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Enantioselective Parallel Synthesis Using Polymer-Supported Chiral Co(salen) Complexes

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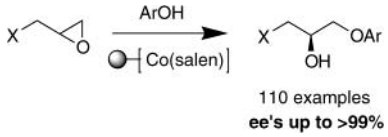
ABSTRACT



The kinetic resolution of epoxides with phenols catalyzed by a polymer-supported Co(salen) complex is applied to the first enantioselective catalytic synthesis of parallel libraries. The corresponding 1-aryloxy-2-alcohols are obtained in high yield, purity, and enantiomeric excess. Further elaboration with diversity elements provides highly efficient access to important classes of pharmacologically active compounds.

Interest in the construction of large libraries of synthetic compounds with targeted properties continues to grow despite the fact that the range of chemical transformations that has been applied thus far with success to library synthesis remains quite limited. Indeed, there are relatively few known reactions that are generally effective enough for use in combinatorial synthesis. For example, despite the enormous research activity that has been undertaken in asymmetric catalysis during the last several years,[1] to date no enantioselective catalytic reactions have been applied directly in the synthesis of parallel libraries.[2,3] This can be ascribed to the fact that few existing asymmetric methods provide high yield and enantioselectivity for a broad range of substrates under a given set of conditions, and those that do almost all involve reactions of a single reagent (e.g. an oxidant, reductant, or specific nucleophile) rather than a family of reagents (Figure 1a). To exploit the true power of combinatorial strategies in the context of asymmetric catalysis, it would clearly be most desirable to implement enantioselective reactions between families of reacting partners (Figure 1b).

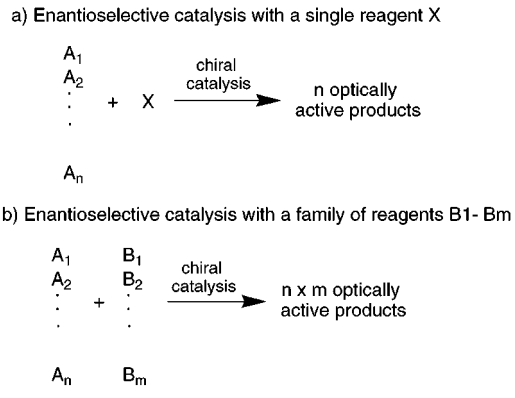


Figure 1.

Very recently, we reported the kinetic resolution of epoxides with phenols catalyzed by Co(salen) complex **1a**

(1) *Comprehensive Asymmetric Catalysis*, Vols. 1−3; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999.

(2) (a) For an example of the application of catalytic reactions to yield libraries of racemic compounds, see: Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1996**, *118*, 8977. (b) For the evaluation of a chiral catalyst against a mixture of substrates, see: Gao, X.; Kagan, H. B. *Chirality* **1998**, *10*, 120.

(3) For a discussion of the possible role of enantioselectivity in library synthesis, see: Annis, D. A.; Helluin, O.; Jacobsen, E. N. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1907.

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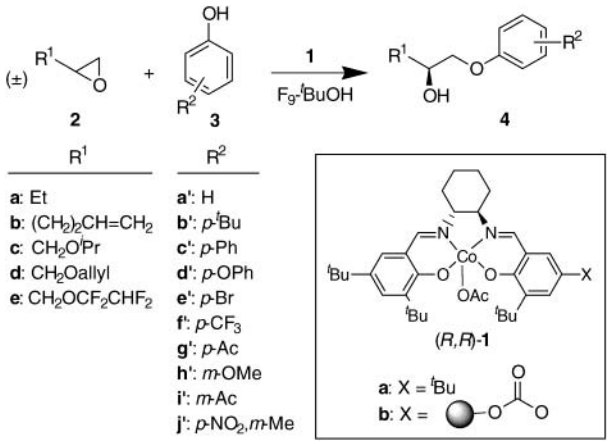
(Scheme 1).[4] The catalyst can also be attached covalently to polystyrene resin (**1b**) with no deleterious effects on reactivity or enantioselectivity, even after repeated recycling of the catalyst.[5] Encouraged by the generality of the phenolic kinetic resolution with respect to both the terminal epoxide and the phenol derivative, we envisioned an application in which parallel libraries could be synthesized from a group of inexpensive, racemic epoxides and a variety of phenols to provide the corresponding 1-aryloxy-2-alcohols in high yield and enantiopurity. We report here the successful attainment of this objective.

Scheme 1

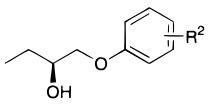
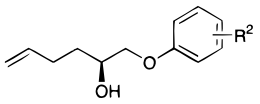
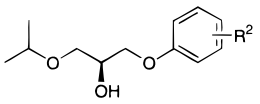
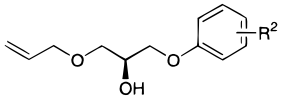
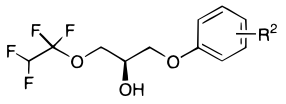


A series of five different terminal epoxides (**2a**−**e**) and ten different phenols (**3a′**−**j′**) was selected for the initial experiment. To access the ring-opened products in highest enantiopurity, the kinetic resolution reactions were carried out using the racemic epoxides as solvents (6−9 equiv relative to the phenol derivative).[6,7] All reactions were maintained at 4 °C for the first 6 h, and then the temperature of the system was raised to 25 °C for 2 h; this led to complete consumption of phenol in all cases. After separation of the catalyst by filtration, excess epoxide was removed by evaporation. Although this protocol restricts the scope of library synthesis to volatile epoxides, the significant (>100 °C) boiling point difference between the epoxide substrate and the aryloxy alcohol products renders the method quite general nonetheless. The catalysts could be reused with no loss of activity or selectivity after washing and reoxidation with 10% acetic acid in toluene.

All 50 ring-opened products were characterized by EI mass spectrometry and analyzed for yield and purity by GC or HPLC. The enantiomeric excesses were determined for 20 randomly selected samples (Table 1).

(4) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086.
(5) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147.
(6) Catalytic amounts of $(CF_3)_3COH$ were added to enhance enantioselectivity and rate in the phenolic kinetic resolution. See ref 4.
(7) Nishizawa, K.; Ohgami, Y.; Matsuo, N.; Kisida, H.; Hirohara, H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1293.

Table 1. Yield, Purity, and ee Determination of 20 Randomly Selected Members of Library **4**

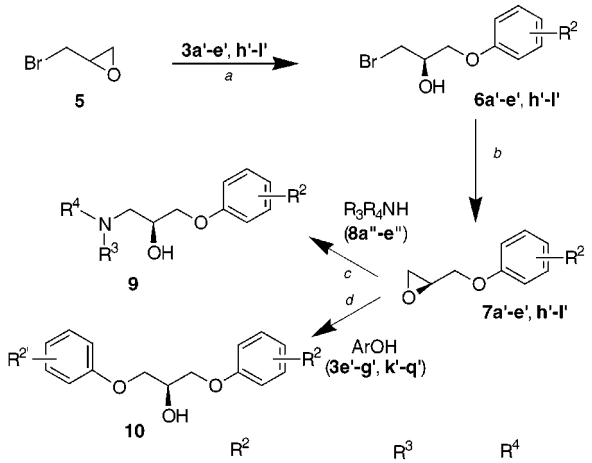
Aryloxy-2-alcohols **4**		yield (%)[a]	purity (%)[b]	ee
	**a'**	55	100	98
	b'	quant.	100	98.5
	d'	90	100	98.5
	f'	90	98	90
a series	**h'**	95	98	>99
	**c'**	95	99	99
	e'	quant.	99	97
	f'	quant.	96	93.5
b series	**i'**	quant.	97	99
	**e'**	quant.	98	94
	h'	95	95	>99
	i'	quant.	95	98.5
c series	**j'**	95	97[d]	87
	**b'**	quant.	96	-
	d'	90	93[d]	97
	g'	95	94	84
d series	**j'**	quant.	95[d]	81
	**a'**	95	100	95
	c'	90	100	93
	g'	95	100	94
e series				

[a] Yields were determined by ^{1}H NMR by dissolving each product in $CDCl_3$ and integrating with internal standard. [b] Purity was assayed by GC analysis. [c] ee's were determined by HPLC analysis on Chiralcel AS and AD columns. The absolute configuration of the product **4ad′** was assigned by comparison of the sign of optical rotation with the literature value.[7] Others are assigned by analogy. [d] Purity was assayed by HPLC analysis.

All products except one were obtained in excellent (≥90%) yield and purity; the lower yield for **4aa′** can be ascribed to losses due to evaporation as a result of the relative volatility of that product. For all of the aryloxy alcohol derivatives examined, the ee's were determined to be >80%. Phenols bearing electron-withdrawing substituents at the para position afforded the poorest results, with product ee's between 81 and 93.5%, whereas all others led to adduct formation in 93 to >99% ee. Ortho-substituted phenols were not included in this library, but results from trial experiments revealed that *o*-halophenols were reactive under the conditions used for the synthesis of library **4**, and the resulting adducts were obtained in >90% ee. In contrast, *o*-alkyl-substituted phenols proved unreactive under the same conditions.

Epibromohydrin (**5**) is an especially interesting substrate for study in the phenolic kinetic resolution, partly because it is susceptible to facile racemization and therefore dynamic kinetic resolution[4] and also because the ring-opened products **6** are readily elaborated with additional diversity elements (Scheme 2). The reaction of **5** with ten different phenols (**3a′**−**e′**,**h′**−**l′**) was carried out in the presence of 1.2 mol % of (*R*,*R*)-**1b**. The intermediate bromohydrin derivatives **6a′**−**e′**,**h′**−**l′** were observed to undergo slow transformation to the corresponding aryl glycidyl ethers **7** under the conditions

Scheme 2

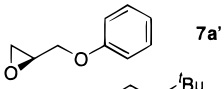
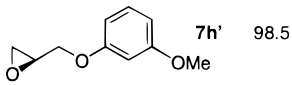
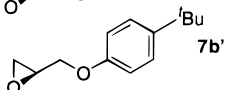
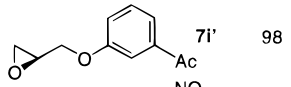
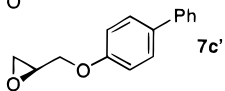
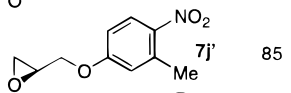
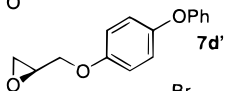
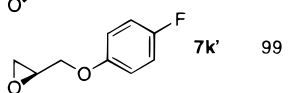
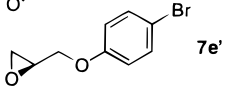
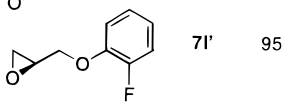


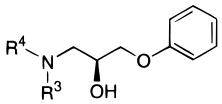
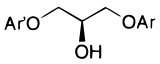
[a] (*R*,*R*)-**1b**, F_9-^{t}BuOH, (CH_2Cl_2), 4 °C (6 h), 25 °C (2 h). [b]KOH, ether, 3 h. [c]Aliphatic amines: $Yb(OTf)_3$, CH_2Cl_2, (polystyrene methyl isocyanate, 2 h), 25 °C. Anilines: $Cu(OTf)_2$, ether, 25 °C. [d](*S*,*S*)-**1b**, F_9-^{t}BuOH, CH_2Cl_2, 4 °C (3 h), 25 °C (3 h).

of catalysis. To effect complete conversion to **7**, the crude reaction mixtures were treated with powdered KOH after catalyst removal by filtration. The aryl glycidyl ether derivatives **7a′**−**e′**,**h′**−**l′** were thus generated in nearly quantitative yield and high ee (Table 2).

The set of ten aryl glycidyl ether derivatives **7** was subjected to ring opening with a set of five different amines to provide a parallel library of 50 different enantioenriched aryloxy propanolamines **9** (Scheme 2). This class of compounds, of which propanolol[8] is an especially significant example, has found widespread application in medicine.[9] Reaction of **7** with aliphatic amines **8a″**−**d″** was effected in the presence of 10 mol % of $Yb(OTf)_3$ at room temperature in dichloromethane.[10] After GC analysis indicated complete consumption of **7**, ytterbium salts were removed by filtration of the solutions through pads of silica gel, and excess amine was removed by evaporation (or, in the case of nonvolatile amines **8b″** and **8d″** by sequestration with resin-bound methyl isocyanate[11]). Aniline **8e″** was added cleanly to glycidyl ethers **7** in the presence of 10 mol % of $Cu(OTf)_2$ with complete regioselectivity for terminal attack.[12] Determination of the enantiomeric excess of three library members

Table 2. Aryl Glycidyl Ether Intermediates **7** and Selected Members of Libraries **9** and **10**

Aryl glycidyl ether	ee (%)[a]	Aryl glycidyl ether **7**	ee (%)[a]
 **7a'**	98	 **7h'**	98.5
 **7b'**	98.5	 **7i'**	98
 **7c'**	98	 **7j'**	85
 **7d'**	98.5	 **7k'**	99
 **7e'**	97	 **7l'**	95

Members of library **9** and **10**		yield (%)[b]	purity (%)[c]	ee
	**9a'c"**	81	96	98
	9a'd"	85	94	97.5
	9a'e"	87	95	98
	**10a'o'**	96	98	>99
	10b'p'	94	98	>99
	10d'f'	83	95	>99
	10h'e'	96	91	>99
	10i'n'	92	97	>99

[a] ee's were determined by HPLC analysis on Chiralcel AD, OB, OJ, and OD columns. [b] Yields were determined gravimetrically. [c] Purity was assayed by HPLC analysis.

(Table 2, compounds **9a′c″**, **9a′d″**, and **9a′e″**) confirmed that ring opening occurred without compromising the enantiopurity of the starting epoxides. Experiments with primary amines and anilines under similar conditions led to isolation of ring-opened products of lower purity (<90%) as a result of competing double alkylation pathways.

The preparation of 1,3-diaryloxy-2-propanol library **10** (Scheme 2) was explored by treating five of the aryl glycidyl ether derivatives (**7a′**,**b′**,**d′**,**h′**,**i′**) with a set of ten phenols in the presence of the resin-bound Co(salen) catalyst (*S*,*S*)-**1b**. As anticipated, the use of the *S*,*S* enantiomer of the catalyst—the antipode to the one used to generate the starting aryl glycidyl ether derivatives from epibromohydrin—led to a further refinement of the optical purity of the bisphenol adducts **10**. Upon completion of the reaction, the catalyst was removed by filtration and excess phenol separated by solid-supported liquid extraction[13] to provide products in chemical purities exceeding 90%. As with libraries **4** and **9**, the identity of all compounds was verified by mass spectrometric analysis. Five representatives of the 50-member library **10** were assayed for enantiopurity, and in all cases

(8) Crowther, A. F.; Smith, L. H. *J. Med. Chem.* **1968**, *11*, 1009.
(9) (a) Wright, J. L.; Gregory, T. J.; Heffner, T. G.; MacKenzie, R. G.; Pugsley, T. A.; Meulen, S. V.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1377. (b) Walsh, D. A. Chen, Y.-H.; Green, J. B.; Nolan, J. C.; Yanni, J. M. *J. Med. Chem.* **1990**, *33*, 1823. (c) Baker, N. R.; Byrne, N. G.; Economides, A. P.; Javed, T. *Chem. Pharm. Bull.* **1995**, *43*, 1045.
(10) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433.
(11) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882.
(12) Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287.
(13) Johnson, C. R.; Zhang, P.; Fantauzi, M.; Hecker, M.; Yagar K. M. *Tetrahedron* **1998**, *54*, 4097.

only a single enantiomer could be detected by HPLC analysis (Table 2). To our knowledge, these are the first examples of syntheses of 1,3-diaryloxy-2-propanol derivatives in enantiopure form.

In conclusion, we have identified a synthetically useful enantioselective catalytic process that is suitable for automated parallel synthesis. In addition, the phenolic kinetic resolution reaction provides highly efficient access to important classes of pharmacologically active compounds. Although the present method was applied only to the synthesis of relatively small libraries of 50 members each, the chiral Co(salen) catalysts have displayed remarkable generality both with respect to terminal epoxide and nucleophile, and we anticipate that a wide variety of analogous structures will be accessible by this method.

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Supporting Information Available: Experimental procedures for the preparation of solid-supported catalysts **1b**, and compound libraries **4**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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