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ARTICLE *in* CHEMINFORM · JUNE 1999

Impact Factor: 0.74 · DOI: 10.1021/ja9910917

Asymmetric Catalytic Synthesis of α-Aryloxy Alcohols: Kinetic Resolution of Terminal Epoxides via Highly Enantioselective Ring-Opening with Phenols

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Received April 6, 1999

Enantiopure α-aryloxy alcohols (**1**) are valuable targets for asymmetric synthesis as a result of their role as key synthetic intermediates in a variety of pharmaceutically important compounds.[1] In principle, access to these building blocks may be provided by several routes, including asymmetric reduction of aryloxy ketones[2] or the ring opening of enantiopure terminal epoxides with phenols. Of these, the latter is probably the most versatile and direct, but available methods for the addition of phenols to epoxides are extremely limited. No catalytic methods have been devised for phenolic opening of terminal epoxides,[3] and forcing conditions are required for the uncatalyzed reaction, such as heating epoxide in the presence of a phenoxide salt to high temperatures in a polar solvent. These thermal methods are generally low-yielding and are particularly unsuitable for sensitive substrates. Thus, despite the recent discovery of general methods for accessing terminal epoxides in high optical purity,[4] the development of routes to enantiopure α-aryloxy alcohols via epoxide ring-opening with phenols remains an unsolved problem.

The ready accessibility of terminal epoxides in racemic form renders kinetic resolution of terminal epoxides with phenols a potentially attractive route to **1** (Scheme 1, Nu = OAr). The high selectivities obtained in the recently reported hydrolytic kinetic resolution of terminal epoxides with catalyst **3b**[4] (Scheme 1, Nu = OH) suggested that (salen)Co(III) complexes might also serve as effective catalysts for the enantioselective addition of phenols to epoxides. This strategy has proven successful, and we report here the first examples of kinetic resolution of epoxides with phenols, with the isolation of 1-aryloxy 2-alcohols (**1**) in high ee's and yields.

Reaction of 2.2 equiv of (±)-1,2-epoxyhexane (**2a**) with phenol (**4a**) in the presence of (salen)Co(OAc) complex **3b** (0.044 equiv) in *tert*-butyl methyl ether (TBME) led to 61% conversion of phenol after 55 h at room temperature, with 1-phenoxy-2-hexanol (**1a**) generated in 94% ee. Encouraged by the observation of high enantioselectivity in this reaction, we evaluated a variety of reaction parameters with the goal of identifying a more reactive system. The identity of the counterion for the (salen)cobalt complex proved to be important in this context, with the perfluoro *tert*-butoxide complex displaying superior reactivity. Thus, the use of complex **3c**[5] under conditions otherwise identical to those outlined above resulted in 80% conversion of phenol in 18 h and formation of 1-phenoxy-2-hexanol as the major product in 96% ee. Small amounts of 1,2-diol were also generated, presumably as a result of epoxide hydrolysis with adventitious water,[4] but this pathway could be suppressed easily by the inclusion of 3 Å molecular sieves in the reaction mixture. The optimized procedure afforded the product in 97% isolated yield based on phenol and 98% ee (Table 1, entry 1).[6,7]

Scheme 1

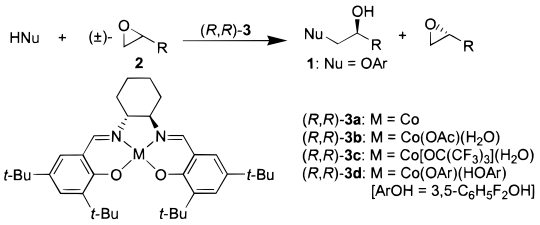

Table 1. Kinetic Resolution of Terminal Epoxides with Phenol Catalyzed by **3c**[a]

entry	R	equiv **1c**	temp (°C)	yield (%)[b]	ee (%)[c]
1	$(CH_2)_3CH_3$ (**2a**)	0.044	25	97	98
2	CH_2Cl (**2b**)	0.044	−15	97	99
3	CH_2O(allyl) (**2c**)	0.044	4	93	97
4	*c*-C_6H_{11} (**2d**)	0.088	−15	99	97
5	$C(O)CH_2CH_3$ (**2e**)	0.088	−20	96	96
6	CO_2CH_3 (**2f**)	0.044	−20	98	96
7	C_6H_5 (**2g**)	0.044	−25	*e*	n.d.

[a] Reactions run 5 M in TBME for 4 to 18 h, unless otherwise noted. See Supporting Information for details. [b] Isolated yield based on phenol. [c] Determined by chiral HPLC analysis or chiral GC analysis. [d] Reaction run in CH_3CN. [e] GC/MS of crude reaction mixture indicated formation of a 2:1 ratio of regioisomeric products.

A series of terminal epoxides were screened in the kinetic resolution with phenol, and results are summarized in Table 1. Both electron-rich (entries 1 and 4) and electron-poor (entries 2,3,5 and 6) epoxides as well as epoxides with a range of steric properties reacted with complete regioselectivity to provide the corresponding α-aryloxy alcohols in excellent yields and ee's. In contrast, reaction with styrene oxide resulted in a mixture of regioisomeric ring-opened products (entry 7). In general, the stereoselectivities in the kinetic resolution displayed a strong temperature dependence, such that reactions providing moderate ee's at room temperature could be rendered significantly more selective simply by lowering the reaction temperature. For example, in the reaction of phenol with methyl glycidate, the following data were obtained: 25 °C, 85% ee; 4 °C, 90% ee; −20 °C, 96% ee. There was correspondingly little effect of temperature on reaction rate, with all of the above reactions reaching completion within 16−24 h.

The phenolic kinetic resolution was found to have a broad substrate scope with respect to the phenol (Table 2). Alkyl

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(2) For examples of asymmetric reductions of α-arlyoxy ketones, see: (a) Takahashi, H.; Sakuraba, S.; Takea, H.; Achiwa, K. *J. Am. Chem. Soc.* **1990**, *112*, 5877. (b) Gooding, O.; Colin, B.; Cooper, G.; Jackson, D. *J. Org. Chem.* **1993**, *58*, 3681. (c) Yuan, R.; Watanabe, S.; Kuwabata, S.; Yoneyama, H. *J. Org. Chem.* **1997**, *62*, 2494. (d) Kang, S. B.; Ahn, E. J.; Kim, Y.; Kim, Y. H. *Tetrahedron Lett.* **1996**, *37*, 9317. (e) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1986**, *27*, 3547.

(3) Shibasaki has reported the asymmetric catalytic ring opening of meso epoxides with 4-methoxyphenol using a Ga(BINOL) catalyst system: Lida, T.; Yamamoto, N.; Matsunaga, S.; Shigeki, M.; Woo, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2223.

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

(5) Commercially available (salen)Co complex **3a** was effectively oxidized to (salen)Co(III) complex **3c** simply by stirring **3a** and $(CF_3)_3COH$ in CH_2Cl_2 open to the atmosphere for 45 min and then removing the solvent by rotary evaporation. See Supporting Information.

(6) General procedure for the kinetic resolutions in Table 1 and Table 2: A 10 mL flask was charged with 86 mg (0.100 mmol) of **3c** and 100 mg MS 3A. Epoxide (5.00 mmol) and phenol (2.25 mmol) were added at the indicated reaction temperature, and then TBME (0.15 mL) was added. The reaction was stirred at the indicated temperature until GC analysis indicated complete conversion of phenol, at which time 75 mg (0.30 mmol) pyridinium *p*-toluenesulfonate was added. The reaction mixture was filtered through a pad of silica and washed with 50% EtOAc/hexanes. The filtrate was concentrated and purified by chromatography on silica gel with EtOAc/hexanes or Kugelrohr distillation under reduced pressure. The enatiomeric purity was determined by GC or HPLC.

(7) Full experimental procedures, spectral data for new compounds, and ee determinations are presented in the Supporting Information.

10.1021/ja9910917 CCC: $18.00
Published on Web 06/10/1999

Table 2. Kinetic Resolution of 1,2-Epoxyhexane with Phenols Catalyzed by **3c**[a]

4 (1.00 equiv) **2a** (2.20 equiv)

entry	R	**3c** (equiv)	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	H (**4a**)	0.044	25	12	97	98
2	*p*-CH_3 (**4b**)	0.044	25	12	95	97
3	*m*-CH_3 (**4c**)	0.044	25	16	99	99
4	*o*-CH_3 (**4d**)	0.044	25	120	<5[d]	n.d.
5	*p*-Br (**4e**)	0.044	−15	12	92	99
6	*o*-Br (**4f**)	0.088	−30	48	98	92
7	*p*-OCH_3 (**4g**)	0.088	4	18	75	99
8	*p*-NO_2 (**4h**)	0.088	−20	18	93	91
9	*p*-$(CH_2)_2$NHBoc (**4i**)	0.044	25	12	86	99
10	1-Naphthol (**4j**)	0.044	25	96	*e*	

[a] See Supporting Information for full experimental details. [b] Isolated yield based on phenol. [c] Determined by chiral HPLC analysis. [d] Determined by GC analysis of crude reaction mixture. [e] No reaction as determinedby GC analysis.

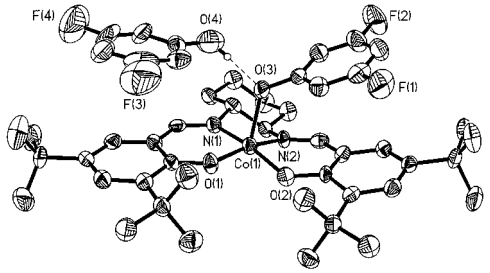
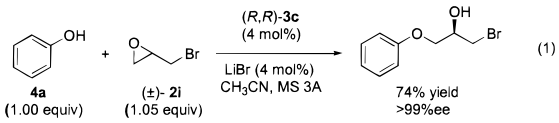


Figure 1. ORTEP diagram of (salen)Co(OAr)(HOAr) complex **3d** (Ar = 3,5 F_2-C_6H_3).

substitution at the para- or meta-positions on the phenol had little influence on yield or ee (entries 2 and 3). While ortho-substituted alkyl phenols displayed poor reactivity, the successful use of *o*-bromophenol in the kinetic resolution (entry 6) allows access to a wide range of ortho-substituted aryl ethers through subsequent cross-coupling reactions. Overall, phenols with a wide range of electronic properties participated in the ring-opening reaction with good yields and ee's.[8]

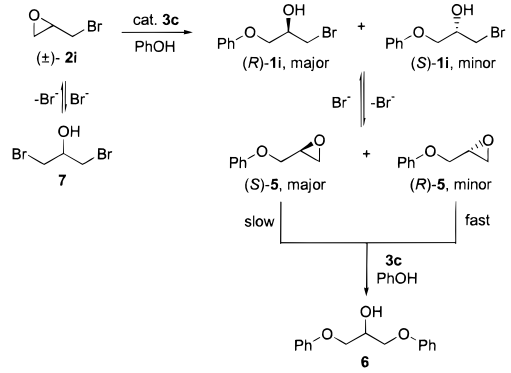
Epibromohydrin is prone to undergo racemization in the presence of bromide ion,[9] and this substrate therefore emerged as a promising candidate for dynamic kinetic resolution under the conditions of the phenolic ring-opening reaction. Reaction of (±)-epibromohydrin (1.05 equiv) with phenol (1.00 equiv) in the presence of (*R*,*R*)-**3c** and LiBr (4 mol %) in CH_3CN led to formation of bromohydrin **1i** in >99% ee and 74% yield (eq 1).



4a (1.00 equiv) (±)- **2i** (1.05 equiv) 74% yield >99%ee

The exceptionally high enantioselectivity obtained for the ring-opening product can be ascribed in part to a secondary resolution pathway involving the ring opening of transiently formed aryl glycidyl ether **5** (Scheme 2).[10] Consistent with this mechanism, the double addition byproduct **6** was generated in 1−2% yield. The dynamic kinetic resolution of epibromohydrin via phenolic ring-opening thus provides a highly efficient route to enantiopure aryl glycidyl ether derivatives.

Scheme 2



A general mechanistic pattern has begun to emerge for asymmetric epoxide ring-opening reactions, wherein the catalyst can serve a dual role of Lewis acid activator of the epoxide and counterion for nucleophile delivery.[3,11] In that context, we sought to identify the active catalyst in the phenolic kinetic resolution reaction and, in particular, to evaluate the possible intermediacy of a (salen)Co(phenoxide) complex. Addition of 3,5-difluorophenol to a CH_2Cl_2 solution of **3a** under air led to an immediate darkening of the solution and isolation of a black solid (**3d**) upon solvent evaporation. This material exhibited mass spectral and solution ^1H, ^{19}F, and ^{13}C NMR (DMSO-d_6) properties consistent with a complex of formula (salen)Co(OAr)(HOAr) (Ar = 3,5 F_2-C_6H_3).[12] X-ray crystallographic analysis of a single-crystal grown from heptane confirmed this formulation and revealed a rare example of a five-coordinate square pyramidal cobalt−aryloxide complex with a molecule of ArOH hydrogen-bonded to the aryloxide oxygen (Figure 1).[13] The characterization of **3d** is consistent with the intermediacy of a (salen)Co(aryloxide) complex in the reaction with epoxides, and this is further supported by the observation of stoichiometric aryloxide transfer from **3d** to (±)-1,2-epoxyhexane (2.2 equiv) to provide the corresponding α-aryloxy alcohol as the sole product in >99% ee.

The (salen)Co(III)-catalyzed kinetic resolution of terminal epoxides with phenols provides a highly practical route to 1-aryloxy-2-alcohols using an operationally simple procedure and a readily accessible catalyst. The reaction exhibits extraordinary generality with respect to the steric and electronic properties and degree of functionalzation of the epoxides and the phenol. This constitutes the first case where an entire class of nucleophiles—rather than a single nucleophile such as N_3^- or OH^-—can be used for the kinetic resolution of terminal epoxides. This raises the interesting possibility of applying this methodology to the enantioselective catalytic synthesis of parallel libraries of ring-opened products. Our efforts in this area are underway.

Acknowledgment. This work was sponsored by NIH (GM-43214). The crystal structure analysis was performed by Dr. Matthew S. Sigman and Dr. Richard Staples. We thank D. Allen Annis for helpful discussions.

Supporting Information Available: Complete experimental procedures and chiral chromatographic analyses of racemic and enantiomerically enriched ring-opening products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA9910917

(8) Lower limits for the values of k_{rel} for the reactions described in Tables 1 and 2 were determined using the equation $k_{rel} = \ln[1 - c(1 + ee)]/\ln[1 - c(1 - ee)]$ where ee is the enantiomeric excess of the product and the conversion c is set to be the isolated yield of the ring-opened product. The values for k_{rel} thus determined ranged from 42 (Table 2, entry 8) to greater than 300 (Table 1, entry 2, Table 2, entries 3, 4, 7, 9). Calculations for each entry are presented in the Supporting Information.

(9) (a) Furrow, M. E.; Schaus, S.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776. (b) Schaus, S. E.; Jacobsen, E. N. *Tetrahedron Lett.* **1996**, *37*, 7937.

(10) Catalytic asymmetric ring closure of 1,3-dichloro-2-propanol with optically active (salen)Co complexes in the presence of K_2CO_3 has been reported, but we have no evidence for such a pathway in the present system. Takfichi, R.; Arihara, M.; Ishimori, M.; Tsuruta, T. *Tetrahedron* **1980**, *36*, 3391.

(11) (a) Hansen, K.; Leighton, J.; Jacobsen, E. *J. Am. Chem. Soc.* **1996**, *118*, 10924. (b) McCleland, B.; Nugent, W.; Finn, M. *J. Org. Chem.* **1998**, *63*, 6656.

(12) The ^1H NMR also reveals the presence of a small amount of a C_2 symmetric compound we formulate as the (salen)Co(III)$(DMSO)_2^+$ complex.

(13) For related structures, see: (a) Cesari, M.; Neri, C.; Percgo, G.; Perrotti, E.; Zazzetta, A. *J. Chem. Soc., Chem. Commun.* **1970**, 276. (b) Bailey, N. A.; McKenzie, E. D.; Worthington, J. M. *J. Chem. Soc., Dalton Trans.* **1977**, 763. (c) Huilan, C.; Deyan, H.; Tian, L.; Hong, Y.; Wenxia, T.; Chen, J. Zheng, P.; Chen, C. *Inorg. Chem.* **1996**, *35*, 1502.