheme 1). Also, 1-methylcyclohexene oxide was rearranged with high enantioselectivity (see Table 1, entries 1−2).

Encouraged by our preliminary results, we started investigating the possibility of broadening the scope of the reaction. A group of racemic cyclic epoxides were prepared and resolved via the preferential rearrangement of one of the enantiomers to an allylic alcohol when treated with Li-**1** (10 mol %). All reactions were performed at 0 °C using an excess of DBU[9] and LDA as the stoichiometric base. To produce both the unreacted epoxide and the allylic alcohol in high ees, the reaction was quenched either shortly before or after 50% conversion (Table 1).

The 1-alkyl-substituted cyclohexene oxides investigated produced enantioenriched epoxides and tertiary alcohols in up to 99% ee at conversions close to 50%. The best results were obtained for the rearrangement of 1-*tert*-butylcyclohexene oxide, where both the epoxide **10** and the allylic alcohol **11** were formed with excellent asymmetric induction at 58% conversion[10] (Table 1, entry 8). The rearrangement of 1-methyl cyclohexene oxide (entries 1 and 2) produces the highly enantioenriched allylic alcohol **5**. This is particularly interesting since 1-methylcyclohex-2-en-1-ol is an aggregation pheromone of the beetle *Dendroctonus pseudosugae* Hopkins. Ethyl-substituted epoxide was resolved giving **6** with moderate enantioselectivity (≤70% ee), while the enantiomeric excess of the corresponding allylic alcohol obtained was high (90%) (entries 3 and 4). When the alkyl substituent in the 1-position was changed to the more bulky isopropyl, the epoxide was enriched in up to 92% ee (entries 5 and 6). Unfortunately, the two enantiomers of the allylic alcohol product could not be separated either by chiral GC or derivatization (Mosher ester). From the results, it is obvious that the selectivity of the reaction is related to the size of the substituent in the 1-position. The more bulky this substituent is, the more selective the reaction is.

Other 1-*tert*-butyl-substituted cyclic epoxides were treated and gave encouraging results, but they were inferior to the six-membered ring analogue. The 1-*tert*-butylcyclopentene oxide **16** gave moderate ees, 79% for the allylic alcohol **17** at 41% conversion (entry 12), while the 1-*tert*-cycloheptene oxide **18** leads to the corresponding allylic alcohol **19** (41% conversion) in 94% ee (entry 14). Unfortunately, we were

(7) Asami, M.; Suga, T.; Honda, K.; Inoue, S. *Tetrahedron Lett.* **1997**, *38*, 6425−6428.

(8) Asami, M.; Sato, S.; Honda, K.; Inoue, S. *Heterocycle* **2000**, 3, 1029−1032.

(9) The beneficiary effect of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in the catalytic rearrangement reaction has been shown earlier; see: Asami, M.; Ishizaki, T.; Inoue, S. *Tetrahedron: Asymmetry* **1994**, *5*, 793−796 and refs 6 and 3c therein.

(10) Also, about 10% yield of 2-*tert*-butylcyclohex-2-en-1-ol was obtained in the reaction.

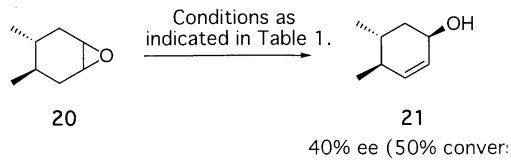
not able determine the enantiomeric purity of the epoxide using chiral GC.

In earlier investigations, a competing β-hydrogen abstraction in the *exo*-cyclic position was detected for 1-alkyl-substituted epoxides.[11] This feature was also observed for some of the substrates investigated. However, the byproduct was formed in small amounts (<15%), except in the case of 1-methyl-cycloheptene oxide where the abstraction occurs exclusively on the *exo*-cyclic position and leads to a racemic allylic alcohol.

Furthermore, we were interested in 2,2-disubstituted cyclohexene oxides as substrates because of the fact that they only have one β-hydrogen cis to the epoxide oxygen accessible to the chiral base. This should make these substrates good candidates for the kinetic resolution. Two substrates were synthesized and tested. As expected, we obtained very good to excellent ees for both candidates. The 2,2-dimethyl-cyclohexene oxide **12** was tried first; the reaction was stopped at 52% conversion, and the allylic alcohol **13** was obtained in 94% ee and the epoxide **12** in 99% ee (entry 9). When the methyl substituents were replaced by a spiro ring, the allylic alcohol **15** was obtained in 90% ee after 56% conversion, while the enantiomeric excess of the epoxide was 93% (entry 10).

Racemic *trans*-4,5-dimethylcyclohexene oxide **20** was also subjected to the rearrangement reaction in order to achieve a kinetic resolution (Scheme 2). However, the enantioselectivity dropped dramatically when the center of chirality was moved to the 4- and 5-positions of the epoxide ring.

Scheme 2. Kinetic Resolution of *trans*-4,5-Dimethyl Cyclohexene Oxide



The allylic alcohols were easily separated from the epoxide substrates by column chromatography after the resolution. This makes the procedure highly useful for the preparation of both enantioenriched epoxides and allylic alcohols.

Acknowledgment. This work was supported by the Swedish Natural Research Council (NFR), the Swedish Research Council for Engineering Sciences (TFR), and the Swedish Council for Strategic Research (SSF).

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

OL025983E

(11) Crandall, J. K.; Lin, L.-H. C. *J. Org. Chem.* **1968**, *33*, 2375−2378. See also ref 3a.