

A Practical Method for the Synthesis of Highly Enantioenriched *trans*-1,2-Amino Alcohols

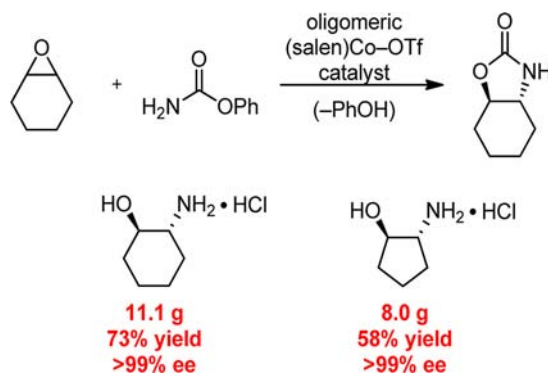
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ABSTRACT



A highly enantioselective addition of phenyl carbamate to *meso*-epoxides has been developed to efficiently generate protected *trans*-1,2-amino alcohols. This transformation is promoted by an oligomeric $(\text{salen})\text{Co}-\text{OTf}$ catalyst and has been used to prepare two useful 2-aminocycloalkanol hydrochlorides in enantiopure form on a multigram scale from commercially available starting materials.

Enantioenriched *trans*-1,2-amino alcohols are useful building blocks for the preparation of complex molecules and chiral catalysts, as well as ligands and auxiliaries for asymmetric synthesis.¹ Catalytic asymmetric approaches to synthesize this class of compounds have been developed, but their application on a preparative scale has been limited.² A chief concern in known methods is the use of hydrazoic acid as an ammonia equivalent,^{2a,b} since this reagent is potentially dangerous and requires special safety measures. Bartoli has demonstrated that carbamates can be employed successfully in $(\text{salen})\text{Co}(\text{III})$ -catalyzed kinetic resolutions of terminal epoxides.³ However, there

are no known examples of enantioselective carbamate additions to *meso* epoxides, which are intrinsically much less reactive than terminal epoxides in $(\text{salen})\text{Co}(\text{III})$ -catalyzed reactions.

Bimetallic mechanisms have been established for $(\text{salen})\text{metal}$ -catalyzed nucleophilic ring opening of both terminal and *meso*-epoxides,⁴ and polymer-supported, dendrimeric, and oligomeric $(\text{salen})\text{Co}(\text{III})$ complexes have been developed to facilitate cooperativity between metal centers.⁵ These multimetallic complexes have been shown to

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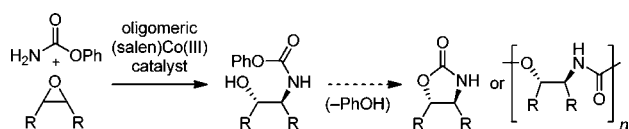
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display striking improvements in both rate and selectivity in relation to their monomeric analogs.⁶ Herein we report the use of an oligomeric (salen)Co–OTf complex^{5c,f,7} to catalyze the highly enantioselective addition of phenyl carbamate to *meso*-epoxides (Scheme 1). This reaction enables an efficient, operationally simple, and scaleable approach to protected *trans*-1,2-amino alcohols in high enantiomeric excess from commercially available starting materials.

In preliminary studies, we found that oligomeric (salen)Co–OTf complexes provide marked improvements in reactivity in the kinetic resolution of 1,2-epoxyhexane with *tert*-butyl carbamate.^{5f} For example, only 0.2 mol % of the oligomeric complex **3** was needed to effectively catalyze this reaction, whereas under similar conditions 4.4 mol % of a related monomeric (salen)Co(III) was required.^{3a}

Scheme 1. Oligomeric (salen)Co(III)-Catalyzed Carbamate Addition to *meso*-Epoxides



The addition of carbamates to cyclohexene oxide was selected as a model reaction, and it was found that phenyl carbamate was particularly effective as a nucleophilic reacting partner.^{8,9} Clean addition to cyclohexene oxide with subsequent intramolecular cyclization was observed to afford *trans*-4,5-disubstituted oxazolidinone product **1** (Table 1).¹⁰ The cyclization appears to be relatively rapid, as the initial addition intermediate is not detectable. While both monomeric and oligomeric (salen)Co–OTf complexes were found to catalyze this transformation, both the rate and enantioselectivity were far superior with the oligomeric catalyst **3** (entry 3). The best balance of rate and enantioselectivity was achieved in reactions carried out at 50 °C, with oxazolidinone **1** obtained in 91% yield and 95% ee after 24 h (entry 4).

(6) For an example in the context of enantioselective intramolecular openings of oxetanes, see: Loy, R. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 2786–2787.

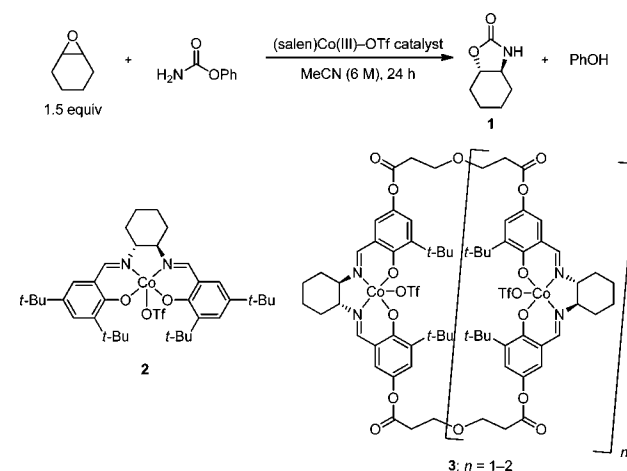
(7) For applications of this catalyst in total synthesis, see: (a) Chae, J.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 3336–3339. (b) Snider, B. B.; Zhou, J. *Org. Lett.* **2006**, *8*, 1283–1286. (c) Adachi, M.; Zhang, Y.; Leimkuhler, C.; Sun, B.; LaTour, J. V.; Kahne, D. E. *J. Am. Chem. Soc.* **2006**, *128*, 14012–14013. (d) McGowan, M. A.; Stevenson, C. P.; Schiffler, M. A.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6147–6150. (e) Rajapaksa, N. S.; McGowan, M. A.; Rienzo, M.; Jacobsen, E. N. *Org. Lett.* **2013**, *15*, 706–709.

(8) Aryl carbamates are uniquely effective nucleophiles in this transformation; *tert*-butyl carbamate, methyl carbamate, benzyl carbamate, *S*-phenyl thiocarbamate, acetamide, trifluoroacetamide, or trichloroacetamide all proved unreactive.

(9) A correlation between reaction rate and the electronics of a series of substituted aryl carbamates was observed, with electron-deficient carbamates proceeding most rapidly. For a comparison of the reaction rates of electronically substituted carbamates, see the Supporting Information.

(10) For a (salen)Al-catalyzed method for the synthesis of *cis*-4,5-disubstituted oxazolidinones from epoxides and isocyanates, see: Baronsky, T.; Beattie, C.; Harrington, R. W.; Irfan, R.; North, M.; Osende, J. G.; Young, C. *ACS Catal.* **2013**, *3*, 790–797.

Table 1. Catalyst and Reaction Optimization



entry ^a	catalyst (mol %)	temp (°C)	yield ^b (%)	ee ^c (%)
1	2 (5)	23	3	n.d.
2	2 (5)	50	33	21
3	3 (1)	23	21	97
4	3 (1)	50	91	95

^a Reactions run on a 0.5 mmol scale. ^b Yield determined by ¹H NMR analysis relative to *p*-xylene as an internal standard. ^c Enantiomeric excess determined by GC analysis using commercial chiral columns.

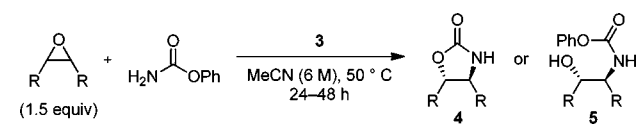
The addition of phenyl carbamate to a variety of *meso*-epoxides was evaluated under the optimized reaction conditions (Table 2). Epoxides with unsaturation in the ring were viable substrates, but underwent reaction with slower rates than cyclohexene oxide (entries 2–3). Carbamate addition to five-membered ring epoxide derivatives proceeded with very high enantioselectivity (entries 4–5). The products from these reactions did not undergo intramolecular cyclization, presumably due to the unfavorable strain in *trans*-fused 5–5 ring systems.¹¹ Instead, the monomeric addition product was generated together with carbamate-bridged oligomers (Scheme 2). However, this mixture could be subjected to hydrolysis by treatment with base to liberate the *trans*-1,2-amino alcohol in high overall yield (see below).

The practical applicability of the carbamate addition protocol is illustrated in the preparation of *trans*-2-amino-cyclohexanol hydrochloride (**6**) and *trans*-2-aminocyclopentanol hydrochloride (**7**) on a multigram scale using 0.5 and 1 mol % of catalyst, respectively (Scheme 3).^{12,13}

(11) (a) Chang, S.; McNally, D.; Shary-Tehrany, S.; Hickey, M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109–3118. (b) Allinger, N. L.; Tribble, M. T.; Miller, M. A.; Wertz, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 1637–1648.

(12) Compounds **6** and **7** were also prepared on a 10 mmol scale without a recrystallization step, providing the following results: **6** (1.4 g, 91% yield, 94% ee); **7** (1.2 g, 86% yield, 98% ee). The difference in yields between the 10 and 100 mmol-scale reactions is a result of the recrystallization procedure.

(13) For classical resolution approaches to these compounds, see: (a) Schifflers, I.; Rantanen, T.; Schmidt, F.; Bergmans, W.; Zani, L.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2320–2331. (b) Schifflers, I.; Bolm, C. *Org. Synth.* **2008**, *85*, 106–117. For an alternative method, see: (c) Overman, L. E.; Sugai, S. *J. Org. Chem.* **1985**, *50*, 4154–4155.

Table 2. Substrate Scope


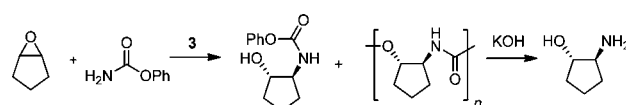
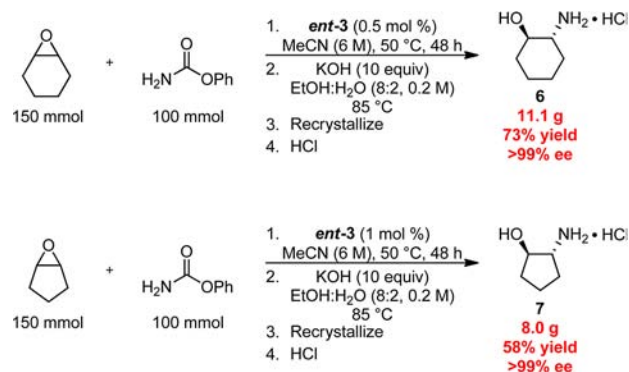
entry ^a	substrate	product	catalyst loading (mol %)	time (h)	yield ^b (%)	ee ^c (%)
1			1	24	94	96
2			2	48	84	96
3			2	48	63	95
4			1	24	66	>99
5			1	24	49	>99

^a Reactions run on a 1.0 mmol scale. ^b Isolated yield of purified product. ^c Enantiomeric excess determined by GC or HPLC analysis on commercial chiral columns.

Following the catalytic reaction, the reaction mixture was subjected to basic deprotection conditions and the products were recrystallized as the hydrochloride salts in > 99% ee. These amino alcohols are versatile building blocks for organic synthesis and can readily be transformed into a variety of valuable chiral products.^{13a,14}

In summary, we have developed an efficient protocol for the catalytic enantioselective synthesis of protected *trans*-1,2-amino alcohols in high yield and enantiomeric excess.

(14) Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197–4199.

Scheme 2. (salen)Co(III)-Catalyzed Carbamate Addition to Cyclopentene Oxide**Scheme 3.** Preparative-Scale Reactions

Crucial to this development was the use of an oligomeric (salen)Co–OTf complex as the catalyst and aryl carbamate nucleophiles. This method is amenable to large-scale synthesis due to the low catalyst loadings and high concentration used, its operational simplicity, and the use of inexpensive, commercially available starting materials.

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Supporting Information Available. Complete experimental procedures and characterization data, ¹H and ¹³C NMR spectra, GC and HPLC traces of racemic and enantioenriched protected *trans*-1,2-amino alcohol and 2-aminocycloalkanol hydrochloride products, and data comparing the reaction rates of electronically substituted carbamates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.