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# A highly regioselective azidolysis of 2,3-epoxy amines: an unexpected [Ti(O-*i*-Pr)$_2$(N$_3$)$_2$] mediated C-2 opening

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ABSTRACT

The Lewis acid-catalysed regioselective azidolysis of 2,3-epoxy amines has been investigated. The results obtained demonstrated that using TMSN$_3$ as a source of azide, the appropriate choice of Lewis acid allowed to direct the regiochemistry of the ring opening. The present methodologies provide a powerful tool in organic synthesis for the preparation of diaminoalcohol moieties.



Epoxides are important synthons in organic chemistry because they can be easily prepared in an optically active form and their reactions with various nucleophiles lead to interesting regio- and stereoselective ring opened products.

Among these, the diaminoalcoholic moiety is widespread in nature as part of many biologically active natural products and also as the key component of a variety of synthetic compounds with multiple applications in medicinal chemistry as therapeutically active agents or as pharmacological tools.

Examples are the hydroxyethylamine (HEA) transition state isostere, found in many peptidomimetic protease inhibitors such as HIV protease,[1] renine,[2] γ-secretase,[3] human β-secretase (BACE-1),[4] malarial plasmepsins I and II[5] and in the natural products as (−)-balanol[6] and its regioisomer ophiocordin[7] (Fig. 1).

The azidolysis of epoxides is a subject of continuous interest.[8] During our study concerning the synthesis of new HIV-protease inhibitors,[9] we were intrigued by the controlled azidolysis of 2,3-epoxy amines to obtain the corresponding azido derivatives, direct precursors of hydroxyethylamine (HEA) isosters.

Since apart from few reports concerning only cyclic substrates,[10] to our best knowledge this reactivity has never been extensively exploited, we focused our attention towards this goal. With this purpose we decided to use TMSN$_3$ as the azide source in the presence of three different Lewis acids: BF$_3$·OEt$_2$ (method A), ZnCl$_2$ (method B) and Ti(*O*-*i*-Pr)$_4$ (method C), which were already successfully employed on 2,3-epoxy alcohols or esters.[11] The C-3 opening always observed with these methods was generally explained invoking a cyclic chelate transition state model **3** between the Lewis acid and the two oxygens of epoxy derivatives (Fig. 2) with an intermolecular attack of the nucleophiles.[12]

Our preliminary studies were restricted, for convenience, to racemic compounds;[13] the 2,3-epoxy amines were synthesized in satisfactory yield from the corresponding allylic alcohols through the sequence described in Scheme 1: (i) epoxidation of allylic alcohol, (ii) transformation of the hydroxyl function in a good leaving group such as the mesylate, (iii) nucleophilic substitution with the suitable amine (Scheme 1).

When 2,3-epoxy amines **10a–f** were submitted to **A** or **B** methods, the expected 3-azido-2-hydroxy amines **11a–f** were obtained (as demonstrated by spin–spin decoupling experiments on the peracetylated derivatives) in good chemical yield and excellent regioisomeric ratio, independently from the steric hindrance of R′ (Table 1).

On the contrary, an unexpected behaviour was observed when the same 2,3-epoxy amines **10a–c** and **10e–f** were treated with [Ti(O-*i*-Pr)$_2$(N$_3$)$_2$], prepared in situ by refluxing Ti(*O*-*i*-Pr)$_4$ and TMSN$_3$ in benzene for at least 5 h (until the solution became clear) and adding successively the substrates.[14] Under these reaction conditions, the only isolated products were **12a–c** and **12e–f**, highlighting the nucleophilic attack at C-2 position, rarely reported for any epoxy derivatives.

Apart from particular cases with steric and/or electronic bias and an epoxide opening developed by using NaN$_3$-(CH$_3$O)$_3$B system,[15] in general this regioselectivity is presumed to be due to

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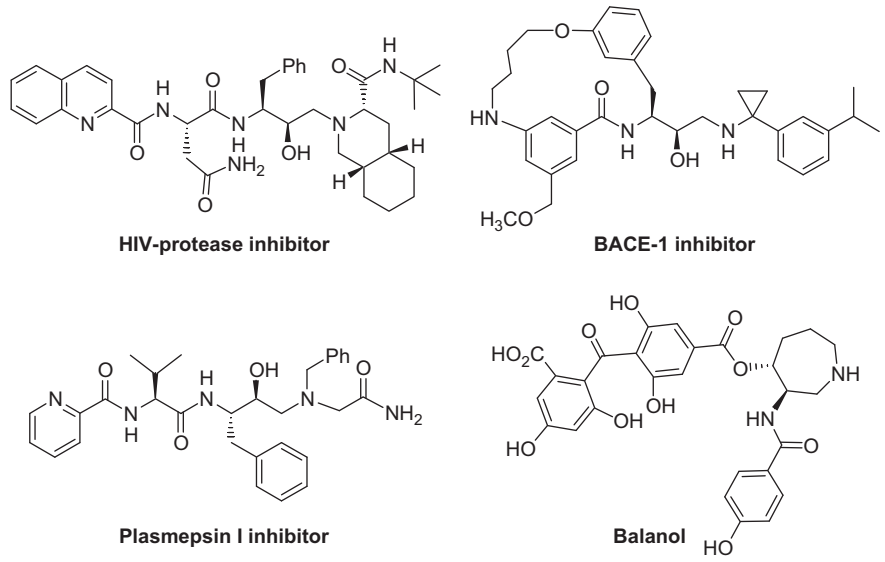



**Figure 1.** Examples of HEA isoster containing compounds.

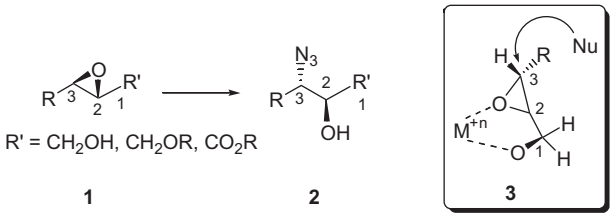
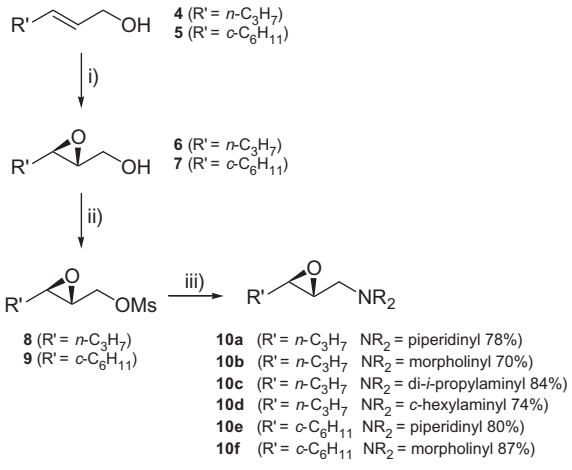
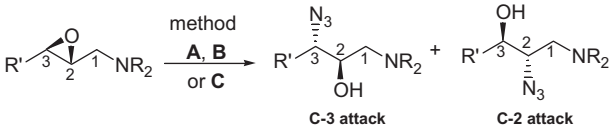



**Figure 2.** Hypothesized cyclic chelate T.S.




**Scheme 1.** Synthesis of 2,3-epoxy amines; (i) *m*-CPBA, $CH_2Cl_2$, rt, 97–98%; (ii) $CH_3SO_2Cl$, $Et_3N$, DMAP, $CH_2Cl_2$, rt, 88–95%; (iii) amine $R_2NH$, neat, 50 °C, 70–87%.

**Table 1**
Lewis acid-mediated azidolysis of 2,3-epoxy amines[17,18]




| Entry | Epoxide | Method[a] | C3:C2[b] | Yield azide[c] | | Time (h) |
|---|---|---|---|---|---|---|
| | | | | 11 | 12 | |
| 1 | **10a** | **A** | >95:5 | 85 | — | 6 |
| 2 | **10a** | **B** | >95:5 | 76 | — | 45 |
| 3 | **10a** | **C** | <5:95 | — | 82 | 0.8 |
| 4 | **10b** | **A** | >95:5 | 98 | — | 4 |
| 5 | **10b** | B | >95:5 | 97 | — | 45 |
| 6 | **10b** | **C** | <5:95 | — | 84 | 1 |
| 7 | **10c** | A | >95:5 | 78 | — | 1.5 |
| 8 | **10c** | B | >95:5 | 87 | — | 45 |
| 9 | **10c** | **C** | <5:95 | — | 97 | 2 |
| 10 | **10d** | **A** | >95:5 | 98 | — | 5 |
| 11 | **10d** | **B** | >95:5 | 88 | — | 45 |
| 12 | **10d** | **C** | >95:5 | 94 | — | 8 |
| 13 | **10e** | **A** | >95:5 | 92 | — | 3 |
| 14 | **10e** | **B** | >95:5 | 98 | — | 45 |
| 15 | **10e** | **C** | <5:95 | — | 96 | 4 |
| 16 | **10f** | **A** | >95:5 | 86 | — | 4 |
| 17 | **10f** | **B** | >95:5 | 95 | — | 45 |
| 18 | **10f** | **C** | <5:95 | — | 92 | 2 |

[a] Method A: $TMSN_3$ (1 mmol), $BF_3{\cdot}Et_2O$ (2 mmol), $CH_2Cl_2$, rt; method B: $TMSN_3$ (1.2 mmol), $ZnCl_2$ (0.04 mmol), neat, 70 °C; method C: $TMSN_3$ (1.04 mmol), Ti(*O-i*-Pr)$_4$ (1.84 mmol), benzene, 90 °C.
[b] The major regioisomer was the only product detected (NMR analysis).
[c] Isolated yield based on epoxides **10a–f**.

an initial coordination of the reagent to the C-1 functional group (often a hydroxyl), followed by an intramolecular delivery of nucleophile to the proximal C-2 carbon.[16] It is noteworthy that also in this case the regiochemistry is independent of the steric hindrance in C-3.

Since the reaction of [Ti(O-*i*-Pr)$_2$(N$_3$)$_2$] on 2,3-epoxy alcohols is reported to give a strong C-3 regioselectivity, we prepared the 2,3-epoxy amine **10d** with a secondary amine at C-1 (entry 12), to test whether the presence of a proton at the C-1 heteroatom was crucial for the course of the reaction.

Actually, the latter example (entry 12) showed that the presence of the proton seemed to be important to direct the regioselectivity of the nucleophilic attack, since in this case only the C-3 derivative **11d** was detected.

To better understand the particular behaviour of the [Ti(O-*i*-Pr)$_2$(N$_3$)$_2$], we have recently undertaken quantum mechanic studies. The preliminary results seemed to be in agreement with the experimental data, indicating that there are different orientations

between the epoxides and the source of nucleophile, namely [Ti(O-*i*-Pr)$_2$(N$_3$)$_2$], depending on whether $NR_2$ is a tertiary or secondary amine. More comprehensive computational studies as well as the extension of the methodologies at the 2,3-aziridine amines are currently under investigation.

In conclusion, we have reported a Lewis acid-mediated regioselective azidolysis of 2,3-epoxy amines, using $TMSN_3$ as the source of azide. It is of interest to note that the appropriate choice of Lewis acid allows to direct, when $NR_2$ is a tertiary amine, the regioselectivity of the ring opening in C-3 or C-2 position.

Considering the occurrence of the diaminoalcohol moieties in the structure of many biologically active compounds, the present methodologies could represent a powerful tool in organic synthesis for the preparation of interesting molecules.

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13. For the purpose of this work, it is not mandatory to have optically active compounds, all the molecules are intended as racemates and the stereochemistry is only reported as the relative one.
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17. *Typical procedure for method A*: To a stirred solution of the 2,3-epoxy amine (1 mmol) in dry $CH_2Cl_2$ (3 mL) were added $TMSN_3$ (1 mmol) and $BF_3$ $OEt_2$ (2 mmol) dropwise and the solution was stirred at room temperature. After 2 h (TLC monitoring), the reaction was diluted with $CH_2Cl_2$, washed with $NaHCO_3$ (3 mL), brine (3 × 3 mL), dried over $Na_2SO_4$ and the solvent removed under reduced pressure. The crude product was characterized without further purification.
*Typical procedure for method B*: 1 mmol of the 2,3-epoxy amine (1 mmol), azidotrimethylsilane (1.2 mmol) and zinc chloride (0.04 mmol) were stirred at 68 °C for 15 h, at which time an additional 0.04 mmol of zinc chloride was added. After a total reaction time of 48 h, the reaction mixture at 20 °C was treated with THF (0.64 mL), acetic acid (0.064 mL) and HCl conc. (0.027 mL) and then stirred for 30 min. The reaction mixture was diluted with EtOAc (10 mL) and washed with $NaHCO_3$ sol.sat (3 mL). The aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic phases were washed with brine (3 × 4 mL), dried ($Na_2SO_4$), and concentrated in vacuo.
*Typical procedure for method C*: A solution of 1.84 mmol of Ti(*O*-*i*-Pr)$_4$ and 1.04 mmol of $TMSN_3$ in 4 mL of benzene was heated at 90 °C for 4 h. To the heating yellow solution was added 1 mmol of 2,3-epoxy amine in 1 mL of benzene and reflux was continued for 0.8–4 h. The solution was then cooled to 0 °C, 15% $H_2SO_4$ (8.2 mL) solution was added, and the mixture was stirred vigorously for 1 h. Then the reaction mixture was diluted with EtOAc (10 mL), washed with $NaHCO_3$ sol.sat. (3 mL)) and brine (1 mL), dried ($Na_2SO_4$) and the solvent was removed in vacuo. The resulting product was characterized without further purification.
18. *NMR data for representative compounds*.
*(3R*,2S*)-3-Azido-1-piperidin-1-yl-hexan-2-ol* ***11a***: $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.94 (t, *J* = 6.9 Hz, 3H), 1.24–1.68 (m, 10H), 2.23–2.47 (m, 4H), 2.50–2.68 (m, 3H), 3.34–3.48 (m, 1H), 3.67 (ddd, *J* = 5.1, 5.1, 9.6 Hz, 1H); $^{13}$C NMR (75.4 MHz, $CDCl_3$, 25 °C): 13.8, 19.6, 24.2, 26.1, 32.5, 54.6, 59.9, 65.5, 68.5.
*(3R*,2S*)-3-Azido-1-morpholin-4-yl-hexan-2-ol* ***11b***: $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.92 (t, 3H), 1.20-1.72 (m, 4H), 2.34–2.50 (m, 4H), 2.55–2.82 (m, 3H), 3.33–3.55 (m, 1H), 3.58–3.89 (m, 5H); $^{13}$C NMR (75.4 MHz, $CDCl_3$, 25 °C): 13.6, 19.5, 32.3, 53.5, 59.8, 65.1, 66.7, 68.4.
*(3R*,2S*)-3-Azido-1-diisopropylamino-hexan-2-ol* ***11c***: $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.89 (t, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 6H), 1.05 (d, *J* = 6.6 Hz, 6H), 1.28–1.34 (m, 5H), 2.81 (dd, *J* = 5.3, 14.1 Hz, 1H), 2.74 (dd, *J* = 6.9, 14.1 Hz, 1H), 3.07 (sep, *J* = 6.5 Hz, 2H), 3.42 (ddd, *J* = 3.0, 5.3, 8.3 Hz, 1H), 3.60 (m, 1H); $^{13}$C NMR (75.4 MHz, $CDCl_3$, 25 °C): 13.9, 18.8, 19.7, 20.6, 34.2, 46.8, 49.3, 64.9, 68.2.
*(3R*,2S*)-3-Azido-1-cyclohexylamino-hexan-2-ol* ***11d***: $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): δ= 0.95 (t, *J* = 7.0 Hz, 3H), 1.01-1.85 (m, 14H), 2.31–2.55 (m, 1H), 2.62 (dd, *J* = 8.9, 12.2 Hz, 1H), 2.82 (dd, *J* = 3.6, 12.2 Hz, 1H), 2.87–3.05 (br s, 2H), 3.31–3.45 (m, 1H), 3.56 (ddd, *J* = 3.6, 5.3, 8.9 Hz, 1H); $^{13}$C NMR (75.4 MHz, $CDCl_3$, 25 °C): 13.7, 19.4, 24.4, 24.5, 24.8, 29.3, 29.5, 32.6, 47.2, 58.1, 65.4, 69.3.
*(2S*,3R*)-2-Azido-1-piperidin-1-yl-hexan-3-ol* ***12a***: $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.95 (t, *J* = 7.0 Hz, 3H), 1.30–1.68 (m, 10H), 2.24–2.63 (m, 5H), 2.69 (dd, *J* = 5.9, 13.4 Hz, 1H), 3.53 (td, *J* = 5.9, 2.8 Hz, 1H), 3.64–3.76 (m, 1H), 4.58 (br s, 1H); $^{13}$C NMR (75.4 MHz, $CDCl_3$, 25 °C): 14.0, 19.0, 23.8, 25.9, 35.6, 55.4, 60.1, 61.8, 73.0.
*(2S*,3R*)-2-Azido-1-morpholin-4-yl-hexan-3-ol* ***12b***: $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$= 0.93 (t, *J* = 7.0 Hz, 3H), 1.36–1.64 (m, 4H), 2.59 (dt, *J* = 4.6, 14.0 Hz, 4H), 2.68 (d, *J* = 6.0 Hz, 2H), 3.44–3.60 (m, 2H), 3.60–3.68 (m, 1H), 3.70 (t, *J* = 4.5 Hz, 4H); $^{13}$C NMR (75.4 MHz, $CDCl_3$, 25 °C): 13.9, 18.9, 36.1, 54.2, 60.1, 62.2, 66.8, 72.6.
*(2S*,3R*)-2-Azido-1-diisopropylamino-hexan-3-ol* ***12c***: $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.80 (t, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 6H), 1.02 (d, *J* = 6.6 Hz, 6H), 1.43 (m, 5H), 2.75 (t, *J* = 4. 4 Hz, 2H), 3.07 (quint, *J* = 6.7 Hz, 2H), 3.40 (m, 1H), 3.58 (m, 1H); $^{13}$C NMR (75.4 MHz, $CDCl_3$, 25 °C): 13.8, 18.8, 19.9, 20.7, 36.2, 46.8, 48.3, 64.5, 71.8.