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

Joseph M. Ready and Eric N. Jacobsen
Department of Chemistry and Chemical Biology
Harvard University, Cambridge, Massachusetts 02138

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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 pharmacologically important compounds. In principle, access to these building blocks may be provided by several routes, including asymmetric reduction of arylxy ketones 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, 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, 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 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.

Reactions 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-phenoxo-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)Co(III) complex proved to be important in this context, with the perfluoro tert-butoxide complex displaying superior reactivity. Thus, the use of complex 3c under conditions otherwise identical to those outlined above resulted in 80% conversion of phenol in 18 h and formation of 1-phenoxo-2-hexanol as the major product in 96% yield.

Table 1. Kinetic Resolution of Terminal Epoxides with Phenol Catalyzed by 3c

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>equiv 1e</th>
<th>temp (°C)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH3)2CH</td>
<td>0.044</td>
<td>25</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>CH2Cl2</td>
<td>0.044</td>
<td>15</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>CH2O(allyl)</td>
<td>0.044</td>
<td>4</td>
<td>93</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>c-C6H5CH2</td>
<td>0.088</td>
<td>15</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>c-O(CH2CH2O)3</td>
<td>0.088</td>
<td>20</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>CO2CH2F2</td>
<td>0.044</td>
<td>20</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>C6H5H2</td>
<td>0.044</td>
<td>25</td>
<td>n.d.</td>
<td></td>
</tr>
</tbody>
</table>

* Reactions run 5 M in TBME for 4 to 18 h, unless otherwise noted. See Supporting Information for details. 4 Isolated yield based on phenol. 5 Determined by chiral HPLC analysis or chiral GC analysis. 6 Reaction run in CH2CN. 7 GC/MS of crude reaction mixture indicated formation of a 2:1 ratio of regioisomeric products. ee. Small amounts of 1,2-diol were also generated, presumably as a result of epoxide hydrolysis with adventitious water, 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).

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 stereochemistries 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).

(5) Commercially available (salen)Co complex 3a was effectively oxidized to (salen)Co(III) complex 3c simply by stirring 3a and (CF3)2COH in CH2Cl2 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 10.0 mL flask was charged with 86 mg (0.10 mmol) of 3c and 100 mg MS 3A. Epoxide (5.00 mmol) and propan-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 the epoxide, 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 enantiomeric 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.
The exceptionally high enantioselectivity obtained for the ring-opening reaction with phenols provides a highly practical route to enantiopure aryl glycidyl ether derivatives.

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. 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 CH2Cl2 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, 19F, and 13C NMR (DMSO-d6) properties consistent with a complex of (salen)Co(phenolate) (Ar = 3,5-F2-C6H3). 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). The characterization of 3d is consistent with the intermedacy of a (salen)Co(aryl oxide) complex in the reaction with epoxides, and this is further supported by the observation of stoichiometric aryl oxide transfer from 3d to (±)-1,2-epoxyhexane (2.2 equiv) to provide the corresponding α-aryl 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-aryl-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 functionalization of the epoxides and the phenol. This constitutes the first case where an entire class of nucleophiles—rather than a single nucleophile such as N3− 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.

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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.

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(12) The 1H NMR also reveals the presence of a small amount of a C2 symmetric compound we formulate as the (salen)Co(III)(DMSO)2 complex.