# Stereocontrolled Synthesis of 3-Substituted Azetidinic Amino Acids

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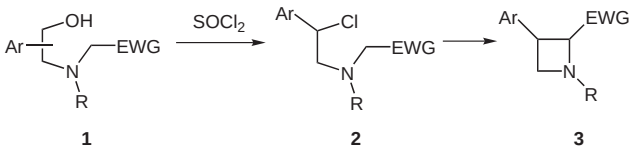
**Abstract:** A set of enantiomerically pure N-disubstituted β-amino alcohols was chlorinated by treatment with thionyl chloride. This reaction gave a mixture of regioisomeric chlorides that could be equilibrated to the more stable regioisomer by heating in DMF. The chlorides thus obtained were engaged in an intramolecular anionic ring-closure and gave access to fully protected enantio- and diastereomerically pure 2,3-*cis*-disubstituted azetidinic amino acids. One of the latter was deprotected and included in a short peptide sequence.

**Key words:** azetidines, amino acids, amino alcohols, asymmetric synthesis

We recently reported a synthesis of functionalized azetidines from β-amino alcohols based on a 4-*exo*-*tet* anionic ring-closure.[1] Key steps involved in this synthesis rely on (i) a chlorination of the hydroxyl in a N-disubstituted β-amino alcohol **1** and (ii) an intramolecular alkylation of the produced chloride **2** induced by deprotonation α to the EWG group, to give functionalized azetidine **3** in good overall yield (Scheme 1). Given the availability of β-amino alcohols in enantiomerically pure form, this synthesis provides an original entry to the preparation of azetidines and led us to explore the reactivity of this understudied class of heterocycles towards ring expansions[2] or ring-opening[3] processes. This anionic ring-closure was found to be general and compatible with nitriles,[1] esters[4] or phosphonates[5] acting as EWG group. The electrophilic partner was also experienced with an α,β-unsaturated ester, providing azetidinic amino acids evaluated as ligands for the glutamate receptors and transporters.[6]




1 2 3

**Scheme 1**

However, this synthetic sequence relies heavily on the chlorination step, whose regioselectivity was found to be dependent on the substitution pattern in the starting amino alcohol **1**. As a matter of fact, chlorination of a β-amino alcohol induces the formation of an aziridinium ion, which is then opened by the chloride anion (Figure 1).[7] When an aryl group is present in the substrate, such as in aziridinium **4**, then the chloride anion exclusively attacks the benzylic position, giving one regioisomeric chloride with overall retention of configuration compared to the starting amino alcohol. In contrast, when an alkyl-substituted aziridinium **5** is involved, the opening by the chloride anion is not regioselective, giving two regioisomeric chlorides and thus hampering the generality of this synthesis.

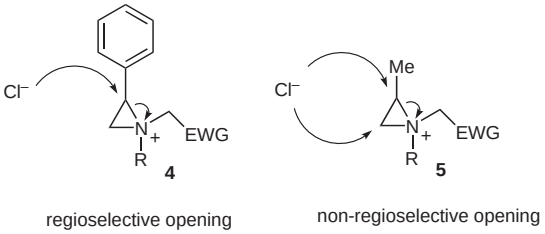



**Figure 1**

We wish to report herein a solution to this regioselectivity problem involving alkyl-substituted aziridinium intermediates, thus extending considerably the scope of this reaction. This was applied to the synthesis of enantiomerically pure 3-substituted azetidinic amino acids[8] that can be envisioned as conformationally constrained amino acids the latter being the topic of extensive research for synthetic and medicinal chemists.[9]

The β-amino alcohol substrates **7**–**15** were prepared in order to study the regioselectivity of the chlorination step (Table 1). These compounds were made either from commercially available enantiomerically pure β-amino alcohols (for **7**–**12**) or from (*S*)-*O*-benzyl tyrosinol[10] following a two-step sequence involving N-benzylation (PhCHO, 4 Å MS, then $NaBH_4$) and N-alkylation with either bromoacetonitrile (for **7**–**9**: $K_2CO_3$, MeCN) or *tert*-butyl bromoacetate (for **10**–**15**: $NaHCO_3$, NaI, DMF). Amino alcohols **14** and **15** were prepared from the corresponding epoxides by reaction with either isopropylamine or benzylamine in the presence of β-cyclodextrin (β-CD) following our previously described methodology.[11] The resulting amino alcohols **16**, **17** were obtained with good yields and high ee (Scheme 2) and were transformed into **14** and **15** through the above-described two-step procedure.

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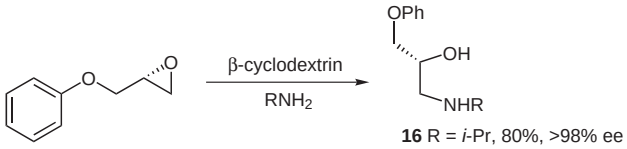
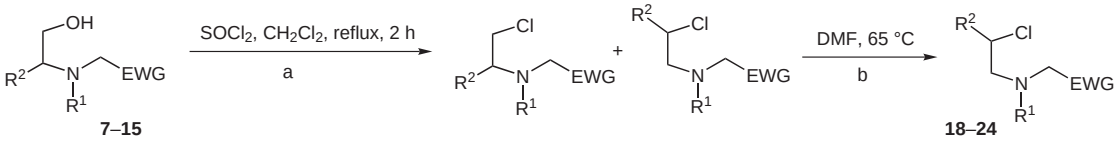
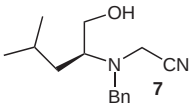
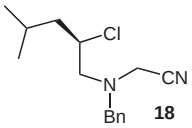
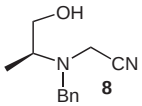
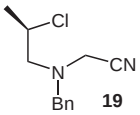
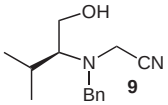
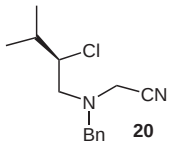
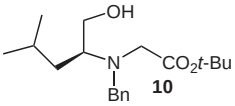
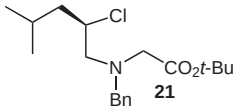
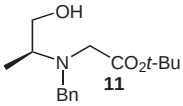
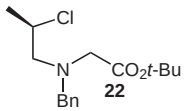
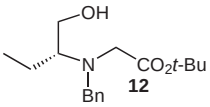
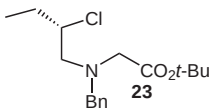
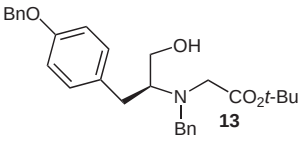
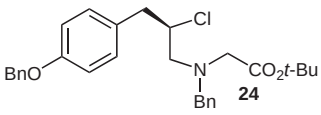
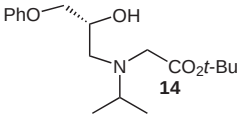
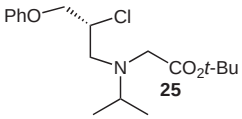
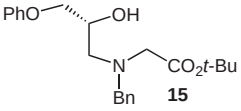
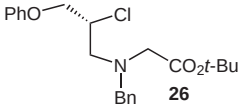



**Scheme 2**

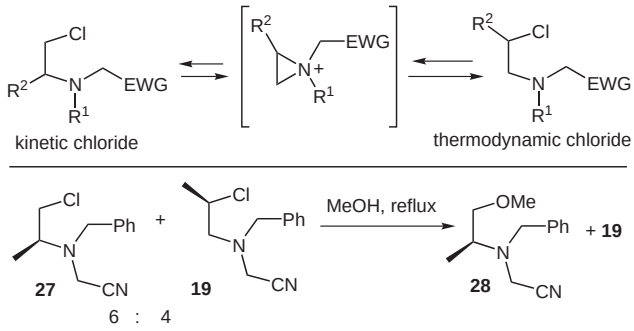
All these β-amino alcohols were chlorinated by treatment with thionyl chloride in $CH_2Cl_2$ to furnish a regioisomeric mixture of chlorides in good yields. Heating this mixture in DMF at 65 °C for the time specified in Table 1 resulted in a complete equilibration to give the secondary chlorides **18**–**26**. These conditions were adjusted in order to minimize degradation and the secondary chlorides were obtained in high overall yields and >98% regioisomeric purity.

**Table 1** Regioselective Chlorination of β-Amino Alcohols




| Entry | Substrate | Step a Yield (%), regioisomeric ratio | Step b Yield (%), time for equilibration | Product | Overall yield (%)[a] |
|---|---|---|---|---|---|
| 1 |  **7** | 90 (1:1) | 95 65 h |  **18** | 85 |
| 2 |  **8** | 93 (1:1) | 95 60 h |  **19** | 88 |
| 3 |  **9** | 90 (1:1) | 98 65 h |  **20** | 88 |
| 4 |  **10** | 80 (1:1) | 95 65 h |  **21** | 76 |
| 5 |  **11** | 90 (2:1) | 95 60 h |  **22** | 85 |
| 6 |  **12** | 92 (1:1) | 95 80 h |  **23** | 83 |
| 7 |  **13** | 93 (2:3) | 95 65 h |  **24** | 88 |
| 8 |  **14** | 90 (2:1) | 95 60 h |  **25** | 85 |
| 9 |  **15** | 83 (4:1) | 77 60 h |  **26** | 64 |

[a] Yield of pure isolated product.




**Scheme 3**

The high regioselectivity obtained in this chlorination can be explained by the occurrence of an equilibration through an intermediate aziridinium ion (Scheme 3). Upon heating in DMF, both primary and secondary chlorides can produce an aziridinium ion through intramolecular alkylation. Chloride anion can then re-attack this electrophilic intermediate to give either primary or secondary chloride. The accumulation of the secondary chloride in the reaction mixture can be explained by the fact that it is less prone to give back the aziridinium ion, due to the crowding of the electrophilic center. It should be noted that a very similar behavior with azetidinium ions has been recently reported.[12] The long reaction times required for equilibration suggest that the opening at the less hindered position to give back the primary chloride is a more rapid process. Therefore, the primary chloride is the kinetic product, and the secondary chloride the thermodynamic product and these compounds are obtained without erosion of the optical purity, as demonstrated by the high optical purity of the azetidines derived from these products (vide supra). The kinetic opening by a nucleophile at the less hindered position can be easily evidenced: heating a 6:4 mixture of chlorides derived from **8** in MeOH gave a mixture of primary ether **28** and unreacted secondary chloride **19**: no trace of secondary ether could be detected in the reaction mixture.

The regioselectivity issue being solved, we next focused on the nucleophilic ring-closure in order to form the azetidine ring. Therefore, chlorides **18**–**20** bearing a cyanomethyl moiety on the nitrogen were treated with LiHMDS at –78 °C, following our previously described conditions.[1] Cyclization occurred in high yield with **18** and **19**, but not with **20**, in which the electrophilic center is more sterically crowded. However, the 2,3-diastereoselectivity was low in all cases, and the diasteroisomers were not easily separable. We therefore switched to the use of chlorides **21**–**26**, bearing a large *tert*-butyl ester, hoping to increase the diastereoselectivity. As a matter of fact, the enolates derived from these esters proved to be less reactive than their amino nitrile homologues, and it was crucial to use HMPA as an additive (10% volume with THF) to induce the cyclization with these substrates. Nonetheless, under these conditions, cyclized compounds were obtained in good yields, and we were pleased to note that cyclization occurred with total 2,3-*cis*-diastereoselectivity. Results of these experiments are summarized in Table 2.

Particularly noteworthy in these experiments is the high 2,3-*cis*-diastereoselectivity observed in the course of the cyclization. The 2,3-relative configuration in the produced azetidines was determined by NOE experiments performed with **36** and **39** (NOE enhancements are shown in Figure 2). The optical purity of the azetidine **36** and *ent*-**36** was determined by NMR using (*S*)-α-(trifluoromethyl)benzyl alcohol as chiral solvent[13] and was found to be greater than 95%, demonstrating that no erosion of the optical purity occurred during the equilibration process. The rationalization of the observed *cis*-2,3-diastereoselectivity is not simple. The first question to be answered is whether the reaction is kinetically controlled or if further enolization of the produced azetidine induces a thermodynamic control. In order to address this point, we have treated azetidine **36** under the conditions of the cyclization (LiHMDS in THF–HMPA) followed by quenching at 0 °C with methanol-$d_4$. Since the starting product was recovered unchanged and did not show any incorporation of deuterium, we can conclude that it is not enolized in the reaction mixture. This observation is, however, not sufficient to conclude that a kinetic control is operating, since we cannot rule out an enolization of a 2,3-*trans* azetidine into the observed 2,3-*cis* isomer.

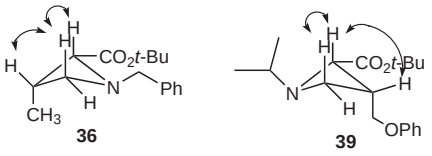
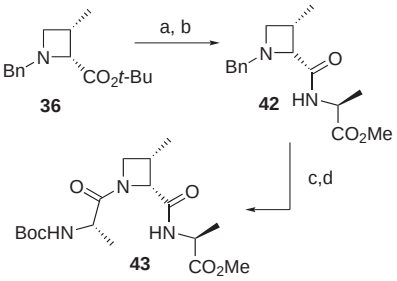


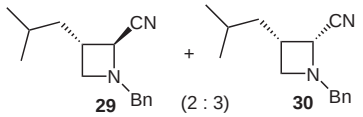
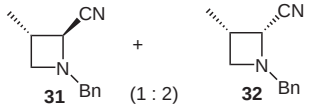
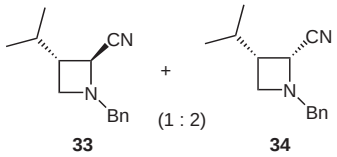
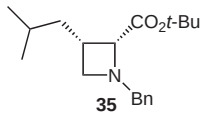
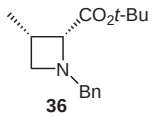
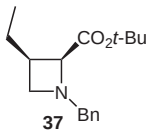
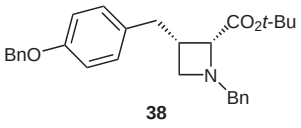
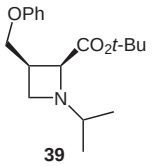
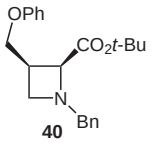

**Figure 2** NOE enhancements in **36** and **39**.

In order to demonstrate that these azetidinic amino acids are suitable for peptide chemistry, amino acid **36** was included in a tripeptide, as shown in Scheme 4. Thus, cleavage of the *tert*-butyl ester in **36** with TFA was followed by coupling with L-AlaOMe to give **42**. N-debenzylation of **42** was then followed by coupling with L-*N*-Boc-Ala, to furnish tripeptide **43** with modest yield. The use of the BOP reagent proved to be necessary for this step to attain a reasonable yield.




**Scheme 4** *Reagents and conditions*: (a) TFA, $CH_2Cl_2$, r.t., 0.5 h, 95%; (b) L-AlaOMe·HCl, $Et_3N$, BOP, MeCN, 16 h, r.t., 65%; (c) $Pd(OH)_2$, $H_2$, MeOH, AcOH, r.t., 3 h, 95%; (d) L-*N*-BocAla, $Et_3N$, BOP, MeCN, 16 h, r.t., 50%.

**Table 2** Intramolecular Alkylation of Chlorides **18**–**26**

| Entry | Substrate | Conditions | Products | Yield (%)[a] |
|---|---|---|---|---|
| 1 | **18** | LiHMDS, THF, –78 °C to –10 °C |  **29** (2 : 3) **30** | 95 |
| 2 | **19** | LiHMDS, THF, –78 °C to 0 °C |  **31** (1 : 2) **32** | 60 |
| 3 | **20** | LiHMDS, THF, –78 °C to 0 °C |  **33** (1 : 2) **34** | 25 |
| 4 | **21** | LiHMDS, THF–HMPA –78 °C to 0 °C |  **35** | 73 |
| 5 | **22** | LiHMDS, THF–HMPA –78 °C to 0 °C |  **36** | 80 |
| 6 | **23** | LiHMDS, THF–HMPA –78 °C to –20 °C |  **37** | 85 |
| 7 | **24** | LiHMDS, THF–HMPA –78 °C to –40 °C |  **38** | 50[b] |
| 8 | **25** | LiHMDS, THF–HMPA –78 °C to 0 °C |  **39** | 50 |
| 9 | **26** | LiHMDS, THF–HMPA –78 °C to 0 °C |  **40** | 75 |

[a] Yield of pure isolated product.
[b] A 20% yield of elimination product was produced with this substrate.

In conclusion, we have shown that diastereo- and enantiomerically pure *cis*-2,3-substituted azetidines can be prepared in a straightforward way from β-amino alcohols.[14] Applications of these azetidinic amino acids will be reported in due course.

## Acknowledgment

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## References and Notes

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(2) (a) Couty, F.; Durrat, F.; Prim, D. *Tetrahedron Lett.* **2003**, *44*, 5209. (b) Couty, F.; Durrat, F.; Evano, G.; Prim, D. *Tetrahedron Lett.* **2004**, *45*, 7525.
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**Typical Procedure for the Preparation of Chloride 19.**

To a solution of amino alcohol **11** (1.20 g, 4.30 mmol) in $CH_2Cl_2$ (30 mL) was added $SOCl_2$ (0.64 mL, 8.81 mmol) at 0 °C and it was then refluxed for 3 h. After the completion of the reaction, the excess $SOCl_2$ was neutralized by a sat. aq solution of $NaHCO_3$ (10 mL). Extraction of the reaction mixture using $Et_2O$ followed by usual workup gave a mixture of chlorides (2:1 ratio) that were purified by flash chromatography (EtOAc–PE 1:9, 1.15 g, 90%).The formed chlorides (1.15 g) were then dissolved in DMF (10 mL) and heated at 60 °C for 60 h. DMF was removed under vacuo and the obtained chloride was filtered on silica gel (EtOAc–PE 1:9) and gave pure chloride **22** (1.09 g, 95%) as a thick oil. $R_f$ 0.85 (EtOAc–PE 9:1); $[\alpha]_D^{20}$ –6.6 (*c* 0.7, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.37 (br s, 12 H), 2.80 (dd, *J* = 13.7, 6.8 Hz, 1 H), 2.93 (dd, *J* = 13.7, 6.8 Hz, 1 H), 3.19 (s, 2 H), 3.78 (d, *J* = 3.4 Hz, 2 H), 3.87–3.94 (m, 1 H), 7.14–7.20 (m, 5 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 23.0, 28.2, 55.7, 56.2, 58.7, 62.5, 81.0, 127.2, 128.7, 128.9, 139.0, 170.7. MS (CI, $NH_3$ gas): *m/z* (%) = 320 (27) [M + $K^+$], 264 (8), 242 (61).

**Typical Procedure for the Azetidine Formation, Starting with Chloride 22.**

To a solution of chloride **22** (1.50 g, 5.04 mmol) in THF (20 mL) and HMPA (2 mL) was added dropwise at –90 °C a solution of LiHMDS (1 M solution in THF, 7.56 mL, 7.56 mmol). The reaction was monitored by TLC and then quenched by the addition of an aq sat. solution of $NH_4Cl$ (10 mL) at 0 °C. Extraction of the reaction mixture using $Et_2O$ gave, after usual workup, a residue that was purified by flash chromatography (EtOAc–PE 1:9) to give *cis*-azetidine **36** (1.05 g, 80%). $R_f$ 0.85 (EtOAc–PE 15:85); $[\alpha]_D^{20}$ +91.3 (*c* 0.4, $CHCl_3$). $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 7.0 Hz, 3 H), 1.40 (s, 9 H), 2.58–2.69 (m, 1 H), 2.90–3.10 (m, 2 H), 3.54 (d, *J* = 12.5 Hz, 1 H), 3.68 (d, *J* = 8.0 Hz, 1 H), 3.74 (d, *J* = 12.5 Hz, 1 H), 7.18–7.39 (m, 5 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 15.5, 28.2, 28.6, 56.8, 61.6, 67.3, 80.6, 127.0, 128.2, 129.2, 137.5, 170.8. MS (CI, $NH_3$ gas): *m/z* (%) = 300 (10), 284 (74), 262 (28) [$M^+$], 206 (100). Anal. Calcd for $C_{16}H_{23}NO_2$ (%): C, 73.53; H, 8.87; N, 5.36. Found: C, 73.39; H, 9.01; N, 5.42.