Practical Access to Highly Enantioenriched C-3 Building Blocks via Hydrolytic Kinetic Resolution

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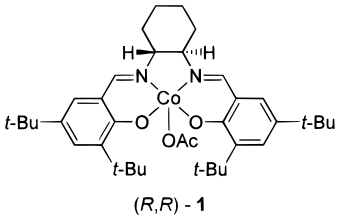
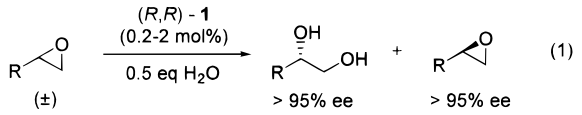
Received July 9, 1998

Kinetic resolution (KR) can be a highly effective strategy for the preparation of optically pure compounds, particularly if the corresponding racemates are readily available and a practical procedure for KR can be applied.[1] In this light, the recently disclosed hydrolytic kinetic resolution (HKR) reaction catalyzed by (salen)Co complex **1** (eq 1) constitutes



(*R*,*R*) - **1**

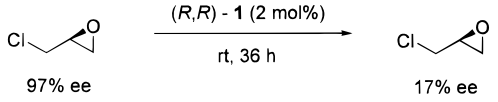


(1)

a very attractive approach toward the preparation of enantiopure terminal epoxides.[2] The features of the HKR include the following: the use of water as the nucleophile for epoxide ring opening; the high accessibility of racemic terminal epoxides; the low loadings and recyclability of the commercially available catalyst;[3] and the ease of product separation from unreacted epoxide due to large boiling point and polarity differences.

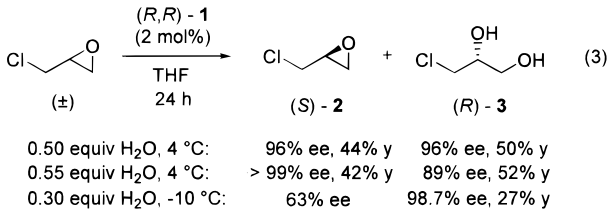
Epihalohydrins and glycidol derivatives are particularly attractive substrates for HKR because the racemates are available inexpensively and on a large scale, and the chiral three-carbon (C-3) building blocks derived from these compounds are extremely versatile synthetic intermediates. In the initial report on the HKR,[2] epichlorohydrin was the only C-3 substrate evaluated and its resolution was described to afford recovered epoxide in 44% yield and 98% ee, but the diol was obtained in only 38% yield and 86% ee. In this paper, we describe a highly optimized protocol for the HKR of epichlorohydrin to provide either epoxide or diol in >99% ee,[4,5] as well as the highly efficient *dynamic* HKR of epibromohydrin. The HKR methodology is also shown to be applicable to a variety of important glycidol derivatives.

Epihalohydrins are susceptible to racemization catalyzed by adventitious halide ion, and this stands as a critical issue in any kinetic resolution of these substrates. Indeed, this racemization pathway has been used to advantage in the resolution of epichlorohydrin with $TMSN_3$ catalyzed by the Cr analogue of **1**.[6] In that case, racemization was rapid enough relative to the ring-opening pathway to allow for a dynamic kinetic resolution affording the ring-opened product in 76% yield and 97% ee. In contrast, racemization of epichlorohydrin was found to take place only very slowly relative to hydrolysis under hydrolytic conditions with Co catalyst **1** (eq 2). This racemization was suppressed by



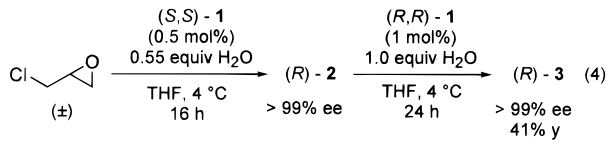
(2)

addition of THF as solvent, thereby allowing the HKR of (±)-epichlorohydrin with 0.50 equiv of H_2O to provide both epoxide and diol in 96% ee and in isolated yields of 44% and 50%, respectively (eq 3). Enantiopure epichlorohydrin (>99% ee) could be obtained in 42% isolated yield by resolution under the same conditions using 0.55 equiv of water. In both cases, catalyst **1** could be regenerated and reused with no loss of activity or enantioselectivity (see the Supporting Information).



(3)

The HKR product of epichlorohydrin, chloropropane diol **3**, is also a very valuable chiral C-3 building block,[7] and conditions were sought for its production in high optical purity. The HKR of epichlorohydrin at reduced temperature and lower conversion (−10 °C, 0.3 equiv of H_2O) gave (*R*)-**3** in 98.7% ee and 27% yield (eq 3). This corresponds to a selectivity factor in the HKR of epichlorohydrin of at least 218. Enantiopure (*R*)-**3** (>99% ee) was easily obtained by HKR of epichlorohydrin to >99% ee with (*S*,*S*)-**1**, as described above, followed by vacuum distillation of the epoxide and THF and subsequent ring opening of the resolved epoxide using (*R*,*R*)-**1**. This sequence, which takes advantage of the equal availability of both enantiomers of catalyst **1**, provides an attractive route to (*R*)-**3** or (*S*)-**3** in 41% overall isolated yield from racemic epichlorohydrin (eq 4).



(4)

In contrast to the slow rate of racemization observed for epichlorohydrin under HKR conditions, epibromohydrin was found to undergo racemization relatively rapidly. Thus, at

(1) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1987; Vol. 14, pp 249−330.

(2) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

(3) (*S*,*S*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II): Aldrich catalog no. 47, 460-6. (*R*,*R*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II): Aldrich catalog no. 47, 459-2. The corresponding Co(III) complex **1** is generated either in situ in the HKR or in a discrete step by exposure of the Co(II) complex to air in the presence of AcOH. See the Supporting Information for complete experimental details.

(4) For an alternative route to enantioenriched epichlorohydrin employing asymmetric catalysis, see: Takeichi, T.; Arihara, M.; Ishimori, M.; Tsuruta, T. *Tetrahedron* **1980**, *36*, 3391.

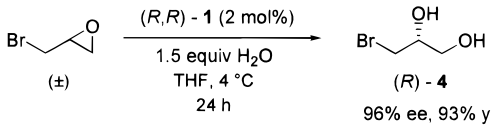
(5) For the synthesis of enantiopure epichlorohydrin by enzymatic resolution of 2,3-dichloro-1-propanol, see: Kasai, N.; Tsujimura, K.; Suzuki, T. Jpn. Patent JP 02 257 895, 1990; *Chem. Abstr.* **1991**, *114*, 41064q.

(6) Schaus, S. E.; Jacobsen, E. N. *Tetrahedron Lett.* **1996**, *37*, 7937.

(7) For the synthesis of **3** and **4** by asymmetric dihydroxylation, see: Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448.

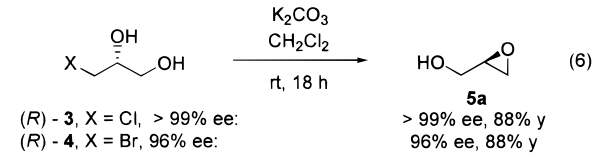
S0022-3263(98)01332-2 CCC: $15.00
Published on Web 09/05/1998

50% conversion in the hydrolysis of epibromohydrin with (*R*,*R*)-**1**, epoxide was recovered in only 6% ee while diol was produced in 96% ee. As a result, epibromohydrin was evaluated as a possibly viable substrate for dynamic kinetic resolution.[8] The reaction of racemic epoxide with 1.5 equiv of H_2O in THF in the presence of 2 mol % of (*R*,*R*)-**1** gave diol **4**[6] in 96% ee and 93% isolated yield (eq 5). This, therefore, represents a particularly effective example of dynamic kinetic resolution from the point of view of both enantioselectivity and yield.



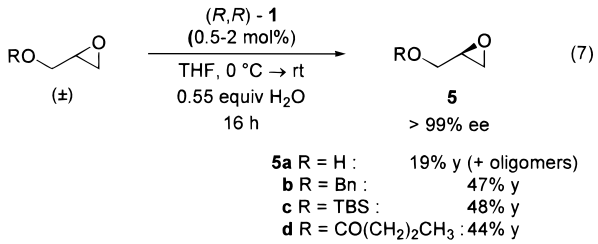
(5)

Diols **3** and **4** are immediate precursors to glycidol (**5a**), another broadly useful C-3 building block.[9] Upon treatment with potassium carbonate, enantiopure (*R*)-**3** obtained as described above was converted to (*R*)-**5a** in 88% isolated yield and >99% ee (eq 6). In the same manner, (*R*)-**4** was converted to (*R*)-**5a** in 88% yield. These HKR/cyclization sequences represent straightforward, efficient methods for the synthesis of enantioenriched glycidol[10] from racemic epichlorohydrin or epibromohydrin.



(6)

The HKR of glycidol itself provided resolved epoxide in low yield as a result of the participation of undesired oligomerization pathways (eq 7). In contrast, the HKR was found to be highly effective in the resolution of glycidol derivatives. Under standard conditions employing 0.5 mol % (*R*,*R*)-**1** and 0.55 equiv of H_2O, benzyl glycidyl ether,[11] *tert*-butyldimethylsilyl glycidyl ether, and glycidyl butyrate[12] were each obtained in >99% ee and 47%, 48%, and 44% yield, respectively.



(7)

The high enantioselectivity in the HKR of epichlorohydrin and glycidol derivatives makes it possible to isolate either epoxide or the corresponding diols in high ee. We are hopeful that the ready access to C-3 building blocks in enantiopure form provided by the HKR methodology will have a significant enabling impact on the use of these intermediates in pharmaceutical and natural product synthesis.

Acknowledgment. This work was sponsored by the NIH (GM-43214). We gratefully acknowledge predoctoral fellowship support to S.E.S. from the Ford Foundation and a James Flack Norris undergraduate summer scholarship to M.E.F. from the Northeastern Section of the ACS.

Supporting Information Available: Complete experimental procedures and chiral chromatographic analyses of racemic and enantiomerically enriched **2**−**5** (13 pages).

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(8) For a review, see: Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.

(9) For a review of the synthetic applications of glycidol and glycidol derivatives, see: Hansen, R. H. *Chem. Rev.* **1991**, *91*, 437.

(10) For the synthesis of glycidol by asymmetric epoxidation of allyl alcohol, see: (a) Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 3710. (b) Hanson, R. M.; Ko, S. Y.; Gao, Y.; Masamune, H.; Klunder, J. M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(11) For the enzymatic resolution of benzyl glycidyl ether, see: (a) Weijers, C. A. G. M. *Tetrahedron: Asymmetry* **1997**, *8*, 639. (b) Pederson, R. L.; Liu, K. K.-C.; Rutan, J. F.; Chen, L.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 4897.

(12) For the enzymatic resolution of glycidyl butyrate, see: Ladner, W. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1984**, *106*, 7250.