Kinetic Resolution of Terminal Epoxides via Highly Regioselective and Enantioselective Ring Opening with $TMSN_3$. An Efficient, Catalytic Route to 1,2-Amino Alcohols

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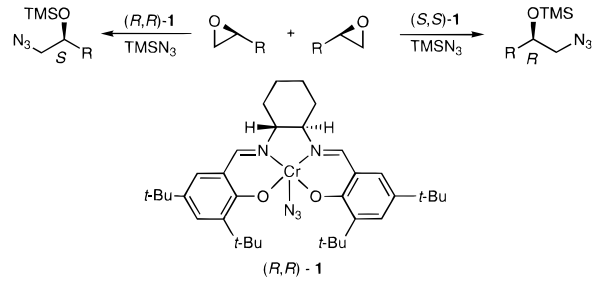
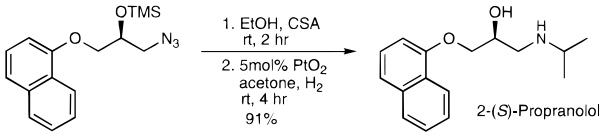
The value of enantiopure 1,2-amino alcohols lies in their utility both as intermediates for the synthesis of a wide range of biologically important compounds[1] and as precursors to effective and versatile ligands for asymmetric catalysis.[2] Existing synthetic routes to amino alcohols rely heavily on the chiral pool,[2b] and particularly on the reduction of α-amino acids. While this approach provides ready access to many 2-amino-1-ols, the regioisomerically transposed 1-amino-2-ols cannot be prepared by this method. Asymmetric routes to the latter, synthetically-valuable compounds include the nitroaldol reaction,[3] hydrocyanation of aldehydes,[4] asymmetric dihydroxylation,[5] and the ring opening of enantiopure epoxides by amines or amine equivalents.[6] The latter approach is direct and particularly appealing, especially in light of the advances in the development of enantioselective catalytic methods for the synthesis of epoxides.[7] Still, there are several classes of epoxides that are not easily accessed by asymmetric catalysis, with terminal alkyl-substituted epoxides certainly heading the list in terms of importance.

Given the accessibility of a wide range of racemic terminal epoxides at low cost, a kinetic resolution strategy for the synthesis of optically pure 1-amino-2-alkanols becomes viable. In this communication, we report the application of the recently developed (salen)Cr-catalyzed epoxide ring-opening reaction[8] to the efficient synthesis of 1-azido-2-trimethylsiloxyalkanes from racemic epoxides (Scheme 1). The viability of this strategy is illustrated in practical syntheses of (*S*)-propranolol, a widely-used anti-hypertensive agent,[9] and (*R*)-9-[2-(phosphonomethoxy)propyl]adenine (PMPA), a compound recently demonstrated to display prophylactic activity against SIV infection.[10]

Scheme 1



Scheme 2



The reaction of neat (±)-propylene oxide with 0.5 equiv of $TMSN_3$ in the presence of (salen)CrN_3 complex (*R*,*R*)-**1** (1 mol %) resulted in clean conversion to a mixture of epoxide and ring-opened product after 18 h at 0 °C. Removal of the highly volatile unreacted epoxide by rotary evaporation, followed by distillation of the residue at 24 °C/<1 mm Hg, afforded 1-azido-2-trimethylsiloxypropane in essentially quantitative yield based on theory and in 97% ee (Table 1, entry 1).[11] Careful analysis of the product by GC revealed that the regioisomeric product was formed to an almost negligible extent (<1%).

This method was found to be applicable to a series of other terminal epoxides (Table 1). Unbranched alkyl-substituted epoxides proved to be the best substrates with regard to enantioselectivity, with k_{rel} values exceeding 100 (entries 2, 3).[12] The kinetic resolution of epichlorohydrin led to highly enriched 1-azido-3-chloro-2-trimethylsiloxypropane (entry 4), a reaction that is particularly noteworthy given the availability of the racemic substrate and the functional versatility of the optically active product. Epoxides bearing branched alkyl substituents displayed reduced reactivity but no loss of enantioselectivity in the ring opening (entry 8). As has been demonstrated previously in the context of meso epoxides,[8] excellent functional group tolerance was exhibited in these (salen)Cr-catalyzed reactions (entries 9−11). The kinetic resolution of 3,3-diethoxypropene oxide (entry 10) provided the ring-opened product in 96% isolated yield and 89% ee, despite the presence of a potentially epimerizable stereogenic center in the product.

(1) (a) Shioiri, Y.; Hamada, Y. *Heterocycles* **1988**, *27*, 1035. (b) Barlow, C. B.; Bukhari, S. T.; Guthrie, R. D.; Prior, A. M. *Asymmetry in Carbohydrates*; Dekker: New York, 1979; pp 81−99.

(2) (a) Pfaltz, A. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, CT, 1995; pp 61−94. (b) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935. (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (d) Denmark, S. E.; Nakijima, N.; Nicaise, O. J.-C.; Faucher, A.-M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884.

(3) (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (b) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851. (c) Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 855. (d) Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 2657. (e) Shibasaki, M.; Sasai, H. *J. Synth. Org. Chem., Jpn.* **1993**, *51*, 972. (f) Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372.

(4) See (a) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555. (b) Nitta, H.; Yu, D.; Kudo, M.; Mori, A.; Inoue, S. *J. Am. Chem. Soc.* **1992**, *114*, 7969, and references therein.

(5) Chang, H.-T.; Sharpless, K. B. *Tetrahedron Lett.* **1996**, *37*, 3219. A breakthrough in the direct, asymmetric catalytic synthesis of amino alcohols from alkenes was also reported recently by the Sharpless group: Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451.

(6) (a) Askin, D.; Eng, K. K.; Rossen, K.; Purick, R. M.; Wells, K. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 673. (b) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437. (c) Klunder, J. M.; Ko, S. Y., Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 3710.

(7) (a) Jacobsen, E. N. In *Comprehensive Organometallic Chemistry II*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Hegedus, L. S., Eds.; Pergamon: New York, 1995; Vol. 12, Chapter 11.1. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.1. (c) Jacobsen, E. N. *Ibid.* Chapter 4.2. (d) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189.

(8) (a) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (b) Leighton, J. L.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 389.

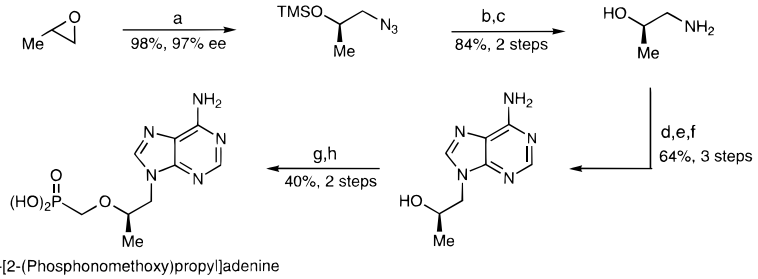
(9) (a) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2267. (b) Also see refs 6c and 3c.

(10) (a) Tsai, C.-C.; Follis, K. E.; Sabo, A.; Beck, T. W.; Grant, R. F.; Bischofberger, N.; Benveniste, R. E.; Black, R. *Science* **1995**, *270*, 1197.

(11) An oven dried 10 mL flask equipped with a stir bar was charged with 32 mg (0.05 mmol) of (*R*,*R*) -**1**. The flask was sealed, purged with N_2, and cooled to 0 °C in an ice bath, followed by the sequential addition of (±)-propylene oxide (350 μL, 5.0 mmol) and $TMSN_3$ (330 μL, 2.5 mmol). The reaction was allowed to stir at 0−2 °C for 18 h, upon which time the remaining epoxide was removed by rotary evaporation, and the desired product was vacuum distilled (24 °C/<1 mm Hg) into a cooled collection flask to yield 0.425 g (2.45 mmol, 98%) of a colorless oil. Chiral GC analysis (Cyclodex-B) indicated that the 1-azido-2-trimethylsiloxypropane was obtained in 97% ee.

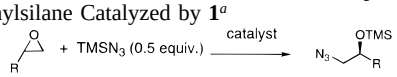
(12) The values for k_{rel} were calculated using the equation $k_{rel} = \ln[1 - c(1 + ee)]/\ln[1 - c(1 - ee)]$, where ee is the enantiomeric excess of the product and c is the conversion. The conversion was set to equal the isolated yield of the ring-opened product, so calculated values for k_{rel} actually represent lower limits. For leading references on kinetic resolution, see: (a) Eliel, E. L.; Wilen, S. H.; Mander, L. M. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; pp 395−415. (b) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Interscience: New York, 1987; Vol. 14, p 249.

Scheme 3[a]



[a]Reagents: (a) 0.5 equiv $TMSN_3$, 0.5 mol % (*S*,*S*)-**1**, 0 °C → rt; 98%, 97% ee; (b) CSA (cat.), MeOH, 92%; (c) 10% Pd/C, MeOH, H_2, 91%; (d) 5-amino-4,6-dichloropyrimidine, TEA, *n*-BuOH, Δ, 82%; (e) $HC(OEt)_3$, conc. HCl, rt, 86%; (f) NH_3, 65 °C, 91%; (g) NaH, DMF, diethylphosphonomethoxytosylate, 0 °C → rt, 44%; (h) i. TMSBr, CH_3CN, rt; ii. H_2O, acetone, 4 °C, 92%.

Table 1. Kinetic Resolution of Monosubstituted Epoxides with Azidotrimethylsilane Catalyzed by **1**[a]



entry	R	cat. mol %	yield (%)[b]	ee (%)	k_{rel}[c]
1	CH_3	1.0	98	97[d]	230
2	CH_2CH_3	2.0	83	97[f]	140
3	$(CH_2)_3CH_3$	2.0	89	97[d]	160
4	CH_2Cl	2.0	94	95[e]	100
5	$CH_2OTBDMS$	3.0	96	96[e]	150
6	CH_2O(1-naphthyl)	5.0	74	93[g]	48
7	$CH_2C_6H_5$	2.0	94	93[f]	71
8	*c*-C_6H_{11}	2.0	84[h]	97[f]	140
9	$(CH_2)_2CH{=}CH_2$	2.0	94	98[d]	280
10	$CH(OEt)_2$	2.0	96	89[e]	44
11	CH_2CN	2.0	80	92[e]	45

[a] Reactions were run without solvent for 18−50 h at 0−2 °C. [b] Isolated yield of the azido silyl ether based on $TMSN_3$. [c] See ref 12. [d] Determined by chiral GC analysis of the azido silyl ether. [e] Determined by chiral GC analysis of the azido alcohol. [f] Determined by chiral GC analysis of the azido *O*-acetate derivative. [g] Determined by chiral HPLC analysis of the azido silyl ether. [h] Isolated yield of the azido alcohol.

Tolerance for Lewis basic functionality such as cyano groups (entry 11) is also noteworthy.

A wide range of synthetic applications of this kinetic resolution procedure are readily envisaged. The synthesis of propranolol outlined in Scheme 2 serves to illustrate the efficient and straightforward elaboration of the azido silyl ether products of the ring-opening reaction to a biologically important amino alcohol derivative. Kinetic resolution of the racemic epoxide derived from epichlorohydrin and 1-naphthol afforded the corresponding azido silyl ether in 74% isolated yield and in 93% ee (entry 6). In a one-pot, two-step procedure, transformation to (*S*)-propranolol was accomplished by desilylation followed by azide reduction and *in situ* reductive alkylation in the presence of acetone.[3c]

The synthesis of (*R*)-PMPA[13] was effected similarly in a highly efficient manner via kinetic resolution of propylene oxide (Scheme 3). A desilylation/reduction sequence yielded the synthetically important amino alcohol (*R*)-1-amino-2-propanol in excellent yield. Further transformation of this compound to (*R*)-PMPA was accomplished using known methods by conversion of the amine to an adenine base,[14] followed by alkylation of the alcohol and standard deprotection of the phosphonate.[15]

In conclusion, the application of (salen)CrN_3-catalyzed epoxide ring-opening reaction to the kinetic resolution of racemic terminal epoxides allows not only the recovery of epoxides with high enantiomeric excess,[8a] but also the clean production of 1-azido-2-trimethylsiloxyalkanes in good yield and very high enantiopurity. The synthetic utility of these amino alcohol precursors, combined with the ready accessibility of the racemic epoxides and of the catalyst,[16] renders this an immediately useful alternative to existing methods. In addition, the extremely high enantioselectivity on such simple substrates as propylene oxide with attendant broad substrate generality suggest very intriguing mechanisms for chiral recognition by this catalyst system. This, along with the expansion of this methodology to other classes of nucleophiles and electrophiles, constitutes the subject of our sustained efforts.

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Supporting Information Available: Chromatographic analyses of all racemic and enantiomerically enriched azido silyl ethers or derivatives, full characterization of all isolated products, and complete experimental procedures for the syntheses of (*R*)-PMPA and (*S*)-propranolol (18 pages). See any current masthead page for ordering and Internet access instructions.

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(13) (*R*)-PMPA has recently been synthesized from the chiral pool utilizing D-(−)-lactic acid as the enantiopure starting material: Holy, A.; Masojídková, M. *Collect. Czech. Chem. Commun.* **1995**, *60*, 1196.

(14) For preparation of 9-[2-(hydroxypropyl)]adenine see: Schaeffer, H. J.; Vince, R. *J. Med. Chem.* **1967**, *10*, 689.

(15) For similar phosphonomethoxytosylate alkylation reactions, see: Yu, K-L; Bronson, J. J.; Yang, H.; Patick, A.; Alam, M.; Brankovan, V.; Datema, R.; Hitchcock, M. J. M.; Martin, J. C. *J. Med. Chem.* **1992**, *35*, 2958.

(16) For catalyst preparation, see ref 8b. The catalysts used in this study were prepared using $AgBF_4$ instead of $AgClO_4$ but were identical to previous catalyst batches in all other respects. For ligand preparation, see: Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939. Both enantiomers of the ligand are also commercially available (Aldrich).