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Towards a chemo-enzymatic method for the asymmetric synthesis of β-amino tertiary alcohols†‡

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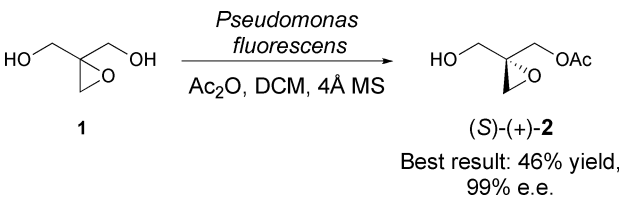
The synthesis of a number of β-amino tertiary alcohols has been achieved *via* ring-opening of an unsymmetrical epoxide with primary and secondary amines. The results revealed that primary amines give symmetrical triol products following an undesired acyl migration reaction, whereas secondary amines give the desired chiral (racemic) products. Furthermore, we demonstrate that asymmetric products can be formed using enantiomerically pure epoxide and aromatic amines without any loss of enantiomeric excess.

Tertiary alcohols and their derivatives are an important class of compound, which are found in numerous natural products and pharmaceuticals; they also represent useful chemical building blocks for synthetic manipulation to other useful products.[1–3] In particular, β-amino tertiary alcohols are present in natural products including pumiliotoxin A and other alkaloids from the poison dart frogs of the dendrobates genus,[4] setoclavine,[5] paraherquamide A,[6] and the anticancer compound vincristine.[7] Likewise, numerous biologically active non-natural compounds possess this moiety.[8–10] Despite the importance of tertiary alcohols, a general asymmetric synthesis of them still provides a challenge to the synthetic community. Current methods towards the development of enantiomerically enriched tertiary alcohols include: the enantioselective addition of organometallic reagents to ketones[1–3,11,12] as well as various enzymatic methods by kinetic resolution[13] and desymmetrisation.[14] However, due to the almost spherical, bulky shape of tertiary alcohols, their direct enzymatic resolution is difficult, as enzymes are unable to distinguish between the enantiomers efficiently.[13]

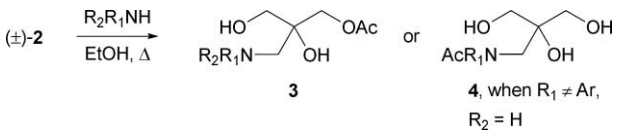
Recently, we published a method for the desymmetrisation of the prochiral diol (2-hydroxymethyl-oxiranyl)-methanol (**1**), in which the enantiopure epoxide **2** was isolated in 46% yield with 97-99% enantiomeric excess, Scheme 1.[15]



Scheme 1 Desymmetrisation of prochiral diol (**1**).

The motivation behind that work was to develop an asymmetric synthesis of a suitable building block that could be further developed into a method for the synthesis of enantiopure tertiary alcohols in an efficient and economical manner by opening the epoxide.[16–21] Herein, we report our results on the extension of that work regarding the conversion of the aforementioned enantiomerically pure epoxide to the corresponding asymmetric tertiary alcohol.

In our previous work,[15] we established the enzymatic conditions necessary to obtain the enantiopure epoxide **2**, and our attempts to develop the method into an asymmetric synthesis of tertiary alcohols began by ascertaining the conditions needed to open the epoxide with a range of amines on racemic material, Scheme 2.



Scheme 2 Synthesis of β-amino tertiary alcohols.

Initial experiments conducted to open the epoxide set out with conditions closely related to established procedures, which included the use of catalysts; microwave irradiation and by varying the equivalents of amine nucleophile used. Unfortunately, all these attempts failed to produce material in sufficient quantities due to low conversion of the starting material.[16–21] Eventually, suitable conditions were found which opened the epoxide in good to excellent yields: the epoxide was heated in the presence of the amine (3 eq.) at reflux, in ethanol, for 1 h. Table 1 outlines the results of this screen displaying isolated yields which vary from 21-96%. The results highlighted a few points that are worthy of further discussion: 1] it appears as though secondary and primary aromatic amines give the desired product **3** (entries 1-5, 10, 12, 14, 16, 17); and 2] primary amines, give the required epoxide ring-opened product, but, in such cases, the acetate group seemingly migrates from oxygen onto the newly introduced nitrogen atom during the course of the reaction to give triol **4** (entries 6-9, 11, 13, 15); the structures of two of the products of this rearrangement (amine = propargylamine and allylamine, entries 9 and 11, respectively) have been proved by X-ray crystallography, Fig. 1.[22]

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‡ Electronic supplementary information (ESI) available: Experimental details. CCDC reference numbers 736703–736704. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b916013b

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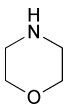
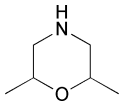
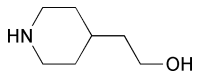
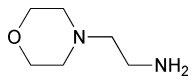
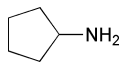
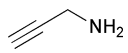
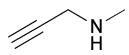
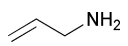
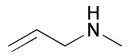
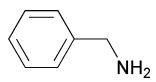
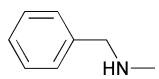
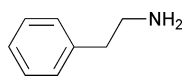
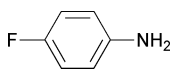
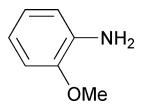
Table 1 Results of amine addition to epoxide (±)-**2**[a]

Entry	Compound	Amine	Isomer[b]	Yield (%)[c]
1	**5**		**3**	—[d]
2	**6**		**3**	55
3	**7**		**3**	76
4	**8**		**3**	84
5	**9**		**3**	77
6	**10**		**4**	89
7	**11**		**4**	21
8	**12**		**4**	31
9	**13**		**4**	93
10	**14**		**3**	80[e,f]
11	**15**		**4**	96
12	**16**		**3**	55[e,f]
13	**17**		**4**	74
14	**18**		**3**	63
15	**19**		**4**	54
16	**20**		**3**	96
17	**21**		**3**	93

[a] *Reagents and conditions*: Epoxide **2** was dissolved in ethanol (0.1 M), the amine added (3 equivalents) and the reaction heated to reflux for 1 h. [b] See Scheme 2. [c] Isolated yields. [d] Trace product was observed after 1 h or 4 h at reflux. [e] The reaction was purified by the removal of excess amine under high vacuum. [f] Reaction left for 4 h.

As can be seen from the X-ray structures (Fig. 1) and NMR data (supporting information†), the result of this acyl migration means these products are symmetrical and thus would not give asymmetric products with enantiomerically pure epoxide.

To confirm that the formation of isomer **3** (Scheme 2) was due to the use of secondary amines, which lack a replaceable hydrogen atom in the epoxide ring-opened product, thus preventing acyl migration, and not due to other, unknown factors, three secondary *N*-methylated amines were reacted alongside the analogous primary amines (entries 9 and 10; 11 and 12; 13 and 14) and indeed it was found that the products of the *N*-methylated compounds (entries 10, 12 and 14) gave the desired isomer **3** exclusively without the concomitant acyl migration seen in the cases with the primary amines, as expected, albeit in a slightly lower yield. The low yield of entry 1 is surprising, however, repeating the reaction numerous times resulted in the isolation of a compound determined to be *N*-acyl pyrrolidine, presumably formed *via* an intermolecular acyl transfer reaction between (±)-**2** and pyrrolidine. It is assumed that the reduced steric bulk and the higher nucleophilicity of pyrrolidine, compared to the other 6-membered ring amines, is the cause of this undesired by-product being formed; as evidenced by the good yields with the less reactive, more bulky amines. Also, the product from the reaction with 2,6-dimethylmorpholine produced a complex mixture of isomers since the amine used was obtained as a mixture of *cis* and *trans*-isomers (entry 4), however, mass spectral data was indicative of the desired product (HRMS FAB $[M+H]^+$ 262.1648 $C_{12}H_{23}O_5N+H^+$ requires 262.1654).

We assume that the reduced nucleophilicity of the primary aromatic amines prevents the acyl migration seen with aliphatic primary amines. From empirical observation, we believe that the migration occurs after epoxide-opening has taken place and not *via* acylation of the amine nucleophile followed by ring-opening with the formed acetamide as nucleophile. In the case of allylamine, carrying out the reaction at room temperature did not prevent acyl migration taking place, however, the use of a suitable protecting group (*e.g.* Bn) may allow a switch in the isomer being produced by temporarily forming a secondary amine which can be deprotected later.

Under the basic conditions used we did not detect any products resulting from epoxide ring-opening at the more hindered carbon.

Following on from the work using racemic epoxide **2**, outlined in Table 1, we turned our attention to the reaction using enantiomerically enriched (97% ee)[15] epoxide to determine if the conditions would allow us to develop an asymmetric synthesis of tertiary alcohols. Compounds **20** and **21** were amenable to enantiomeric separation using HPLC with a chiral stationary phase, and thus were the compounds used to establish if the enantiomeric excess of the starting material was maintained in the ring-opened products. Indeed, when the enantiomerically pure epoxide (*S*)-(+)-**2** was used, no loss of enantiomeric excess was observed with 4-fluoroaniline and *o*-anisidine, Table 2, confirming that the method is suitable for the synthesis of enantiomerically pure β-amino tertiary alcohols.[23]

In summary, we have developed a method for the asymmetric synthesis of β-amino tertiary alcohols *via* ring-opening of an enantiomerically pure epoxide with primary aromatic amines. The enantiomeric excess of the epoxide is maintained in the tertiary

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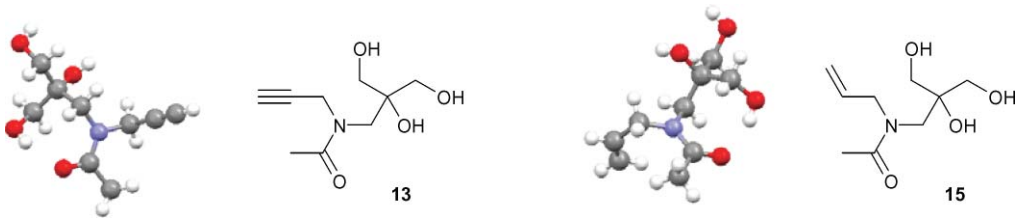

Fig. 1 X-Ray crystal structures of **13** and **15**.

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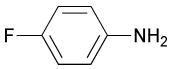
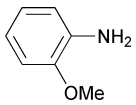
Table 2 Results of aromatic amine addition to (*S*)-(+)-**2**[a]

Entry	Amine	Isomer[b]	Ee (%)[c]
1		**3**	97
2		**3**	97

[a] *Reagents and conditions*: See ref 23. [b] See Scheme 2. [c] Determined using HPLC.

alcohol products, and thus we believe the method should be applicable to the synthesis of similar β-amino tertiary alcohols.

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22 X-Ray crystallographic data: **13**: $C_9H_{15}NO_4$, $M = 201.22$, monoclinic, $P2(1)/c$, $a = 9.2759(13)$, $b = 14.318(2)$, $c = 7.9435(11)$ Å, $\beta = 110.024(3)$, $V = 991.2(2)$ Å^3, $T = 100(2)$ K, $Z = 4$, $\mu = 0.106$ mm^{-1}, 5675 reflections collected, of which 2032 were unique, $R_{int} = 0.0588$, CCDC 736704; **15**: $C_9H_{17}NO_4$, $M = 203.24$, monoclinic, $P2(1)/c$, $a = 9.763(6)$, $b = 14.702(10)$, $c = 7.816(5)$ Å, $\beta = 108.886(10)$, $V = 1061.5(12)$ Å^3, $T = 100(2)$ K, $\mu = 0.099$ mm^{-1}, 3837 reflections collected, of which 1297 were unique, $R_{int} = 0.1552$, CCDC 736703. Because the crystal was weakly diffracting, it was necessary to use rigid bond and similarity restraints on the anisotropic atomic displacement parameters to avoid them becoming unrealistic, leading to the application of a total of 108 restraints‡.
23 These reactions were performed in "one-pot" as follows: To a solution of **1** (100 mg, 0.96 mmol), Amano L, AK (200 mg, 2 wt. eq.) and molecular sieves (4 Å) in dichloromethane (10 ml, 0.1 M) was added acetic anhydride (1.8 equivalents) and the reaction left for one hour at 37 °C. The mixture was filtered through Celite® and the filtrate was reduced *in vacuo*. Ethanol (10 ml, 0.1 M) and the corresponding amine (see Table 2) was added and the mixture heated at reflux for 4 hours. The mixture was reduced *in vacuo* and purified by column chromatography (SiO_2; 20% EtOH in EtOAc). The enantiomeric purity was determined by HPLC; Agilent 1100 Series. Chiralpack AD, 1 ml/min, 80/20 isohexene in EtOH at 25 °C.