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Highly Diastereoselective *anti*-Dihydroxylation of 3-*N*,*N*-Dibenzylaminocyclohex-1-ene *N*-Oxide

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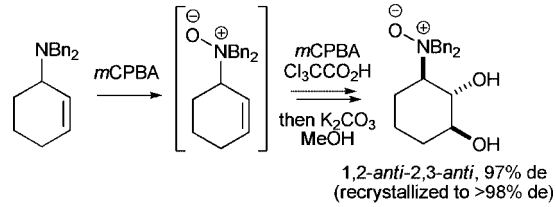
ABSTRACT



Oxidation of 3-*N*,*N*-dibenzylaminocyclohex-1-ene *N*-oxide in the presence of Cl_3CCO_2H proceeds with high levels of *anti*-diastereoselectivity (97% de), with no competing side reactions, allowing access to 1,2-*anti*-2,3-*anti*-3-aminocyclohexane-1,2-diol after deprotection.

Tertiary amine *N*-oxides have long been known within organic chemistry.[1] They have found use as intermediates in, for example, [1,2]- and [2,3]-Meisenheimer rearrangements,[2] Cope eliminations,[3] and Polonovski reactions[4] and are well-known in alkaloid chemistry (e.g., within the strychnos, ergoline, and opium families), often facilitating structure elucidation or promoting interesting skeletal rearrangements.[5] Nonetheless, their utility in synthesis remains underdeveloped.[1,6] As part of our ongoing research program directed toward the synthesis of the amino diol motif,[7−9] and recognizing that *N*-oxidation of allylic amines competes with oxidative functionalization of the olefin, we recently achieved the highly chemo- and diastereoselective, ammonium-directed epoxidation of 3-*N*,*N*-dibenzylaminocy-

(1) For a review of the synthetic utility of tertiary amine *N*-oxides, see: Albini, A. *Synthesis* **1992**, 263.

(2) Meisenheimer, J. *Chem. Ber.* **1919**, *52*, 1667. For selected synthetic applications, see: Davies, S. G.; Smyth, G. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2467. Majumdar, K. C.; Jana, G. H. *J. Org. Chem.* **1997**, *62*, 1506. Arnone, A.; Metrangolo, P.; Novo, B.; Resnati, G. *Tetrahedron* **1998**, *54*, 7831. Buston, J. E. H.; Coldham, I.; Mulholland, K. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2327.

(3) Cope, A. C.; LeBel, N. A. *J. Am. Chem. Soc.* **1960**, *82*, 4656. For a review, see: Gallagher, B. M.; Pearson, W. H. *Chemtracts: Org. Chem.* **1996**, *9*, 126. For selected synthetic applications, see: O'Neil, I. A.; Ramos, V. E.; Ellis, G. L.; Cleator, E.; Chorlton, A. P.; Tapolczay, D. J.; Kalindjan, S. B. *Tetrahedron Lett.* **2004**, *45*, 3659. Henry, N.; O'Neil, I. A. *Tetrahedron Lett.* **2007**, *48*, 1691.

(4) Polonovski, M.; Polonovski, M. *Bull. Soc. Chim. Fr.* **1927**, *41*, 1190. For a review, see: Grierson, D. *Org. React.* **1990**, *39*, 85.

(5) Bentley, K. W. *The Chemistry of the Morphine Alkaloids*; Oxford University Press: Oxford, 1954; Albini, A. *Heterocycles* **1992**, *34*, 1973.

(6) For selected examples of the use of *N*-oxides in synthesis, see: Tokitoh, N.; Okazaki, R. *Chem. Lett.* **1985**, 241. O'Neil, I. A.; Turner, C. D.; Kalindjian, S. B. *Synlett* **1997**, 777. O'Neil, I. A.; Bhamra, I.; Gibbons, P. D. *Chem. Commun.* **2006**, 4545. Oh, K.; Ryu, J. *Tetrahedron Lett.* **2008**, *49*, 1935.

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(8) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3762.

(9) For selected recent examples, see: Cailleau, T.; Cooke, J. W. B.; Davies, S. G.; Ling, K. B.; Naylor, A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 3922. Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655. Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665. Davies, S. G.; Durbin, M. J.; Goddard, E. C.; Kelly, P. M.; Kurosawa, W.; Lee, J. A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2009**, *7*, 761.

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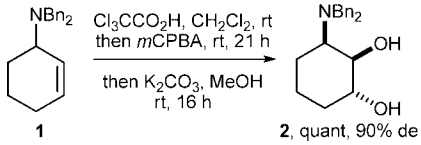
clohex-1-ene **1** with *m*CPBA employing a strategy reliant on in situ *N*-protection against oxidation via protonation with Cl_3CCO_2H. Epoxide ring opening by Cl_3CCO_2H, followed by transesterification, gave 3-*N*,*N*-dibenzylaminocyclohexane-1,2-diol **2** in 90% de (Scheme 1).[7] We hypothesized that

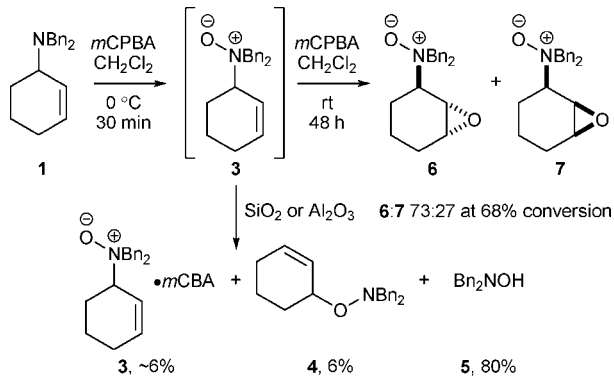
Scheme 1. Ammonium-Directed Dihydroxylation of 3-*N*,*N*-Dibenzylaminocyclohex-1-ene **1**



an alternative diastereoselective olefin functionalization protocol would be available through *N*-oxidation of 3-*N*,*N*-dibenzylaminocyclohex-1-ene **1** to give the corresponding *N*-oxide followed by further oxidation of the olefin. We delineate herein our results within this area.

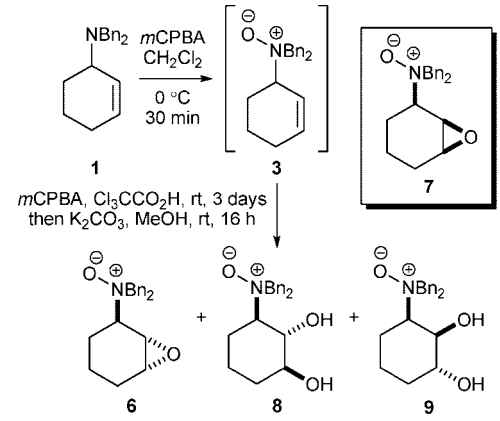
Our initial studies were directed toward preparation of *N*-oxide **3**. Treatment of amine **1** with *m*CPBA (1.5 equiv) at 0 °C in CD_2Cl_2 gave *N*-oxide **3** as a mixture with excess *m*CPBA and *m*-chlorobenzoic acid (*m*CBA). As expected, attempted basic aqueous workup and purification on basic alumina gave an impure sample of *N*-oxide **3** as a mixture with *m*CBA (~6%), and hydroxylamines **4** (6%) and **5** (80%) as the major products. This suggests that a Meisenheimer rearrangement (to give hydroxylamine **4**) or Cope elimination (to give hydroxylamine **5** and cyclohexa-1,3-diene) was occurring, indicating that the presence of acid is necessary to suppress rearrangement or fragmentation of **3**, presumably by protonation on, or by hydrogen bonding to, the oxygen atom.[10,11] With *N*-oxide **3** in hand, olefinic dihydroxylation was investigated. Treatment of **3** with 3 equiv of *m*CPBA gave 68% conversion after 48 h to a 73:27 mixture of the diastereoisomeric epoxides *anti*-**6** and *syn*-**7** (Scheme 2). The relative configurations within **6** and **7** were assigned by comparison to authentic samples (vide infra).

Scheme 2. Epoxidation of 3-*N*,*N*-Dibenzylaminocyclohex-1-ene *N*-Oxide **3**



Olefinic oxidation of *N*-oxide **3** in the presence of Cl_3CCO_2H was next investigated. In situ treatment of a freshly prepared sample of **3** with 1 equiv of Cl_3CCO_2H followed by 3 equiv of *m*CPBA gave a complex mixture of products. Transesterification with K_2CO_3 in MeOH gave a 55:15:30 mixture of epoxide **6** and diols **8** and **9**, respectively, suggesting that the ring opening of epoxide **7** by Cl_3CCO_2H is much faster than that of epoxide **6**. When 5 equiv of Cl_3CCO_2H were employed, 68% de in favor of diol **8** was noted; when 10 equiv of Cl_3CCO_2H were used, **8** was produced in 97% de. No traces of **6** or **7** were noted in either case, consistent with an increased rate of epoxide ring opening with increasing concentration of Cl_3CCO_2H. Recrystallization of the crude reaction mixture gave **8** in >98% de and 63% yield (Scheme 3). The relative configuration

Scheme 3. *anti*-Dihydroxylation of 3-*N*,*N*-Dibenzylaminocyclohex-1-ene *N*-Oxide **3** in the Presence of Trichloroacetic Acid



Cl_3CCO_2H equiv.	conversion %	**6**:**8**:**9** ratio	yield of **8** (de) %
1	100	55:15:30	-
5	100	0:84:16	-
10	100	0:98.5:1.5	63 (>98)

within the major diastereoisomer **8** resulting from this oxidation protocol was unambiguously established by single crystal X-ray analysis (Figure 1). Within the solid-state structure, hydrogen bonding is observed between the C(2)-hydroxyl substituent and the oxygen atom of the *N*-oxide group, which is consistent with the known stabilizing effect of hydrogen bonding on the *N*-oxide moiety.[11,12] Meanwhile, the relative configuration within the minor diastereoisomer **9** was unambiguously established through the synthesis of an authentic sample by *N*-oxidation of the known *N*,*N*-dibenzylamino diol **2**[8] (Scheme 4) and subsequent analysis by X-ray crystallography (Figure 2). *N*-Oxide **9** cocrystallized

(10) Aliphatic amine *N*-oxides have long been known to form stable salts with organic acids; for a recent example of the use of acid to suppress rearrangement of an *N*-oxide, see: Bernier, D.; Blake, A. J.; Woodward, S. *J. Org. Chem.* **2008**, *73*, 4229. Indeed, a sample of *N*-oxide **3** in CD_2Cl_2 (prepared via treatment of amine **1** with *m*CPBA) was found to be largely unchanged after 10 days, although the formation of ~5% of *N*-oxide epoxide **6** was observed.

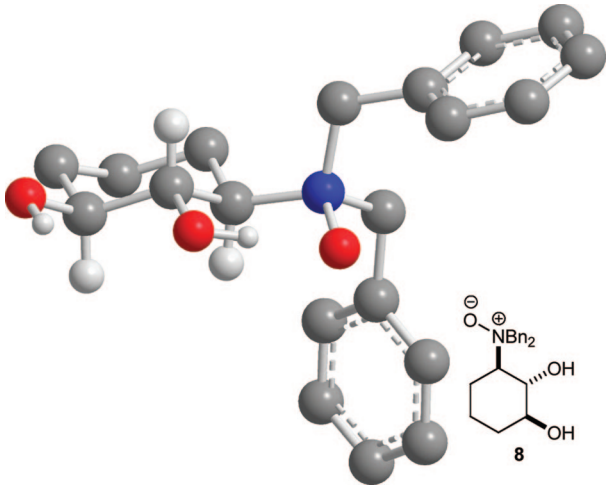
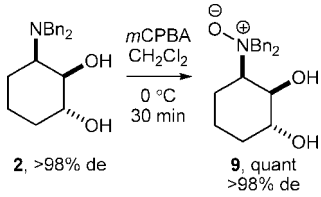


Figure 1. Chem 3D representation of the X-ray crystal structure of **8** (some H atoms omitted for clarity).

Scheme 4. Preparation of an Authentic Sample of 3-*N*,*N*-Dibenzylaminocyclohexane-1,2-diol *N*-Oxide **9**



with two molecules of *m*CBA in the asymmetric unit, and within the crystal lattice hydrogen bonding is observed between the carboxylic acid group of one of the *m*CBA molecules and both the C(2)-hydroxyl group and the oxygen atom of the *N*-oxide.[11,13]

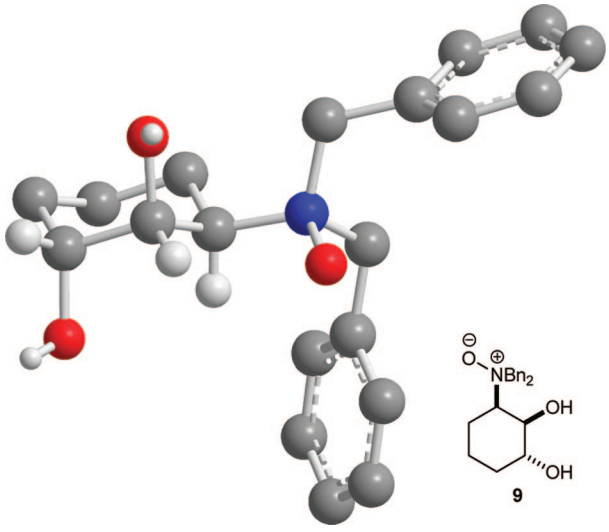
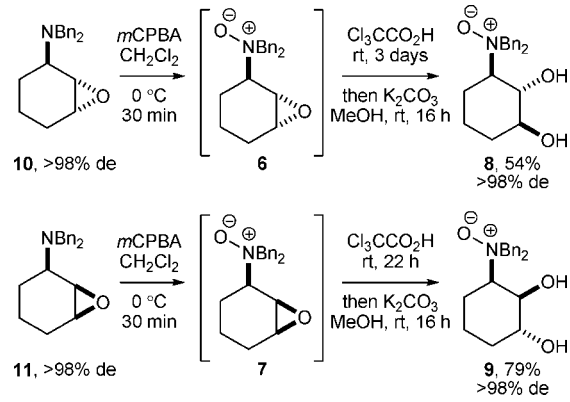


Figure 2. Chem 3D representation of the X-ray crystal structure of **9** (some H atoms and both *m*CBA molecules omitted for clarity).

Treatment of the known epoxides *anti*-**10**[8] and *syn*-**11**[7] with *m*CPBAgave authentic samples of **6** and **7**. Addition of 2 equiv of Cl_3CCO_2H to *syn*-**7** and transesterification after 22 h gave **9** in >98% de. Analogous ring opening of *anti*-**6** was found to occur much more slowly and required treatment with 5 equiv of Cl_3CCO_2H over 3 days to achieve complete conversion. Transesterification with K_2CO_3/MeOH gave **8** in >98% de (Scheme 5). These results demonstrate that the ring openings of both *anti*-**6** and *syn*-**7** by Cl_3CCO_2H are highly regioselective and are consistent with the ring opening of **7** proceeding via a chair-like transition state with the *N*,*N*-dibenzylamino *N*-oxide group in a pseudoequatorial site to give the *trans*-diaxial product,[14] with ring opening of **6** proceeding via a twist-boat-like transition state (vide infra). The production of mixtures of **8** and **9** upon olefinic oxidation of *N*-oxide **3** in the presence of 1 or 5 equiv of Cl_3CCO_2H is therefore consistent with loss of stereoselectivity in the initial epoxidation step rather than erosion of regioselectivity in the epoxide ring opening step.

Scheme 5. Regio- and Stereoselective Ring Opening of *N*-Oxide Epoxides **6** and **7** by Trichloroacetic Acid



Stereoselective *anti*-epoxidation of **3** in the presence of 10 equiv of Cl_3CCO_2H suggests that the protonated *N*,*N*-dibenzylamino *N*-oxide group[15] does not participate in hydrogen-bonded delivery of the oxidant to the *syn*-face of the olefin.[16,17] The stereochemical outcome is consistent with the oxidation proceeding either under steric control or through minimization of the dipoles of the protonated amine *N*-oxide and the peracid[18] to give protonated *anti*-epoxide

(11) The stabilization of *N*-oxides through intramolecular hydrogen-bonding has been documented; for instance, see: O'Neil, I. A.; Potter, A. J. *Chem. Commun.* **1998**, 1487, and references cited therein.

(12) A similar solution phase conformation for *N*-oxide **8** in $CDCl_3$ was inferred from determination of the interproton distances by analysis of the NOE build-up curves; see: Esposito, G.; Pastore, A. *J. Magn. Reson.* **1988**, *76*, 331. Claridge, T. D. W. *High-Resolution NMR Techniques in Organic Chemistry*, 2nd ed.; Elsevier Science Ltd: Oxford, 1999; Chapter 8.

(13) The second molecule of *m*CBA within the asymmetric unit of the crystal structure of *N*-oxide **9** is involved with hydrogen bonding with the C(1)-hydroxyl substituent of **9**.

(14) Fürst, A.; Plattner, P. A. *12th Int. Congr. Pure Appl. Chem. New York* **1951**, 409.

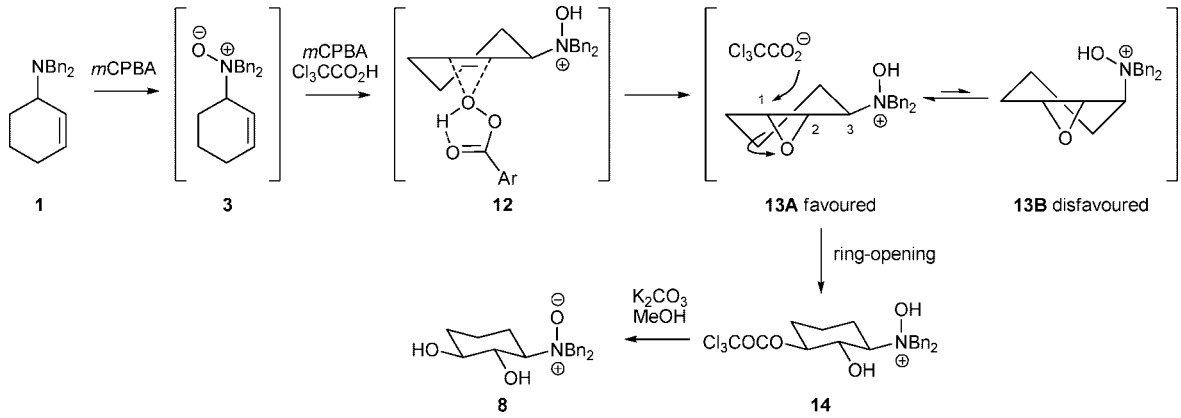


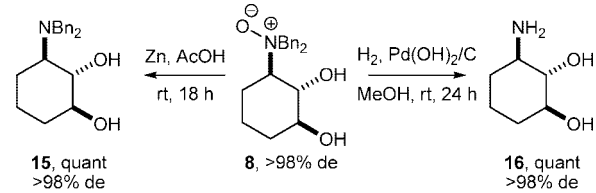
Figure 3. Postulated mechanism for the dihydroxylation of tertiary allylic amine *N*-oxide **3** in the presence of Cl_3CCO_2H.

N-oxide **13**. This presumably resides in conformation **13A**, with the protonated C(3)-*N*,*N*-dibenzylamino *N*-oxide group occupying a pseudoequatorial position. Regioselective ring opening of **13A** at C(1) followed by transesterification gives **8**. The acid catalyzed ring opening of epoxides is known to proceed via a late transition state[19] which, in this case, favors attack at C(1) of **13A** where the electron-withdrawing inductive effect of the protonated *N*,*N*-dibenzylamino *N*-oxide moiety is lower. This presumably overrides any propensity of **13** to undergo ring opening through a chair-like transition state via attack at C(2) of **13A** to give the corresponding *trans*-diaxial product[14] (Figure 3).

Treatment of **8** with activated zinc dust gave the known *N*,*N*-dibenzylamino diol **15**,[8] while hydrogenolysis of **8** gave the known amino diol **16**,[8] in quantitative yield and >98% de in both cases (Scheme 6).

In conclusion, stereoselective anti-dihydroxylation of 3-*N*,*N*-dibenzylaminocyclohex-1-ene *N*-oxide offers a short, high yielding route for the preparation of 1,2-*anti*-2,3-*anti*-3-aminocyclohexane-1,2-diol after global hydrogenolytic deprotection. The stereochemical outcome is complementary to the selectivity previously reported by us in the corresponding ammonium-directed case and is consistent with epoxidation proceeding under steric or dipolar control on the face *anti* to the tertiary amine *N*-oxide group. Evaluation of the scope and utility of this novel transformation, for example in the application to the total asymmetric synthesis of amino sugars, is ongoing within this laboratory.

Scheme 6. *N*-Deprotection of 3-*N*,*N*-Dibenzylaminocyclohexane-1,2-diol *N*-Oxide **8**



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Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Protonation of *N*-oxide **3** by Cl_3CCO_2H is to be expected due to the differences in pK_a of the two species (for Cl_3CCO_2H, $pK_a = 0.65$; for a tertiary amine *N*-oxide, $pK_a \sim 4.5$); see: Bell, R. P.; Higginson, W. C. E. *Pro. Royal Soc.* **1949**, *197*, 141. Dippy, J. F. J.; Hughes, S. R. C.; Rozanski, A. *J. Chem. Soc.* **1959**, 2492.

(16) For a discussion of the stereochemistry of epoxidation in some homoallylic cyclohexene alcohols, see: Koèovsky, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1759.

(17) Trost recently reported the *syn*-epoxidation of 3-[(4′-methylpyridin-2′-yl)methyl]cyclohex-1-ene *N*-oxide by *m*CPBA; see: Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092.

(18) Crossley, N. S.; Darby, A. C.; Henbest, H. B.; McCullough, J. J.; Nicholls, B.; Stewart, M. F. *Tetrahedron Lett.* **1961**, *2*, 398.

(19) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. Addy, J. K.; Parker, R. E. *J. Chem. Soc.* **1963**, 915.