Published in final edited form as:

Org Lett. 2013 June 21; 15(12): 2895–2897. doi:10.1021/ol401013s.

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

James A. Birrell and Eric N. Jacobsen

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

Eric N. Jacobsen: jacobsen@chemistry.harvard.edu

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

Correspondence to: Eric N. Jacobsen, jacobsen@chemistry.harvard.edu.

Supporting Information Available Complete experimental procedures and characterization data, ^1H and ^{13}C NMR spectra, GC and HPLC traces of racemic and enantioenriched protected *trans*-1,2-amino alcohol and 2-aminocycloalkanol hydrochloride products, data comparing the reaction rates of electronically substituted carbamates.

metal centers.⁵ These multimeric complexes have been shown to display striking improvements in both rate and selectivity in relation to their monomeric equivalents.⁶ Herein we report the use of an oligomeric (salen)Co–OTf complex^{5e–f,7} to catalyze the highly enantioselective addition of phenyl carbamate to *meso*-epoxides (Scheme 1). This reaction enables an efficient, operationally-simple, and scalable 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}

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).

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 additon 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-aminocyclohexanol 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} Following the catalytic reaction, the reaction mixture was subjected to basic deprotection conditions and the products 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. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the NIH (GM-43214).

References

1. (a) Ager DJ, Prakash I, Schaad DR. *Chem Rev.* 1996; 96:835–876. [PubMed: 11848773] (b) Fache F, Schulz E, Tommasino ML, Lemaire M. *Chem Rev.* 2000; 100:2159–2231. [PubMed: 11749286] (c) Bergmeier SC. *Tetrahedron.* 2000; 56:2561–2576. (d) Anaya de Parrodi C, Juaristi E. *Synlett.* 2006:2699–2715.
2. (a) Nugent WA. *J Am Chem Soc.* 1992; 114:2768–2769. (b) Martínez LE, Leighton JL, Carsten DH, Jacobsen EN. *J Am Chem Soc.* 1995; 117:5897–5898. (c) Schneider C, Sreekanth AR, Mai E. *Angew Chem, Int Ed.* 2004; 43:5691–5694. (d) Carrée F, Gil R, Collin J. *Org Lett.* 2005; 7:1023–1026. [PubMed: 15760129] (e) Arai K, Salter MM, Yamashita Y, Kobayashi S. *Angew Chem, Int Ed.* 2007; 46:955–957.
3. (a) Bartoli G, Bosco M, Carlone A, Locatelli M, Melchiorre P, Sambri L. *Org Lett.* 2004; 6:3973–3975. [PubMed: 15496077] (b) Bartoli G, Bosco M, Carlone A, Locatelli M, Melchiorre P, Sambri L. *Org Lett.* 2005; 7:1983–1985. [PubMed: 15876035]
4. (a) Hansen KB, Leighton JL, Jacobsen EN. *J Am Chem Soc.* 1996; 118:10924–10925. (b) Nielsen LPC, Stevenson CP, Blackmond DG, Jacobsen EN. *J Am Chem Soc.* 2004; 126:1360–1362. [PubMed: 14759192]
5. (a) Annis DA, Jacobsen EN. *J Am Chem Soc.* 1999; 121:4147–4154. (b) Breinbauer R, Jacobsen EN. *Angew Chem, Int Ed.* 2000; 39:3604–3607. (c) Ready JM, Jacobsen EN. *J Am Chem Soc.* 2001; 123:2687–2688. [PubMed: 11456948] (d) Ready JM, Jacobsen EN. *Angew Chem, Int Ed.* 2002; 41:1374–1377. (e) White DE, Jacobsen EN. *Tetrahedron: Asymmetry.* 2003; 14:3633–3638. (f) White, DE. PhD Thesis. Harvard University; Cambridge, Massachusetts: 2005. (g) Zheng X, Jones CW, Weck M. *J Am Chem Soc.* 2007; 129:1105–1112. [PubMed: 17263391] (h) Madhavan N, Jones CW, Weck M. *Acc Chem Res.* 2008; 41:1153–1165. [PubMed: 18793027] (i) Thomas RM, Widger PCB, Ahmed SM, Jeske RC, Hirahata W, Lobkovsky EB, Coates GW. *J Am Chem Soc.* 2010; 132:16520–16525. [PubMed: 21043488] (j) Haak RM, Wezenberg SJ, Kleij AW. *Chem Commun.* 2010; 46:2713–2723.
6. For an example in the context of enantioselective intramolecular openings of oxetanes, see: Loy RN, Jacobsen EN. *J Am Chem Soc.* 2009; 131:2786–2787. [PubMed: 19199427]
7. For applications of this catalyst in total synthesis, see: Chae J, Buchwald SL. *J Org Chem.* 2004; 69:3336–3339. [PubMed: 15132539] Snider BB, Zhou J. *Org Lett.* 2006; 8:1283–1286. [PubMed: 16562872] Adachi M, Zhang Y, Leimkuhler C, Sun B, LaTour JV, Kahne DE. *J Am Chem Soc.* 2006; 128:14012–14013. [PubMed: 17061868] McGowan MA, Stevenson CP, Schiffler MA, Jacobsen EN. *Angew Chem, Int Ed.* 2010; 49:6147–6150. Rajapaksa NS, McGowan MA, Rienzo M, Jacobsen EN. *Org Lett.* 2013; 15:706–709. [PubMed: 23331099]
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 RW, Irfan R, North M, Osende JG, Young C. *ACS Catal.* 2013; 3:790–797.
11. (a) Chang S, McNally D, Shary-Tehrany S, Hickey MJ, Boyd RH. *J Am Chem Soc.* 1970; 92:3109–3118. (b) Allinger NL, Tribble MT, Miller MA, Wertz DH. *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: Schiffers I, Rantanen T, Schmidt F, Bergmans W, Zani L, Bolm C. *J Org Chem.* 2006; 71:2320–2331. [PubMed: 16526780] Schiffers I, Bolm C. *Org Synth.* 2008; 85:106–117. For an alternative method, see: Overman LE, Sugai S. *J Org Chem.* 1985; 50:4154–4155.
14. Schaus SE, Larrow JF, Jacobsen EN. *J Org Chem.* 1997; 62:4197–4199.

Scheme 1. Oligomeric $(\text{salen})\text{Co}(\text{III})$ -Catalyzed Carbamate Addition to *meso*-Epoxides

Scheme 2.
(salen)Co(III)-Catalyzed Carbamate Addition to Cyclopentene Oxide

Scheme 3.
Preparative-Scale Reactions

Table 1**Catalyst and Reaction Optimization**

entry ^a	catalyst (mol %)	temperature (°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

^aReactions run on a 0.5 mmol scale.

^bYield determined by ^1H NMR analysis relative to *p*-xylene as internal standard.

^cEnantiomeric excess determined by GC analysis using commercial chiral columns.

Table 2

Substrate Scope

<div><div><div><div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div><div></div><div></div><div></div></div><div><div><div><div><div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div></div>						
--	--	--	--	--	--	--

entry ^a	substrate	product	catalyst loading (mol %)	time (h)	yield ^b (%)	ee ^c (%)
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.