

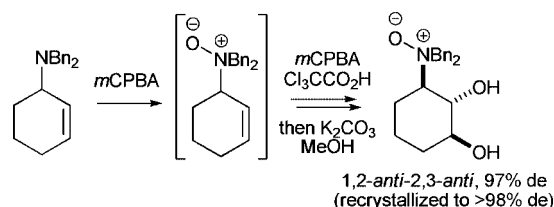
# Highly Diastereoselective *anti*-Dihydroxylation of 3-*N,N*-Dibenzylaminocyclohex-1-ene *N*-Oxide

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## ABSTRACT



Oxidation of 3-*N,N*-dibenzylaminocyclohex-1-ene *N*-oxide in the presence of  $\text{Cl}_3\text{CCO}_2\text{H}$  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.<sup>1</sup> They have found use as intermediates in, for example, [1,2]- and [2,3]-Meisenheimer rearrangements,<sup>2</sup> Cope eliminations,<sup>3</sup> and Polonovski reactions<sup>4</sup> 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.<sup>5</sup> Nonetheless, their utility in synthesis remains underdeveloped.<sup>1,6</sup> As part of our ongoing research program

directed toward the synthesis of the amino diol motif,<sup>7–9</sup> 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*-dibenzylaminocyclohex-1-ene *N*-oxide.

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(2) Meisenheimer, J. *Chem. Ber.* **1919**, 52, 1667. For selected synthetic applications, see: Davies, S. G.; Smyth, G. D. *J. Chem. Soc., Perkin Trans. I* **1996**, 2467. Majumdar, K. C.; Jana, G. H. *J. Org. Chem.* **1997**, 62, 1506. Arnone, A.; Metrangola, P.; Novo, B.; Resnati, G. *Tetrahedron* **1998**, 54, 7831. Buston, J. E. H.; Coldham, I.; Mulholland, K. R. *J. Chem. Soc., Perkin Trans. I* **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.; Kalindjian, S. B. *Tetrahedron Lett.* **2004**, 45, 3659. Henry, N.; O'Neil, I. A. *Tetrahedron Lett.* **2007**, 48, 1691.

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

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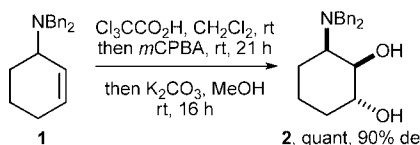
(7) Aciro, C.; Claridge, T. D. W.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, 6, 3751.

(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.

clohex-1-ene **1** with *m*CPBA employing a strategy reliant on in situ *N*-protection against oxidation via protonation with  $\text{Cl}_3\text{CCO}_2\text{H}$ . Epoxide ring opening by  $\text{Cl}_3\text{CCO}_2\text{H}$ , followed by transesterification, gave 3-*N,N*-dibenzylaminocyclohexane-1,2-diol **2** in 90% de (Scheme 1).<sup>7</sup> We hypothesized that

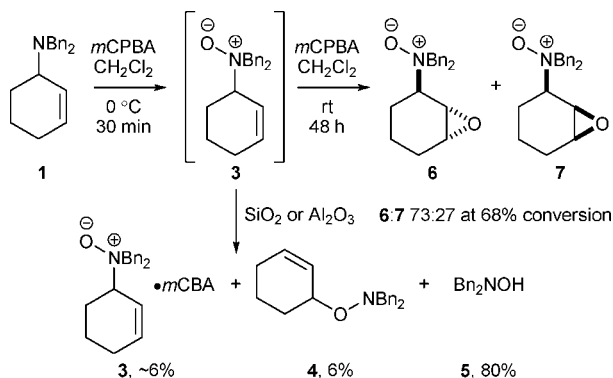
**Scheme 1.** Ammonium-Directed Dihydroxylation of 3-*N,N*-Dibenzylaminocyclohex-1-ene **1**



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.

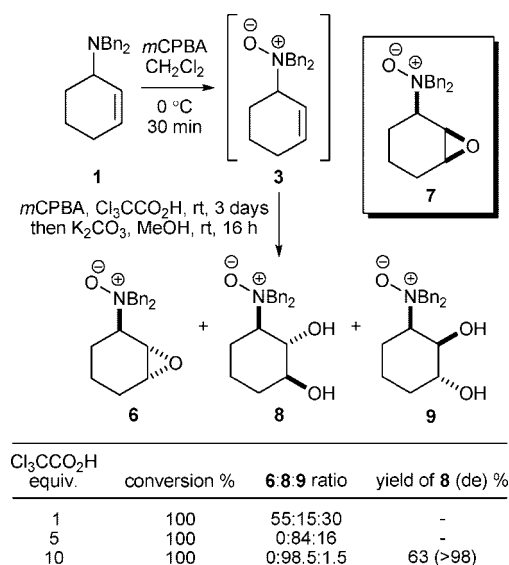
Our initial studies were directed toward preparation of *N*-oxide **3**. Treatment of amine **1** with *m*CPBA (1.5 equiv) at 0 °C in  $\text{CD}_2\text{Cl}_2$  gave *N*-oxide **3** as a mixture with excess *m*CPBA and *m*-chlorobenzoic acid (*m*CBA). As expected, attempted basic aqueous workup and purification 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.<sup>10,11</sup> 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**



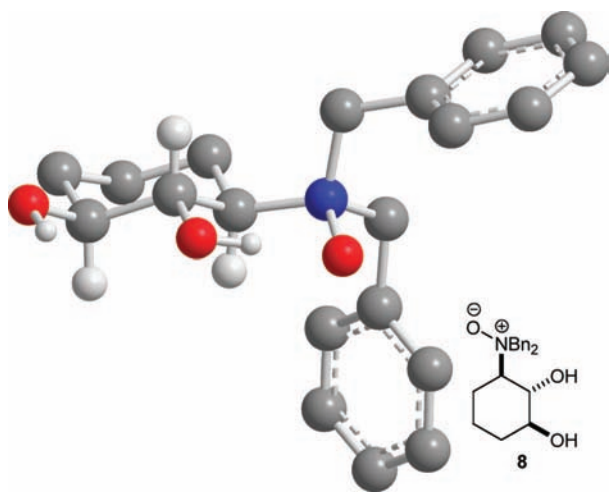
Olefinic oxidation of *N*-oxide **3** in the presence of  $\text{Cl}_3\text{CCO}_2\text{H}$  was next investigated. In situ treatment of a freshly prepared sample of **3** with 1 equiv of  $\text{Cl}_3\text{CCO}_2\text{H}$  followed by 3 equiv of *m*CPBA gave a complex mixture of products. Transesterification with  $\text{K}_2\text{CO}_3$  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  $\text{Cl}_3\text{CCO}_2\text{H}$  is much faster than that of epoxide **6**. When 5 equiv of  $\text{Cl}_3\text{CCO}_2\text{H}$  were employed, 68% de in favor of diol **8** was noted; when 10 equiv of  $\text{Cl}_3\text{CCO}_2\text{H}$  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  $\text{Cl}_3\text{CCO}_2\text{H}$ . 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



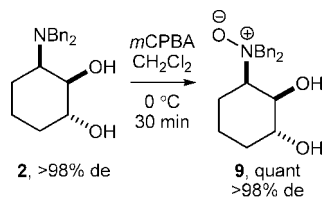
within the major diastereoisomer **8** resulting from this oxidation protocol was unambiguously established by single crystal X-ray analysis (Figure 1). Within the solid-state structure, hydrogen bonding is observed between the C(2)-hydroxyl substituent and the oxygen atom of the *N*-oxide group, which is consistent with the known stabilizing effect of hydrogen bonding on the *N*-oxide moiety.<sup>11,12</sup> 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**<sup>8</sup> (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  $\text{CD}_2\text{Cl}_2$  (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.

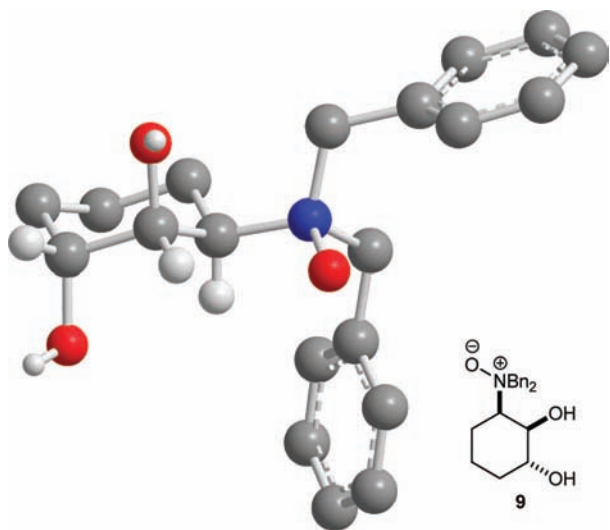


**Figure 1.** Chem 3D representation of the X-ray crystal structure of **8** (some H atoms omitted for clarity).

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



with two molecules of *mCBA* in the asymmetric unit, and within the crystal lattice hydrogen bonding is observed between the carboxylic acid group of one of the *mCBA*

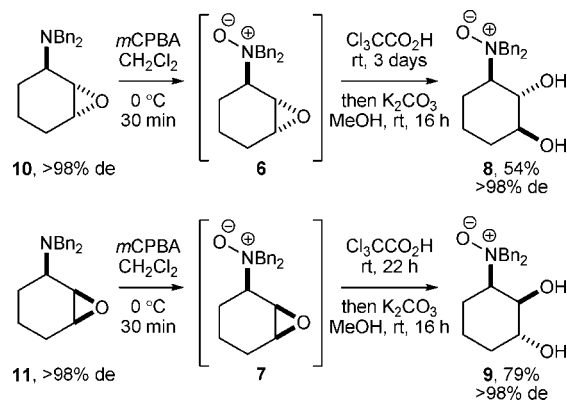


**Figure 2.** Chem 3D representation of the X-ray crystal structure of **9** (some H atoms and both *mCBA* molecules omitted for clarity).

molecules and both the C(2)-hydroxyl group and the oxygen atom of the *N*-oxide.<sup>11,13</sup>

Treatment of the known epoxides *anti*-**10**<sup>8</sup> and *syn*-**11**<sup>7</sup> with *mCPBA* gave authentic samples of **6** and **7**. Addition of 2 equiv of  $\text{Cl}_3\text{CCO}_2\text{H}$  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  $\text{Cl}_3\text{CCO}_2\text{H}$  over 3 days to achieve complete conversion. Transesterification with  $\text{K}_2\text{CO}_3/\text{MeOH}$  gave **8** in >98% de (Scheme 5). These results demonstrate that the

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



ring openings of both *anti*-**6** and *syn*-**7** by  $\text{Cl}_3\text{CCO}_2\text{H}$  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,<sup>14</sup> 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  $\text{Cl}_3\text{CCO}_2\text{H}$  is therefore consistent with loss of stereoselectivity in the initial epoxidation step rather than erosion of regioselectivity in the epoxide ring opening step.

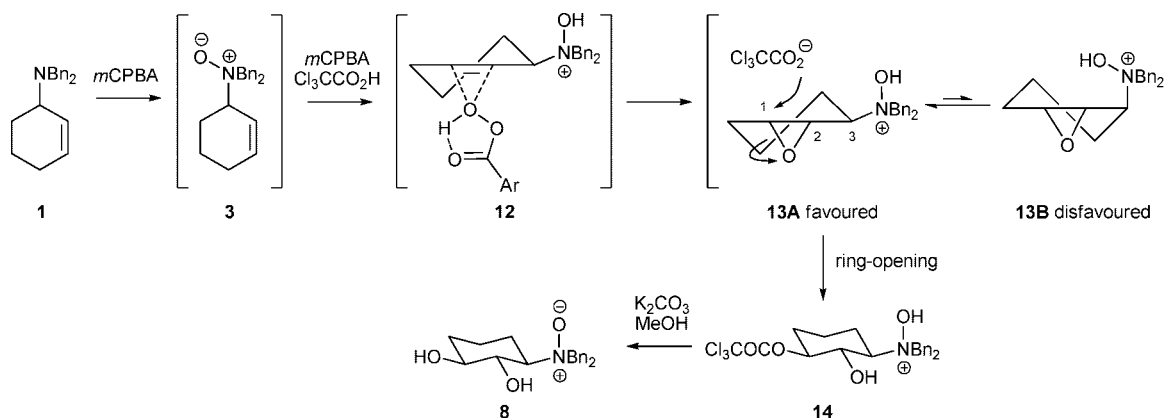
Stereoselective *anti*-epoxidation of **3** in the presence of 10 equiv of  $\text{Cl}_3\text{CCO}_2\text{H}$  suggests that the protonated *N,N*-dibenzylamino *N*-oxide group<sup>15</sup> does not participate in hydrogen-bonded delivery of the oxidant to the *syn*-face of the olefin.<sup>16,17</sup> 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<sup>18</sup> 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  $\text{CDCl}_3$  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 *mCBA* 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.



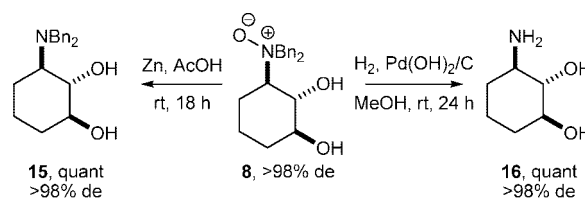
**Figure 3.** Postulated mechanism for the dihydroxylation of tertiary allylic amine *N*-oxide **3** in the presence of  $\text{Cl}_3\text{CCO}_2\text{H}$ .

*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<sup>19</sup> 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<sup>14</sup> (Figure 3).

Treatment of **8** with activated zinc dust gave the known *N,N*-dibenzylamino diol **15**,<sup>8</sup> while hydrogenolysis of **8** gave the known amino diol **16**,<sup>8</sup> 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

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



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.

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**Supporting Information Available:** Experimental procedures, characterization data, and copies of  $^1\text{H}$  and  $^{13}\text{C}$  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  $\text{Cl}_3\text{CCO}_2\text{H}$  is to be expected due to the differences in  $\text{p}K_a$  of the two species (for  $\text{Cl}_3\text{CCO}_2\text{H}$ ,  $\text{p}K_a = 0.65$ ; for a tertiary amine *N*-oxide,  $\text{p}K_a \sim 4.5$ ); see: Bell, R. P.; Higginson, W. C. E. *Proc. 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: Kočovský, 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.