Ammonium-directed dihydroxylation of 3-aminocyclohex-1-enes: development of a metal-free dihydroxylation protocol†‡

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Treatment of 3-aminocyclohex-1-enes with *m*CPBA in the presence of trichloroacetic acid gives the corresponding 1,2-*anti*-2,3-*syn*-1-trichloroacetoxy-2-hydroxy-3-aminocyclohexane with high levels of diastereoselectivity (90% de). This is consistent with a mechanism of oxidation involving hydrogen-bonded delivery of the oxidant by the allylic ammonium ion formed *in situ*, followed by highly regioselective ring-opening of the intermediate epoxide by trichloroacetic acid. The effect of conformational constraints upon the oxidation reaction is also examined.

Introduction

The epoxidation of allylic alcohols is a widely studied synthetic transformation in organic chemistry,[1] with high levels of stereocontrol having been observed in substrate-directed epoxidation of both cyclic[2] and acyclic[3] allylic alcohols. The related epoxidation of allylic amines has been much less widely studied, presumably due to facile *N*-oxidation upon treatment with oxidising agents,[4] although examples employing carbamate, amide and sulfonamide protecting groups have been reported.[5] The chemoselective olefinic oxidation of allylic amines[6] has been achieved upon treatment of the requisite amine with F_3CCO_2H followed by trifluoroperacetic acid.[7,8] More recently, Asensio *et al.* have shown that **1** undergoes *syn*-directed oxidation upon treatment with *m*CPBA to give **2** in >98% de.[9] Aggarwal *et al.* have also demonstrated that oxidation of the ammonium *p*-toluenesulfonate salt **3** with Oxone proceeds with high levels of *syn*-selectivity (>90% de) to generate epoxide **4** in 73% yield.[10] Additionally, Harrity *et al.* have demonstrated that spiropiperidine ammonium trifluoroacetate salt **5** undergoes diastereoselective epoxidation upon treatment with *m*CPBA[11] to give **6** (Fig. 1).

We have previously communicated a method to effect the dihydroxylation of 3-(*N*,*N*-dibenzylamino)cyclohex-1-ene upon treatment with Cl_3CCO_2H followed by *m*CPBA.[12] However, the method described was not found to be robust or generally applicable. We therefore describe herein our full investigations into the development of a reliable experimental protocol applicable to the dihydroxylation of primary, secondary and tertiary amines.

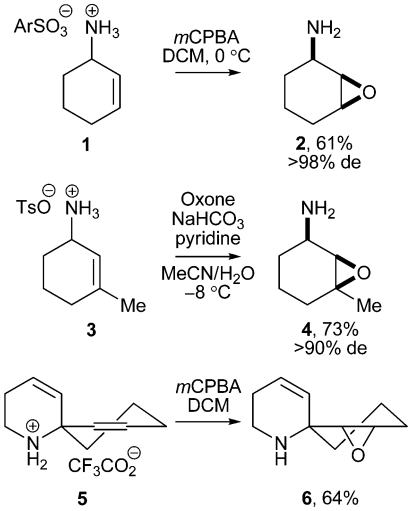

Fig. 1 Ammonium-directed oxidations of allylic amines [Ar = *p*-ClC_6H_4].

Results and discussion

Development of an ammonium-directed oxidation protocol

In order to probe the oxidation protocol, 3-(*N*,*N*-dibenzylamino)cyclohex-1-ene **9** was chosen as model system for reaction optimisation. Tertiary allylic amine **9** was synthesised from cyclohexene *via* Wohl–Ziegler allylic bromination[13] and subsequent bromide displacement with dibenzylamine, giving **9** in 41% yield after chromatographic purification. However, a more experimentally facile (and scalable) preparation of **9** involved benzylation of secondary allylic amine **8** (prepared from **7** and benzylamine) with benzyl bromide, with subsequent acid/base extraction giving **9** in 70% yield on a >80 g scale (Scheme 1).

The formation of ammonium species **10** from tertiary allylic amine **9** in the presence of Cl_3CCO_2H was examined. Amine **9** was added in 0.1 eq aliquots to a solution of Cl_3CCO_2H (1 eq) in $CDCl_3$, and the distribution of products was monitored by ^1H NMR spectroscopy. A pronounced difference in δ_H of the vinylic protons was observed (for **9**, C(1)*H* and C(2)*H* appear as a multiplet at δ_H 5.65–5.85 ppm), indicating the time-averaged

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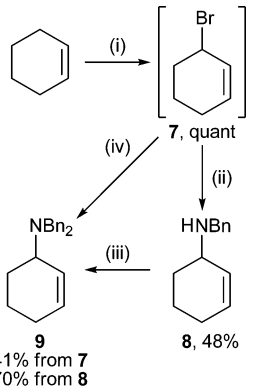
† Dedicated to Professor Gordon H. Whitham, to honour his 80th year.

‡ Electronic supplementary information (ESI) available: Additional experimental information. CCDC reference number 679350. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b808811j



Scheme 1 *Reagents and conditions*: (i) NBS, AIBN, CCl_4, 80 °C, 1.5 h; (ii) benzylamine, K_2CO_3, THF, 50 °C, 3 days; (iii) BnBr, Hünig's base, DMAP, DCM, rt, 24 h; (iv) dibenzylamine, K_2CO_3, THF, 50 °C, 3 days.

signal and fast exchange between amine **9** and ammonium **10**. The difference in chemical shift ($\Delta\delta$) between the values of δ_H for C(1)*H* and C(2)*H* increased with increasing equivalents of Cl_3CCO_2H, although a plateau was noted at approximately 4–5 equivalents, suggesting that the equilibrium lies predominately to the right and the ammonium **10** predominates in solution under these conditions. This result suggests that 5 eq of Cl_3CCO_2H may be sufficient to effect efficient *N*-protonation (Fig. 2).

The effect of number of equivalents of Cl_3CCO_2H on the product distribution of the oxidation reaction was assessed. Initial treatment of **9** in DCM (0.07 M) with 1.2 eq of *m*CPBA,[14] followed by aqueous work-up after 21 h, returned a mixture of products. Similarly, when **9** was treated with either 1 eq or 2 eq of Cl_3CCO_2H for 5 min, followed by the addition of *m*CPBA, a mixture of products was observed. However, when 4 eq of Cl_3CCO_2H was utilised, a 33 : 67 mixture of **9** and trichloroacetate **11** (90% de)[15,16] was generated, although other minor unidentifiable by-products were also noted in the ^{1}H NMR spectrum of the crude reaction mixture. Under the same conditions 5 eq of Cl_3CCO_2H gave a crude reaction mixture whose ^{1}H NMR spectrum indicated only the presence of **9** and trichloroacetate **11** (90% de) in a 31 : 69 ratio. Reaction optimisation showed that quantitative conversion to **11** was achieved when **9** in DCM (0.36 M) was treated with 5 eq of Cl_3CCO_2H followed by 1.6 eq *m*CPBA (Scheme 2). The relative 1,2-*anti*-2,3-*syn*-configuration of **11** was initially assigned by a combination of ^{1}H NMR ^3J coupling constant and NOE analyses (assuming a chair conformation is adopted in which the *N*,*N*-dibenzylamino moiety lies in an equatorial site), and subsequently unambiguously proven *via* single crystal X-ray analysis‡ of the trichloroacetate salt **12** (Fig. 3).

A range of carboxylic acids, ranging in acid strength from acetic acid to trifluoroacetic acid, was next screened for their efficacy in promoting chemoselective olefinic oxidation. Here, **9** was treated with an excess (5 eq) of the requisite carboxylic acid followed by *m*CPBA (1.6 eq) over 21 h, followed by basification, and the product distribution was analysed by ^{1}H NMR spectroscopy.[16] These results demonstrated that AcOH ($pK_a = 4.76$)[17] and $ClCH_2CO_2H$ ($pK_a = 2.86$)[17] were ineffective at promoting olefinic oxidation, giving rise to complex mixtures of products. In the

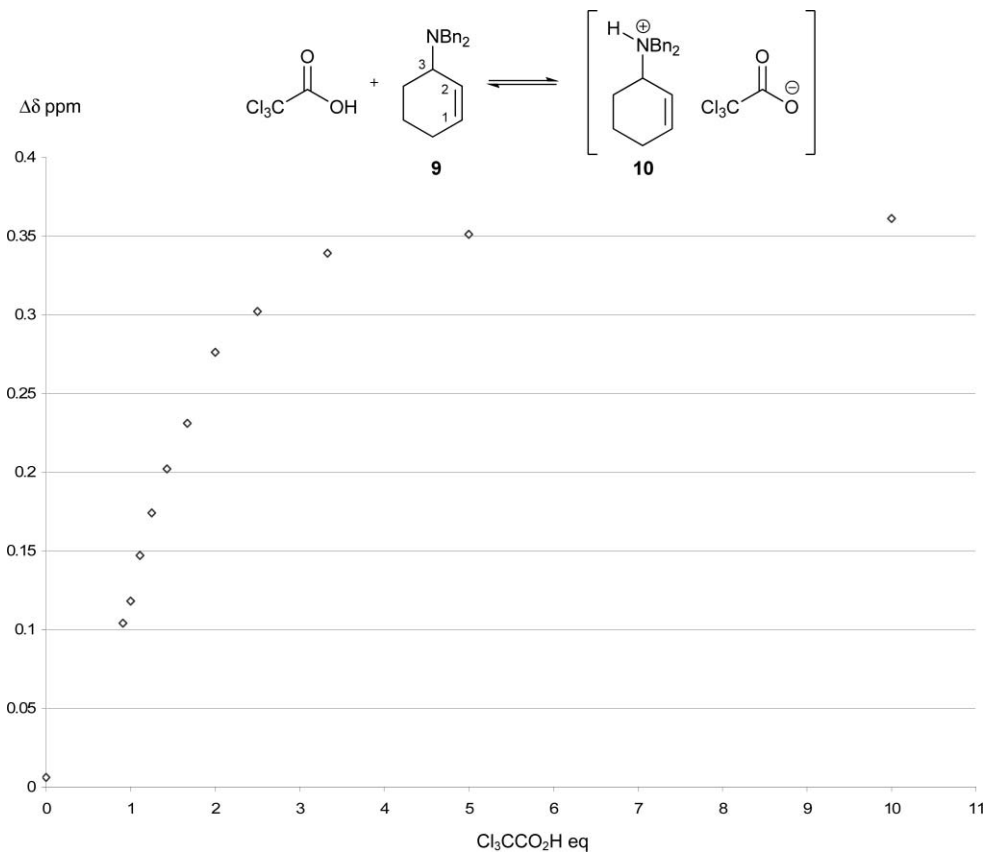
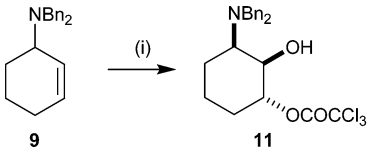


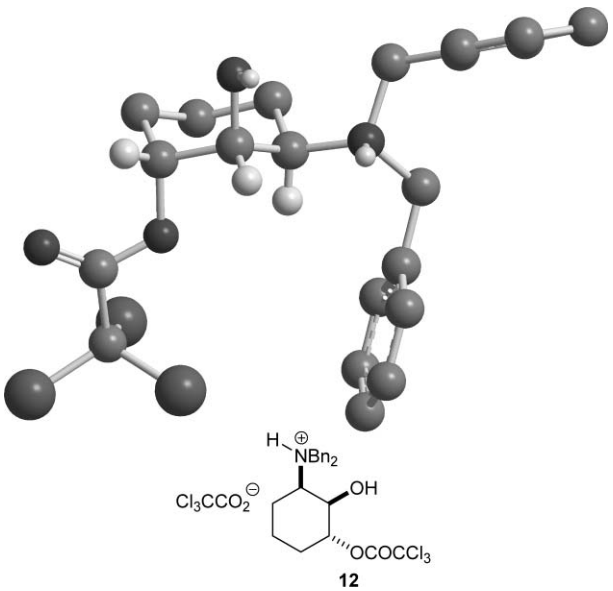
Fig. 2 Difference in chemical shift ($\Delta\delta$) between C(1)*H* and C(2)*H* upon addition of Cl_3CCO_2H to **9**.



9 11

Cl_3CCO_2H eq	*m*CPBA eq	Conc M	**9**:**11**	de of **11** %
1	1.2	0.07	-	-
2	1.2	0.07	-	-
4	1.2	0.07	33:67	90
5	1.2	0.07	31:69	90
5	1.6	0.36	<1:>99	90

Scheme 2 *Reagents and conditions*: (i) Cl_3CCO_2H, *m*CPBA, DCM, 21 h, rt then $NaHCO_3$ (0.1 M, aq).

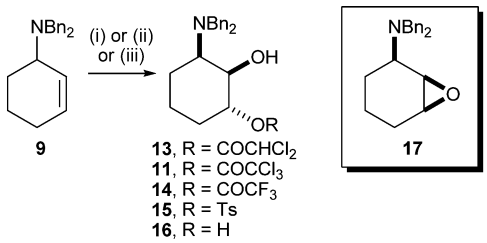


12

Fig. 3 Chem 3D representation of the X-ray crystal structure of **12** (some H atoms and the $Cl_3CCO_2^-$ counterion omitted for clarity).

case of Cl_2CHCO_2H ($pK_a = 1.29$),[17] however, the corresponding dichloroacetate ester **13** was observed as the major product, in 87% de. Oxidation in the presence of F_3CCO_2H ($pK_a = -0.25$)[17] gave a 53 : 47 mixture of trifluoroacetate **14** (90% de) and diol **16** (90% de), presumably a result of the lability of the trifluoroacetate group under the basic aqueous work-up conditions. The effectiveness of *N*-protection with a sulfonic acid in this reaction was also assessed *via* the application of TsOH ($pK_a = -6.5$),[17] giving **15** in 90% de after aqueous work-up. In accordance with the increased acidity of TsOH over Cl_3CCO_2H, optimisation studies revealed that only 3 eq of TsOH were necessary to effect efficient *N*-protonation in this reaction protocol. The utility of mineral acids was also examined, although treatment of **9** with aq HCl ($pK_a = -7$)[17] in 1,4-dioxane followed by *m*CPBA returned starting material, and addition of aq H_2SO_4 ($pK_a1 = -9$)[17] gave a 9 : 61 : 30 mixture of **9**, 1,2-*anti*-2,3-*syn* diol **16** (90% de) and *syn*-epoxide **17** (90% de) respectively, along with other unidentifiable products (Scheme 3).

The relative configurations within the major diastereoisomers **13**, **14** and **15** were assigned by analogy to that unambiguously proven for **11**. Additionally, ^{1}H NMR ^3J coupling constant and NOE analyses were supportive of the relative 1,2-*anti*-2,3-*syn*-configuration within **15**, and transesterification of **11**, **13** and **14** (as a 53 : 47 mixture of **14**:**16**) upon treatment with K_2CO_3 in

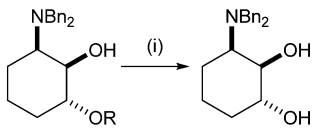


9 **13**, R = $COCHCl_2$
11, R = $COCCl_3$
14, R = $COCF_3$
15, R = Ts
16, R = H
17

Acid	pK_a	Procedure	Product	de[a] %
Cl_2CHCO_2H	1.29	(i)	**13**	87
Cl_3CCO_2H	0.65	(i)	**11**	90
F_3CCO_2H	−0.25	(i)	**14**	90
TsOH	−6.5	(ii)	**15**	90
H_2SO_4	−9[b]	(iii)	**16**	90

Scheme 3 *Reagents and conditions*: (i) **9** (1 eq) in DCM (0.36 M), Brønsted acid (5 eq), then *m*CPBA (1.6 eq), rt, 21 h, then $NaHCO_3$ (0.1 M, aq); (ii) **9** (1 eq) in DCM (0.36 M), TsOH (3 eq), then *m*CPBA (1.6 eq), rt, 21 h, then $NaHCO_3$ (0.1 M, aq); (iii) **9** (1 eq) in 1,4-dioxane (0.36 M), H_2SO_4 (5 eq), then *m*CPBA (1.6 eq), 0 °C to rt, 21 h, then $NaHCO_3$ (0.1 M, aq) [[a] Determined from analysis of the ^{1}H NMR spectrum of the crude reaction product. [b] First ionisation].

MeOH, gave the common 1,2-*anti*-2,3-*syn*-*N*-protected amino diol **16** in 90% de in each case. ^{1}H NMR ^3J coupling constant and NOE analyses were supportive of the assigned 1,2-*anti*-2,3-*syn*-configuration within **16** (Scheme 4).

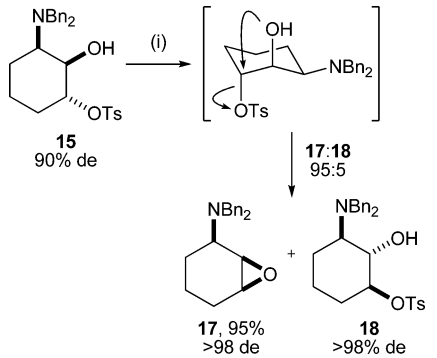


11, R = $COCCl_3$
13, R = $COCHCl_2$
14, R = $COCF_3$
16

Scheme 4 *Reagents and conditions*: (i) K_2CO_3, MeOH, rt, 16 h.

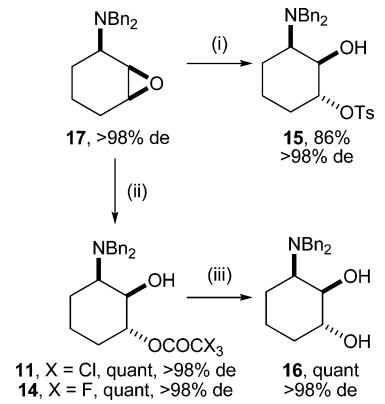
In order to probe the intermediacy of *syn*-epoxide **17** in this oxidation reaction, it was envisaged that **17** could be prepared through base-promoted elimination of TsOH from **15**. Treatment of **15** (90% de) with DBU gave a 95 : 5 mixture of *syn*-epoxide **17** (>98% de) and 1,2-*anti*-2,3-*anti*-tosylate **18** (>98% de)[16] respectively, with chromatographic purification giving *syn*-epoxide **17** in 95% yield and >98% de. The observation that base-mediated epoxide formation from 1,2-*anti*-2,3-*syn*-tosylate **15** is faster than that from 1,2-*anti*-2,3-*anti*-tosylate **18** is consistent with the former proceeding *via* a favourable chair-like transition state that places the *N*,*N*-dibenzylamino group equatorial, whilst the latter would presumably have to proceed *via* an unfavourable twist-boat-like transition state (Scheme 5).

Treatment of **17** (>98% de) with TsOH (5 eq) proceeded with complete regio- and diastereocontrol to give, after basification, **15** in >98% de and 86% yield. Epoxide opening of **17** with Cl_3CCO_2H (5 eq) and basification furnished **11** in >98% de and quantitative yield. An authentic sample of **14** was also prepared upon ring-opening of **17** with F_3CCO_2H. Transesterification of either **11** or **14** with K_2CO_3/MeOH gave a sample of **16** in >98% de. Attempted direct formation of **16** upon ring-opening of **17** with H_2SO_4 in aqueous dioxane gave 72% conversion to **16** in >98% de, and was accompanied by the formation of unidentified by-products. It was also noted that treatment of **17** with *meta*-chlorobenzoic



Scheme 5 *Reagents and conditions*: (i) DBU, DCM, rt, 24 h.

acid returned only starting material, whilst addition of a 1.6 : 5 mixture of *meta*-chlorobenzoic acid/Cl_3CCO_2H gave, after basic work-up, **11** only, indicating that no competitive ring-opening of **17** by *meta*-chlorobenzoic acid was occurring under the oxidation reaction conditions (Scheme 6).



Scheme 6 *Reagents and conditions*: (i) TsOH, DCM, rt, 16 h, then $NaHCO_3$ (0.1 M, aq); (ii) X_3CCO_2H, DCM, rt, 16 h, then $NaHCO_3$ (0.1 M, aq); (iii) K_2CO_3, MeOH, rt, 16 h.

The 1,2-*anti*-2,3-*syn*-arrangement within the major diastereoisomeric *N*,*N*-dibenzylamino diol **16** resulting from this oxidation protocol is consistent with a mechanism involving initial protonation of the amine **9** to give the corresponding ammonium **10**. Subsequent oxidation with *m*CPBA directs epoxidation to the *syn*-face of the allylic C=C, *via* a hydrogen-bonded transition state **19** analogous to the Bartlett[18] and Henbest[19] studies on the corresponding allylic alcohol, to give *syn*-epoxide **17** as the corresponding ammonium trichloroacetate salt **20**. This presumably resides in the more stable conformation **20A**, where the *N*,*N*-dibenzylammonium moiety lies equatorial. This conformer favours nucleophilic attack by the conjugate base of the Brønsted acid protecting agent at the C(1)-oxirane carbon, giving a chair-like transition state leading to the *trans*-diaxial product **11**, in accordance with the Fürst–Plattner rule.[20] This is also consistent with the acid-catalysed ring-opening of epoxides proceeding *via* a late transition state,[21] thus promoting attack at the C(1)-oxirane carbon where the electron-withdrawing inductive effect of the *N*,*N*-dibenzylammonium moiety is lower (Fig. 4).

Conformational effects upon reaction diastereoselectivity and rate

In order to probe the effect of conformation upon the reaction diastereoselectivity, the oxidations of the diastereoisomers of 3-(*N*,*N*-dibenzylamino)-5-*tert*-butylcyclohex-1-ene *syn*-**21** and *anti*-**22** (both prepared from 4-*tert*-butylcyclohexanol)[22] were investigated. Treatment of *syn*-**21** with 5 eq of Cl_3CCO_2H and *m*CPBA followed by basic aqueous work-up and transesterification with K_2CO_3 in MeOH gave 1,2-*anti*-2,3-*syn*-**23** as a single diastereoisomer in quantitative yield. The relative stereochemistry within **23** was assigned by ^{1}H NMR ^3J coupling constant analysis, assuming that **23** preferentially adopts a chair ground-state conformation in solution which places both the bulky *tert*-butyl and *N*,*N*-dibenzylamino groups in equatorial sites. Analogous treatment of *anti*-**22** gave a 22 : 78 mixture of epoxide **24** and its ring-opened product 1,2-*anti*-2,3-*syn*-**25** as single diastereoisomers in each case, and in quantitative yield. The stereochemistry within **25** was assigned on the basis of ^{1}H NMR ^3J coupling constant analysis, assuming that **25** preferentially adopts a distorted chair conformation in solution which places the *tert*-butyl group in an equatorial site, and the *N*,*N*-dibenzylamino group midway between an axial and equatorial site.[23] These results suggest that both positions for the *N*,*N*-dibenzylamino group (an equatorial site in *syn*-**21** and midway between an axial and equatorial site in *anti*-**22**) are equally effective in promoting a highly diastereoselective *syn*-oxidation reaction (Scheme 7).

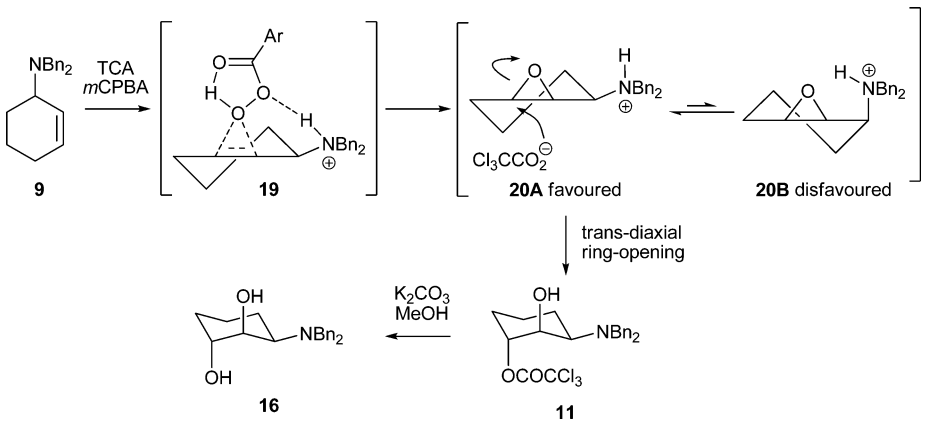
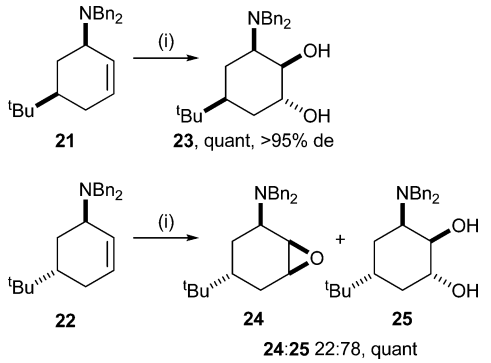


Fig. 4 Postulated mechanism for the oxidation of **9** with Cl_3CCO_2H and *m*CPBA [Ar = *m*-ClC_6H_4].



Scheme 7 *Reagents and conditions*: (i) Cl_3CCO_2H, *m*CPBA, DCM, rt, 21 h, then K_2CO_3, MeOH, rt, 16 h.

The effect of conformational constraints on the rate of the oxidation reaction was next determined. Initially, the progress of the oxidation of 3-(*N*,*N*-dibenzylamino)cyclohexene **9** was studied by ^{1}H NMR spectroscopy. Treatment of **9** with 5 eq of Cl_3CCO_2H gave ammonium **10**. Upon subsequent addition of *m*CPBA, the consumption of ammonium **10** was monitored by calculating an average integration of the peaks due to C(1)*H* (δ_H 6.27–6.36 ppm) and C(2)*H* (δ_H 5.87–5.94 ppm), whilst the consumption of peracid was monitored by calculating an average integration of the peaks at δ_H 7.86–7.89 and 7.93–7.96 ppm. The generation of ammonium **12** was monitored by calculating an average integration of the peaks due to C(1)*H* (δ_H 5.10–5.17 ppm), C(3)*H* (δ_H 3.65–3.72 ppm), and N(CH_AH$_B$Ph)$_2$ (δ_H 5.31–5.41 ppm). The integral values obtained from the ^{1}H NMR spectra were converted to concentration values using the known initial concentrations of **10** (0.36 M), **12** (0 M), and *m*CPBA (0.58 M). These data were used to determine the rate coefficient (k) by application of the integrated form of the rate law for a second-order reaction,[24] giving $k = 3.5 \times 10^{-4}$ ($\pm 0.2 \times 10^{-4}$) mol^{-1} dm^3 s^{-1} (Fig. 5).

The oxidation of *syn*-**21** was next monitored by ^{1}H NMR spectroscopy. Addition of 5 eq of Cl_3CCO_2H to *syn*-**21** gave ammonium **26**. Upon addition of *m*CPBA the consumption of ammonium **26** was monitored by calculating an average integration of the peaks due to C(1)*H* (δ_H 6.24–6.32 ppm) and C(2)*H* (δ_H 5.84–5.93 ppm), and the consumption of peracid was monitored in an analogous fashion to that previously described. The generation of ammonium **27** was monitored by calculating an average integration of the peaks due to C(1)*H* (δ_H 5.20–5.24 ppm), C(3)*H* (δ_H 3.64–3.72 ppm), and N(CH_AH$_B$Ph)$_2$ (δ_H 5.33–5.41 ppm). Analogous treatment of the data to that described for oxidation of **9** gave $k = 3.3 \times 10^{-4}$ ($\pm 0.2 \times 10^{-4}$) mol^{-1} dm^3 s^{-1} (Fig. 6).

Similarly, the oxidation of *anti*-**22** was monitored by ^{1}H NMR spectroscopy. Addition of 5 eq of Cl_3CCO_2H to *anti*-**22** gave ammonium **28**. Upon addition of *m*CPBA the consumption of ammonium **28** was monitored by calculating an average integration of the peaks due to C(1)*H* (δ_H 6.51–6.60 ppm) and C(2)*H* (δ_H at 5.95–6.05 ppm), and the consumption of peracid was monitored in an analogous fashion to that previously described. The generation of ammonium **30** was monitored by integration of the peaks due to N(CH_AH$_B$Ph)$_2$ (δ_H 5.25–5.32 ppm). The growth and decay of a signal at δ_H 3.68–3.73 ppm was attributed as arising from C(3)*H* within the intermediate epoxide ammonium **29**, consistent with **29** being an intermediate *en route* to **30**. In this case the rate coefficient was calculated as $k = 5.9 \times 10^{-4}$ ($\pm 0.2 \times 10^{-4}$) mol^{-1} dm^3 s^{-1} (Fig. 7).

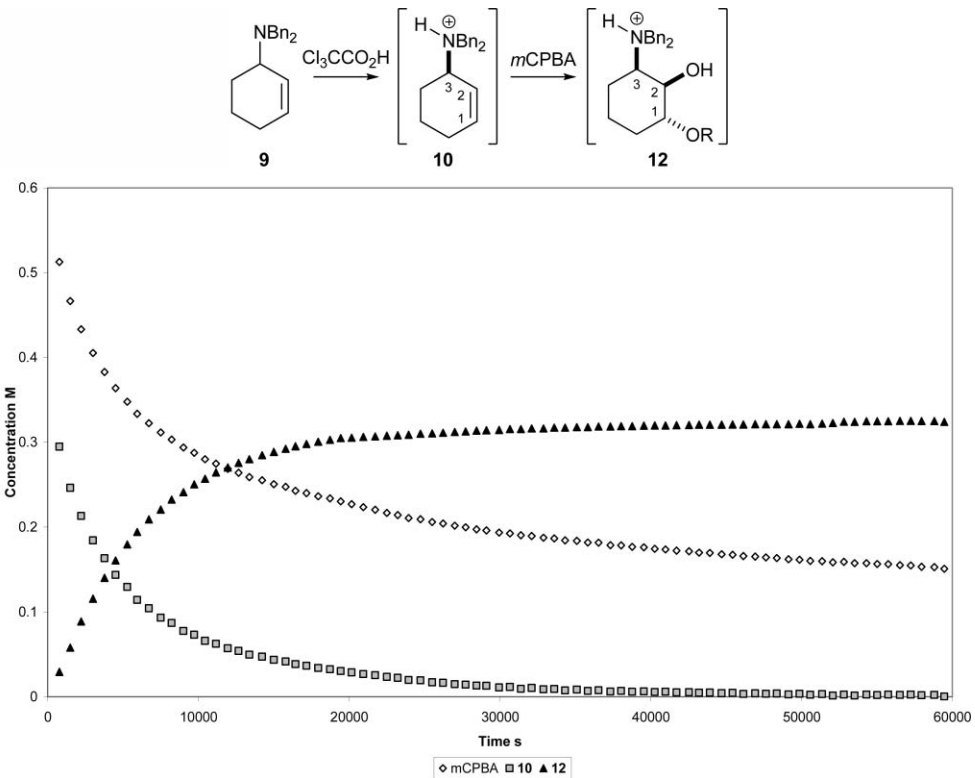


Fig. 5 Real-time ^{1}H NMR measurements for Cl_3CCO_2H- and *m*CPBA-promoted dihydroxylation of **9** [R = $COCCl_3$; for brevity, for **10** and **12**, the $Cl_3CCO_2^-$ counterions are not shown].

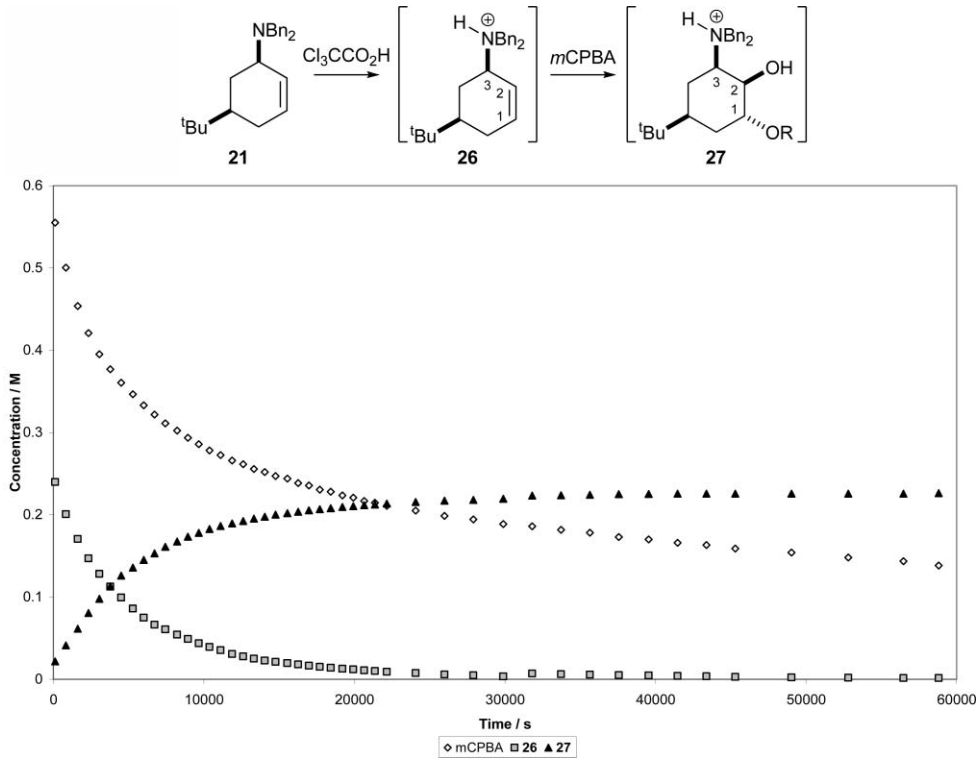


Fig. 6 Real-time ^{1}H NMR measurements for Cl_3CCO_2H- and *m*CPBA-promoted dihydroxylation of *syn*-**21** [R = $COCCl_3$; for brevity, for **26** and **27**, the $Cl_3CCO_2^-$ counterions are not shown].

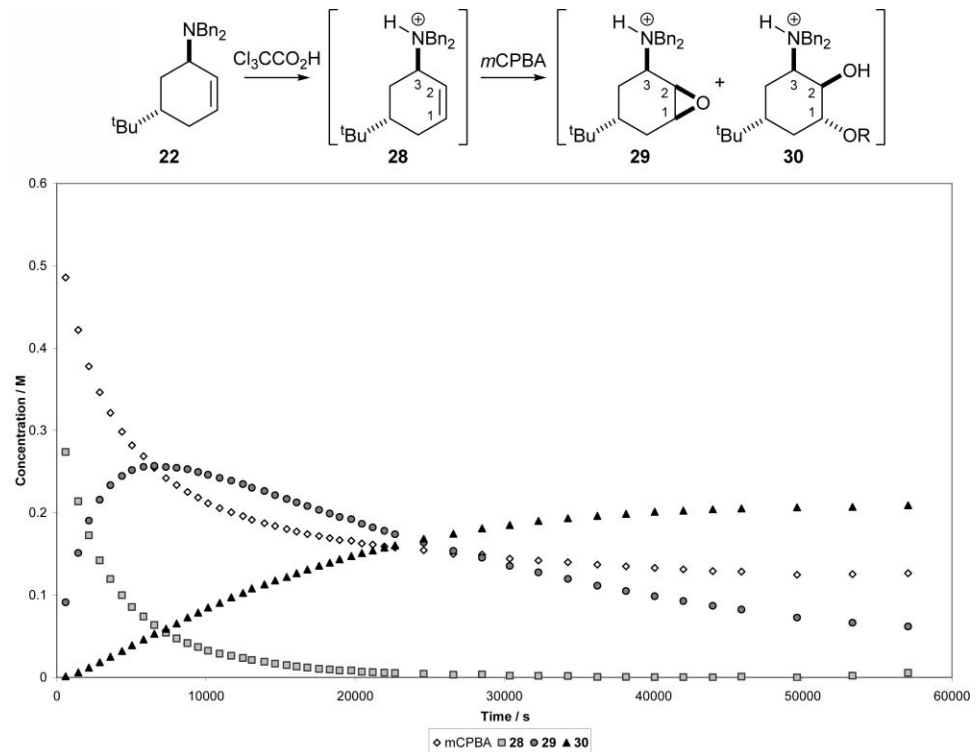


Fig. 7 Real-time ^{1}H NMR measurements for Cl_3CCO_2H- and *m*CPBA-promoted dihydroxylation of *anti*-**22** [R = $COCCl_3$; for brevity, for **28–30**, the $Cl_3CCO_2^-$ counterions are not shown].

Whitham and co-workers investigated the preferred geometry of the transition state proposed by Henbest for the epoxidation of cyclohex-2-enol **31** by performing the oxidation of the diastereoisomers of 5-*tert*-butylcyclohex-2-enol *syn*-**32** (having the hydroxyl group locked in an pseudoequatorial site of a half-chair conformation) and *anti*-**33** (having the hydroxyl group locked in a pseudoaxial site of a half-chair conformation).[25] Very high levels of *syn*-diastereoselectivity were achieved for epoxidation of **31** and *syn*-**32** (>95% de) but were lower for *anti*-**33** (66% de). Furthermore, the relative rates of oxidation of **31**:*syn*-**32**:*anti*-**33** were determined to be 5 : 7 : 1. These rate data suggest that the pseudoequatorial hydroxyl group in *syn*-**32** is efficient at promoting a rapid, highly diastereoselective oxidation reaction, whilst the pseudoaxial hydroxyl group within *anti*-**33** is much less effective, presumably due to the conformational restriction preventing adoption of the optimal reactive geometry in the transition state.[26] The intermediate rate of oxidation of **31** is consistent with this species existing as a mixture of the two possible half-chair conformations in solution. In the ammonium-directed oxidation of **9**, *syn*-**21** and *anti*-**22**, very high levels of *syn*-diastereoselectivity (≥90% de) were observed in each case, and the relative rates of oxidation of **9**:*syn*-**21**:*anti*-**22** were determined to be 1 : 1 : 2. The similarity in the rates of oxidation of **9** and *syn*-**21** in this system presumably reflects the similarity in the preferred half-chair conformations of each species, with the bulky *N*,*N*-dibenzylamino group showing a pronounced preference to adopt a pseudoequatorial site within a half-chair conformation for **9**, and both the *tert*-butyl and *N*,*N*-dibenzylamino substituents adopting pseudoequatorial sites in a half-chair conformation for *syn*-**21**. The faster rate of oxidation for *anti*-**22** is in contrast to the results obtained by Whitham on the analogous allylic alcohol system, but is consistent with the preferred conformation of *anti*-**22** (and therefore ammonium **28**) being a distorted half-chair which places the ammonium in a more optimal reactive geometry within the hydrogen-bonded transition state originally proposed by Henbest (Fig. 8).

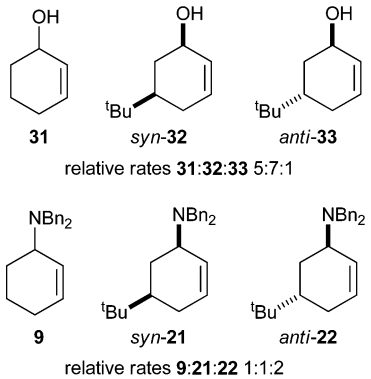


Fig. 8 Relative rates of oxidation of allylic alcohols **31–33**, and allylic amines **9**, **21** and **22**.

In order to investigate this hypothesis, MacroModel molecular modelling[27] was carried out on ammonium *syn*-**26**, for which a half-chair conformation was predicted with the *N*,*N*-dibenzylammonium substituent occupying a pseudoequatorial site. For *anti*-**28** a distorted half-chair conformation was predicted, with the *N*,*N*-dibenzylammonium substituent midway between a pseudoaxial and pseudoequatorial site[28] (Fig. 9).

The conformations of epoxide ammoniums **34** (derived from *syn*-**21**) and **29** (derived from *anti*-**22**) were modelled, and found at minima of –42.2 and –37.5 kJ mol^{-1} respectively. From analysis of these minimised energy conformations the ring-opening of **34** at C(1) would traverse a chair-like transition state, while the ring-opening of **29** at C(1) would traverse a twist-boat-like transition state. This is consistent with the observation by ^{1}H NMR spectroscopy of an epoxide intermediate in the oxidation of *anti*-**22**, presumably due to a longer lifetime of this intermediate arising from a slower rate of ring-opening *in situ* (Fig. 10).

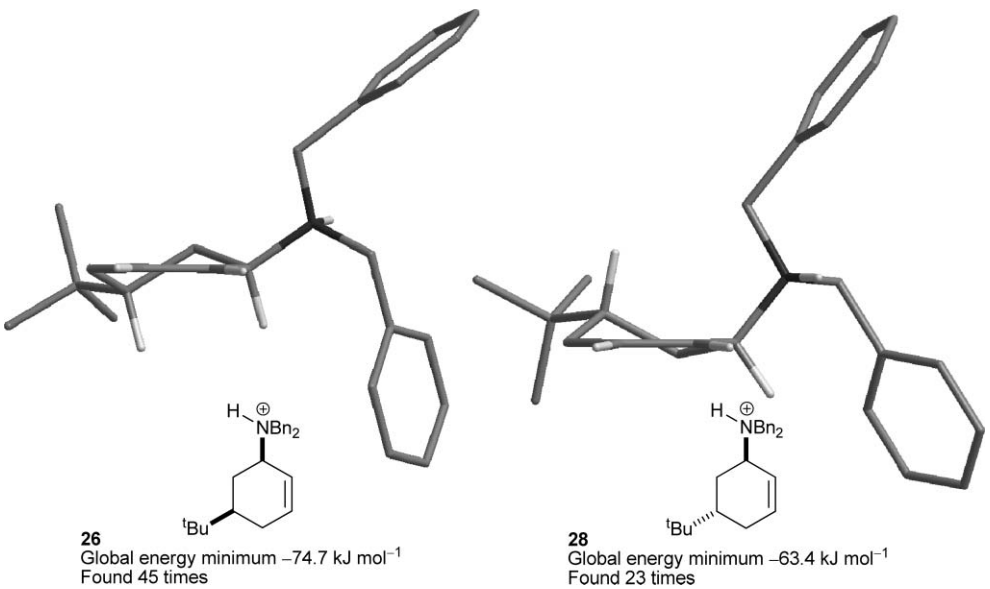


Fig. 9 Chem 3D representation of the MacroModel global energy predictions of for ammoniums **26** and **28** (some H atoms omitted for clarity).

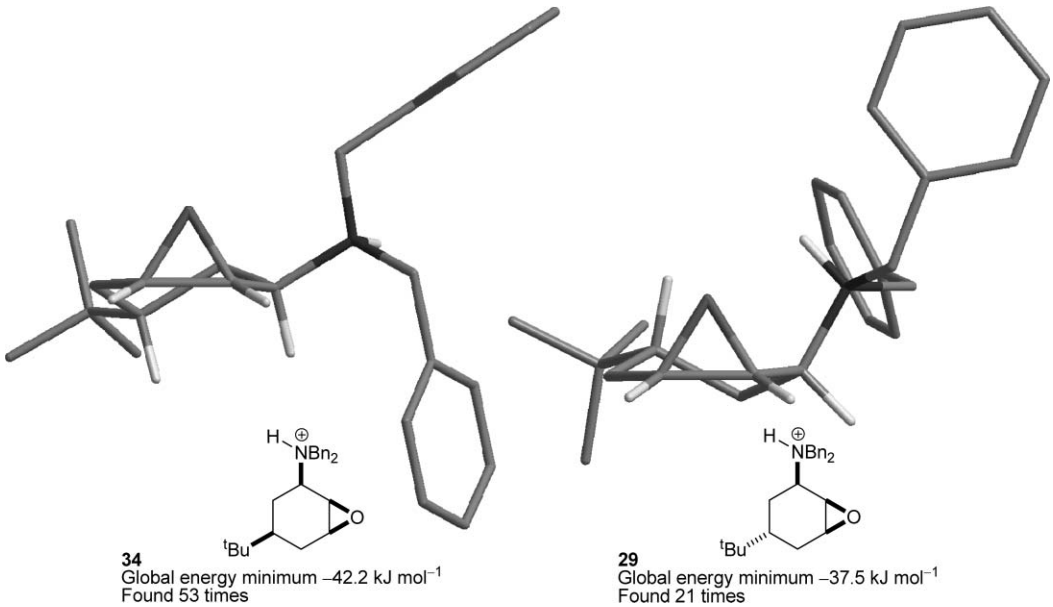
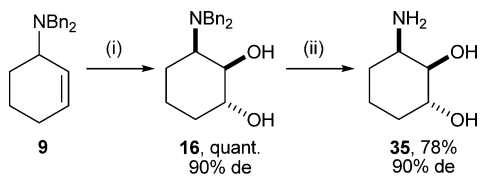


Fig. 10 Chem 3D representation of the MacroModel global energy predictions of for epoxide ammoniums **34** and **29** (some H atoms omitted for clarity).

"One-pot" dihydroxylation: Application to tertiary, secondary and primary amines

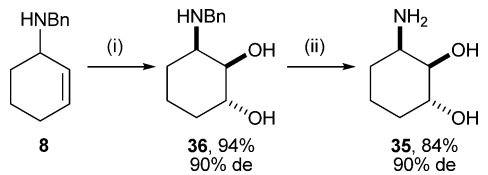
The viability of a "one-pot" dihydroxylation procedure was next examined. After treatment of allylic amine **9** with Cl_3CCO_2H and *m*CPBA for 21 h, sat aq Na_2SO_3, followed by MeOH and then K_2CO_3, were added to the crude reaction mixture, affording *N*,*N*-dibenzylamino diol **16** directly, in quantitative yield and 90% de, on a >10 g scale. Subsequent hydrogenolytic *N*-debenzylation gave 3-aminocyclohexane-1,2-diol **35** in 78% overall yield and 90% de (Scheme 8).



Scheme 8 *Reagents and conditions*: (i) Cl_3CCO_2H (5 eq), *m*CPBA, DCM, rt, 24 h, then Na_2SO_3 (sat aq), then K_2CO_3, MeOH, rt, 24 h; (ii) H_2 (1 atm), $Pd(OH)_2/C$, MeOH.

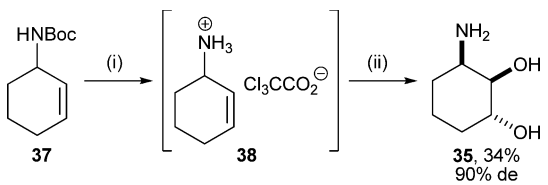
The applicability of this oxidation protocol to secondary and primary amines was next investigated. Thus, 3-(*N*-benzylamino)-cyclohex-1-ene **8** was treated under the optimum oxidation and transesterification conditions, followed by column chromatography on neutral alumina to give 1,2-*anti*-2,3-*syn*-**36** in 90% de and 94% yield. The relative configuration within **36** was assigned by analogy to the tertiary amine case, and subsequently proven through hydrogenolysis to furnish amino diol **35** in 90% de and 84% yield (Scheme 9).

In order to access the corresponding primary amine, *N*-deprotection of **37** with Cl_3CCO_2H (5 eq) generated trichloroacetate salt **38** *in situ*. To this mixture was added *m*CPBA giving, after transesterification and column chromatography on neutral alumina, amino diol **35** in 90% de and 34% yield, which was



Scheme 9 *Reagents and conditions*: (i) Cl_3CCO_2H (5 eq), *m*CPBA, DCM, rt, 21 h, then Na_2SO_3 (sat aq), then K_2CO_3, MeOH, rt, 16 h; (ii) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h.

spectroscopically identical to those samples prepared from tertiary amine **9** and secondary amine **8** (Scheme 10).



Scheme 10 *Reagents and conditions*: (i) Cl_3CCO_2H (5 eq), rt; (ii) *m*CPBA (1.6 eq), rt, 21 h, then K_2CO_3, MeOH, rt, 16 h.

Conclusion

In conclusion, primary, secondary and tertiary 3-aminocyclohex-1-enes are susceptible to highly chemo- and diastereoselective olefinic dihydroxylation upon treatment with either Cl_3CCO_2H or TsOH and *m*CPBA. The high levels of stereoselectivity observed are consistent with the formation of an ammonium ion *in situ* that directs epoxidation with *m*CPBA to the *syn*-face, with subsequent regio- and stereoselective *trans*-diaxial epoxide opening and hydrolysis generating the corresponding 1,2-*anti*-2,3-*syn*-3-aminocyclohexane-1,2-diol. The application of this protocol to facilitate the synthesis of all the diastereoisomers of 3-aminocyclohexane-1-2-diol is reported in the following paper.

Experimental

General experimental

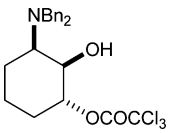
Water was purified by an Elix® UV-10 system. *m*CPBA was supplied as a 70–77% slurry in water (Aldrich) and titrated according to the procedure of Swern[14] immediately before use. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed either on Kieselgel 60 silica on a glass column, or on a Biotage SP4 automated flash column chromatography platform.

Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

General procedure for ammonium-directed dihydroxylation

The requisite acid was added to a stirred solution of the requisite allylic amine in DCM, and the resultant solution was stirred at rt for 5 min. Freshly titrated *m*CPBA was then added and the solution was stirred at rt for 21 h. The mixture was then diluted with DCM and washed with sat. aq. Na_2SO_3 until starch–iodide paper indicated that no *m*CPBA was present. The organic layer was washed four times with 0.1 M aq. $NaHCO_3$, dried and concentrated *in vacuo*.

(1*RS*,2*RS*,3*RS*)-1-Trichloroacetoxy-2-hydroxy-3-(*N*,*N*-dibenzylamino)cyclohexane 11



Following the *general procedure*, Cl_3CCO_2H (294 mg, 1.81 mmol), **9** (100 mg, 0.36 mmol) in DCM (1 mL), and *m*CPBA (81%, 122 mg, 0.58 mmol) gave **11** as a colourless oil (165 mg, quant, 90% de); ν_{max} (film) 3424 (O–H), 2941 (C–H), 1762 (C=O); δ_H (400 MHz, $CDCl_3$) 1.50–1.97 (6 H, m, C(4)H_2, C(5)H_2, C(6)H_2), 2.91 (1 H, br s, OH), 2.99–3.08 (1 H, m, C(3)H), 3.74 (1 H, d, *J* 14.4, N(C$H_A$$H_B$Ph)$_2$), 3.94 (1 H, d, *J* 14.4, N(CH$_A$$H_B$Ph)$_2$), 4.14–4.19 (1 H, m, C(2)H), 5.14–5.20 (1 H, m, C(1)H), 7.22–7.38 (10 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.8, 22.6, 24.2 (*C*(4), *C*(5), *C*(6)), 54.9 (N(*C*H$_2$Ph)$_2$), 57.5 (*C*(3)), 67.8 (*C*(2)), 77.9 (*C*(1)), 89.9 (*C*Cl$_3$), 127.0 (*p-Ph*), 128.5, 128.6 (*o-*, *m-Ph*), 139.8 (*i-Ph*), 161.0 (*C*=O); *m*/*z* (ESI$^+$) 456 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{25}{}^{35}Cl_3NO_3^+$ ([M + H]$^+$) requires 456.0895; found 456.0891.

Rate studies of the ammonium-directed dihydroxylation reaction

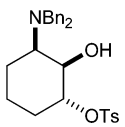
A solution of **9** (15 mg, 0.054 mmol) in $CDCl_3$ (0.15 mL) was prepared in a 3 mm NMR tube. Cl_3CCO_2H (44 mg, 0.27 mmol) was added and the tube was shaken for 5 min. *m*CPBA (87% by wt, 17 mg, 0.087 mmol) was then added, and the progress of the reaction was monitored by ^{1}H NMR spectroscopic analysis.

X-Ray crystal structure determination for 12

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite-monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[29]

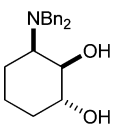
12: $C_{17.5}H_{18}Cl_{6.67}N_{0.67}O_{4.67}$, M = 548.69, monoclinic, space group *C*2/*c*, *a* = 24.5125(2) Å, *b* = 9.82110(10) Å, *c* = 30.9595(4) Å, β = 106.7096(5)°, *V* = 7138.47(13) Å^3, *Z* = 12, μ = 0.823 mm^{-1}, colourless plate, crystal dimensions = 0.2 × 0.2 × 0.3 mm^3. A total of 7984 unique reflections were measured for 5 < θ < 27 and 5826 reflections were used in the refinement. The final parameters were $wR_2 = 0.095$ and $R_1 = 0.092$ [$I > 3\sigma(I)$]. CCDC 679350.‡

(1*RS*,2*RS*,3*RS*)-1-*p*-Toluenesulfonyloxy-2-hydroxy-3-(*N*,*N*-dibenzylamino)cyclohexane 15



Following the *general procedure*, TsOH (206 mg, 1.08 mmol), **9** (100 mg, 0.36 mmol) in DCM (1 mL), and *m*CPBA (87%, 117 mg, 0.58 mmol) gave **15** as a green oil (167 mg, quant, 90% de); ν_{max} (film) 3050 (O–H), 2946 (C–H); δ_H (400 MHz, $CDCl_3$) 1.43–1.85 (6H, m, C(4)H_2, C(5)H_2, C(6)H_2), 2.44 (3H, s, ArCH_3), 2.92–3.13 (2H, br m, C(3)H, OH), 3.77 (4H, AB system, N(CH_2Ph)$_2$), 4.03–4.09 (1H, m, C(2)H), 4.75–4.79 (1H, m, C(1)H), 7.23–7.37 (12H, m, *Ar*, *Ph*), 7.75–7.81 (2H, d, *J* 7.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.2 (*C*H$_2$), 21.7 (Ar*C*H$_3$) 23.4, 25.1 (*C*H$_2$), 54.6 (N(*C*H$_2$Ph)$_2$), 58.4 (*C*(3)), 67.4 (*C*(2)), 80.1 (*C*(1)), 127.0, 127.8, 128.5, 128.6, 129.9, 133.9, 139.8, 144.8 (*Ar*, *Ph*); *m*/*z* (ESI$^+$) 466 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}NO_4S^+$ ([M + H]$^+$) requires 466.2047; found 466.2045.

(1*RS*,2*RS*,3*RS*)-3-(*N*,*N*-Dibenzylamino)cyclohexane-1,2-diol 16



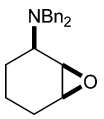
K_2CO_3 (500 mg) was added to a stirred solution of **11** (164 mg, 0.36 mmol) in MeOH (5 mL), and the resultant suspension was stirred at rt for 16 h then concentrated *in vacuo*. H_2O (10 mL) was added and the mixture was extracted with DCM (4 × 10 mL). The combined organic extracts were then washed with brine (50 mL), dried and concentrated *in vacuo*. Purification *via* flash column

chromatography (gradient elution, eluent 0%→100% EtOAc in 40–60 °C petrol) gave **16** as a viscous, pale yellow oil (112 mg, quant, 90% de); ν_{max} (film) 3407 (O–H), 3027, 2937 (C–H); δ_H (400 MHz, $CDCl_3$) 1.43–1.89 (6H, m, C(4)H_2, C(5)H_2, C(6)H_2), 2.14 (1H, br s, O*H*), 3.10–3.20 (1H, m, C(3)*H*), 3.69–3.78 (2H, d, *J* 14.4, N(CH_APh)$_2$), 3.81–3.91 (3H, m, C(2)*H*, N(CH_BPh)$_2$), 3.99–4.06 (1H, m, C(1)*H*), 7.22–7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.9, 23.8, 28.1 (*C*(4), *C*(5), *C*(6)), 55.0 (N(*C*H$_2$Ph)$_2$), 58.3 (*C*(3)), 70.5 (*C*(1)), 71.1 (*C*(2)), 127.0 (*p-Ph*), 128.5, 128.7 (*o-*, *m-Ph*), 139.8 (*i-Ph*); *m/z* (ESI$^+$) 312 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}NO_2^+$ ([M + H]$^+$) requires 312.1958; found 312.1952.

"One-pot" dihydroxylation protocol

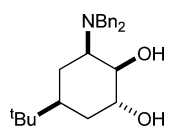
Cl_3CCO_2H (29.5 g, 0.18 mol) was added to a stirred solution of **9** (10 g, 36 mmol) in DCM (100 mL) and the resultant solution was stirred at rt for 5 min. Freshly titrated *m*CPBA (87%, 11.5 g, 58 mmol) was then added and the solution was stirred at rt for 21 h. Sat. aq. Na_2SO_3 was then added until starch–iodide paper indicated that no *m*CPBA was present. MeOH (500 mL) and K_2CO_3 (10 g) were then added and the resultant suspension was stirred at rt for 16 h before being concentrated *in vacuo*. H_2O (500 mL) was then added and the mixture was extracted with DCM (4 × 500 mL). The combined organic extracts were washed with brine (1 L), dried and concentrated *in vacuo* to give **16** as a viscous, pale yellow oil (11.4 g, quant, 90% de).

(1*RS*,2*SR*,3*SR*)-1,2-Epoxy-3-(*N*,*N*-dibenzylamino)-cyclohexane 17



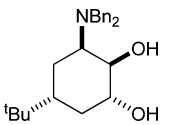
DBU (7.94 mL, 52.8 mmol) was added to a stirred solution of **15** (22.3 g, 49 mmol, 90% de) in DCM (100 mL) at rt and the reaction mixture was stirred for 24 h. 10% aq. $CuSO_4$ (500 mL) was added and the mixture was extracted with DCM (3 × 500 mL). The combined organic extracts were washed with H_2O (3 × 500 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, eluent 0%→100% Et_2O in 40–60°C petrol) gave **17** as a colourless oil (13.6 g, 95%, >98% de); ν_{max} (film) 3061, 2938 (C–H); δ_H (400 MHz, $CDCl_3$) 1.11–1.39 (1H, m, C(5)H_A), 1.55–1.96 (5H, m, C(4)H_2, C(5)H_B, C(6)H_2), 3.00–3.10 (1H, m, C(3)*H*), 3.11–3.17 (1H, m, C(1)*H*), 3.37 (1H, app d, *J* 4.0, C(2)*H*), 3.75 (2H, d, *J* 14.1, N(CH_AH$_B$Ph)$_2$), 3.96 (2H, d, *J* 14.1, N(CH$_A$$H_B$Ph)$_2$), 7.24–7.53 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.3, 21.6, 23.1 (*C*(4), *C*(5), *C*(6)), 51.7 (*C*(1)), 54.7 (N(*C*H$_2$Ph)$_2$), 55.0 (*C*(2)), 55.7 (*C*(3)), 126.7 (*p-Ph*), 128.2, 128.6 (*o-*, *m-Ph*), 140.7 (*i-Ph*); *m/z* (ESI$^+$) 294 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{24}NO^+$ ([M + H]$^+$) requires 294.1852; found 294.1853.

(1*RS*,2*RS*,3*RS*,5*SR*)-3(-*N*,*N*-Dibenzylamino)-5-*tert*-butylcyclohexane-1,2-diol 23



Cl_3CCO_2H (44 mg, 0.27 mmol) was added to a solution of *syn*-**21** (13 mg, 0.039 mmol) in $CDCl_3$ (0.15 mL) in a 3 mm NMR tube. After 5 min, *m*CPBA (87% by wt, 17 mg, 0.086 mmol) was added and the progress of the reaction monitored by ^{1}H NMR spectroscopy. After completion the reaction mixture was transferred to a round-bottom flask and sat. aq. Na_2SO_3 was added until starch–iodide paper indicated that no *m*CPBA remained. MeOH (1 mL) and K_2CO_3 (50 mg) were added and the suspension stirred for 24 h before being concentrated *in vacuo*. H_2O (2 mL) was added and the mixture was extracted with DCM (4 × 2 mL). The combined organic extracts were washed with brine (10 mL), dried, and concentrated *in vacuo* to give **23** as a colourless oil (14 mg, quant, >95% de); ν_{max} (film) 3376 (O–H), 3085, 3063, 3028, 2950, 2689 (C–H); δ_H (400 MHz, $CDCl_3$) 0.81 (9H, s, C*Me*$_3$), 1.06–1.17 (1H, app q, *J* 12.1, C(4)H_{ax}), 1.40 (1H, br tt, *J* 12.3, 2.8, C(5)*H*), 1.50 (1H, td, *J* 13.0, 2.8, C(6)H_{ax}), 1.59–1.66 (1H, m, C(6)H_{eq}), 1.72–1.80 (1H, m, C(4)H_{eq}), 3.06 (1H, br dt, *J* 12.1, 3.0, C(3)*H*), 3.77 (2H, d, *J* 16.0, N(CH_AH$_B$Ph)$_2$), 3.87 (2H, d, *J* 16.0 N(CH$_A$$H_B$Ph)$_2$), 4.01 (1H, app br t, *J* 2.5, C(2)*H*), 4.15 (1H, app q, *J* 3.0, C(1)*H*), 7.19–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.7 (*C*(4)), 27.4 (C*Me*$_3$), 28.4 (*C*(6)), 32.2 (*C*Me$_3$), 40.2 (*C*(5)), 54.9 (N(*C*H$_2$Ph)$_2$), 59.9 (*C*(3)), 69.3 (*C*(2)), 70.2 (*C*(1)), 126.9 (*p-Ph*), 128.4, 128.5 (*o-*, *m-Ph*), 139.2 (*i-Ph*); *m/z* (ESI$^+$) 368 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{34}NO_2^+$ ([M + H]$^+$) requires 368.2584; found 368.2584.

(1*RS*,2*RS*,3*RS*,5*RS*)-3-(*N*,*N*-Dibenzylamino)-5-*tert*-butylcyclohexane-1,2-diol 25



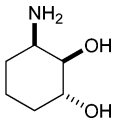
Cl_3CCO_2H (44 mg, 0.27 mmol) was added to a solution of *anti*-**22** (18 mg, 0.054 mmol) in $CDCl_3$ (0.15 mL) in a 3 mm NMR tube. After 5 min, *m*CPBA (87% by wt, 17 mg, 0.086 mmol) was added and the progress of the reaction monitored by ^{1}H NMR spectroscopy. After completion the reaction mixture was transferred to a round-bottom flask and sat. aq. Na_2SO_3 was added until starch–iodide paper indicated that no *m*CPBA remained. MeOH (1 mL) and K_2CO_3 (50 mg) were added and the suspension stirred for 24 h before being concentrated *in vacuo*. H_2O (2 mL) was added and the mixture was extracted with DCM (4 × 2 mL). The combined organic extracts were washed with brine (10 mL), dried, and concentrated *in vacuo* to give a 22 : 78 mixture of **24**:**25** as a colourless oil (20 mg); ν_{max} (film) 3354 (O–H), 3068, 3032, 2956, 2871 (C–H); *m/z* (ESI$^+$) 368 ([M + H]$^+$, **25**, 100%), 350 ([M + H]$^+$, **24**, 74%); HRMS (ESI$^+$) $C_{24}H_{34}NO_2^+$ ([M + H]$^+$, **25**) requires 368.2584; found 368.2582.

Data for **24**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.84 (9H, s, C*Me*$_3$), 3.67 (2H, d, *J* 12.0, N(CH_AH$_B$Ph)$_2$), 3.97 (2H, d, *J* 12.0, N(CH$_A$$H_B$Ph)$_2$).

Data for **25**: δ_H (400 MHz, $CDCl_3$) 0.93 (9H, s, C*Me*$_3$), 1.03 (1H, app q, *J* 12.5, C(6)H_{ax}), 1.17–1.37 (1H, m, C(4)H_{ax}), 1.57 (1H, br tt, *J* 12.9, 3.4, C(5)*H*), 2.05 (1H, br ddd, *J* 12.4, 6.8, 3.0, C(6)H_{eq}), 2.15–2.23 (1H, m, C(4)H_{eq}), 3.21 (1H, dd, *J* 9.6, 7.3, C(2)*H*), 3.33 (1H, app t, *J* 6.6, C(3)*H*), 3.43 (2H, d, *J* 13.1, N(CH_AH$_B$Ph)$_2$), 3.85 (1H, ddd, *J* 11.4, 9.6, 4.3, C(1)*H*), 3.95 (2H, d, *J* 13.1, N(CH$_A$$H_B$Ph)$_2$), 7.20–7.45 (10H, m, *Ph*); δ_C (100 MHz,

$CDCl_3$) 23.5 (*C*(4)), 27.3 (CMe_3), 32.3 (*C*(6)), 32.8 (CMe_3), 43.0 (*C*(5)), 56.1 (*C*(3)), 56.4 ($N(CH_2Ph)_2$), 73.4 (*C*(1)), 75.0 (*C*(2)), 127.5 (*p-Ph*), 128.6, 129.0 (*o-*, *m-Ph*), 138.8 (*i-Ph*).

(1*RS*,2*RS*,3*RS*)-3-Aminocyclohexane-1,2-diol 35



$Pd(OH)_2$/C (50 mg) was added to a vigorously stirred suspension of **16** (100 mg, 0.32 mmol) in degassed MeOH (1 mL) and the resultant suspension was stirred at rt under H_2 (1 atm) for 24 h. The suspension was then filtered through a pad of Celite (eluent MeOH) and the filtrate was concentrated *in vacuo* to give **35** as a pale yellow solid (33 mg, 78%, 90% de); mp 115–116 °C; ν_{max} (KBr) 3355 (O–H), 2936, 2867 (C–H); δ_H (400 MHz, d_4-MeOH) 1.34–1.46 (1H, m, C(6)H_A), 1.47–1.66 (4H, m, C(4)H_2, C(5)H_2), 1.74–1.87 (1H, m, C(6)H_B), 3.02–3.12 (1H, m, C(3)*H*), 3.52 (1H, dd, *J* 5.3, 3.3, C(2)*H*), 3.74–3.82 (1H, m, C(1)*H*); δ_C (100 MHz, d_4-MeOH) 18.6, 29.2 (*C*(4), *C*(5), *C*(6)), 49.9 (*C*(3)), 70.0 (*C*(1)), 74.2 (*C*(2)); *m/z* (ESI^+) 132 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_6H_{14}NO_2^+$ ($[M + H]^+$) requires 132.1019; found 132.1022.

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