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Ring Expansion of 2-(1-Hydroxyalkyl)azetidines to 4-(2-Chloroethyl)-oxazolidinones

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Keywords: Ring expansion / Nitrogen heterocycles / Synthetic methods / Azetidines / Oxazolidinones

2-(1-Hydroxyalkyl)azetidines react with bis(trichloromethyl) carbonate (BTC) after basic treatment to afford 4-(2-chloroethyl)oxazolidinones. The scope of this rearrangement was examined in detail and its efficiency was shown to depend on the class of the reacting alcohol and on the substitution pattern on the azetidine ring.

Introduction

Oxazolidinones are among the most popular heterocycles in organic chemistry due to the seminal work of Evans[1] who introduced these scaffolds as chiral auxiliaries that became cornerstones of asymmetric synthesis.[2] More recently, the discovery of Linezolid (**1**, Figure 1), the first clinically useful oxazolidinone antibacterial agent,[3] has brought to light another important application of these heterocycles. In 2000, this antibiotic was approved by the FDA and was shown to be active against multidrug-resistant Gram-positive pathogens responsible for significant mortality. Synthesis of oxazolidinones relies on the formation of the cyclic carbamate by reaction of a 1,2-amino alcohol with diverse acylating agents such as diethyl carbonate,[4] phosgene,[5] *N*,*N*′-carbonyldiimidazole,[6] or carbon monoxide with catalytic elemental sulfur.[7] Therefore, the ease of preparation of oxazolidinones with functionalized side chains depends heavily on the synthetic availability of the corresponding amino alcohol.[8] In 2003, Ha and Lee demonstrated that 4-(chloromethyl)oxazolidinones **4** resulted from the reaction of the corresponding 2-hydroxyalkyl aziridine **2** with phosgene under basic conditions.[9] This ring expansion involves intermediate *N*-acyl aziridinium **3**, which is opened regioselectively by the chloride anion. In continuation of our interest in the chemistry of azetidines,[10] we decided to evaluate the feasibility of a similar ring expansion starting from 2-(1-hydroxyalkyl)azetidines **5** (Scheme 1). Considering the easy access to the required starting material,[11] this ring expansion would provide an original entry to 4-(2-chloroethyl)oxazolidinones **7**, which are susceptible to further chemical transformations.

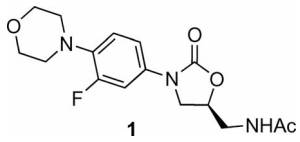
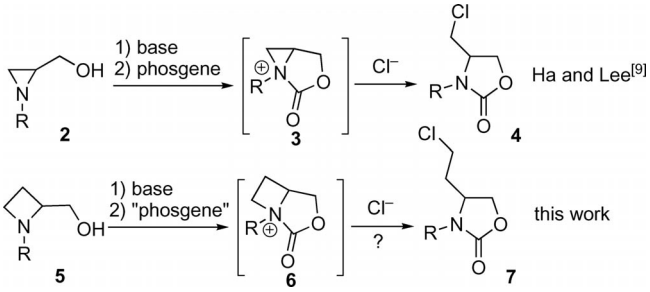


Figure 1. Structure of Linezolid.



Scheme 1. Is the ring expansion of 2-(1-hydroxyalkyl)aziridines transposable to azetidines.

Results and Discussion

2-(1-Hydroxyalkyl)azetidines **8**–**18** chosen to conduct this study were prepared as described previously.[11c] Examples of all classes of alcohols were used to determine the scope of the reaction. Substitution on the azetidine ring was also varied, and the structures of these substrates are depicted in Figure 2. Previously unreported azetidines (±)-**11** and **14**–**18**, as well as known (±)-**8** were prepared according to Scheme 2.

With this array of diversely substituted azetidines, the feasibility of the rearrangement was studied. We chose the best operating conditions described by Ha, that is, formation of the sodium alkoxide by reaction with NaH in THF, followed by reaction with bis(trichloromethyl) carbonate (BTC), as a safer substitute for phosgene. With these conditions, we were delighted to see that (±)-**8** was converted

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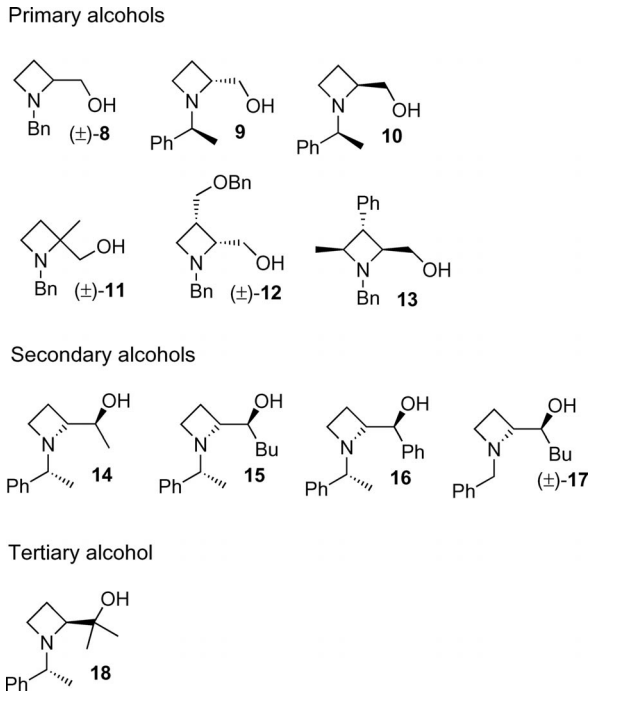
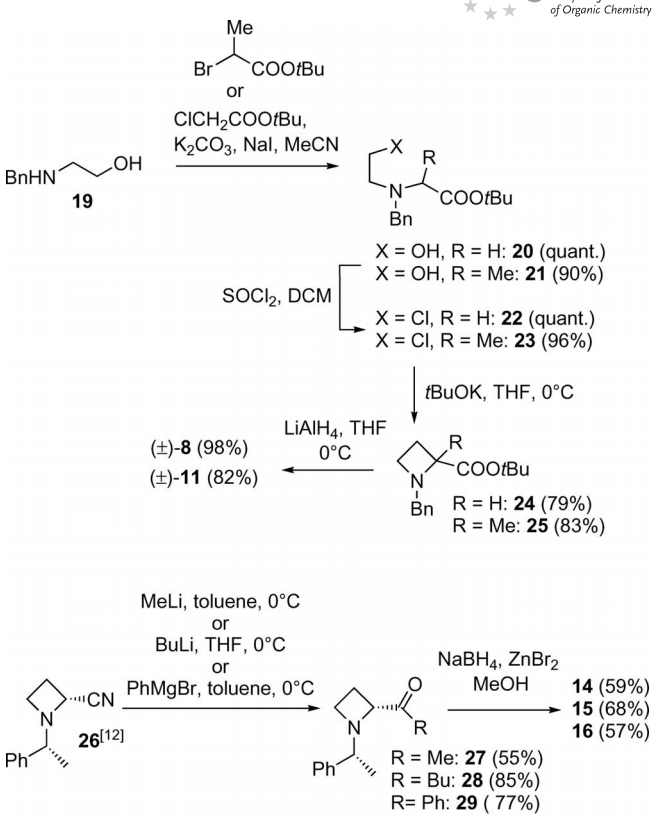


Figure 2. Structure of 2-(1-hydroxyalkyl)azetidines used in this study.



Scheme 2. Synthesis of previously unreported 2-(1-hydroxyalkyl)-azetidines.

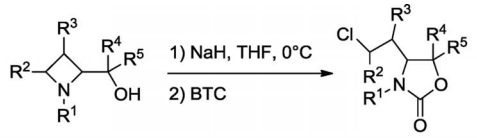
into 4-(2-chloroethyl)oxazolidinone **33** in quantitative yield after 1 h at room temperature. Encouraged by this result, the scope of this reaction was examined with other substrates, and the results are presented in Table 1.

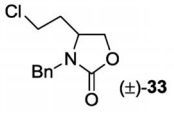
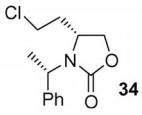
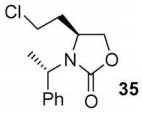
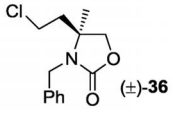
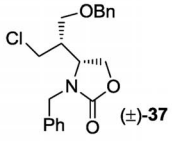
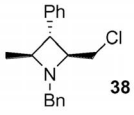
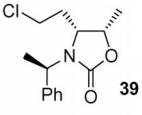
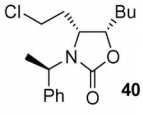
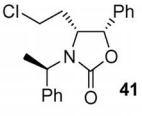
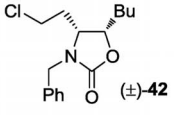
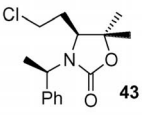
The yield of this reaction appears to depend on the substitution pattern of the starting azetidine. In most cases (Table 1, Entries 2, 4, 5, and 7–10), the reaction was clean. In some cases, the low yields are due to incomplete conversion, as the starting material was easily detected or isolated after workup (20–30% average yield). In other cases, the low yields are explained by side reactions; this is the case for Entry 6, where only 2-(chloromethyl)azetidine **38**[11c] was isolated among unidentified byproducts. Formation of this compound can be explained by attack of the chloride anion at the oxomethylene position instead of at the C-4 position of the azetidinium, which is hindered by the methyl substituent (Scheme 3). This is also the case for (±)-**11** (Table 1, Entry 4). In this experiment, compound **44** was isolated in 19% yield. Its formation was rationalized by the carbocationic nature of the intermediate bicyclic azetidinium, which undergoes a 1,2-hydride shift to furnish aldehyde **44** (Scheme 3). Tertiary alcohol **18** (Table 1, Entry 11) was also reluctant to undergo rearrangement, and most of the starting material was recovered. This lack of reactivity contrasts the work of Ha[9] in the lower homologue series. One possible explanation is the enhanced nucleophilicity of the nitrogen in the azetidine ring, compared to the aziridine. Thus, if the alkoxide is too encumbered (which is especially true with tertiary alcohols), the nitrogen atom of the azetidine competes to react with BTC and gives a double salt, which precipitates in the reaction medium and does not evolve further. Upon basic workup, this salt decomposes and results in starting material. Possible competitive reaction of the amine in the case of primary alcohols is proven experimentally by the nature of side product **44**, whose formation can only be explained by competitive attack on BTC by the nitrogen. Simple steric factors hampering the attack of the chloride anion on intermediate **6** cannot be ruled out.[14]

Starting with secondary alcohol (±)-**17**, attempts to optimize the yield by varying the reaction conditions did not meet with much success. More polar solvents, such as DME, the presence of additives, such as crown ethers, the nature of the base (BuLi or KHMDS), and the addition of phosgene instead of BTC were screened extensively but gave no significant improvement in the yield of (±)-**42**.

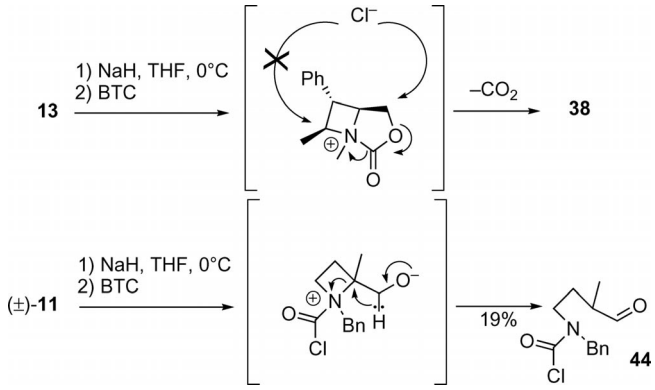
Finally, post functionalization of 4-(2-chloroethyl)oxazolidinone **33** was briefly examined. Substitution of the chloride by azide or cyanide occurred readily to give **45** and **46**, respectively. More interestingly, treatment of **33** with a slight excess amount of BuLi in THF promoted benzylic

Table 1. Scope of the rearrangement.



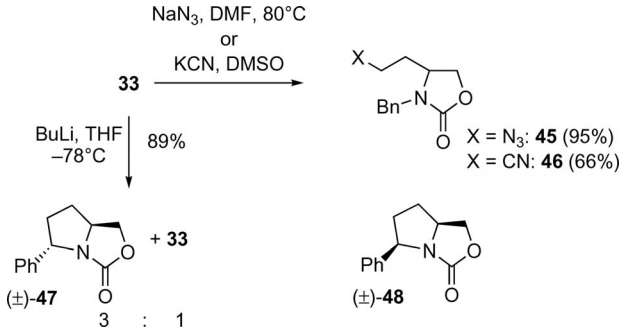
Entry	Substrate	Product	Yield [%][a]
1	(±)-**8**	 (±)-**33**	quant.
2	**9**	 **34**	53
3	**10**	 **35**	83
4	(±)-**11**	 (±)-**36**	35
5	(±)-**12**	 (±)-**37**	37
6	**13**	 **38**	15
7	**14**	 **39**	41
8	**15**	 **40**	33[b]
9	**16**	 **41**	50
10	(±)-**17**	 (±)-**42**	52
11	**18**	 **43**	10

[a] Yield of isolated product. [b] Yield was improved to 48% (86% based on recovered starting material) when KHMDS was used as base instead of NaH.



Scheme 3. Mechanism of formation of side products **38** and **44**.

lithiation followed by kinetically controlled intramolecular alkylation to afford **47** in a diastereoselective manner together with starting material **33** (3:1 ratio by NMR spectroscopy). Protracted reaction time or excess amounts of BuLi did not totally consume the starting material, but induced formation of diastereoisomer **48**,[15] which probably arises from further lithiation of **47**, followed by equilibration (Scheme 4).



Scheme 4. Post functionalization of oxazolidinone **33**.

Conclusions

In conclusion, we have demonstrated that 2-(1-hydroxymethyl)azetidines can be converted into 4-(2-chloroethyl)oxazolidinones by reaction with BTC. The scope of the reaction was examined and was shown to be restricted to primary and secondary alcohols on the azetidinic side chain. Furthermore, azetidines substituted at C-4 or disubstituted at C-2 failed to react or gave side products that allowed insight into the mechanism. Yields are modest, which is attributed to the competitive reaction of the azetidinic nitrogen with BTC that leads to unreactive intermediates. Starting material can be recovered in these cases by simple acidic/basic treatment. Work is in progress to further examine the reactivity of functionalized azetidines with phosgene.

Experimental Section

General Comments: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance spectrometer at 200 or 300 MHz and 75 or 50 MHz, respectively; chemical shifts are reported in ppm from TMS. Optical rotations were determined with a Perkin–Elmer 141 instrument. All reactions were carried out under an atmosphere of argon. Column chromatography was performed on a silica gel 230–400 mesh by using various mixtures of diethyl ether (Et_2O), ethyl acetate (AcOEt), petroleum ether (PE), and cyclohexane (CyH). TLCs were run on Merck Kieselgel $60F_{254}$ plates. THF and toluene were dried by a dehydrating system MB-SPS 800 (Mbraun). Dichloromethane (DCM) was distilled from calcium hydride. The mention of a "usual workup" means: (i) decantation of the organic layer, (ii) extraction of the aqueous layer with specified solvent, (iii) drying of the combined organic layers with $MgSO_4$, (iv) solvent evaporation under reduced pressure. Isomeric ratios were determined by NMR spectroscopic analysis of crude reaction mixtures before purification. High-resolution mass spectra (HRMS) were obtained with a Water Micromass Q-Tof Micro instrument.

***tert*-Butyl Ester 24:** To a solution of *N*-benzylethanolamine **19** (5 g, 33.1 mmol) in acetonitrile (150 mL) was added sodium iodide (1 g, 6.7 mmol), K_2CO_3 (4.7 g, 34 mmol), and *tert*-butyl chloroacetate (5 mL, 35 mmol). The reaction mixture was heated at reflux overnight, cooled to room temperature, and concentrated under reduced pressure. The residue was partitioned between water and ether, washed with 5 wt.-% aqueous $Na_2S_2O_3$, and treated following usual workup to afford a quantitative yield of **20**. This residue was dissolved in DCM (200 mL) and thionyl chloride (4.7 mL, 63.9 mmol) was added dropwise. After heating the mixture at reflux for 1 h, it was cooled to room temperature and neutralized by careful addition of a saturated aqueous solution of $NaHCO_3$ (*caution*: gas evolution!). Usual workup (DCM) gave quantitative yield of **22**. Crude **22** was dissolved in dry THF (300 mL) and *t*BuOK (4.48 g, 40 mmol) was added portionwise at 0 °C. The reaction mixture was stirred at room temperature for 15 min and hydrolyzed by the addition of a saturated aqueous solution of NH_4Cl (15 mL). Partial concentration under reduced pressure was followed by usual workup (AcOEt) to give crude **24**, which was purified by flash chromatography (PE/AcOEt, 85:15; R_f = 0.4). Compound **24** was obtained as an oil (6.45 g, 79% overall) that showed spectroscopic data in accordance with literature data.[16]

2-(1-Hydroxyalkyl)azetidine (±)-8: To a solution of ester **24** (6 g, 24.5 mmol) in THF (100 mL) was added portionwise $LiAlH_4$ (1.9 g, 49 mmol). The reaction mixture was stirred for 2 h at 0 °C and hydrolyzed by successive dropwise addition of water (1.9 mL), 2 M NaOH (1.9 mL), and water (3.8 mL). After stirring at room temperature for 2 h, THF (50 mL) was added, and the reaction mixture was filtered. The solid was washed with THF (3 × 50 mL), and the filtrate was concentrated under reduced pressure to give **8** as a clear oil that crystallized on standing (m.p. 68 °C, 4.25 g, 98%). This compound was used for the next steps and showed spectroscopic data in accordance with literature data.[17]

β-Amino Alcohol 21: Following the procedure described above for **20** by using *tert*-butyl 2-bromopropionate[18] as alkylating agent, compound **21** was obtained as an oil (8.3 g, 90%) after purification by flash chromatography (PE/AcOEt, 8:2; R_f = 0.6). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (d, J = 7.1 Hz, 3 H, Me), 1.48 (s, 9 H, *t*Bu), 2.72–2.92 (m, 2 H, NCH_2), 3.41 (q, J = 7.1 Hz, 1 H, C*H*Me), 3.45–3.54 (m, 2 H, CH_2OH), 3.73 (d, part of AB syst., J = 14 Hz, 1 H, NC*H*HPh), 3.80 (d, part of a AB syst., J = 14 Hz, 1 H, NCH*H*Ph), 7.27–7.34 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 28.2 (CH_3), 52.0, 55.3 (CH_2), 58.0, (CH), 58.8 (CH_2), 81.1 (Cq), 126.9, 127.2, 127.5 (CHAr), 139.4 (CqAr), 173.1 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 3490, 2976, 1721, 1141, 729, 697 cm^{-1}. HRMS: calcd. for $C_{16}H_{26}NO_3$ [M + H]$^+$ 280.1913; found 280.1898.

β-Amino Chloride 23: Following the procedure described above for **22**, compound **23** was obtained as an oil (8.2 g, 96%) and was used as such for the next step. R_f = 0.8 (PE/AcOEt, 8:2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (d, J = 7.2 Hz, 3 H, Me), 1.48 (s, 9 H, *t*Bu), 2.88–3.152 (m, 2 H, NCH_2), 3.33–3.42 (m, 3 H, C*H*Me and CH_2Cl), 3.77 (d, part of AB syst., J = 14.3 Hz, 1 H, NC*H*HPh), 3.90 (d, part of a AB syst., J = 14.3 Hz, 1 H, NCH*H*Ph), 7.24–7.37 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1, 28.3 (CH_3), 43.0, 53.1, 56.5 (CH_2), 59.2 (CH), 81.0 (Cq), 127.1, 128.3, 128.5 (CHAr), 139.9 (CqAr), 173.1 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 2977, 1722, 1367, 1141, 728, 697 cm^{-1}. HRMS: calcd. for $C_{16}H_{25}ClNO_2$ [M + H]$^+$ 298.1496; found 298.1479.

***tert*-Butyl Ester 25:** Following the procedure described above for the preparation of **24**, compound **25** was obtained as an oil (6.6 g, 83%) after purification by flash chromatography (PE/AcOEt, 9:1; R_f = 0.7). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 3 H, Me), 1.49 (s, 9 H, *t*Bu), 1.81–1.93 (m, 1 H, 3-H), 2.48–2.60 (m, 1 H, 3′-H), 2.99–3.10 (m, 1 H, 4-H), 3.16–3.26 (m, 1 H, 4′-H), 3.55 (d, part of AB syst., J = 12.7 Hz, 1 H, NC*H*HPh), 3.80 (d, part of a AB syst., J = 12.7 Hz, 1 H, NCH*H*Ph), 7.28–7.32 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 28.2 (CH_3), 28.4, 49.0, 55.7 (CH_2), 68.3 (CH), 80.6 (Cq), 126.9, 128.3, 128.8 (CHAr), 138.5 (CqAr), 174.0 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 2920, 2851, 1710, 1260, 759, 701 cm^{-1}. HRMS: calcd. for $C_{16}H_{24}NO_2$ [M + H]$^+$ 262.1729; found 262.1780.

β-Amino Alcohol (±)-11: Following the procedure described above for the reduction of **24**, compound **11** was obtained as an oil (3.6 g, 82%) and was used as such for the next step. R_f = 0.2 (DCM/MeOH/16 M aq. NH_3, 94.5:5:0.5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (s, 3 H, Me), 1.51–1.62 (m, 1 H, 3-H), 2.32–2.46 (m, 1 H, 3′-H), 2.99–3.14 (m, 3 H, 4-H and 5-H), 3.20–3.29 (m, 1 H, 4′-H), 3.47 (d, part of AB syst., J = 13.1 Hz, 1 H, NC*H*HPh), 3.65 (d, part of a AB syst., J = 13.1 Hz, 1 H, NCH*H*Ph), 7.26–7.31 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2 (CH_3), 25.3, 48.8, 54.3, 66.0 (CH_2), 66.9 (Cq), 127.1, 128.2, 128.4 (CHAr), 138.5 (CqAr) ppm. HRMS: calcd. for $C_{12}H_{18}NO$ [M + H]$^+$ 192.1388; found 192.1380.

Ketone 27: MeLi (1.6 M in diethyl ether, 3.36 mL, 5.37 mmol) was added dropwise to a solution of **26**[13] (500 mg, 2.69 mmol) in toluene (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and hydrolyzed by the addition of a saturated aqueous solution of NH_4Cl (15 mL). Usual workup gave a crude oil, which was a mixture of **27** and the corresponding imine. The residue was purified by flash chromatography (PE/AcOEt, 9:1; R_f = 0.3) to give compound **27** as an oil (300 mg, 55%). $[\alpha]_D^{20}$ = +1.3 (c = 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, J = 9 Hz, 3 H, Me), 2.06–2.26 (m, 2 H, 3-H), 2.39 (s, 3 H, CH_3CO), 2.78–2.86 (m, 1 H, 4-H), 3.15 (dt, J = 2.7, 7.3 Hz, 1 H, 4′-H), 3.44 (q, J = 6.5 Hz, 1 H, CHPh), 3.74 (t, J = 8.7 Hz, 1 H, 2-H), 7.26–7.33 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (CH_2), 21.3, 25.3 (CH_3), 49.9 (CH_2), 67.6, 71.5 (CH), 127.2, 128.4 (CHAr), 142.9 (CqAr), 211.1 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 2965, 2840, 1703, 1451, 1348, 697 cm^{-1}. HRMS: calcd. for $C_{13}H_{18}NO$ [M + H]$^+$ 204.1388; found 204.1368.

Ketone 28: BuLi (1.6 M in hexane, 2.85 mL, 4.57 mmol) was added dropwise to a solution of **26**[13] (425 mg, 2.28 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h

and hydrolyzed by the addition of a saturated aqueous solution of NH_4Cl (15 mL). Usual workup gave a crude oil, which was a mixture of **28** and the corresponding imine. This residue was dissolved in AcOEt (50 mL) and silica gel (10 g) was added. This suspension was stirred overnight at room temperature, filtered, and concentrated under reduced pressure. Purification by flash chromatography (PE/Et_2O, 1:1; R_f = 0.5) gave compound **28** as an oil (477 mg, 85%). $[\alpha]_D^{20}$ = +152 (c = 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.2 Hz, 3 H, Me), 1.06 (d, J = 6.5 Hz, 3 H, Me), 1.22–1.44 (m, 2 H, CH_2), 1.52–1.67 (m, 2 H, CH_2), 2.00–2.20 (m, 2 H, CH_2CO), 2.57–2.83 (m, 3 H, 4-H and 3-H), 3.12 (dt, J = 2.8, 7.6 Hz, 1 H, 4′-H), 3.38 (q, J = 6.5 Hz, 1 H, CHPh), 3.72 (t, J = 8.7 Hz, 1 H, 2-H), 7.26–7.34 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 20.9 (CH_2), 21.3 (CH_3), 22.5, 25.5, 49.8 (CH_2), 67.6, 71.4 (CH) 127.1, 127.3, 128.3 (CHAr), 142.9 (CqAr), 212.3 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 2956, 1631, 1453, 1180, 729, 697 cm^{-1}. HRMS: calcd. for $C_{16}H_{24}NO$ $[M + H]^+$ 246.1858; found 246.1847.

Ketone 29: Following the above procedure with PhMgBr and running the reaction in toluene instead of THF, compound **29** was obtained as a yellow solid (350 mg, 77%) after purification by flash chromatography (PE/AcOEt, 7:3; R_f = 0.5). M.p. 62 °C. $[\alpha]_D^{20}$ = +1.6 (c = 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.19 (d, J = 6.5 Hz, 3 H, Me), 2.17–2.46 (m, 2 H, 3-H), 2.85–2.97 (m, 1 H, 2-H), 3.15–3.24 (m, 1 H, 2′-H), 3.49 (q, J = 6.5 Hz, 1 H, C*H*Ph), 4.53 (t, J = 8.8 Hz, 1 H, 2-H), 7.26–7.63 (m, 10 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0 (CH_3), 23.9, 50.3 (CH_2), 68.4, 69.4 (CH), 126.8, 127.2, 127.6, 128.4, 128.6, 133.2 (CHAr), 135.7, 143.4 (CqAr), 199.3 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 2964, 2851, 1687, 1596, 1447, 1369, 1219, 876, 699 cm^{-1}. HRMS: calcd. for $C_{18}H_{20}NO$ $[M + H]^+$ 266.1545; found 266.1536.

2-(1-Hydroxyalkyl)azetidine 14: To a solution of ketone **28** (336 mg, 1.66 mmol) in MeOH (10 mL) was added $ZnBr_2$ (412 mg, 1.83 mmol). The reaction mixture was stirred at room temperature for 30 min followed by the portionwise addition of $NaBH_4$ (95 mg, 2.49 mmol). After stirring for an additional 30 min., ethylene diamine (0.5 mL, 7.47 mmol) was added, and the mixture was stirred for 1.5 h. AcOEt (25 mL) and water (25 mL) were added, and the organic layer was separated. The aqueous layer was extracted with AcOEt (25 mL), washed with 1 N NaOH (25 mL) and 20% aq. NH_3 (25 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (PE/AcOEt, 1:1; R_f = 0.3), to give compound **14** as an oil (202 mg, 59%). $[\alpha]_D^{20}$ = +97 (c = 1.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.01 (d, J = 6.3 Hz, 3 H, Me), 1.22 (d, J = 6.6 Hz, 1 H, Me), 1.65–1.79 (m, 1 H, 3-H), 1.98–2.17 (m, 1 H, 3-H), 2.61–2.74 (m, 1 H, 2-H), 2.92–3.01 (m, 1 H, 2′-H), 3.32 (dt, J = 6.5, 8.0 Hz, 1 H, 2-H), 3.48 (q, J = 6.6 Hz, 1 H, CHPh), 3.76–3.85 (m, 1 H, C*H*OH), 7.26–7.30 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 16.6, 22.3 (CH_3), 49.3 (CH_2), 66.1, 67.1, 69.1 (CH), 127.1, 128.4 (CHAr), 143.7 (CqAr) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 3495, 2844, 1452, 1025, 757, 699 cm^{-1}. HRMS: calcd. for $C_{13}H_{20}NO$ $[M + H]^+$ 206.1545; found 206.1517.

2-(1-Hydroxyalkyl)azetidine 15: Following the above procedure described for **14**, compound **15** was obtained as an oil (306 mg, 68%) after purification by flash chromatography (PE/AcOEt, 1:1; R_f = 0.6). $[\alpha]_D^{20}$ = +88 (c = 0.9, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.9 Hz, 3 H, Me), 1.22 (d, J = 6.9 Hz, 1 H, Me), 1.27–1.55 (m, 6 H, CH_2), 1.64–1.79 (m, 1 H, 3-H), 1.98–2.17 (m, 1 H, 3-H), 2.59–2.74 (m, 1 H, 4-H), 2.92–2.99 (m, 1 H, 4′-H), 3.39 (dt, J = 3.3, 8.3 Hz, 1 H, 2-H), 3.48 (q, J = 6.5 Hz, 1 H, CHPh), 3.60–3.68 (m, 1 H, C*H*OH), 7.24–7.28 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3) 14.8 (CH_2), 22.3 (CH_3), 23.0, 28.2, 31.4 49.6 (CH_2), 67.1, 68.3, 70.31 (CH), 127.1, 128.4 (CHAr), 143.6 (CqAr) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 3416, 2834, 1047, 726, 696 cm^{-1}. HRMS: calcd. for $C_{16}H_{26}NO$ $[M + H]^+$ 248.2014; found 248.2013.

2-(1-Hydroxyalkyl)azetidine 16: Following the above procedure described for **14**, compound **16** was obtained as a solid (305 mg, 57%); after purification by flash chromatography (PE/AcOEt, 75:25; R_f = 0.4). M.p. 93 °C. $[\alpha]_D^{20}$ = +121 (c = 0.9, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.40 (d, J = 6.4 Hz, 1 H, Me), 2.68 (q, J = 8.2 Hz, 1 H, 4-H), 2.98–3.05 (m, 1 H, 4′-H), 3.56–3.70 (m, 2 H, 2-H and C*H*Me), 4.84 (d, J = 3.0 Hz, 1 H, C*H*OH), 7.27–7.39 (m, 10 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8 (CH_2), 22.1 (CH_3), 48.9, 66.9, 69.1, 72.1 (CH), 125.6, 127.0, 128.1, 128.4 (CHAr), 140.0, 143.4 (CqAr) ppm. IR (NaCl, Nujol) $\tilde{\nu}_{max}$ = 3500, 2862, 1450, 762, 698 cm^{-1}. HRMS: calcd. for $C_{18}H_{22}NO$ $[M + H]^+$ 268.1718; found 268.1701.

Ketone 31: Following the procedure for the preparation of **28**, compound **31** was obtained as an oil (1.18 g, 88%) after purification by flash chromatography (PE/AcOEt, 1:1; R_f = 0.2). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.5 Hz, 3 H, Me), 1.13–1.31 (m, 2 H, CH_2), 1.36–1.51 (m, 2 H, CH_2), 2.10–2.30 (m, 3 H, C*H*HCO and 3-H), 2.46–2.62 (m, 1 H, CH*H*CO), 2.87–2.99 (m, 1 H, 4-H), 3.27–3.35 (m, 1 H, 4′-H), 3.57 (d, part of AB syst., J = 12.5 Hz, 1 H, NC*H*HPh), 3.67 (t, J = 8.7 Hz, 1 H, 2-H), 3.73 (d, part of AB syst., J = 12.5 Hz, 1 H, NCH*H*Ph), 7.26–7.31 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.8, 22.3, 25.1, 32.1, 50.9, 63.0 (CH_2), 71.4 (CH), 127.3, 128.4, 129.0 (CHAr), 137.4 (CqAr), 212.0 (CO) ppm. HRMS: calcd. for $C_{16}H_{24}NO$ $[M + H]^+$ 246.1658; found 246.1847.

2-(1-Hydroxyalkyl)azetidine (±)-17: Following the procedure described above for the reduction of **24**, compound **17** was obtained as an oil (633 mg, 88%) and was used as such for the next step. R_f = 0.2 (PE/AcOEt, 1:1). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.5 Hz, 3 H, Me), 1.18–1.35 (m, 6 H, CH_2), 1.71–1.85 (m, 1 H, 3-H), 2.07–2.95 (m, 1 H, 3′-H), 2.83–2.95 (m, 1 H, 4-H), 3.22–3.35 (m, 3 H, 2-H, 4′-H and C*H*OH), 3.53 (d, part of AB syst., J = 12.7 Hz, 1 H, NC*H*HPh), 3.70 (d, part of a AB syst., J = 12.7 Hz, 1 H, NCH*H*Ph), 7.27–7.30 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 16.0, 22.8, 27.9, 31.0, 51.0, 61.5 (CH_2), 68.4, 69.5 (CH) 127.1, 128.3, 128.6 (CHAr), 138.1 (CqAr) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 2927, 1453, 1167, 1028, 733, 698 cm^{-1}. HRMS: calcd. for $C_{15}H_{24}NO$ $[M + H]^+$ 234.1858; found 234.1855.

2-(1-Hydroxyalkyl)azetidine 18: MeLi (1.6 M in diethyl ether, 6 mL, 9.51 mmol) was added dropwise to a solution of **32** (740 mg, 3.17 mmol) in THF (13 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and hydrolyzed by the addition of a saturated aqueous solution of NH_4Cl (45 mL). Usual workup gave a residue, which was purified by flash chromatography (PE/AcOEt, 5:5; R_f = 0.1) to give compound **18** as an oil (396 mg, 57%). $[\alpha]_D^{20}$ = +1.5 (c = 1.36, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.67 (s, 3 H, Me), 1.01 (s, 3 H, Me), 1.32 (d, J = 6.5 Hz, 3 H, Me), 1.84–2.02 (m, 2 H, 3-H), 2.29 (br. s, 1 H, O*H*), 3.01–3.09 (m, 1 H, 4-H), 3.23 (m, 2 H, 2-H and 4′-H), 3.57 (q, J = 6.5 Hz, 1 H, CHPh), 7.22–7.35 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9 (CH_3), 18.1 (CH_2), 24.0, 26.7 (CH_3), 46.8 (CH_2), 65.1 (CH), 69.9 (CqOH), 73.2 (CH_2), 127.4, 127.7, 128.5 (CHAr), 144.4 (CqAr) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 3572, 3428, 2969, 1452, 1370, 1164, 946, 749, 699 cm^{-1}. HRMS: calcd. for $C_{14}H_{21}NO$ $[M + H]^+$ 220.1701; found 220.1698.

General Procedure for the Reaction of 2-(1-Hydroxyalkyl)azetidines with BTC: Sodium hydride (60 wt.-% in mineral oil, 470 mg,

11.85 mmol) was added portionwise to a solution of azetidine (3.95 mmol) in dry THF (30 mL) at 0 °C. After the suspension was stirred at 0 °C for 10 min, bis(trichloromethyl) carbonate (470 mg, 1.58 mmol) was added, and the mixture was stirred at room temperature for 1 h. After that time, the reaction mixture was treated with a saturated aqueous solution of NH_4Cl (20 mL) and water (20 mL). Usual workup (AcOEt) gave a residue that was purified by flash chromatography. Unreacted starting material was recovered by alkaline treatment of the aqueous layer (1 N NaOH), followed by extraction with AcOEt.

Oxazolidinone 33: Yield: 2.33 g, quant. No purification by flash chromatography needed. Oil. R_f = 0.8 (PE/AcOEt, 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.89–1.96 (m, 1 H, C*H*HCH$_2$Cl), 2.13–2.26 (m, 1 H, CH*H*CH$_2$Cl), 3.47 (t, J = 6.4 Hz, 2 H, CH_2Cl), 3.68–3.81 (m, 1 H, 4-H), 4.05 (dd, J = 8.4, 6.4 Hz, 1 H, 5-H), 4.13 (d, part of AB syst., J = 15.3 Hz, 1 H, NC*H*HPh), 4.41 (t, J = 8.6 Hz, 1 H, 5′-H), 4.74 (d, part of AB syst., J = 15.3 Hz, 1 H, NCH*H*Ph), 7.31–7.43 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.5, 39.9, 46.4 (CH_2) 53.0 (CH), 67.3 (CH_2), 128.1, 128.2, 128.9 (CHAr), 135.7 (CqAr), 158.3 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 3490, 2928, 1452, 758, 699 cm^{-1}. HRMS: calcd. for $C_{12}H_{14}ClNO_2Na$ [M + Na]$^+$ 262.0614; found 262.0611.

Oxazolidinone 34: Yield: 529 mg, 53%. Purified by flash chromatography (PE/AcOEt, 1:1; R_f = 0.75). M.p. 63 °C. $[\alpha]_D^{20}$ = –69 (c = 0.7, DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62 (d, J = 7.1 Hz, 3 H, Me), 1.85–1.97 (m, 1 H, C*H*HCH$_2$Cl), 2.06–2.18 (m, 1 H, CH*H*CH$_2$Cl), 3.25–3.41 (m, 2 H, CH_2Cl), 3.92 (dd, J = 5.8, 8.2 Hz, 1 H, C*H*HO), 4.18 (t, J = 8.9 Hz, 1 H, CH*H*O), 5.06 (q, J = 8.9 Hz, 1 H, NC*H*MePh), 7.20–7.34 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8 (Me), 36.7 (*C*H$_2$CH$_2$Cl), 39.9 (*C*H$_2$Cl), 52.9, 53.1 (CH), 67.1 (CH$_2$O), 127.3, 128.1, 128.9 (CHAr), 139.0 (CqAr), 158.0 (CO) ppm. HRMS: calcd. for $C_{13}H_{17}ClNO_2$ [M + H]$^+$ 254.0948; found 254.0951.

Oxazolidinone 35: Yield 830 mg, 83%. Purified by flash chromatography (PE/AcOEt, 1:1; R_f = 0.80). Oil. $[\alpha]_D^{20}$ = +4 (c = 1.1, DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.53 (m, 1 H, C*H*HCH$_2$Cl), 1.59–1.70 (m, 1 H, CH*H*CH$_2$Cl), 1.63 (d, J = 7.1 Hz, 3 H, Me), 3.20–3.25 (m, 2 H, CH_2Cl), 3.93 (dd, J = 8.1, 8.3 Hz, 1 H, C*H*HO), 3.95–4.05 (m, 1 H, 3-H), 4.35 (t, J = 8.1 Hz, 1 H, CH*H*O), 5.06 (q, J = 7.1 Hz, 1 H, NC*H*MePh), 7.19–7.37 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 (Me), 35.5 (*C*H$_2$CH$_2$Cl), 40.1 (*C*H$_2$Cl), 51.7, 52.1 (CH), 67.3 (CH$_2$O), 127.0, 127.9, 128.7 (CHAr), 141.0 (CqAr), 158.2 (CO) ppm. HRMS: calcd. for $C_{13}H_{16}ClNO_2Na$ [M + Na]$^+$ 276.0767; found 276.0766.

Oxazolidinone 36: Yield 349 mg, 35%. Purified by flash chromatography (PE/AcOEt, 75:25; R_f = 0.5). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (s, 3 H, Me), 1.08–2.03 (m, 2 H, CH_2CH$_2$Cl), 3.13–3.22 (m, 1 H, CH$_2$C*H*HCl), 3.32–3.41 (m, 1 H, CH$_2$C*H*HCl), 3.92 (d, part of AB syst., J = 8.9 Hz, 1 H, NC*H*HPh), 4.19 (d, part of AB syst., J = 8.9 Hz, 1 H, NC*H*HPh), 4.32 (s, 2 H, NCH$_2$Ph), 7.21–7.28 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2 (Me), 38.8 (*C*H$_2$CH$_2$Cl), 40.7 (*C*H$_2$Cl), 44.4 (CH$_2$), 60.8 (Cq), 72.8 (CH$_2$O), 127.2, 127.8, 128.2 (CHAr), 137.7 (CqAr), 158.1 (CO) ppm. HRMS: calcd. for $C_{13}H_{16}ClNO_2Na$ [M + Na]$^+$ 276.0767; found 276.0769.Compound **44** (190 mg, 19%) was also isolated by flash chromatography. (PE/AcOEt, 75:25; R_f = 0.7). Oil. ^{1}H NMR (200 MHz, $CDCl_3$, 2 rotamers, 1:1 ratio): δ = 1.04 (d, J = 7.1 Hz, 3 H, Me, one rotamer), 1.07 (d, J = 7.1 Hz, 3 H, Me, one rotamer), 1.49–1.58 (m, 1 H, C*H*HCHMe), 1.89–1.96 (m, 1 H, CH*H*CHMe), 2.25–2.28 (m, 1 H, C*H*Me), 3.27–3.36 (m, 2 H, NCH$_2$), 4.49 (d, part of AB syst., J = 14.8 Hz, 1 H, NC*H*HPh, one rotamer), 4.55 (d, part of AB syst., J = 14.8 Hz, 1 H, NCH*H*Ph, one rotamer), 4.65 (s, 2 H, NCH_2Ph, one rotamer), 7.22–7.31 (m, 5 H, Ar), 9.50 (d, J = 1.1 Hz, 1 H, CHO) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.4 (Me), 27.4 and 28.3 (CH_2, two rotamers), 43.7 and 43.8 (CH two rotamers), 47.0 and 48.0 (CH_2 two rotamers), 52.5 and 54.4 (CH_2, two rotamers), 127.2, 128.2, 128.9, (CHAr), 135.3 and 135.6 (CqAr two rotamers), 203.2 and 203.5 (CO) ppm. HRMS: calcd. for $C_{13}H_{16}ClNO_2Na$ [M + Na]$^+$ 276.0767; found 276.0763.

Oxazolidinone: 37: Yield 529 mg, 37%. Purified by flash chromatography (PE/AcOEt, 75:25; R_f = 0.6). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25–2.35 (m, 1 H, C*H*CH$_2$Cl), 3.43–3.72 (m, 4 H, CH_2O and CH_2Cl), 3.82–3.91 (m, 1 H, 4-H), 4.11 (d, part of AB syst., J = 15.2 Hz, 1 H, NC*H*HPh), 4.15–4.22 (m, 2 H, CH_2O), 4.44 (s, 2 H, CH_2OBn), 4.81 (d, part of AB syst., J = 15.2 Hz, 1 H, NCH*H*Ph), 7.21–7.37 (m, 10 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.7 (*C*H$_2$CH$_2$Cl), 41.7 (CH), 46.6 (CH$_2$), 56.3 (CH), 64.3, 67.6, 73.6 (CH$_2$), 127.2, 127.6, 127.8, 127.9, 128.2, 129.0 (CHAr), 135.4, 137.4 (CqAr), 158.6 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 2929, 1747, 1450, 749, 698, 685 cm^{-1}. HRMS: calcd. for $C_{30}H_{22}ClNO_3Na$ [M + Na]$^+$ 382.1186; found 382.1183.

Chloroazetidine 38: Yield: 85 mg, 15%. Purified by flash chromatography (PE/AcOEt, 95:5; R_f = 0.17). $[\alpha]_D^{20}$ = –5.1 (c = 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, J = 6.0 Hz, 3 H, Me), 2.81–2.87 (m, 1 H, 3-H), 3.07–3.16 (m, 1 H, 4-H), 3.31–3.39 (m, 3 H, 2-H, CH_2Cl), 3.71 (d, part of AB syst., J = 12.7 Hz, 1 H, NCH*H*Ph), 3.78 (d, part of AB syst., J = 12.7 Hz, 1 H, NC*H*HPh), 7.11–7.32 (m, 10 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (Me), 47.7 (CH$_2$Cl), 49.9 (CH), 61.4 (NCH$_2$), 65.8, 69.4 (CH), 126.7, 127.2, 127.5, 128.3, 128.4, 129.4 (CHAr), 138.0, 140.2 (CqAr) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 3028, 2918, 1602, 1452, 1366, 1109, 739, 695 cm^{-1}. HRMS: calcd. for $C_{18}H_{21}ClN$ [M + H]$^+$ 286.1363; found 286.1367.

Oxazolidinone 39: Yield: 382 mg, 41%. Purified by flash chromatography (PE/AcOEt, 75:25; R_f = 0.45). M.p. 61 °C. $[\alpha]_D^{20}$ = +2.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, J = 7.2 Hz, 3 H, Me), 1.70 (d, J = 7.2 Hz, 3 H, Me), 1.95–2.18 (m, 2 H, CH_2CH$_2$Cl), 3.30–3.46 (m, 2 H, CH_2Cl), 3.60 (dt, J = 3.2, 8.0 Hz, 1 H, 4-H), 4.48–4.57 (m, 1 H, 5-H), 5.13 (q, J = 7.2 Hz, 1 H, NC*H*MePh), 7.29–7.42 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 18.7 (Me), 32.1 (*C*H$_2$CH$_2$Cl), 40.6 (*C*H$_2$Cl), 53.1, 55.7 (CH), 74.0 (CH$_2$O), 127.2, 128.0, 128.9 (CHAr), 139.6 (CqAr), 157.8 (CO) ppm. HRMS: calcd. for $C_{14}H_{18}ClNO_2Na$ [M + Na]$^+$ 290.0924; found 290.0923.

Oxazolidinone 40: Yield: 357 mg, 33%. Purified by flash chromatography (PE/AcOEt, 75:25; R_f = 0.64). Oil. $[\alpha]_D^{20}$ = –13.3 (c = 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.6 Hz, 3 H, Me), 1.15–1.60 (m, 6 H, CH$_2$), 1.69 (d, J = 7.2 Hz, 3 H, Me), 1.93–2.17 (m, 2 H, CH_2CH$_2$Cl), 3.40 (br. t, J = 7.5 Hz, 2 H, CH_2Cl), 3.56 (dt, J = 3.4, 7.2 Hz, 1 H, 4-H), 4.25–4.35 (m, 1 H, 5-H), 5.11 (q, J = 7.2 Hz, 1 H, NC*H*MePh), 7.30–7.38 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 18.6 (Me), 22.3, 28.0, 28.8, 32.5, 40.4 (CH$_2$), 53.2, 55.5, 78.3 (CH), 127.1, 127.9, 128.8 (CHAr), 139.6 (CqAr), 157.7 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 2979, 1735, 1219, 1064, 765, 699 cm^{-1}. HRMS: calcd. for $C_{17}H_{24}ClNO_2Na$ [M + Na]$^+$ 332.1229; found 332.1393.

Oxazolidinone 41: Yield: 513 mg, 50%. Purified by flash chromatography (PE/AcOEt, 6:4; R_f = 0.4). M.p. 81 °C. $[\alpha]_D^{20}$ = +8.6 (c = 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (d, J = 7.2 Hz, 3 H, Me), 1.81–1.92 (m, 2 H, CH_2CH$_2$Cl), 2.44–2.57 (m, 1 H, CH*H*Cl), 2.89–3.01 (m, 1 H, CH*H*Cl), 3.91 (dt, J = 3.8, 7.7 Hz, 1 H, 4-H), 5.18 (q, J = 7.2 Hz, 1 H, NC*H*MePh), 5.46 (d, J = 7.6 Hz, 1 H, 5-H), 7.32–7.44 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2 (Me), 32.9 (*C*H$_2$CH$_2$Cl), 40.0 (*C*H$_2$Cl),

53.6, 56.2, 78.9 (CH), 126.3, 127.0, 127.2, 128.1, 128.7, 129.0 (CHAr), 134.0, 139.7 (CqAr), 157.4 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 1746, 1405, 1200, 733, 699, 651 cm^{-1}. HRMS: calcd. for $C_{19}H_{20}ClNO_2Na$ $[M + Na]^+$ 352.1080; found 352.1085.

Oxazolidinone 42: Yield: 529 mg, 52%. Purified by flash chromatography (PE/AcOEt, 8:2; R_f = 0.62). Oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.2 Hz, 3 H, Me), 1.22–1.75 (m, 6 H, CH_2), 2.05 (q, J = 6.8 Hz, 2 H, CH_2CH_2Cl), 3.50 (br. t, J = 6.7 Hz, 2 H, CH_2Cl), 3.73 (q, J = 6.8 Hz, 1 H, 4-H), 4.10 (d, part of AB syst., J = 15.3 Hz, 1 H, NCHHPh), 4.38–4.48 (m, 1 H, 5-H), 4.84 (d, part of AB syst., J = 15.3 Hz, 1 H, NCHHPh), 7.29–7.36 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (Me), 22.4, 27.9, 29.0, 30.6, 40.8 (CH_2), 46.8 (CH), 55.0 (CH_2), 77.9 (CH), 128.0, 128.9 (CHAr), 136.1 (CqAr), 158.1 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 2955, 1740, 1413, 760, 700, 672 cm^{-1}. HRMS: calcd. for $C_{16}H_{23}ClNO_2$ $[M + H]^+$ 296.1417; found 296.1452.

Oxazolidinone 43: Yield: 99 mg, 10%. Purified by flash chromatography (PE/AcOEt, 50:50; R_f = 0.7). Oil. $[\alpha]_D^{20}$ = +12.3 (c = 0.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, Me), 1.39 (s, 3 H, Me), 1.65–1.71 (m, 2 H, CH_2CH_2Cl), 1.74 (d, J = 7.1 Hz, Me), 3.29–3.34 (m, 2 H, CH_2Cl), 3.67–3.72 (m, 1 H, 4-H), 5.09 (q, J = 7.1 Hz, NCHMePh), 7.29–7.44 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.6, 21.9, 28.3 (Me), 32.1 (CH$_2$CH$_2$Cl), 40.8 (CH_2Cl), 51.9 (CH), 55.0, 60.1 (CH_2), 80.0 (CqO), 126.9, 127.7, 128.6 (CHAr), 141.2 (CqAr), 157.3 (CO) ppm. HRMS: calcd. for $C_{15}H_{20}ClNO_2Na$ $[M + Na]^+$ 304.0932; found 304.1080.

Oxazolidinone 45: A suspension of **33** (162 mg, 0.676 mmol) and sodium azide (219 mg, 3.38 mmol) in DMF (3 mL) was heated at 80 °C for 12 h. The reaction mixture was partitioned between water and ethyl acetate. Usual workup gave an oil that was dried under high vacuum to remove trace amounts of DMF and to afford **45** as a clear oil (166 mg, 89%). R_f = 0.5 (PE/AcOEt, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.59–1.77 (m, 1 H, CHHCH$_2$N$_3$), 1.87–2.02 (m, 1 H, CHHCH$_2$N$_3$), 3.30 (t, J = 6.6 Hz, 2 H, CH_2N$_3$), 3.60–3.75 (m, 1 H, 4-H), 4.01 (dd, J = 8.8, 6.6 Hz, 1 H, 5-H), 4.14 (d, J = 15.3 Hz, 1 H, NCHHPh), 4.36 (t, J = 8.7 Hz, 1 H, 5′-H), 4.72 (d, J = 15.3 Hz, 1 H, NCHHPh), 7.28–7.43 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.3 (CH$_2$CH$_2$N$_3$), 44.4 (CH$_2$N$_3$), 46.3 (NCH$_2$Ph), 53.0 (CH), 67.3 (CH_2O), 128.1, 128.2, 128.9 (CHAr), 135.8 (CqAr), 158.3 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 2926, 2094, 1739, 1417, 1090, 1025, 701 cm^{-1}. HRMS: calcd. for $C_{12}H_{14}N_4O_2Na$ $[M + Na]^+$ 269.1014; found 269.1002.

Oxazolidinone 46: A solution of **33** (100 mg, 0.42 mmol) and potassium cyanide (136 mg, 2.1 mmol) in DMSO (3 mL) was heated at 110 °C for 1 h. The reaction mixture was partitioned between water and ethyl acetate. Usual workup gave a crude oil that was purified by chromatography to give **46** (66 mg, 66%) as a clear oil. R_f = 0.15 (PE/AcOEt, 6:4). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.72–1.90 (m, 1 H, CHHCH$_2$CN), 1.87–2.05 (m, 1 H, CHHCH$_2$CN), 2.29 (t, J = 6.6 Hz, 2 H, CH_2CN), 3.72–3.79 (m, 1 H, 4-H), 4.02 (dd, J = 8.8 and 6.6 Hz, 1 H, 5-H), 4.17 (d, J = 15.4 Hz, 1 H, NCHHPh), 4.39 (t, J = 8.7 Hz, 1 H, 5′-H), 4.72 (d, J = 15.4 Hz, 1 H, NCHHPh), 7.28–7.39 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2 (CH$_2$CH$_2$CN), 27.4 (CH$_2$N$_3$), 53.4 (NCH$_2$Ph), 60.4 (CH), 66.2 (CH_2O), 119.3 (CN), 128.1, 128.3, 129.1 (CHAr), 135.4 (CqAr), 158.1 (CO) ppm. IR (NaCl, film) $\tilde{\nu}_{max}$ = 2926, 2246, 1737, 1419, 1244, 1090, 1031, 702 cm^{-1}. HRMS: calcd. for $C_{13}H_{14}N_2O_2Na$ $[M + Na]^+$ 253.0831; found 253.0953.

Oxazolidinone 47: To a solution of **33** (240 mg, 1 mmol) in THF (10 mL) cooled to –78 °C was added dropwise a solution of nBuLi (1.6 M in hexanes, 0.875 mL, 1.4 mmol). The reaction mixture was stirred at –78 °C for 50 min and then hydrolyzed by the addition of aqueous saturated NH_4Cl solution (5 mL). Addition of water and AcOEt was followed by usual workup to give 180 mg of a 1:3 mixture of **33** and **47** (89%). An analytical sample of **47** was isolated by preparative TLC (PE/AcOEt, 6:4); R_f = 0.8 (for **33**) and 0.75 (for **47**). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.50–1.76 (m, 1 H, CHHCH), 1.90–2.25 (m, 2 H, CH_2CH), 2.60–2.80 (m, 1 H, CHHCH), 4.02–4.23 (m, 1 H, CH$_2$CHN), 4.20 (dd, J = 3.4, 8.8 Hz, 1 H, CHHO), 4.60 (dd, J = 8.0, 8.8 Hz, 1 H, CHHO), 4.91 (t, J = 5.2 Hz, 1 H, NCHPh), 7.19–7.33 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.9, 35.7 (CH_2), 59.8, 61.8 (CH), 67.7 (CH_2O), 125.5, 127.2, 128.6 (CHAr), 142.4 (CqAr), 161.7 (CO) ppm. IR (NaCl, film): $\tilde{\nu}_{max}$ = 2936, 1739, 1225, 1078, 1047, 699 cm^{-1}. HRMS: calcd. for $C_{12}H_{13}NO_2Na$ $[M + Na]^+$ 226.0844; found 226.0851.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectroscopic data for oxazolidinones **33**–**37** and **39**–**43**.

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[1] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
[2] D. A. Evans, A. S. Kim in *Handbook of Reagents for Organic Synthesis: Reagents, Auxiliaries and Catalysts for C–C Bond Formation* (Eds.: R. M. Coates, S. Denmark), Wiley, New York, **2000**, pp. 91–101.
[3] M. R. Barbachyn, C. W. Ford, *Angew. Chem. Int. Ed.* **2003**, *42*, 2010–2023.
[4] J. R. Gage, D. A. Evans, *Org. Synth. Coll. Vol.* **1993**, *VIII*, 528–531.
[5] J. B. Hyne, *J. Am. Chem. Soc.* **1959**, *81*, 6058–6061.
[6] A. K. Saund, B. Prashad, A. K. Koul, J. M. Bachhawat, N. K. Marthur, *Int. J. Peptide Protein Res.* **1973**, *5*, 7–10.
[7] F. Applegath, US Patent 2857392, **1958** [*Chem. Abstr.* **1959**, *53*, 5286d].
[8] For examples of oxazolidinones with a 4-bromoethyl or 4-methanesufonyloxyethyl side chain, see inter alia: a) H. L. Sham, H. Stein, J. Cohen, *J. Chem. Soc., Chem. Commun.* **1987**, 1792–1793; b) A. Genevois-Borella, J.-C. Florent, C. Monneret, D. S. Grierson, *Tetrahedron Lett.* **1990**, *31*, 4879–4882; c) A. Tarnowski, T. Bär, R. R. Schmidt, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 573–576; d) D.-R. Hou, J. H. Reibenspies, K. Burgess, *J. Org. Chem.* **2001**, *66*, 206–215; e) A. Tarnowski, O. Retz, T. Bar, R. R. Schmidt, *Eur. J. Org. Chem.* **2005**, 1129–1141; f) G. Yang, J. Schmieg, M. Tsuji, R. W. Franck, *Angew. Chem.* **2004**, *116*, 3906–3910; g) T. Hakogi, Y. Monden, S. Iwana, S. Katsumura, *Org. Lett.* **2000**, *2*, 2627–2629.
[9] C. S. Park, M. S. Kim, T. B. Sim, D. K. Pyun, C. H. Lee, J.-W. Chang, H.-J. Ha, *J. Org. Chem.* **2003**, *68*, 43–49.
[10] a) G. S. Singh, M. D'hoogue, N. De Kimpe, "Azetidines, Azetines and Azete: Monocyclic" in *Comprehensive Heterocyclic Chemistry III*, Elsevier, Oxford, **2008**, vol. 2.01, pp. 1–110; b) F. Couty, "Synthesis of Azetidines" in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations* (Ed.: D. Enders), Thieme, New York, **2009**; vol. 40a, pp. 773–817F; c) F. Couty, G. Evano, *Synlett* **2009**, *19*, 3053–3064.
[11] a) F. Couty, D. Prim, *Tetrahedron: Asymmetry* **2002**, *13*, 2619–2624; b) B. Drouillat, F. Couty, O. David, G. Evano, J. Marrot, *Synlett* **2008**, *9*, 1345–1348; c) F. Durrat, M. Vargas-Sanchez, F. Couty, G. Evano, J. Marrot, *Eur. J. Org. Chem.* **2008**, 3286–3297.

[12] F. Couty, G. Evano, M. Vargas-Sanchez, G. Bouzas, *J. Org. Chem.* **2005**, *70*, 9028–9031.
[13] A. Alex, B. Larmanjat, J. Marrot, F. Couty, O. David, *Chem. Commun.* **2007**, 2500–2502.
[14] S.-M. Han, S.-H. Ma, H.-J. Ha, W.-K. Lee, *Tetrahedron* **2008**, *64*, 11110–11114.
[15] M. Haddad, H. Imogaï, M. Larchevèque, *J. Org. Chem.* **1998**, *63*, 5680–5683.
[16] H. H. Wasserman, B. H. Lipshutz, A. W. Tremper, J. S. Wu, *J. Org. Chem.* **1981**, *46*, 2991–2999.
[17] A. G. M. Barrett, P. Dozzo, A. J. P. White, D. J. Williams, *Tetrahedron* **2002**, *58*, 7303–7313.
[18] A. Vollmarr, M. S. Dunn, *J. Org. Chem.* **1960**, *25*, 387–390.

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