Ammonium directed dihydroxylation of *N*,*N*-dibenzylaminocyclohex-2-ene: metal-free syntheses of the diastereoisomers of 3-dibenzylamino-1,2-dihydroxycyclohexane

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Treatment of *N*,*N*-dibenzylaminocyclohex-2-ene with mCPBA in the presence of CCl_3CO_2H gives 1,2-*anti*-2,3-*syn*-1-trichloroacetoxy-2-hydroxy-3-*N*,*N*-dibenzylaminocyclohexane with high diastereoselectivity; this methodology has been used to facilitate the metal-free stereoselective syntheses of all the diastereoisomers of 3-dibenzylamino-1,2-dihydroxycyclohexane.

The epoxidation of allylic alcohols is a widely studied synthetic transformation in organic chemistry, with the tartrate directed asymmetric epoxidation by Sharpless *et al.* arguably the most valuable synthetic protocol developed within this area.[1] High levels of stereocontrol are observed in the substrate directed[2] epoxidation of both cyclic[3] and acyclic allylic alcohols,[4] with the most widely recognised examples in this area being the hydroxyl directed *syn*-epoxidation of cyclohex-2-enol, or *anti*-epoxidation of *O*-protected cyclohex-2-enol derivatives upon oxidation with mCPBA.[5]

The related asymmetric epoxidation reaction of allylic amines has been much less widely studied,[6] presumably due to facile *N*-oxidation upon treatment with oxidising agents.[7] Although Asensio *et al.* have shown that ammonium salts undergo stereoselective *syn*-directed epoxidation upon treatment with mCPBA or dioxiranes,[8,9] this protocol is not applicable for the oxidation of tertiary allylamines, and the product epoxides are susceptible to decomposition at ambient temperature.[10] Harrity *et al.* have also shown that a spiropiperidine ammonium salt undergoes stereoselective directed epoxidation.[11] We communicate herein an ammonium directed, metal-free dihydroxylation protocol of allylamines that has been applied to the preparation of all the diastereoisomers of 3-dibenzylamino-1,2-dihydroxycyclohexane.[12,13]

Our strategy in this area centred upon protection of the amine by protonation prior to oxidation, with ammonium ion formation proposed to negate *N*-oxidation upon treatment with an oxidising agent. This ammonium ion would simultaneously provide a hydrogen bond donor capable of directing the subsequent epoxidation, the epoxide from which would be capable of regio- and stereoselective ring opening with a suitable nucleophile. To investigate this proposed reaction manifold, the oxidation of *N*,*N*-dibenzylaminocyclohex-2-ene **1** was used as a model system for optimisation. Treatment of amine **1** with trichloroacetic acid and subsequent addition of mCPBA at rt gave, after chromatographic purification on silica, 1,2-*anti*-2,3-*syn*-3-amino-1,2-dihydroxycyclohexane **3** as the sole product in > 98% d.e. and in 80% yield.[14] To probe further the mechanism of this transformation, the crude reaction product from oxidation of amine **1** with mCPBA (containing a single product) was purified on alumina, giving 1,2-*anti*-2,3-*syn*-1-trichloroacetoxy-2-hydroxy-3-*N*,*N*-dibenzylaminocyclohexane **2** in 40% yield and > 98% d.e. The low (40%) isolated yield in the isolation of **2** from the crude reaction product is presumably due to facile trichloroacetate hydrolysis to **3** upon purification; consistent with this hypothesis when **2** was stirred over silica, or subjected to chromatographic purification on silica, amino diol **3** was formed in quantitative yield. The 1,2-*anti*-2,3-*syn*-arrangement within amino diol **3** is consistent with the mechanism of this transformation involving initial protonation of the amine to give the corresponding ammonium ion, which upon subsequent oxidation with mCPBA directs epoxidation to the *syn*-face of the allylic C=C, presumably *via* a hydrogen bonded transition state.[15] The resulting *syn*-epoxide **9** is subsequently opened regioselectively with trichloroacetic acid in a *trans*-diaxial manner, with chromatographic purification on silica promoting hydrolysis of the acetate and giving the amino diol **3**. Alternatively, treatment of amine **1** with TsOH and subsequent oxidation with mCPBA gave 1,2-*anti*-2,3-*syn*-1-*para*-toluenesulfonate-2-hydroxy-3-*N*,*N*-dibenzylaminocyclohexane **4** in > 98% d.e. and in 85% isolated yield, with subsequent *O*-acetylation giving **5**. To invert the configuration at C(2) within **5**, neighbouring group participation of the acetate using a modified Winstein procedure[16] was followed, giving a 50 : 50 mixture of the separable 1,2-*syn*-2,3-*syn*-acetates **6** and **7** in > 98% d.e. in each case and 65% overall yield (two steps) after purification. Subsequent acetate hydrolysis of **6**, or **7**, or the 50 : 50 mixture of **6** and **7**, gave 1,2-*syn*-2,3-*syn*-amino diol **8** in quantitative yield and in > 98% d.e. in each case (Scheme 1).

With the 2,3-*syn*-stereoisomeric combinations of 3-dibenzylamino-1,2-dihydroxycyclohexane in hand, the preparation of the corresponding 2,3-*anti*-stereoisomers was pursued. Treatment of tosylate **4** with DBU gave the *syn*-epoxide **9** in > 98% d.e., which upon regio- and stereoselective opening with TsOH gave tosylate **4**, consistent with the *syn*-epoxide **9** being an intermediate in the oxidation protocol. Alternatively, treatment of *syn*-epoxide **9** with AcOH and subsequent *O*-mesylation gave **10** in quantitative yield. Application of the modified Winstein procedure inverted the configuration at C(2) within **10**, giving 1,2-*syn*-2,3-*anti*-3-amino-1-acetoxy-**11** in > 98% d.e. and 80% yield, with subsequent acetate hydrolysis giving the 1,2-*syn*-2,3-*anti*-amino diol **12** in quantitative yield. The formation of a 50 : 50 mixture of acetates **6** and **7** from **5**, and of a single acetate **11** from **10**, presumably reflects the relative thermodynamic preference of each system. Alternatively,

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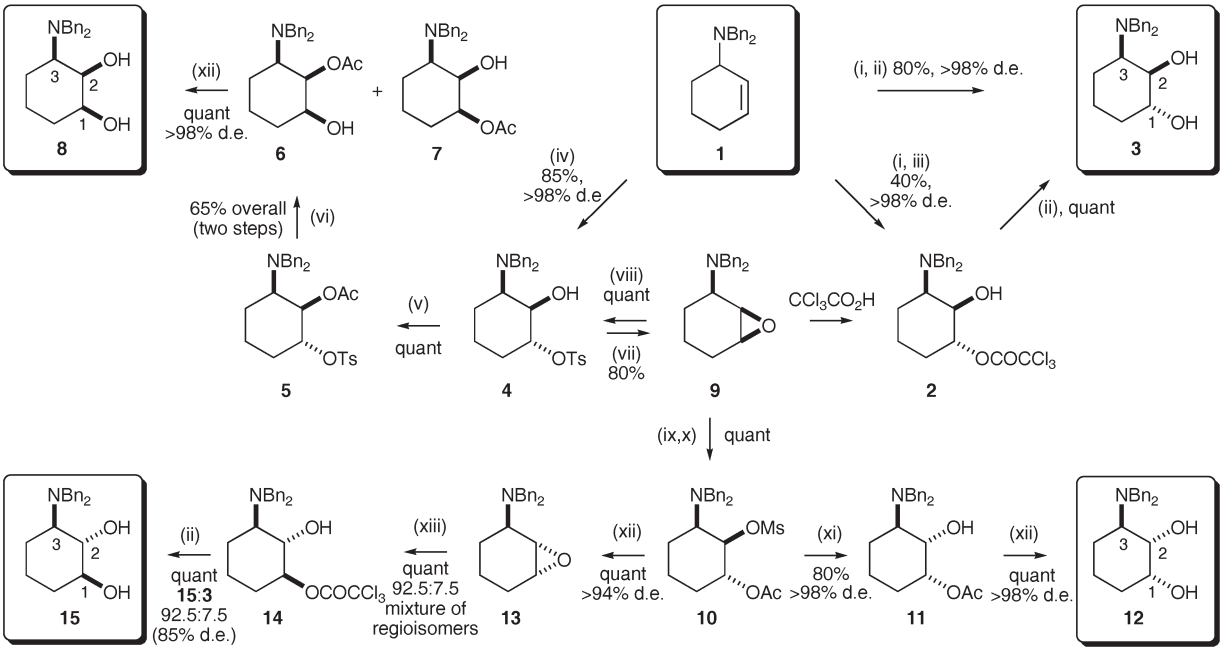
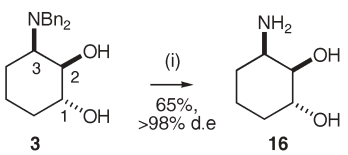


Scheme 1 *Reagents and conditions*: (i). CCl_3CO_2H, DCM, rt, 30 min then mCPBA, rt; (ii). chromatographic purification on silica; (iii). chromatographic purification on alumina; (iv). TsOH, DCM, rt, 30 min then mCPBA, rt; (v). Ac_2O, DMAP, pyridine, rt; (vi). EtOH, Δ; (vii). DBU, DCM, rt; (viii). TsOH, DCM, rt; (ix). AcOH, Δ; (x). MsCl, NEt_3, DMAP, DCM, rt; (xi). EtOH, H_2O, Δ; (xii). K_2CO_3, MeOH, rt; (xiii). CCl_3CO_2H, Δ.

acetate hydrolysis of mesylate **10** and concomitant intramolecular mesylate displacement allowed the isolation of the *anti*-epoxide **13** in quantitative yield without the need for purification. Treatment of epoxide **13** with trichloroacetic acid gave **14** as the major component of a 92.5 : 7.5 mixture of regioisomers in quantitative yield, which upon chromatographic purification on silica gave 1,2-*anti*-2,3-*anti*-amino diol **15** as the major component of a 92.5 : 7.5 mixture of 1,2-*anti*-2,3-*anti*-**15** : 1,2-*anti*-2,3-*syn*-**3** (85% d.e.) in quantitative yield (Scheme 1). The relative configuration within each diastereoisomeric series was confirmed using NMR spectroscopic analysis, consistent in each case with the assumption that the *N*,*N*-dibenzylamino group preferentially adopts a pseudo-equatorial position in a chair conformation. Furthermore, the selective preparation of the four diastereoisomeric amino diols **3**, **8**, **12** and **15** using this methodology confirms the assigned relative configurations within each series.

To demonstrate further the utility of these amino diols in synthesis, *N*-deprotection of **3** to the corresponding primary amine **16** was investigated. Hydrogenolysis of **3** upon treatment with Pearlman's catalyst and H_2 gave the desired 1,2-*anti*-2,3-*syn*-amino diol **16** in 65% yield as a single stereoisomer after purification (Scheme 2).

In conclusion, we have demonstrated that *N*,*N*-dibenzylcyclohex-2-ene is susceptible to stereoselective dihydroxylation upon treatment with either CCl_3CO_2H or TsOH and mCPBA. The high levels of stereoselectivity observed in this reaction are consistent with *in-situ* formation of an ammonium ion that directs epoxidation with mCPBA to the *syn*-face, with subsequent regio- and stereoselective *trans*-diaxial epoxide opening and hydrolysis generating 1,2-*anti*-2,3-*syn*-3-*N*,*N*-dibenzylamino-1,2-dihydroxycyclohexane derivatives. Further protecting group manipulations facilitate the stereoselective synthesis of the four diastereoisomers of 3-dibenzylamino-1,2-dihydroxycyclohexane. A full evaluation of the scope and limitations of this metal-free dihydroxylation protocol, the development of an enantioselective variant and the application of this methodology toward amino carbohydrate synthesis are currently under investigation within our laboratory.



Scheme 2 *Reagents and conditions*: (i). $Pd(OH)_2$ on C, MeOH, H_2 (5 atm).

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