DOI: 10.1002/ejoc.200600200

Nucleophilic Ring-Opening of Azetidinium Ions: Insights into Regioselectivity

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Keywords: Azetidines / Azetidinium ions / Nucleophilic ring-opening / Density functional calculations / Regioselectivity

Enantiopure azetidinium salts presenting various and representative substitution patterns at C-2, C-3 and C-4 have been prepared by alkylation of the corresponding azetidine with methyl trifluoromethanesulfonate. These compounds were treated with an array of nitrogen (azide anion or benzylamine) and oxygen (acetate anion or alkoxides) nucleophiles which provided interesting insights into the regioselectivity of the ring-opening process. Nucleophilic opening occurred in most cases regioselectively at C-4 with azetidinium ions possessing no substituent at this position. On the other hand, highly regioselective opening at C-2 occurred with trisubstituted azetidinium ions bearing a methyl group at C-4. Experimental selectivities together with DFT calculations have allowed a better understanding of the parameters governing the regioselectivities.

Introduction

Owing to the ease of their ring-opening by various nucleophiles, aziridines have been widely used as electrophilic building blocks in synthesis.[1] In contrast, the electrophilic reactivity of their higher homologs, azetidines **1**, is still understudied which is quite amazing since they could act as versatile precursors to various functionalized amine derivatives in which the nitrogen and all three carbon atoms from the azetidine would be incorporated into the skeleton. One explanation for this reactivity having been neglected for years lies in the lack of efficient and general methods for the preparation of azetidines, especially in an enantiomerically pure form.[2] Moreover, the ring strain in azetidines is less important than in aziridines and their nucleophilic ring-opening therefore requires stronger activation. An efficient solution to the activation of this heterocycle towards nucleophiles relies on its transformation into the corresponding cyclic ammonium salt **2**: the amine is then sufficiently activated and a wide range of heteronucleophiles (amines,[3] alkoxides,[4] phenols,[5] carboxylates,[6] sulfur nucleophiles,[7] phosphorus nucleophiles[8] and halides[9]) have been shown to smoothly ring-open these salts. However, few reports have addressed the regioselectivity issue: although it seems that nucleophiles preferably react at the unsubstituted position[3b,5a,6] or at a benzylic site (Figure 1),[5a] there has been no general and extensive study of this process and the introduction of functional groups at the reacting center as well as the influence of the relative configuration of the heterocycle still has to be addressed. As part of our ongoing interest in the chemistry of azetidines,[10] we wish to present herein a full and detailed report[11] on the nucleophilic opening of a range of functionalized azetidinium salts with nitrogen and oxygenated nucleophiles as well as insights into the regioselectivity of this efficient ring-opening process.

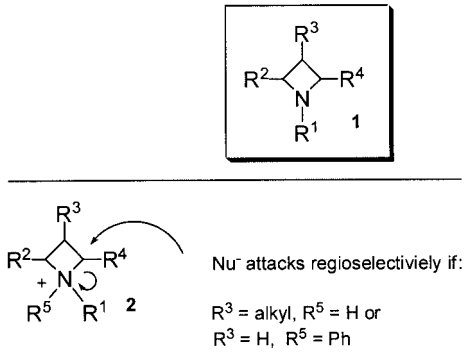

Figure 1. Azetidinium ions as functionalized electrophiles.

Results

Synthesis of Functionalized Azetidinium Salts

The azetidinium salts prepared for this study are depicted in Figure 2. They were all synthesized in good yield by simply treating the corresponding azetidine with methyl trifluoromethanesulfonate (the yields are shown in Figure 2). The starting azetidines[12] can be divided into three categories: those derived from (*R*)-phenylglycinol, which gave azetidinium salts **3**–**7** bearing a variable substituent at C-2 and a

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phenyl substituent at C-3, those derived from (1*R*,2*S*)-ephedrine, which gave azetidinium salts **8**–**11** bearing an additional methyl group at C-4, and those derived from (–)-phenylethylamine, which gave azetidinium salts **12** and **13** unsubstituted at C-3 and C-4.

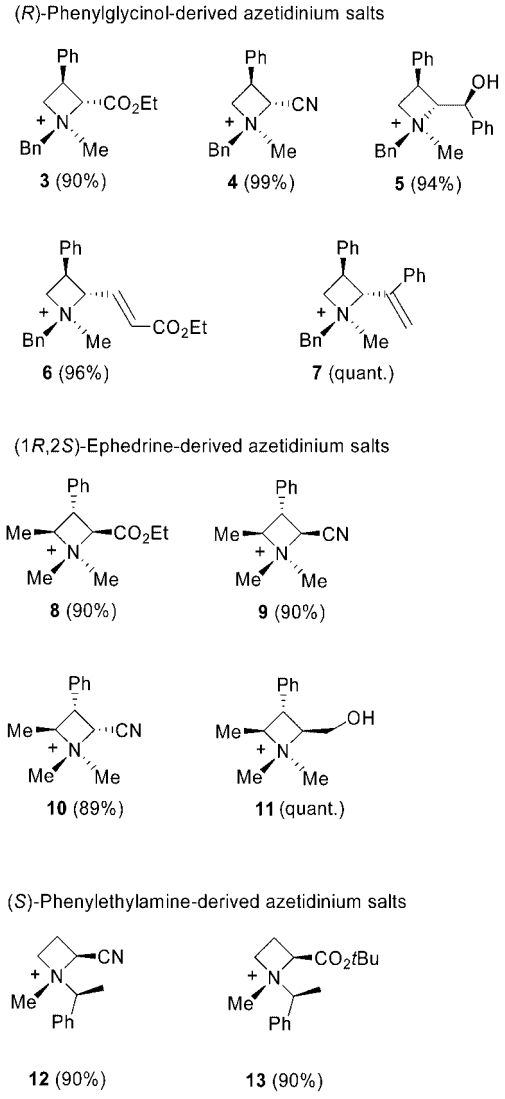


Figure 2. Azetidinium salts prepared by alkylation with methyl trifluoromethanesulfonate.

This alkylation step was found to be highly diastereoselective in the case of *N*-benzyl- or *N*-phenylethyl-substituted azetidines since azetidinium salts **3**–**7** and **12** and **13** were obtained as unique compounds. This stereochemical outcome has already been commented on[12c] for **3**–**7** and the stereochemistries in **12** and **13** were deduced from the same behavior, that is, an attack of the axial lone pair on the nitrogen atom in the conformer having all its substituents in an equatorial position (Figure 3).

Having prepared a set of azetidinium salts with various substitution patterns and stereochemistries, we next studied their opening with various heteronucleophiles.

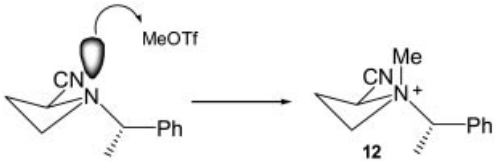


Figure 3. The alkylation of *N*-phenylethyl-substituted azetidines occurs with high diastereoselectivity.

Nucleophilic Ring-Opening with Nitrogen Nucleophiles

Two representative nitrogen nucleophiles were selected for this study: sodium azide and benzylamine. The reactions were conducted overnight in DMF in the case of sodium azide and in dichloromethane in the case of the amine. In all cases 5 equiv. of the nucleophile were used and the results are detailed in Table 1.

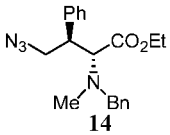
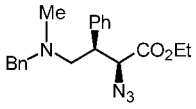
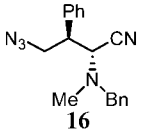
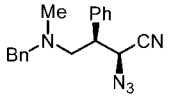
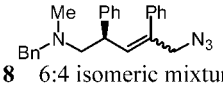
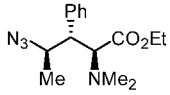
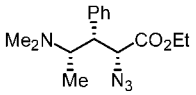
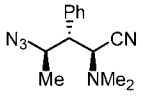
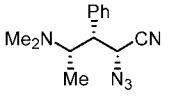
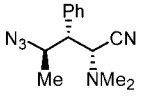
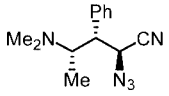
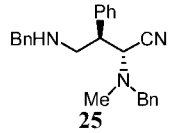
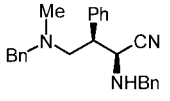
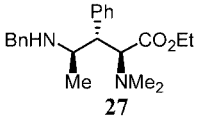
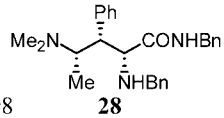
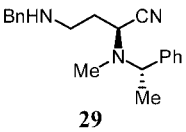
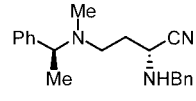
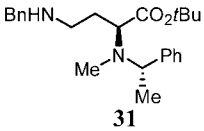
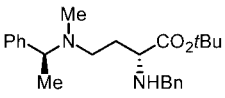
Some general trends can be stated after examination of this first set of experiments. First, the ring-opening reaction with nitrogen nucleophiles is quite efficient and acyclic products are obtained in good yields except in the case of azetidinium **9** (entry 5). Moreover, we were pleased to see that no competitive elimination or S_N1 processes occurred, as evidenced by the diastereoisomeric purity of the products. One exception was however noted in the case of azetidinium salt **7**, which reacts through an exclusive S_N2' reaction to yield trisubstituted alkene **18** as a *Z*/*E* mixture of isomers. In contrast, related alkenylazetidinium salt **6** gave a complex mixture upon reaction with sodium azide.

The regioselectivity of the reaction seems to be governed by the following general parameters: C-2 and C-3 disubstituted azetidinium ions react regioselectively at the unsubstituted C-4 carbon atom (entries 1, 2 and 7) while azetidinium salts possessing a methyl group at C-4 are preferably opened at the C-2 position (entries 5, 6 and 8). Note that the structure of the minor inseparable compound contaminating the product resulting from an attack at C-2 in entry 4 could not be ascertained: from the NMR spectrum of the mixture, all signals except the singlet due to the $N(Me)_2$ group being overlapped. This suggests that the minor compound is an epimer since 2-H signals in the closely related regioisomers **14** and **15** show a difference in chemical shifts of nearly 1 ppm. Finally, the reactivity of azetidinium salts **12** and **13** bearing a single substituent at C-2 (ester or nitrile) was deeply influenced by the nature of that substituent; while **12** was exclusively opened at C-4, the ester **13** induced a reverse of the regioselectivity with opening at C-2 (entries 9 and 10) slightly preferred.

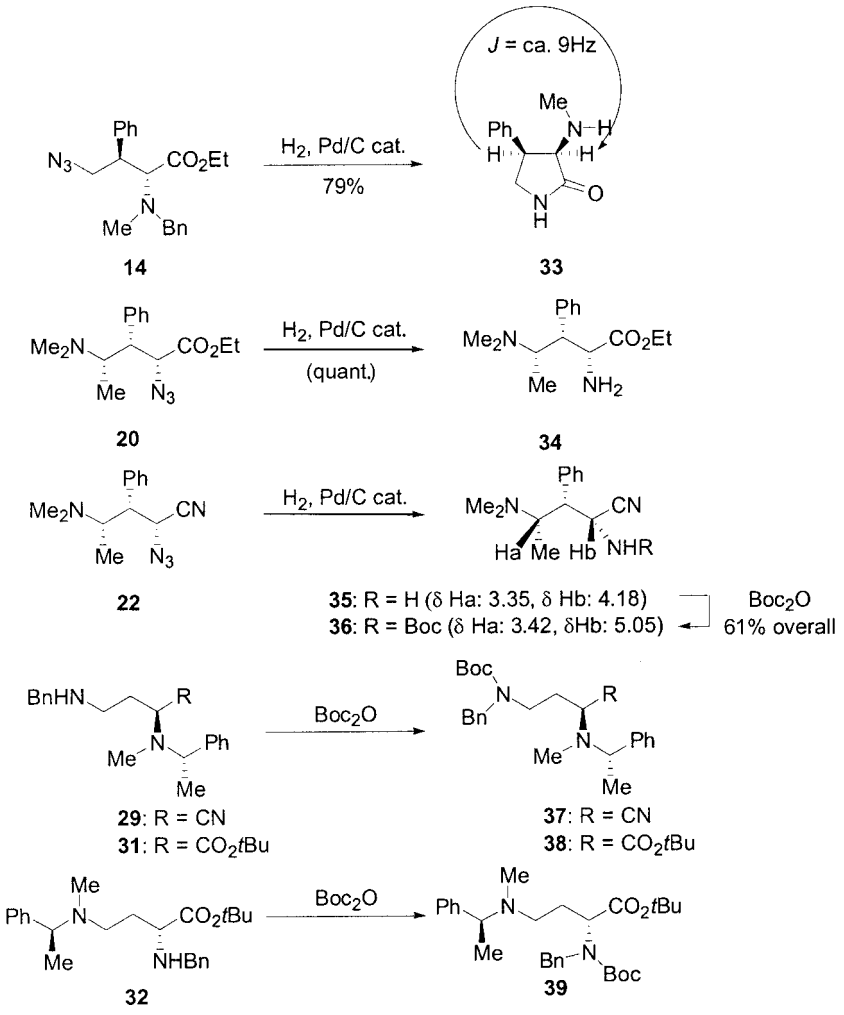
Structure Determination of the Regioisomers Obtained by Chemical Transformation

The structures of the compounds produced upon treatment with nitrogen nucleophiles had to be ascertained by chemical transformation since it was quite hazardous to determine the location of the incoming nucleophile on the basis of chemical shifts only. Thus, compound **14** was subjected to catalytic hydrogenation to give lactam **33** in which

Table 1. Reaction of azetidinium ions with sodium azide and benzylamine.

Entry	Substrate	Nucleophile[a]	Products C-4 Attack	Products C-2 Attack	Yield[b] (%)
1	**3**	NaN_3	 **14**	93:7  **15**	quant.
2	**4**	NaN_3	 **16**	82:18  **17**	quant.
3	**7**	NaN_3	 **18** 6:4 isomeric mixture		88
4	**8**	NaN_3	 **19**	14[c]:86  **20**	quant.
5	**9**	NaN_3	 **21**	> 2:98  **22**	27
6	**10**	NaN_3	 **23**	> 2:98  **24**	quant.
7	**4**	Benzylamine	 **25**	> 98:2  **26**	89
8	**8**	Benzylamine	 **27**	> 2:98  **28**	68
9	**12**	Benzylamine	 **29**	> 98:2  **30**	50
10	**13**	Benzylamine	 **31**	44:56  **32**	53

[a] DMF was used as solvent with sodium azide and DCM was used with benzylamine. [b] Yield of pure isolated product. [c] An inseparable minor compound (14%) contaminated compound **20** (C-2 attack), but we could not determine whether it was the regioisomer **19** or an epimer of **20** (see text).



Scheme 1. Structure determination of the regioisomers obtained.

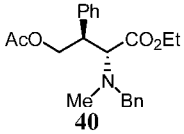
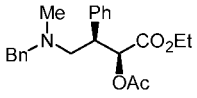
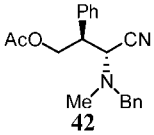
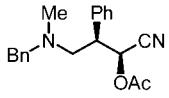
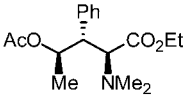
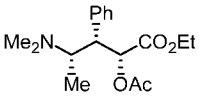
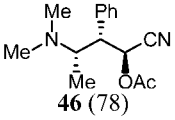
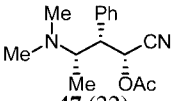
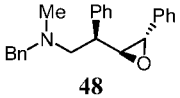
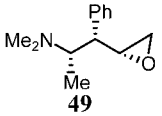
the large coupling constant observed for the proton adjacent to the lactam (ca. 9 Hz) is in accordance with a 3,4-*cis* stereochemistry, as depicted in Scheme 1, and, by deduction, with an attack by the azide at C-4. In contrast, when subjected to the same conditions, compounds **20** and **22**, respectively, gave amines **34** and **35**, and the latter was further protected as the *N*-Boc derivative. Careful analysis of the ^{1}H NMR spectra of **35** and **36** unambiguously allowed the determination of the location of the carbamate in the acyclic skeleton (relevant data shown in Scheme 1). Similarly, compounds **29**, **31** and **32** were also transformed into their *N*-Boc derivatives **37**–**39**; comparison of their ^{1}H NMR chemical shifts with those of the unprotected amine allowed the location of the secondary amine to be determined.

Nucleophilic Ring-Opening with Oxygen Nucleophiles

The acetate anion was chosen as a model oxygenated nucleophile which was delivered overnight as its sodium or caesium salt in DMF at room temperature; sodium triacetoxyborohydride was also found to be an efficient source of acetate anion in refluxing THF. The use of alkoxides acting as inter- or intramolecular nucleophiles was also evaluated. The results of these experiments are collected in Table 2.

Nucleophilic ring-opening with oxygenated nucleophiles shows some discrepancies compared with the results obtained with their nitrogen counterparts. First, the nature of the oxygen nucleophile has a dramatic influence: although sodium acetate reacts readily in some cases (entries 1 and 2), use of the more nucleophilic caesium acetate is sometimes necessary to obtain reasonable-to-good yields (compare entries 4 and 5). Moreover, while benzyl alkoxide led to extensive decomposition when used as an external nucleophile (entry 3), potassium alkoxides act as intramolecular nucleophiles to efficiently give the expected epoxides **48** and **49** (entries 10 and 11). Considering the regioselectivity, the exclusive C-2 attack previously observed in the case of the reaction of C-4-substituted azetidinium salts with nitrogen nucleophiles is still observed when oxygenated nucleophiles are used (entries 5–9). However, and in contrast with previous results (Table 1), the regioselectivity observed for the ring-opening of **3** and **4** is not homogeneous (entries 1 and 2): although azetidinium ion **4** is regioselectively opened at C-4 as previously observed with the azide anion (compare entries 2 of Table 1 and Table 2), azetidinium ion

Table 2. Reaction of azetidinium ions with acetates and alkoxides.

Entry	Substrate	Nucleophile	Products		Yield[a] (%)
			C-4 Attack	C-2 Attack	
1	**3**	AcONa, DMF	 **40**	37:63  **41**	80
2	**4**	AcONa, DMF	 **42**	>98:2  **43**	quant.
3	**4**	$PhCH_2ONa$, DMF		-	decomposition
4	**8**	AcONa, DMF		-	decomposition
5	**8**	AcOCs, DMF	 **44**	>2:98  **45**[c]	21–67[b]
6	**9**	AcOCs, DMF		 **46** (78)  **47** (22)	91
7	**9**	$NaBH(OAc)_3$ THF, reflux	**46** (72) + **47** (28)		67
8	**10**	AcOCs, DMF	**46** (78) + **47** (22)		quant.
9	**10**	$NaBH(OAc)_3$ THF, reflux	**46** (80) + **47** (20)		quant.
10	**5**	KHMDS, 1.2 equiv., THF, −78°C to r.t.	 **48**		[d]
11	**11**	KHMDS, 1.2 equiv., THF, −78°C to r.t.	 **49**		[d]

[a] Yield of pure isolated product. [b] Yields were difficult to reproduce. [c] The absolute stereochemistry at C-2 was not rigorously ascertained (see the Discussion section). [d] These epoxides were not purified since they were unstable on silica gel; exclusive formation of the epoxide was observed in the crude reaction mixture.

3, bearing an ester moiety in place of the nitrile, is preferably opened at C-2, although with a low selectivity, a result which was completely unexpected in view of the reactivity of the azide anion (compare entries 1 of Table 1 and Table 2). This highlights again the determining effects of both the nature of the functional group at C-2 (ester or nitrile) and the incoming nucleophile on the regioselectivity of the reaction.

Interestingly, substrates **9** and **10**, for which C-2 attack is exclusive, afforded two isomers at this C-2 position in the same ratio, regardless of the absolute configuration of the reacting center in the starting material. Diastereoisomers **46** and **47** were separated by flash chromatography and the relative stereochemistry of the major isomer **46** was determined by X-ray crystallography.[13]

Discussion

The surprising and unprecedented low diastereoselectivity observed in this case suggests that an equilibration of substrates **9** and **10** through a deprotonation/reprotonation sequence involving an intermediate ylide **50** occurs prior to ring-opening (Scheme 2). The identical diastereoisomeric ratio obtained starting from **9** or **10** might therefore reflect the ease of opening of these diastereoisomers by the acetate anion. Since the major isomer **46** results from a S_N2 reaction involving the 2,3-*cis* isomer **10**, it can be deduced that this isomer reacts faster than the 2,3-*trans*-**9**. This is in accordance with entries 5 and 6 of Table 1 involving the opening of **9** and **10** by the azide anion; comparison of the yields obtained for each of these substrates (27% for the 2,3-*trans* isomer and quantitative for the 2,3-*cis* isomer) fits well with this assumption.

This epimerization process was easily evidenced by independently treating **9** and **10** overnight with triethylamine in [D_6]acetone. A thermodynamic distribution of **9** (ca. 80%) and **10** (ca. 20%) was obtained in each case with the disappearance of the 2-H proton from the ^{1}H NMR spectra. The occurrence of this possible competitive epimerization and the low yield obtained for product **45** in entry 5 of Table 2 led us to be cautious in determining the absolute configuration at C-2 in **45**. Although the observed coupling constant ^3J for 2-H/3-H fits well with a 2,3-*syn* stereochemistry (J = 4.2 Hz in **45** and 3.7 Hz in **42**), we cannot rule out epimerization prior to the nucleophilic opening.

The higher reactivity of the 2,3-*cis* compound **10** relative to its 2,3-*trans* isomer **9** can be explained by conformational analysis: Figure 4 illustrates the conformational equilibria in the diastereoisomeric salts **9** and **10**. In compound **9**, the equilibrium should strongly favor the conformer **9a** with all its substituents in a pseudoequatorial orientation. This conformer however appears to be less reactive towards nucleophilic ring-opening owing to an unfavorable steric interaction between the phenyl group and the incoming nucleophile. The less stable conformer **9b**, with severe 1,3-diaxial interactions between the substituents, would therefore be the more reactive one. Starting from **10**, its conformer **10b** would also, for the same reasons, be the more reactive one. This conformer is however more stable than **9b** since the cyano group is now in an equatorial position. In this case, the kinetics of the nucleophilic attack should be less hampered by an unfavorable preconformational equilibrium.

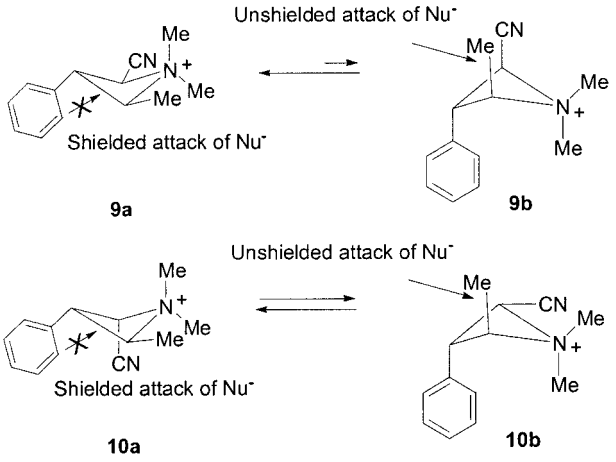
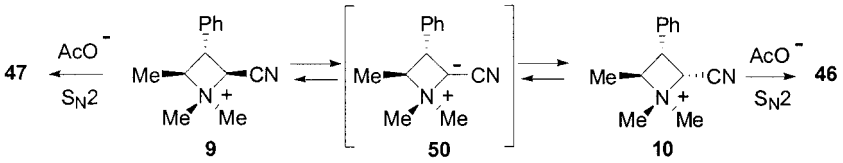


Figure 4. Conformational equilibrium in **9** and **10**.

In order to gain a better understanding of the intimate reaction profile, DFT[14] calculations were performed on model azetidinium ions **51**–**53** and **12** and their reaction at C-2 or C-4 with ammonia or the azide anion (for **12**) (Figure 5). After complete optimization of the substrates, the energies and the optimized structures for each transition state were determined. Two of them, involving C-4 attack on **51** and **52** are depicted in Figure 6. These calculations show that attack at C-4 is favored by 0.66 kcal mol^{-1} in **51**, which is in accordance (although this value is low) with the preferred experimental regioselectivity observed with benzylamine (entry 7, Table 1). This value corresponds to a calculated 76:24 ratio of C-4 versus C-2 attack at 293 K, which is lower than the 2:98 distribution observed experimentally. However, the calculation did not take into account the bulkiness of the nucleophile (benzylamine) and of the *N*-benzyl substituent present in **4**. In contrast, calculations show that C-2 attack on azetidinium ion **52** is favored by a much larger amount (3.4 kcal mol^{-1}) and this fits perfectly



Scheme 2. Epimerization of **9** and **10**.

well with the constantly high regioselectivity observed with C-4 methyl-substituted azetidinium ions. Finally, C-2 attack is preferred by 1.17 kcal mol^{-1} in **53**, while **12** is opened at C-4 ($\Delta\Delta E^{\#}$ = 3.51 kcal mol^{-1}). These last results again highlight the important influence of the moiety (ester or nitrile) linked to C-2 and are in agreement with the experimental regioselectivities (entries 9 and 10, Table 1). More interestingly, the optimized transition state for the disfavored C-4 attack in **52** merits some comments: the long distance between N(NH_3) and C-4 (2.249 Å) relative to the value of 2.097 Å in the transition state involving **51** reflects the difficult approach of the nucleophile due to the shielding of the methyl group. Moreover, the N(NH_3)−C-4−N-1 angle, with a value of 167°, shows an important deviation from the ideal value of 180°. This explains the high energy of this transition state[15] and the excellent regioselectivities observed with related substrates.

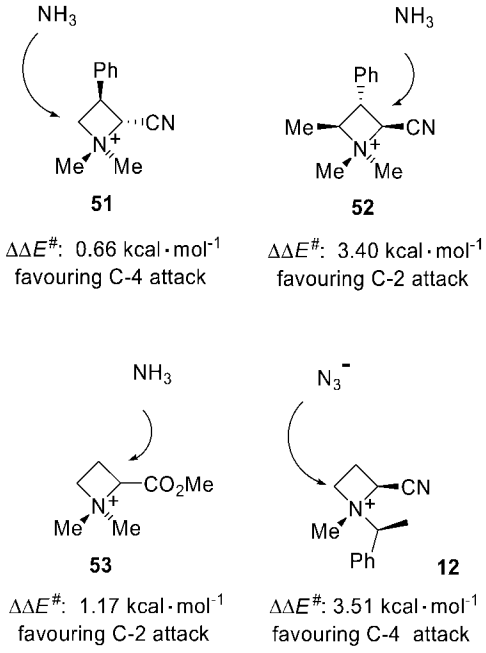


Figure 5. Calculated $\Delta\Delta E^{\#}$ values for C-2 or C-4 attack of ammonia on azetidinium ions **51**–**53** and **12**.

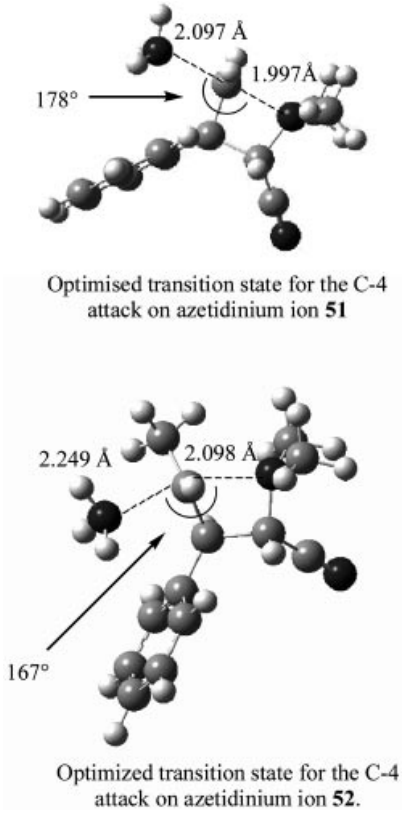


Figure 6. Optimized transition states for the nucleophilic opening by C-4 attack on **51** and **52**.

In conclusion, this work has disclosed several features of azetidine chemistry. First, we have demonstrated that polysubstituted azetidinium ions can react in a highly regioselective way depending on different parameters such as the degree of substitution, the nature of the linked moiety at C-2 (nitrile, ester, alkene) and the nature of the incoming nucleophile. We have also shown that the relative configuration of the substituents on the azetidinium ring is an important parameter for the success of the ring-opening and that a side-reaction involving an epimerization process can take place in some cases. Finally, we have shown that DFT calculations are a good way of predicting the regioselectivity of this nucleophilic ring-opening reaction. Since this reaction produces stereodefined highly functionalized building blocks and considering the new methodologies available for the preparation of enantiopure azetidines,[2] this study should find applications in organic synthesis.

Experimental Section

General Comments: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 spectrometer at 300 and 75 MHz, respectively; chemical shifts are reported in ppm relative to TMS. Optical rotations were determined with a Perkin–Elmer 141 instrument. All the reactions were carried out under argon. Column chromatography was performed on silica gel (230–400 mesh) using various mixtures of diethyl ether (Et_2O), ethyl acetate (AcOEt), petroleum ether (PE) and cyclohexane (CyH). TLC was performed on Merck Kieselgel $60F_{254}$ plates. Melting points were recorded with a Mettler FP61 apparatus and are uncorrected. Infrared spectra were recorded with a Nicolet apparatus. Mass spectra were recorded with a Hewlett-Packard MS Engine HP 5989 B equiped with an Analytica Brandford ESI source. THF and diethyl ether were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. The mention of a "usual work up" means: (i) decanting the organic layer, (ii) extraction of the aqueous layer with diethyl ether, (iii) drying of the combined organic layers with $MgSO_4$ and (iv) solvent evaporation under reduced pressure. Stereoisomeric ratios were determined by NMR analysis of crude reaction mixtures before purification.

General Procedure for the Preparation of Azetidinium Salts: Methyl trifluoromethanesulfonate (0.225 mL, 2 mmol) was added dropwise to a solution of azetidine (1 mmol) in DCM (5 mL) at 0 °C. The reaction mixture was stirred at room temp. for 1 h before evaporating the solvent under reduced pressure. The residue was washed with small quantities of dry diethyl ether and dried under vacuum.

(1*R*,2*R*,3*R*)-1-Benzyl-2-ethoxycarbonyl-1-methyl-3-phenylazetidinium Trifluoromethanesulfonate (3): Yield: 90%; m.p. 135 °C. $[\alpha]_{365}^{20}$ = –5 (*c* = 0.5, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 7.84–7.82 (m, 2 H, Ph), 7.81–7.55 (m, 3 H, Ph), 7.38–7.33 (m, 5 H, Ph), 5.75 (d, *J* = 10.0 Hz, 1 H, 2-H), 5.06 (A part of AB syst., *J* = 13.1 Hz, 1 H, C*H*HPh), 5.01 (B part of. AB syst., *J* = 13.1 Hz, 1 H, CH*H*Ph), 4.95–4.80 (m, 2 H, 3-H, 4-H), 4.58–4.52 (m, 1 H, 4′-H), 4.32 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_3$), 3.55 (s, 3 H, Me), 1.27 (d, *J* = 7.1 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 164.7 (CO), 135.9 (*ipso*-C, Ph), 133.3, 131.4, 130.0, 129.4, 128.8, 128.7, 128.1 (CH Ph), 75.1 (C-2), 68.7 (*C*H$_2$Ph), 66.7 (C-4), 63.5 (CH$_2$O), 46.4 (Me), 37.2 (C-3), 13.8 (Me) ppm. MS (ESI Pos): *m*/*z* = 310.4 [M – OTf]$^+$. $C_{21}H_{24}F_3NO_5S$ (459.48): C 54.89, H 5.26, N 3.05; found C 54.66, H 5.32, N 2.94.

(1*R*,2*R*,3*R*)-1-Benzyl-2-cyano-1-methyl-3-phenylazetidinium Trifluoromethanesulfonate (4): Yield: 99%; m.p. 116 °C. $[\alpha]_D^{20}$ = –34 (*c* = 0.5, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 7.89–7.82 (m, 2 H, Ph), 7.67–7.42 (m, 8 H, Ph), 6.34 (d, *J* = 9.3 Hz, 1 H, 2-H), 5.31–5.14 (m, 4 H, 3-H, 4-H, CH$_2$Ph), 4.91–4.81 (m, 1 H, 4′-H), 3.70 (s, 3 H, Me) ppm. ^{13}C NMR: δ = 133.9 (*ipso*-C, Ph), 133.1, 131.9, 130.5, 129.9, 129.8, 128.4 (CHPh), 128.3 (*ipso*-C, Ph), 112.3 (CN), 69.3, 69.2 (C-4, *C*H$_2$Ph), 65.3 (C-2), 46.9 (Me), 39.6 (C-3) ppm. MS (ESI Pos): *m*/*z* = 263.2 [M – OTf]$^+$. $C_{19}H_{19}F_3N_2O_3S$ (412.4): C 55.33, H 5.26, N 6.79; found C 55.23, H 4.66, N 6.74.

(1*R*,1′*R*,2*R*,3*R*)-1-Benzyl-2-(1′-hydroxyphenylmethyl)-1-methyl-3-phenylazetidinium Trifluoromethanesulfonate (5): Yield: 94%; m.p. 135 °C. $[\alpha]_D^{25}$ = –2 (*c* = 0.5, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 7.84–7.80 (m, 2 H, Ph), 7.63–7.60 (m, 3 H, Ph), 7.35–7.32 (m, 2 H, Ph), 7.21–7.09 (m, 8 H, Ph), 5.66 (br. s, 1 H, OH), 5.36 (br. s, 1 H, C*H*OHPh), 5.17 (d, *J* = 10.0 Hz, 1 H, 2-H), 5.01 (s, 2 H, CH_2Ph), 4.92 (q, *J* = 9.8 Hz, 1 H, 3-H), 4.69 (t, *J* = 10.0 Hz, 1 H, 4-H), 4.52 (t, *J* = 8.5 Hz, 1 H, 4′-H), 3.60 (s, 3 H, Me) ppm. ^{13}C NMR: δ = 140.5, 137.5 (*ipso*-C, Ph), 133.4, 131.5, 130.3, 129.5, 129.3, 129.2, 128.9, 128.5, 128.3, 127.3 (CHPh), 83.1 (C-1′), 69.5 (C-2), 68.8 (*C*H$_2$Ph), 68.3 (C-4), 45.3 (Me), 34.4 (C-3) ppm. MS (ESI Pos): *m*/*z* = 344.3 [M – OTf]$^+$. $C_{25}H_{26}F_3NO_4S$ (493.5): C 60.84, H 5.31, N 2.84; found C 60.91, H 5.40, N 2.99.

(1*R*,2*S*,3*R*,2′*E*)-1-Benzyl-2-(2′-ethoxycarbonylvinyl)-1-methyl-3-phenylazetidinium Trifluoromethanesulfonate (6): Yield: 96%; m.p. 134 °C. $[\alpha]_D^{25}$: –45 (*c* = 0.8, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 7.86–7.82 (m, 2 H, Ph), 7.63–7.53 (m, 3 H, Ph), 7.48–7.32 (m, 5 H, Ph), 7.08 (dd, *J* = 7.1, 15.6 Hz, 1 H, C*H*=CH), 6.45 (dd, *J* = 1.2, 15.6 Hz, 1 H, CH=C*H*), 5.86 (dd, *J* = 7.1, 9.4 Hz, 1 H, 2-H), 5.09 (A part of AB syst., *J* = 13.1 Hz, 1 H, C*H*HPh), 5.04 (B part of AB syst., *J* = 13.1 Hz, 1 H, CH*H*Ph), 4.96 (t, *J* = 10 Hz, 1 H, 4-H), 4.83 (qd, *J* = 1.5, 8.3 Hz, 1 H, 3-H), 4.56 (t, *J* = 8.7 Hz, 1 H, 4′-H), 4.18 (q, *J* = 7.1 Hz, 2 H, CH_2O), 3.37 (s, 3 H, Me), 1.24 (t, *J* = 7.1 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 164.8 (CO), 136.2, 135.2 (*ipso*-C, Ph), 133.2 (*C*=C), 132.1, 131.5 (CHPh), 130.2 (C=*C*), 129.8, 129.2, 129.1, 128.3 (CHPh), 78.9 (C-2), 68.5 (*C*H$_2$Ph), 67.7 (C-4), 61.6 (CH$_2$O), 44.2 (Me), 39.1 (C-3), 14.3 (Me) ppm. MS (ESI Pos): *m*/*z* = 336.4 [M – OTf]$^+$. $C_{23}H_{26}F_3N_2O_5S$ (485.5): C 56.90, H 5.40, N 2.88; found C 57.12, H 5.54, N 2.72.

(1*R*,2*R*,3*R*)-1-Benzyl-1-methyl-3-phenyl-2-(1′-phenylvinyl)azetidinium Trifluoromethanesulfonate (7): Yield: quant.; oil. $[\alpha]_D^{25}$ = +90 (*c* = 1, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 7.50–7.21 (m, 15 H, Ph), 5.96–5.83 (m, 3 H, 2-H, =CH_2), 4.75–4.51 (m, 3 H, 3-H, 4-H, C*H*HPh), 3.89–3.82 (m, 2 H, 4′-H, CH*H*Ph), 2.94 (s, 3 H, Me) ppm. ^{13}C NMR: δ = 139.2, 137.7, 134.6, 132.2 (*ipso*-C, Ph, *CC*H$_2$Ph), 130.9, 129.6, 129.4, 128.7, 127.7, 127.4, 125.6 (CHPh), 80.6 (C-2), 67.9 (CH$_2$Ph), 64.5 (C-4), 43.6 (Me), 37.6 (C-3) ppm. MS (ESI Pos): *m*/*z* = 340.2 [M – OTf]$^+$. $C_{26}H_{26}F_3NO_3S$ (489.5): C 63.79, H 5.35, N 2.86; found C 63.62, H 5.54, N 2.72.

(2*S*,3*S*,4*S*)-2-Ethoxycarbonyl-1,1,4-trimethyl-3-phenylazetidinium Trifluoromethanesulfonate (8): Yield: 90%; oil. $[\alpha]_D^{25}$ = +16 (*c* = 0.4, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 7.56–7.54 (m, 2 H, Ph), 7.45–7.34 (m, 3 H, Ph), 5.60 (d, *J* = 10.8 Hz, 1 H, 2-H), 5.08–4.98 (m, 1 H, 4-H), 4.47 (t, *J* = 10.8 Hz, 1 H, 3-H), 4.36 (q, *J* = 7.1 Hz, 2 H, CH_2O), 3.61 (s, 3 H, Me), 3.39 (s, 3 H, Me), 1.75 (d, *J* = 6.8 Hz, 3 H, Me), 1.29 (t, *J* = 7.1 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 164.8 (CO), 135.0 (*ipso*-C, Ph), 129.7, 129.1, 128.4 (CHPh), 77.9 (C-4), 75.8 (C-2), 63.7 (CH$_2$O), 53.5, 42.0 (C-5, C-6), 44.9 (C-3), 14.1 (C-10), 13.3 (C-7) ppm. MS (ESI Pos): *m*/*z* = 248.2 [M – OTf]$^+$. $C_{16}H_{22}F_3NO_5S$ (397.1): C 48.36, H 5.58, N 3.52; found C 48.29, H 5.64, N 3.49.

(2*S*,3*S*,4*S*)-2-Cyano-1,1,4-trimethyl-3-phenylazetidinium Trifluoromethanesulfonate (9): Yield: 90%; oil. $[\alpha]_D^{25}$ = +17 (*c* = 0.8, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 7.60–7.45 (m, 2 H, Ph), 7.44–7.43 (m, 3 H, Ph), 6.09 (d, *J* = 10.6 Hz, 1 H, 2-H), 5.32–5.22 (m, 1 H, 4-H), 4.81 (t, *J* = 10.6 Hz, 1 H, 3-H), 3.72 (s, 3 H, NMe), 3.66 (s, 3 H, NMe), 1.11 (d, *J* = 6.8 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 133.0 (*ipso*-C, Ph), 130.0, 128.5 (CH Ph), 112.1 (CN), 79.8 (C-4), 65.3 (C-2), 53.4, 43.6 (Me), 46.9 (C-3), 13.6 (Me) ppm. MS (ESI Pos): *m*/*z* = 201.2 [M – OTf]$^+$. $C_{14}H_{17}F_3N_2O_3S$ (350.4): C 47.99, H 4.89, N 8.00; found C 48.12, H 4.89, N 8.00.

(2*R*,3*S*,4*S*)-2-Cyano-1,1,4-trimethyl-3-phenylazetidinium Trifluoromethanesulfonate (10): Yield: 89%; m.p. 122 °C. $[\alpha]_D^{25}$ = –2 (*c* = 0.5, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 7.58–7.42 (m, 5 H, Ph), 6.06 (d, *J* = 9.4 Hz, 1 H, 2-H), 5.74–5.59 (m, 1 H, 4-H), 4.97 (t, *J* = 9.6 Hz, 1 H, 3-H), 3.66 (s, 6 H, 2×Me), 1.81 (d, *J* = 6.6 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 132.7 (*ipso*-C, Ph), 129.9, 129.8, 129.1 (CH Ph), 112.1 (CN), 78.2 (C-4), 69.8 (C-2), 51.1, 43.6 (Me), 46.6 (C-3), 13.9 (Me) ppm. MS (ESI Pos): *m*/*z* = 201.2 [M – OTf]$^+$. $C_{14}H_{17}F_3N_2O_3S$ (350.4): C 47.99, H 4.89, N 8.00; found C 47.86, H 4.90, N 7.88.

(2*S*,3*S*,4*S*)-2-Hydroxymethyl-1,1,4-trimethyl-3-phenylazetidinium Trifluoromethanesulfonate (11): Yield: quant.; oil. $[\alpha]_D^{25}$ = +10 (*c* = 0.4, CH_2Cl_2). ^{1}H NMR ([D$_6$]acetone): δ = 7.49–7.32 (m, 5 H, Ph), 5.26 (br. s, 1 H, OH), 4.91–4.76 (m, 2 H, 2-H, 4-H), 4.21 (dd, *J* = 8.9, 13.9 Hz, 1 H, C*H*HOH), 4.06–3.99 (m, 2 H, 3-H, CH*H*OH), 3.47 (s, 3 H, Me), 3.33 (s, 3 H, Me), 1.66 (d, *J* = 6.8 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 136.0 (*ipso*-C, Ph), 129.8, 128.9, 128.3 (CH Ph), 80.8, 77.3 (C-2, C-4), 58.5 (CH$_2$OH), 54.3, 39.6 (Me), 43.7 (C-3), 13.2 (Me) ppm. MS (ESI Pos): *m*/*z* = 206.2 [M – OTf]$^+$.

(1′*S*,2*S*)-2-Cyano-1-methyl-1-(1-phenylethyl)azetidinium Trifluoromethanesulfonate (12): Yield: 90%; R_f = 0.1 (DCM/MeOH, 9:1); m.p. 85 °C, white solid. $[\alpha]_D^{20}$ = –42 (*c* = 0.7, $CHCl_3$). ^{1}H NMR ([D$_6$]acetone): δ = 7.79–7.76 (m, 2 H, C*H*Ar), 7.60–7.51 (m, 3 H, C*H*Ar), 6.24 (t, *J* = 9.9 Hz, 1 H, CNC*H*), 5.38 (q, *J* = 6.8 Hz, 1 H, CH$_3$C*H*), 5.09 (q, *J* = 9.8 Hz, 1 H, NCH*H*), 3.88 (td, *J* = 9.8, 3.2 Hz, 1 H, NC*H*H), 3.45 (s, 3 H, NCH_3), 3.44–3.32 (m, 1 H, CNCHC*H*H), 3.08–2.97 (m, 1 H, CNCHCH*H*), 1.88 (d, *J* = 6.9 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR: δ = 132, 131.9, 130.6, 130.3 (CAr), 113.7 (CN), 74.0 (CH), 63.6 (CH$_2$), 60.3 (CH), 41.9 (CH$_3$), 20.6 (CH$_2$), 13.4 (CH$_3$). CIMS (NH$_3$ gas): *m*/*z* = 351 [MH$^+$], 335, 324.

(1′*S*,2*S*)-2-*tert*-Butoxycarbonyl-1-methyl-1-(1-phenylethyl)azetidinium Trifluoromethanesulfonate (13): Yield: 90%; R_f = 0.2 (DCM/MeOH, 9:1). $[\alpha]_D^{20}$ = +18 (*c* = 1, $CHCl_3$). ^{1}H NMR ([D$_6$]acetone): δ = 7.51–7.49 (m, 2 H, C*H*Ar), 7.34–7.39 (m, 3 H, C*H*Ar), 5.50 (t, *J* = 9.6 Hz, 1 H, 2-H), 4.76 (dd, *J* = 9.7, 19.6 Hz,1 H, 4-H), 3.96 (td, *J* = 3.5, 9.5 Hz, 1 H, 4′-H), 3.07 (s, 3 H, NMe), 2.68–2.88 (m, 2 H, 3-H), 1.60 (d, *J* = 7.0 Hz, 3 H, CH$_3$), 1.10 (s, 9 H, *t*Bu) ppm. ^{13}C NMR: δ = 163.2 (CO), 131.6 (*ipso*-C, Ph), 130.8, 130.1, 129.4

(CHAr), 85.0 (Cq), 73.0, 70.1 (CH), 62.6 (CH_2), 39.4, 27.5 (CH_3), 18.1 (CH_2), 13.5 (CH_3) ppm. CIMS (NH_3 gas): *m*/*z* = 276.3 [M – OTf]$^+$, 220.2, 116.0, 105.0.

General Procedure for the Nucleophilic Ring-Opening of Azetidinium Salts with Sodium Azide: Sodium azide (162 mg, 5 mmol) was added to a solution of azetidinium trifluoromethanesulfonate (1 mmol) in DMF (5 mL). The suspension was stirred at room temp. for 15 h and diluted with water and diethyl ether. The usual work up was then followed by purification by flash chromatography.

Ethyl (2*R*,3*R*)-4-Azido-2-[benzyl(methyl)amino]-3-phenylbutyrate (14): Major regioisomer obtained from azetidinium **3**. Purified by flash chromatography (Et_2O/CyH, 1:9 then 2:8 then 4:6); R_f = 0.61 (Et_2O/PE, 3:7); yield: 93%; oil. $[\alpha]_D^{25}$ = –90 (*c* = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.38–7.19 (m, 10 H, Ph), 4.67 (d, *J* = 4.2 Hz, 1 H, 2-H), 4.17 (q, *J* = 7.1 Hz, 2 H, OCH_2), 3.66 (d, *J* = 13.1 Hz, 1 H, C*H*HPh), 3.54–3.47 (m, 2 H, 3-H, CH*H*Ph), 3.01 (t, *J* = 11.9 Hz, 1 H, 4-H), 2.47 (dd, *J* = 4.2, 12.3 Hz, 1 H, 4′-H), 2.28 (s, 3 H, NMe), 1.22 (t, *J* = 7.1 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 170.2 (C-1), 138.9, 138.1 (*ipso*-C, Ph), 129.2, 128.9, 128.5, 128.4, 127.6, 127.3 (CH Ph), 64.3 (C-2), 62.9 (*C*H_2Ph), 61.7 (CH_2O), 59.3 (C-4), 45.2 (C-3), 42.5 (NMe), 14.2 (Me) ppm. MS (ESI Pos): *m*/*z* = 353 [M + H]$^+$. $C_{20}H_{24}N_4O$ (352.4): C 68.16, H 6.86, N 15.90; found C 68.03, H 6.91, N 15.80.

Ethyl (2*S*,3*R*)-2-Azido-4-[benzyl(methyl)amino]-3-phenylbutyrate (15): Minor regioisomer obtained from azetidinium **3**. Purified by flash chromatography (Et_2O/CyH, 1:9 then 2:8 then 4:6); R_f = 0.63 (Et_2O/PE, 3:7); yield: 7%; oil. ^{1}H NMR ($CDCl_3$): δ = 7.30–7.11 (m, 10 H, Ph), 3.93–3.82 (m, 2 H, CH_2O), 3.77–3.71 (m, 2 H, 4-H, C*H*HPh), 3.63–3.54 (m, 3 H, 2-H, 4′-H, CH*H*Ph), 3.34–3.27 (m, 1 H, 3-H), 2.27 (s, 3 H, NMe), 0.94 (d, *J* = 7.1 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 169.2 (C-1), 139.0, 137.6 (*ipso*-C, Ph), 128.9, 128.8, 128.6, 128.5, 127.6 (CHPh), 67.9 (C-2), 60.0 (CH_2O), 59.4 (*C*H_2Ph), 54.0 (C-4), 44.7 (C-3), 37.8 (NMe), 14.4 (Me) ppm.

(2*R*,3*R*)-4-Azido-2-[benzyl(methyl)amino]-3-phenylbutyronitrile (16): Major regioisomer obtained from azetidinium **4**. Purified by flash chromatography (Et_2O/PE, 5:95 then 1:9); R_f = 0.6 (Et_2O/PE, 1:1); yield: 82%; m.p. 66 °C. $[\alpha]_D^{25}$ = +94 (*c* = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.48–7.24 (m, 10 H, Ph), 3.95 (d, *J* = 11.6 Hz, 1 H, 2-H), 3.88 (A part of a AB syst., *J* = 13.1 Hz, 1 H, C*H*HPh), 3.80 (dd, *J* = 3.9, 12.3 Hz, 1 H, 4-H), 3.70 (dd, *J* = 7.3, 12.3 Hz, 1 H, 4′-H), 3.62 (B part of syst. AB, *J* = 13.1 Hz, 1 H, CH*H*Ph), 3.30–3.22 (m, 1 H, 3-H), 2.46 (s, 3 H, NMe) ppm. ^{13}C NMR: δ = 137.2, 137.0 (*ipso*-C, Ph), 129.2, 129.1, 128.8, 128.6, 128.4, 128.0 (CH Ph), 115.2 (C-1), 60.3 (NCH_2), 59.4 (C-2), 52.9 (C-4), 46.1 (C-3), 38.3 (NMe) ppm. MS (ESI Pos): *m*/*z* = 328.3 [M + Na]$^+$, 279.3 [M – CN]$^+$.

(2*S*,3*R*)-2-Azido-4-[benzyl(methyl)amino]-3-phenylbutyronitrile (17): Minor regioisomer obtained from azetidinium **4**. Purified by flash chromatography (Et_2O/PE, 5:95 then 1:9); R_f = 0.58 (Et_2O/PE, 1:1); yield: 18%; oil. $[\alpha]_D^{25}$ = –88 (*c* = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.26–7.15 (m, 10 H, Ph), 4.88 (d, *J* = 2.9 Hz, 1 H, 2-H), 3.55 (A part of AB syst., *J* = 13.1 Hz, 1 H, C*H*HPh), 3.44 (B part of AB syst., *J* = 13.1 Hz, 1 H, CH*H*Ph), 3.09–3.06 (m, 1 H, 3-H), 2.96 (t, *J* = 11.2 Hz, 1 H, 4-H), 2.45 (dd, *J* = 4.1, 12.3 Hz, 1 H, 4′-H), 2.21 (s, 3 H, NMe) ppm. ^{13}C NMR: δ = 138.5, 136.0 (*ipso*-C, Ph), 129.1, 129.0, 128.8, 128.6, 128.4, 127.5 (CH Ph), 116.2 (C-1), 63.0 (*C*H_2Ph), 57.3 (C-4), 53.1 (C-2), 46.4 (C-3), 42.8 (Me) ppm. MS (ESI Pos): *m*/*z* = 328.3 [M + Na]$^+$, 279.3 [M – CN]$^+$.

(*Z*)- and (*E*)-(2*R*)-(5-Azido-2,4-dipenylpent-3-enyl)(benzyl)methylamine (18): Mixture of isomers obtained from azetidinium **7**. Purified by flash chromatography (Et_2O/CyH, 2:8); R_f = 0.52 (Et_2O/PE, 3:7); yield: 88%; oil. The following signals are characteristic of each isomer. Major isomer: ^{1}H NMR ($CDCl_3$): δ = 7.40–7.12 (m, 15 H, Ph), 6.26 (d, *J* = 9.4 Hz, 1 H, 3-H), 4.32 (s, 2 H, CH_2Ph), 3.70–3.50 (m, 3 H, 1-H, 1′-H, 2-H), 2.37 (s, 2 H, CH_2N_3) ppm. Minor isomer: ^{1}H NMR ($CDCl_3$): δ = 7.40–7.12 (m, 15 H, Ph), 6.00 (d, *J* = 10.2 Hz, 1 H, 3-H), 4.09 (s, 2 H, CH_2Ph), 3.73–3.64 (m, 1 H, 2-H), 3.54–3.40 (m, 2 H, 1-H, 1′-H), 2.14 (s, 2 H, CH_2N_3) ppm.

Ethyl (2*R*,3*S*,4*S*)-2-Azido-4-dimethylamino-3-phenylpentanoate (20): Major regioisomer obtained from azetidinium **8**. Purified by flash chromatography (Et_2O/CyH, 5:95 then 1:9 then 15:85); R_f = 0.44 (Et_2O/CyH, 3:7); yield: 86%; oil. $[\alpha]_D^{25}$ = +13 (*c* = 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.26–7.13 (m, 5 H, Ph), 4.60 (d, *J* = 5.2 Hz, 1 H, 2-H), 4.01 (q, *J* = 7.1 Hz, 2 H, OCH_2), 3.11 (dd, *J* = 5.6, 11.2 Hz, 1 H, 3-H), 3.02–2.92 (m, 1 H, 4-H), 2.19 (s, 6 H, NMe_2), 1.10 (t, *J* = 7.1 Hz, 3 H, Me), 0.58 (d, *J* = 6.4 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 170.1 (C=O), 138.1 (*ipso*-C, Ph), 129.3, 128.5, 127.5 (CH Ph), 64.9 (C-2), 61.3 (CH_2O), 59.9 (C-4), 52.0 (C-3), 40.1 (2 × NMe), 14.3 (Me), 8.7 (Me) ppm. MS (ESI Pos): *m*/*z* = 291 [M + H]$^+$. IR (film): $\tilde{\nu}$ = 3175, 2115, 1685, 1623 cm^{-1}. A yield of 14% of a minor product (based on the integration of a signal due to NMe_2 at δ = 2.26 ppm) contaminated this product. We could not determine however whether it was a regioisomer or an epimer.

(2*R*,3*S*,4*S*)-2-Azido-4-dimethylamino-3-phenylpentanenitrile (22): Unique regioisomer obtained from azetidinium **9**. Purified by flash chromatography (Et_2O/CyH, 5:95 then 1:9 then 15:85); R_f = 0.7 (Et_2O/PE, 1:1); yield: 27%; oil. $[\alpha]_D^{25}$ = +6 (*c* = 0.55, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.32–7.18 (m, 5 H, Ph), 5.14 (d, *J* = 3.1 Hz, 1 H, 2-H), 3.11–3.01 (m, 1 H, 4-H), 2.81 (dd, *J* = 3.1, 11.2 Hz, 1 H, 3-H), 2.30 (s, 6 H, NMe_2), 0.74 (d, *J* = 6.6 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 136.2 (*ipso*-C, Ph), 129.5, 128.8, 128.3 (CH Ph), 116.7 (CN), 58.6 (C-4), 53.3 (C-2), 52.9 (C-3), 40.1 (2 × NMe), 8.52 (Me) ppm. MS (ESI Pos): *m*/*z* = 266.2 [M + Na]$^+$, 244.2 [M + H]$^+$.

(2*S*,3*S*,4*S*)-2-Azido-4-dimethylamino-3-phenylpentanenitrile (24): Unique regioisomer obtained from azetidinium **10**. Purified by flash chromatography (Et_2O/CyH, 1:9); R_f = 0.8 (Et_2O/PE, 1:1); yield: quant.; m.p. 74 °C. $[\alpha]_D^{25}$ = –52 (*c* = 0.6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.38 (br. s, 5 H, Ph), 4.96 (d, *J* = 4.8 Hz, 1 H, 2-H), 3.24 (qd, *J* = 6.4, 13.0 Hz, 1 H, 4-H), 2.99 (dd, *J* = 4.8, 11.4 Hz, 1 H, 3-H), 2.30 (s, 6 H, NMe_2), 0.74 (d, *J* = 6.4 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 136.3 (*ipso*-C, Ph), 129.2, 129.1, 128.6 (CHPh), 115.8 (CN), 59.9 (C-4), 54.1 (C-2), 52.7 (C-3), 40.1 (2 × NMe), 8.4 (Me) ppm. MS (ESI Pos): *m*/*z* = 266.2 [M + Na]$^+$, 244.2 [M + H]$^+$. $C_{13}H_{17}N_5$ (243.3): C 64.17, H 7.04, N 28.78; found C 64.01, H 7.14, N 28.71.

General Procedure for the Nucleophilic Ring-Opening of Azetidinium Salts with Benzylamine: Benzylamine (0.54 mL, 5 mmol) was added to a solution of azetidinium trifluoromethanesulfonate (1 mmol) in CH_2Cl_2 (5 mL). The solution was stirred at room temp. for 5 h. Addition of water and DCM, followed by the usual work up gave a residue which was purified by flash chromatography.

(2*R*,3*R*)-4-Benzylamino-2-[benzyl(methyl)amino]-3-phenylbutyronitrile (25): Unique regioisomer obtained from azetidinium **4**. Purified by flash chromatography (CH_2Cl_2/MeOH, 99:1 then 97:3); R_f = 0.44 (CH_2Cl_2/MeOH, 97:3); yield: 89%; m.p. 128 °C. $[\alpha]_D^{25}$ = +87 (*c* = 0.35, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.37–7.19 (m, 15 H, Ph), 3.84 (d, *J* = 3.3 Hz, 1 H, 2-H), 3.82–3.73 (m, 3 H, NHC*H*$_2$Ph, C*H*HPh), 3.50 (d, *J* = 13.1 Hz, 1 H, CH*H*Ph), 3.34–3.26 (m, 1 H, 3-H), 3.19 (dd, *J* = 4.8, 12.1 Hz, 1 H, 4-H), 2.85 (dd, *J* = 8.3, 12.1 Hz, 1 H, 4′-H), 2.39 (s, 3 H, NMe), 1.56 (br. s, 1 H, NH) ppm.

^{13}C NMR: δ = 140.0, 138.6, 137.4 (*ipso*-C, Ph), 129.2–127.1 (CH Ph), 115.7 (CN), 61.1 (C-2), 60.1 (CH_2Ph), 54.0 (CH_2Ph), 51.1 (C-4), 46.7 (C-3), 38.5 (NMe) ppm. MS (ESI Pos): *m*/*z* = 370.3 [M + H]$^+$. IR (film): $\tilde{\nu}$ = 2289, 1621 cm^{-1}.

(2*R*,3*R*,4*S*)-2-Benzylamino-4-dimethylamino-3-phenylpentanoic Acid Benzylamide (28): Unique regioisomer obtained from azetidinium **8**. Purified by flash chromatography (CH_2Cl_2/MeOH, 99:1 then 97:3); R_f = 0.47 (CH_2Cl_2/MeOH, 97:3); yield: 68%; m.p. 101 °C. $[\alpha]_D^{25}$ = –10 (*c* = 0.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.30–7.07 (m, 15 H, Ph), 6.84 (br. s, 2 H, NH), 4.13 (d, *J* = 5.2 Hz, 2 H, CONHC*H*$_2$), 3.93 (d, *J* = 3.1 Hz, 1 H, 2-H), 3.70 (s, 2 H, NHC*H*$_2$Ph), 3.39 (d, *J* = 10.4 Hz, 1 H, 3-H), 3.05 (br. s, 1 H, 4-H), 2.25 (br. s, 6 H, NMe_2), 0.67 (d, *J* = 6.2 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 173.9 (CO), 140.1, 138.9, 138.5 (*ipso*-C, Ph), 129.4–127.0 (CH Ph), 62.9 (C-2), 58.6 (CH_2Ph), 53.7 (C-3), 52.4 (C-4), 42.9 (CH_2Ph), 40.2 (2×NMe), 8.9 (Me) ppm. MS (ESI Pos): *m*/*z* = 416.3 [M + H]$^+$.

(2*S*)-4-Benzylamino-2-[methyl(1-phenylethyl)amino]butyronitrile (29): Yield: 50%; R_f = 0.2 (Et_2O/EP: 6:4). $[\alpha]_D^{20}$ = –83 (*c* = 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.25–7.09 (m, 10 H, C*H*Ar), 3.67–3.56 (m, 3 H, 2-H, NCH_2Ph), 3.45 (q, *J* = 6.6 Hz, 1 H, CH_3C*H*), 2.63–2.48 (m, 2 H, NHC*H*$_2$), 2.31 (s, 3 H, NC*H*$_3$), 1.88–1.66 (m, 2 H, 3-H), 1.30 (d, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.9, 140.2 (C_qAr), 128.8, 128.4, 128.0, 127.7, 127.2, 127.0 (CHAr), 117.5 (CN), 63.8 (CH), 53.8 (CH_2), 52.6 (CH), 45.3 (CH_2), 33.7 (CH_3), 31.8 (CH_2), 21.6 (CH_3) ppm. CIMS (NH_3 gas): *m*/*z* = 308, 281, 202, 162, 120, 105, 91.

***tert*-Butyl (2*S*)-4-Benzylamino-2-[methyl(1-phenylethyl)amino]butyrate (31):** Yield: 23%; R_f = 0.4 (Et_2O/30% aqueous ammonia: 99:1); oil. $[\alpha]_D^{20}$ = +22 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.13 (m, 10 H, C*H*Ar), 3.73–3.68 (m, 3 H, CH_3C*H*, NHC*H*$_2$Ph), 3.60 (t, *J* = 7.5 Hz, 1 H, 2-H), 2.68 (t, *J* = 6.8 Hz, 2 H, 4-H), 2.05 (s, 3 H, NMe), 1.83 (q, *J* = 6.8, 2 H, 3-H), 1.70 (br. s, 1 H, NH), 1.39 (s, 9 H, CH_3), 1.27 (d, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5 (CO), 146.5, 140.4 (C_qAr), 128.4, 128.1, 127.7, 127.1, 126.9, 126.7 (CHAr), 80.7 (C_q), 62.9 (CH), 59.6 (CH), 54.2 (CH_2), 46.7 (CH_2), 34.6 (CH_3), 29.5 (CH_2), 28.4 (CH_3), 21.2 (CH_3) ppm. FAB MS: *m*/*z* = 421.3 [M + K]$^+$, 405.4 [M + Na$^+$], 389.4, 383.4 [M + H$^+$].

***tert*-Butyl (2*R*)-2-Benzylamino-4-[methyl(1-phenylethyl)amino]butyrate (32):** Yield: 29%; R_f = 0.6 (Et_2O/30% aqueous ammonia, 99:1); oil. $[\alpha]_D^{20}$ = –33 (*c* = 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.22–7.12 (m, 10 H, C*H*Ar), 3.70 (d, *J* = 12.8 Hz, 1 H, PhCH*H*), 3.53–3.44 (m, 2 H, CH_3C*H*, PhC*H*H), 3.09 (t, *J* = 6.2 Hz, 1 H, 2-H), 2.52–2.43 (m, 1 H, 4-H), 2.37–2.28 (m, 1 H, 4′-H), 2.08 (s, 3 H, NC*H*$_3$), 1.86–1.56 (m, 2 H, 3-H), 1.75 (br. s, 1 H, NH), 1.37 (s, 9 H, *t*Bu), 1.26 (d, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.7 (CO), 140.2, 143.8 (C_qAr), 128.4, 128.3, 128.1, 127.7, 126.9, 126.8 (CHAr), 80.9 (C_q), 63.6 (CH), 60.0 (CH), 52.1 (CH_2), 51.1 (CH_2), 38.4 (CH_3), 31.0 (CH_2), 28.2 (CH_3), 18.6 (CH_3) ppm. CIMS (NH_3 gas): *m*/*z* = 383, 148, 105.

Chemical Transformation for Characterization of Regioisomers

(3*R*,4*R*)-3-Methylamino-4-phenylpyrrolidin-2-one (33): A suspension of **14** (153 mg, 0.434 mmol) and palladium on charcoal (10 wt.-%, 15 mg) in ethanol (3 mL) was stirred vigorously under hydrogen for 15 h. Filtration through Celite and evaporation of the solvent under reduced pressure gave a residue that was purified by preparative TLC (CH_2Cl_2/MeOH, 8:2) to give the title compound as a clear oil (65 mg, 79%). R_f = 0.41 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D^{25}$ = –92 (*c* = 0.6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.31–7.17 (m, 5 H, Ph), 3.57–3.47 (m, 2 H, 3-H, 5-H), 3.32 (t, *J* = 9.6 Hz, 1 H, 5′-H), 3.10 (q, *J* = 9.3 Hz, 1 H, 4-H), 2.85 (s, 3 H, NMe), 1.83 (br. s, 2 H, NH, N*H*Me) ppm. ^{13}C NMR: δ = 174.3 (C-2), 139.3 (*ipso*-C, Ph), 128.9, 127.4 (CH Ph), 59.5 (C-3), 52.8 (C-5), 48.7 (C-4), 30.0 (NMe) ppm. MS (ESI Pos): *m*/*z* = 213.1 [M + Na]$^+$, 191.1 [M + H]$^+$.

2-Ethyl (2*R*,3*R*,4*S*)-2-Amino-4-dimethylamino-3-phenylpentanoate (34): Following the procedure described for the preparation of **32** and starting with **20** (160 mg, 0.551 mmol), the title compound was obtained crude in quantitative yield (145 mg). R_f = 0.41 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D^{25}$ = +12 (*c* = 0.75, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.23–7.10 (m, 5 H, Ph), 4.03–3.94 (m, 3 H, 2-H, CH_2O), 3.09–2.94 (m, 2 H, 3-H, 4-H), 2.19 (s, 6 H, NMe_2), 1.41 (br. s, 2 H, NH_2), 1.14 (t, *J* = 7.1 Hz, 3 H, Me), 0.57 (d, *J* = 6.0 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 175.4 (C-1), 139.2 (*ipso*-C, Ph), 129.2, 128.4, 127.1 (CH Ph), 60.5 (OCH_2), 59.2 (C-4), 56.2 (C-2), 53.8 (C-3), 40.2 (2×NMe), 14.3 (Me), 8.7 (Me) ppm. MS (ESI Pos): *m*/*z* = 265 [M + H]$^+$.

(2*R*,3*R*,4*S*)-2-Amino-4-dimethylamino-3-phenylpentanenitrile (35): Following the procedure described for the preparation of **33** and starting with **22** (122 mg, 0.5 mmol), the title compound was obtained crude in quantitative yield (122 mg). R_f = 0.34 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D^{25}$ = –26 (*c* = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.41–7.30 (m, 5 H, Ph), 4.18 (d, *J* = 2.3 Hz, 1 H, 2-H), 3.42–3.31 (m, 1 H, 4-H), 2.91 (dd, *J* = 2.1, 11.4 Hz, 1 H, 3-H), 2.36 (s, 6 H, NMe_2), 0.73 (d, *J* = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 139.0 (*ipso*-C, Ph), 129.0, 128.6, 127.7 (CH Ph), 122.4 (CN), 59.8 (C-2), 53.4 (C-4), 47.7 (C-3), 40.4 (NMe_2), 9.1 (Me) ppm. MS (ESI Pos): *m*/*z* = 230.3 [M + Na]$^+$, 218.3 [M + H]$^+$.

(2*R*,3*R*,4*S*)-2-*tert*-Butoxycarbonylamino-4-dimethylamino-3-phenylpentanenitrile (36): A solution of the above crude **34** (110 mg, 0.452 mmol) and Boc_2O (109 mg, 0.5 mmol) in AcOEt (3 mL) was heated at 60 °C overnight. Evaporation of the solvent under reduced pressure followed by purification of the residue by flash chromatography (Et_2O/PE, 5:95 then 10:90 then 20:80) gave 88 mg (61%) of the title compound. R_f = 0.49 (Et_2O/PE, 3:7). $[\alpha]_D^{25}$ = +12 (*c* = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.39–7.30 (m, 5 H, Ph), 7.02 (br. s, 1 H, NH), 5.05 (d, *J* = 7.3 Hz, 1 H, 2-H), 3.49–3.39 (m, 1 H, 3-H), 2.90 (d, *J* = 10.8 Hz, 1 H, 2-H), 2.38 (s, 6 H, NMe_2), 1.50 (s, 9 H, *t*Bu), 0.75 (d, *J* = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 163.2 (CO), 138.4 (*ipso*-C, Ph), 129.2, 128.3, 128.0 (CH Ph), 118.9 (CN), 80.6 [*C*(Me)$_3$], 60.6 (C-3), 51.9 (C-2), 48.6 (C-1), 40.2 (NMe_2), 28.4 (*t*Bu), 9.4 (Me) ppm. MS (ESI Pos): *m*/*z* = 340.2 [M + Na]$^+$, 318.2 [M + H]$^+$.

***tert*-Butyl (2*S*)-*N*-Benzyl-*N*-{3-cyano-3-[methyl(1-phenylethyl)amino]propyl}carbamate (37):** Following the procedure described for the preparation of **36**, the title compound was prepared. Yield: 78%; R_f = 0.15 (Et_2O/pentane, 2:8); oil. $[\alpha]_D^{20}$ = –75 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, broadened signals due to carbamate): δ = 7.27–7.08 (m, 10 H, C*H*Ar), 4.37–4.12 (m, 2 H, PhC*H*$_2$NBoc), 3.50–3.29 (m, 3 H, 2-H, 4-H, CH_3C*H*), 2.86 (br. m, 1 H, BocNC*H*$_2$Ph), 2.24 (s, 3 H, NMe), 1.75 (br. m, 2 H, 3-H), 1.35 (s, 9 H, CH_3), 1.29 (d, *J* = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5 (CO), 143.7, 138.1 (C_qAr), 128.9, 128.7, 128.5, 127.7, 127.4, 127.1 (CHAr), 117.4 (CN), 80.3 (C_q), 63.9 (CH), 52.3 (CH), 51.4 (CH_2), 43.8 (CH_2), 33.4 (CH_3), 30.6 (CH_2), 28.4 (CH_3), 21.6 (CH_3) ppm. FAB MS: *m*/*z* = 446.3 [M + K]$^+$, 430.3 [M + Na]$^+$, 414.3, 403.4, 387.4, 381.4, 174.2.

***tert*-Butyl (2*S*)-4-[Benzyl(*tert*-butoxycarbonyl)amino]-2-[methyl(1-phenylethyl)amino]butyrate (38):** Yield: 71%; R_f = 0.3 (PE/Et_2O, 9:1); oil. $[\alpha]_D^{20}$ = +24 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, broadened signals due to the carbamate moiety): δ = 7.35–7.20 (m, 10 H, C*H*Ar), 4.54–4.42 (m, 2 H, PhC*H*$_2$N), 3.76 (q, *J* = 6.3 Hz, 1 H,

CH_3CH), 3.52–3.08 (m, 3 H, 2-H, 4-H), 2.10 (s, 3 H, NMe), 2.02–1.88 (m, 2 H, 3-H), 1.47 (s, 18 H, Boc and *t*Bu), 1.31 (d, J = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0 (CO), 146.5, 138.6 (C_qAr), 128.5, 128.3, 127.7, 127.1, 126.1, 126.7 (CHAr), 80.9 (C_q), 79.7 (C_q), 62.9 (CH), 59.3 (CH), 50.2 (CH_2), 44.4 (CH_2), 34.3 (CH_3), 29.7 (CH_2), 28.3 (CH_3), 21.4 (CH_3) ppm. FAB MS: m/z = 505.4.

***tert*-Butyl (2*R*)-2-[Benzyl(*tert*-butoxycarbonyl)amino]-4-[methyl(1-phenylethyl)amino]butyrate ester (39):** Yield: 70%; R_f = 0.5 (Et_2O); oil. ^{1}H NMR ($CDCl_3$, broadened signals due to the carbamate moiety): δ = 7.35–7.23 (m, 10 H, CHAr), 4.63–4.52 (m, 1 H, NCHPh), 4.34–4.15 (m, 2 H, 2-H, NCHPh), 3.72–3.45 (m, 2 H, $CHCH_3$, 4-H), 2.21–2.01 (m, 4 H, NMe, 4′-H), 1.82–1.78 (m, 2 H, 3-H), 1.47, 1.41, 1.37 (three s, 18 H, *t*Bu, ester and carbamate), 1.28 (d, J = 6.8 Hz, 3 H, CH_3) ppm. FAB MS: m/z = 521.4 [M + K]$^+$, 505.4 [M + Na]$^+$, 483.4 [M + H]$^+$, 449.3, 427.3, 371.3, 349.3.

General Procedure for the Nucleophilic Ring-Opening of Azetidinium Salts with Acetate Anion: Sodium (or caesium) acetate (5 mmol) was added to a solution of azetidinium trifluoromethanesulfonate (1 mmol) in DMF (5 mL). The solution was stirred at room temp. for 15 h. Addition of water and diethyl ether followed by the usual work up gave a residue that was examined by NMR and purified by flash chromatography.

General Procedure for the Nucleophilic Ring-Opening of Azetidinium Salts with Sodium Triacetoxyborohydride: A solution of the azetidinium trifluoromethanesulfonate (1 mmol) and sodium triacetoxyborohydride (5 mmol) in THF (5 mL) was refluxed overnight. The mixture was then poured into water (100 mL), basified with sodium carbonate and extracted five times with DCM. The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. The residue was analyzed by proton NMR and purified by flash chromatography (EtO/PE, 3:7).

Ethyl (2*R*,3*S*)-4-Acetoxy-2-[benzyl(methyl)amino]-3-phenylbutyrate (40): Minor regioisomer obtained from the reaction of azetidinium **3** with sodium acetate. Purified by preparative TLC (Et_2O/CyH, 4:6). Yield: 30%; R_f = 0.51 (Et_2O/PE, 4:6); oil. $[\alpha]_D^{25}$ = +89 (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.40–7.21 (m, 10 H, Ph), 4.61 (dd, J = 3.7, 10.9 Hz, 1 H, 4-H), 4.57 (dd, J = 7.3, 10.9 Hz, 1 H, 4′-H), 4.05–3.94 (m, 2 H, CH_2O), 3.88 (A part of AB syst., J = 13.6 Hz, 1 H, CHHPh), 3.76 (d, J = 11.8 Hz, 1 H, 2-H), 3.67 (B part of AB syst., J = 13.6 Hz, 1 H, CHHPh), 3.59–3.51 (m, 1 H, 3-H), 2.41 (s, 3 H, NMe), 1.92 (s, 3 H, Me), 1.06 (t, J = 7.1 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 171.1, 169.3 (C=O), 139.1 (*ipso*-C, Ph), 128.9, 128.8, 128.5, 128.4, 127.2 (CH Ph), 67.4 (C-2), 65.7 (C-4), 59.9 (CH_2O), 59.5 (CH_2Ph), 43.8 (C-3), 37.9 (NMe), 21.0 (CH_3CO), 14.4 (Me) ppm. MS (ESI Pos): m/z = 392.1 [M + Na]$^+$, 370.1 [M + H]$^+$.

Ethyl (2*S*,3*R*)-2-Acetoxy-4-[benzyl(methyl)amino]-3-phenylbutyrate (41): Major regioisomer obtained from the reaction of azetidinium **3** with sodium acetate. Purified by preparative TLC (Et_2O/CyH, 4:6). Yield: 50%; R_f = 0.43 (Et_2O/PE, 4:6); oil. $[\alpha]_D^{25}$ = –69 (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.26–7.10 (m, 10 H, Ph), 5.52 (d, J = 3.7 Hz, 1 H, 2-H), 3.95 (q, J = 7.1 Hz, 2 H, CH_2O), 3.58 (A part of AB syst., J = 13.1 Hz, 1 H, CHHPh), 3.43–3.36 (m, 1 H, 3-H), 3.32 (B part of AB syst., J = 13.1 Hz, 1 H, CHHPh), 2.88 (t, J = 11.8 Hz, 1 H, 4-H), 2.31 (dd, J = 4.8, 12.3 Hz, 1 H, 4′-H), 2.22 (s, 3 H, NMe), 1.92 (s, 3 H, Me), 1.01 (t, J = 7.1 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 170.4, 169.7 (C=O), 138.3 (*ipso*-C, Ph), 129.2, 129.0, 128.4, 128.3, 127.4, 127.2 (CH Ph), 72.6 (C-2), 63.1 (CH_2Ph), 61.2 (CH_2), 58.3 (CH_2), 44.9 (C-3), 42.8 (NMe), 20.8 (MeCO), 14.2 (Me) ppm. MS (ESI Pos): m/z = 392.1 [M + Na]$^+$, 370.1 [M + H]$^+$.

(2*R*,3*S*)-4-Acetoxy-2-[benzyl(methyl)amino]-3-phenylbutyronitrile (42): Unique regioisomer obtained from azetidinium **4**. Purified by flash chromatography (Et_2O/CyH, 2:8 then 3:7). Yield: quant.; R_f = 0.72 (Et_2O/PE, 1:1); oil. $[\alpha]_D^{25}$ = +78 (c = 1.6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.32–7.08 (m, 10 H, Ph), 4.38 (dd, J = 4.1, 11.2 Hz, 1 H, 1-H), 4.25 (dd, J = 6.9, 11.2 Hz, 1 H, 1′-H), 3.82 (d, J = 11.6 Hz, 1 H, 3-H), 3.76 (A part of AB syst., J = 13.1 Hz, 1 H, CHHPh), 3.45 (B part of AB syst., J = 13.1 Hz, 1 H, CHHPh), 3.31–3.23 (m, 1 H, 2-H), 2.35 (s, 3 H, Me), 1.79 (s, 3 H, Me) ppm. ^{13}C NMR: δ = 170.7 (CO), 137.2 (*ipso*-C, Ph), 137.1, 129.2, 129.1, 129.0, 128.8, 128.5, 128.3, 127.9 (CH Ph), 115.3 (CN), 64.3 (C-1), 60.4 (CH_2), 58.9 (C-3), 45.3 (C-2), 38.4 (NMe), 20.9 (Me) ppm. MS (ESI Pos): m/z = 323 [M + H]$^+$. $C_{20}H_{22}N_2O_2$ (322.4): C 74.51, H 6.88, N 8.69; found C 74.39, H 6.78, N 8.55.

Ethyl (2*R* or 2*S*,3*S*,4*S*)-2-Acetoxy-4-dimethylamino-3-phenylpentanoate (45): Unique regioisomer obtained from the reaction of azetidinium **8** with caesium acetate. Purified by flash chromatography (Et_2O/PE, 1:9 then 2:8 then 4:6). Yield: 21–67%; R_f = 0.56 (Et_2O/PE, 7:3); oil. $[\alpha]_D^{25}$ = +4 (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.27–6.91 (m, 5 H, Ph), 5.66 (d, J = 4.2 Hz, 1 H, 2-H), 3.90 (q, J = 7.1 Hz, 2 H, CH_2O), 3.12–3.07 (m, 1 H, 3-H), 3.02–2.96 (m, 1 H, 4-H), 2.17 (s, 6 H, NMe_2), 2.06 (s, 3 H, Me), 0.99 (t, J = 6.8 Hz, 3 H, Me), 0.58 (d, J = 6.3 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 170.3, 170.0 (C=O), 138.3 (*ipso*-C, Ph), 129.5, 128.6, 127.3 (CH Ph), 73.0 (C-2), 60.9 (CH_3CO), 58.9 (CH_2O), 51.4 (C-3), 40.1 (2×NMe), 14.1 (Me), 8.8 (Me) ppm. CIMS (NH_3 Pos): m/z = 308 [M + H]$^+$.

(2*S*,3*S*,4*S*)-2-Acetoxy-4-dimethylamino-3-phenylpentanenitrile (46): Major isomer obtained from nucleophilic ring-opening of **9** and **10** with CsOAc or $NaBH(OAc)_3$. Purified by flash chromatography (Et_2O/PE, 3:7). Yield: see Table 2; R_f = 0.25 (Et_2O/PE, 7:3); m.p. 73–75 °C (dec.). $[\alpha]_D^{25}$ = –1.0 (c = 2.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.31–7.18 (m, 5 H, Ph), 6.00 (dd, J = 5.4, 0.6 Hz, 1 H, 1-H), 3.22–3.14 (m, 1 H, 3-H), 3.09–3.04 (m, 1 H, 2-H), 2.23 (s, 6 H, 2×NMe), 1.88 (d, J = 0.6 Hz, 3 H, $COCH_3$), 0.63 (d, J = 6.4 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 169.2 (C=O), 136.6 (*ipso*-C, Ph), 128.9, 128.7, 127.9 (CH Ph), 116.5 (CN), 64.5 (C-1), 60.0 (C-3), 50.7 (C-2), 39.9 (NMe_2), 20.5 ($COCH_3$), 8.2 (C-4) ppm. CIMS (NH_3 Pos): m/z = 261 [M + H]$^+$. IR (film): $\tilde{\nu}$ = 3180, 2950, 2291, 1751, 1695 cm^{-1}.

(2*R*,3*S*,4*S*)-2-Acetoxy-4-dimethylamino-3-phenylpentanenitrile (47): Minor isomer obtained from nucleophilic opening of **9** and **10** with CsOAc or $NaBH(OAc)_3$. Purified by flash chromatography (Et_2O/PE, 3:7). Yield: see Table 2; R_f = 0.42 (Et_2O/PE, 7:3); oil. $[\alpha]_D^{25}$ = +9.1 (c = 4.47, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.31–7.19 (m, 5 H, Ph), 5.92 (d, J = 3.6 Hz, 1 H, 1-H), 2.99–2.86 (m, 2 H, 3-H, 2-H), 2.16 (s, 6 H, NMe_2), 2.01 (s, 3 H, $COCH_3$), 0.62 (d, J = 5.9 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 169.0 (C=O), 136.7 (*ipso*-C, Ph), 129.4, 128.6, 127.9 (CH Ph), 117.2 (CN), 62.2 (C-1), 58.9 (C-3), 52.3 (C-2), 40.1 (NMe_2), 20.3 ($COCH_3$), 8.7 (Me) ppm. CIMS (NH_3 Pos): m/z = 261 [M + H]$^+$.

General Procedure for Intramolecular Opening with Alkoxides: A solution of KHMDS (0.5 M solution in toluene, 2.4 mL, 1.2 mmol) was added dropwise to a solution of the azetidinium salt (1 mmol) in THF (10 mL) cooled to –78 °C. The temperature was allowed to reach –40 °C and the reaction mixture was treated with water at this temperature. The usual work up (diethyl ether) gave crude epoxides. These products were unstable upon attempted purification by flash chromatography on silica gel.

(2*S*,1′*S*,3′*R*)-Benzyl(methyl)[2-phenyl-2-(3′-phenyloxiran-2′-yl)ethyl]-amine (48): Crude yield: 98%; oil. ^{1}H NMR ($CDCl_3$): δ = 7.38–7.05 (m, 15 H, Ph), 3.57 (d, J = 1.9 Hz, 1 H, 3′-H), 3.42 (AB syst., J = 13.1 Hz, 2 H, CHHPh), 3.08 (dd, J = 2.1, 6.7 Hz, 1 H, 1′-H),

2.93–2.88 (m, 1 H, 2-H), 2.78 (dd, J = 9.1, 12.3 Hz, 1 H, 1-H), 2.56 (dd, J = 5.9, 12.3 Hz, 1 H, 1′-H), 2.19 (s, 3 H, NMe) ppm. ^{13}C NMR: δ = 140.1, 139.2, 137.8 (*ipso*-C, Ph), 128.9–125.7 (CH Ph), 65.7 (C-1′), 63.0 (CH_2Ph), 60.3 (C-1), 58.7 (C-3′), 46.4 (C-2), 42.8 (NMe) ppm. MS (ESI Pos): m/z = 344.2 $[M + H]^+$.

(1*S*,2*S*,1′*R*)-Dimethyl(1-methyl-2-oxiran-2′-yl-2-phenylethyl)amine (49): Crude yield: 99%; oil. ^{1}H NMR ($CDCl_3$): δ = 7.38–7.36 (m, 2 H, Ph), 7.31–7.16 (m, 3 H, Ph), 4.57 (br. s, 1 H, 1′-H), 4.22–4.17 (m, 2 H, 3′-H), 3.97–3.84 (m, 2 H, 2-H, 3′-H), 3.32 (s, 3 H, NMe), 3.26 (s, 3 H, NMe), 1.29 (d, J = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 139.1 (*ipso*-C, Ph), 129.7, 129.1, 128.5 (CH Ph), 77.2 (C-1), 75.1 (C-1′), 74.3 (C-3′), 51.8 (NMe), 46.8 (NMe), 11.3 (Me) ppm. MS (ESI Pos): m/z = 206.3 $[M + H]^+$.

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[14] DFT calculations were carried out using the B3LYP exchange-correlation functionals, together with the standard 6-31G(d) basis set. The optimizations were carried out using the Berny analytical gradient optimization method. The stationary points were characterized by frequency calculations in order to verify that the transition-state structures have one and only one imaginary frequency. All calculations were carried out using the Gaussian 03 suite of programs: M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03* (Revision B-04), Gaussian, Inc., Pittsburgh, PA, **2003**.

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Received: March 7, 2006
Published Online: June 1, 2006

