The Halogen–Lithium Exchange Reaction of 3,3-Dichloro-2-azetidinones: Application to the Synthesis of *cis*-4-Aryl-3-chloro-2-azetidinones

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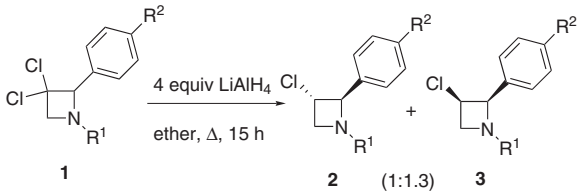
Abstract: A straightforward synthesis of new *cis*-4-aryl-3-chloro-2-azetidinones was developed, using a halogen–lithium exchange reaction on 4-aryl-3,3-dichloro-2-azetidinones. This methodology was further extended to the use of alkyl halides as electrophiles, while more complex electrophiles could not be introduced.

Key words: lactams, lithiation, stereoselectivity, alkylations, azetidinones

Previously, we have reported on the synthesis of 2-aryl-3,3-dichloroazetidines and their ring transformation towards functionalized aziridines via intermediate 2-azetines.[1] The scope of the reactivity of the former strained compounds was further investigated and it was found that reaction of 2-aryl-3,3-dichloroazetidines **1** with lithium aluminum hydride in diethyl ether led to the isolation of a mixture of *trans*-2-aryl-3-chloroazetidines **2** and *cis*-2-aryl-3-chloroazetidines **3** (Scheme 1).[2] A similar reaction on 3,3-dichloroazetidines has been described earlier, i.e. treatment of *cis*-3,3-dichloro-2-methoxy-2,4-diphenylazetidine with lithium aluminum hydride in diethyl ether afforded the corresponding *cis*-3-chloro-2,4-diphenylazetidine in 28% yield.[3]



Scheme 1

In order to characterize unequivocally the new compounds **2** and **3** obtained, their syntheses were performed independently. While this was straightforward for the *trans*-2-aryl-3-chloroazetidines **2** (synthesis of *trans*-4-aryl-3-chloro-2-azetidinones[4] and subsequent reduction with chloroalanes[1,2]), the synthesis of *cis*-2-aryl-3-chloroazetidines **3** proved to be more difficult. The straightforward synthesis of 4-aryl-3-chloro-2-azetidinones by [2+2] cycloaddition between chloroketene and the appropriate imine is known to give exclusively *trans*-stereoselectivity,[4] or mainly *trans*-stereoselectivity when different substituents are present on the aromatic substituent.[5]

Thus, another method to obtain the desired *cis*-derivatives was required. Although some methods are known that give mainly *cis*-stereoselectivity by in situ generation of the ketene from the corresponding acid and an activating compound, these methods were not elaborated for α-halogenated acids.[6,7] Even more so, the stereoselectivity sometimes depends on the α-substituent of the acid and cannot be predicted.[7]

Therefore, the use of halogen–metal exchange reactions on 3,3-dichloroazetidin-2-ones to accomplish the aforementioned goal was investigated. The latter method has already been applied in the chemistry of β-lactams, mainly to 3-bromo or 3,3-dibromo derivatives by means of alkylmagnesium bromide, alkyllithium or dibutylcopperlithium reagents.[8] In most of these cases, the introduction of the 3-(1-hydroxyethyl) side chain in thienamycin or thienamycin-like β-lactams was the purpose of the study.[8a,b,d,f,g]

Here, we wish to report our results on the application of this halogen–metal exchange reaction on 4-aryl-3,3-dichloroazetidin-2-ones en route to stereodefined *cis*-4-aryl-3-chloro-2-azetidinones.

4-Aryl-3,3-dichloro-2-azetidinones **4** were easily obtained by [2+2] cycloaddition between dichloroketene, derived from dichloroacetyl chloride and a base, and the appropriate imine.[1,4] The compounds thus obtained were used as substrates in the subsequent halogen–lithium exchange strategy (Scheme 2). 4-Aryl-3,3-dichloro-2-azetidinones **4**, dissolved in tetrahydrofuran at –78 °C, were treated with *n*-butyllithium. The formation of the enolate **5** can be seen by the appearance of a deep red color after the addition of *n*-butyllithium. This mixture was kept at –78 °C for a given time to allow a complete reaction to occur. Finally, quenching of the intermediate **5** took place by the addition of a suitable electrophile. The results obtained by this sequence are summarized in Table 1. The optimum reaction conditions were determined to be as follows: addition of 1.0–1.5 equivalents of *n*-butyllithium at –78 °C and subsequent stirring at the same temperature for thirty minutes, followed by the addition of 2–5 equivalents of the electrophile and subsequent stirring at room temperature for 3–20 hours.

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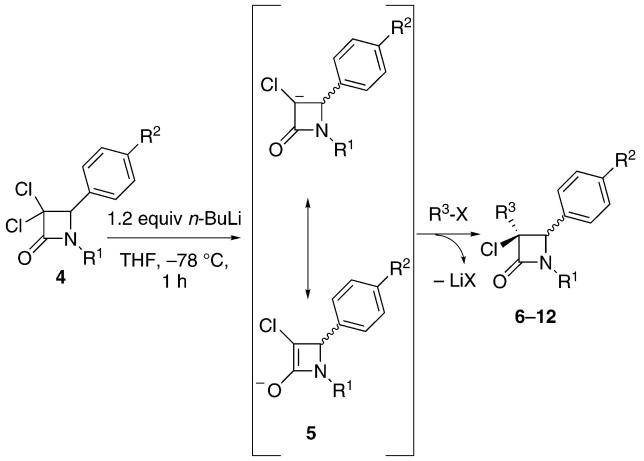
Table 1 Results of the Halogen–Lithium Exchange Reactions Performed on 4-Aryl-3,3-dichloroazetidin-2-ones **4**

Entry	R^1	R^2	Reaction Conditions[a]	R^3	Yield[b] (*cis* + *trans*)[c]
1	*i*-Pr	H	H_2O (5 equiv), –78 °C to r.t., 20 h	H	**6a** + **6b** (1:1.6) 60%
2	*i*-Pr	H	*p*-TsOH (5 equiv), –78 °C to r.t., 20 h	H	**6a** + **6b** (1:0.11) 59%
3	*i*-Pr	Me	*p*-TsOH (5 equiv), –78 °C to r.t., 20 h	H	**7a** + **7b** (1:0.08) 53%
4	*c*-Hex	H	*p*-TsOH (5 equiv), –78 °C to r.t., 20 h	H	**8a** + **8b** (1:0.09) 65%
5	Bn	H	*p*-TsOH (2 equiv), –78 °C to r.t., 3 h	H	**9a** + **9b** (1:0.14) 63%
6	Bn	H	AcOH (2 equiv), –78 °C to r.t., 3 h	H	**9a** (only *cis*) 61%
7	Bn	H	pivalic acid (5 equiv), –78 °C to r.t., 20 h	H	**9a** + **9b** (1:0.22) 61%
8	Bn	H	salicylic acid (2 equiv), –78 °C to r.t., 20 h	H	**9a** + **9b** (1:0.19) 57%
9	*i*-Pr	H	AcOH (2 equiv), –78 °C to r.t., 3 h	H	**6a** + **6b** (1:0.06) 65%
10	*i*-Pr	H	MeI (5 equiv), –78 °C to r.t., 20 h	Me	**10** (only *cis*) 57%
11	*i*-Pr	H	EtBr (5 equiv), –78 °C to r.t., 20 h	Et	**11** (only *cis*) 40%
12	Bn	H	PrBr (5 equiv), –78 °C to r.t., 20 h	Pr	**12** (only *cis*) 23%
13	*i*-Pr	H	$Br(CH_2)_2OSiMe_3$ (5 equiv), –78 °C to r.t., 20 h	$(CH_2)_2OSiMe_3$	–[d]
14	*i*-Pr	H	$ClCO_2Me$ (5 equiv), –78 °C to r.t., 20 h	CO_2Me	–[d]
15	*i*-Pr	H	$MeOCO_2Me$ (5 equiv), –78 °C to r.t., 20 h	CO_2Me	–[d]
16	Bn	H	$NCCO_2Me$ (5 equiv), –78 °C to r.t., 20 h	CO_2Me	–[d]

[a] The halogen–metal exchange was performed by the addition of 1–1.5 equivalents of *n*-BuLi in hexane to a solution of dichloroazetidinone **4** in THF, stirring for 30 min and subsequent addition of the electrophile.
[b] Yields after purification (flash chromatography or recrystallization).
[c] *cis*:*trans* Ratio determined by signal integration in the ^1H NMR spectrum of the crude product.
[d] No reaction product isolated (intractable mixtures).

To synthesize the compounds, which were under focus, namely *cis*-4-aryl-3-chloro-2-azetidinones **6**–**9**, different proton sources were evaluated, i.e. water, *p*-toluenesulfonic acid, glacial acetic acid, pivalic acid and salicylic acid. Glacial acetic acid was prepared by distillation of commercial acetic acid (99+%) in the presence of acetic anhydride.[9] As can be seen from Table 1 (entries 1 to 8), the use of all proton sources allowed to synthesize 4-aryl-3-chloro-2-azetidinones **6**, however, the stereochemical outcome of each reaction was somewhat different. Using 4-aryl-3,3-dichloro-2-azetidinone **4a** with monohydrated *p*-toluenesulfonic acid or glacial acetic acid, mainly *cis*-3-chloro-1-isopropyl-4-phenyl-2-azetidinone (**6a**) was isolated, with the best results for glacial acetic acid (*cis*:*trans* ratio 1:0.06), while using water, a mixture of the *cis*- and *trans*-azetidinones **6a** and **6b** was obtained. The distinction between both stereoisomeric compounds was easily made by means of the coupling constants between the C_3 and C_4 proton (*cis*: J = 5–6 Hz, *trans*: J = 0–2 Hz).[10]

These results were rationalized as follows. The double bond in enolate **5** forms a planar part in the molecule with a sterically hindering aryl group at the allylic position. To



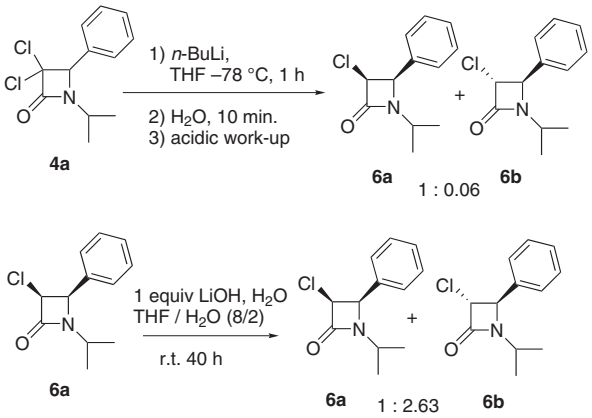
4a, 6 : R^1 = *i*-Pr, R^2 = Ph, R^3 = H
4b, 7 : R^1 = *i*-Pr, R^2 = PhMe, R^3 = H
4c, 8 : R^1 = *c*-Hex, R^2 = Ph, R^3 = H
4d, 9 : R^1 = Bn, R^2 = Ph, R^3 = H
10 : R^1 = *i*-Pr, R^2 = Ph, R^3 = Me
11 : R^1 = *i*-Pr, R^2 = Ph, R^3 = Et
12 : R^1 = Bn, R^2 = Ph, R^3 = Pr

Scheme 2

avoid steric interactions, the incoming electrophile preferentially approaches the intermediate **5** from the opposite face of the space in which the aryl substituent resides. This reasoning satisfactorily explains the formation of *cis*-4-aryl-3-chloro-2-azetidinones **6a**–**9a**. For the formation of substantial amounts of *trans*-4-aryl-3-chloro-2-azetidinones in the case of water (without acid) as electrophile (Table 1, entry 1), the same mechanism can be proposed, but the base lithium hydroxide is formed, which is able to deprotonate the 3-position of *cis*-3-chloro-1-isopropyl-4-phenyl-2-azetidinone (**6a**). In this way, the *cis*-compound **6a** isomerizes to the thermodynamically more stable *trans*-derivative **6b**.

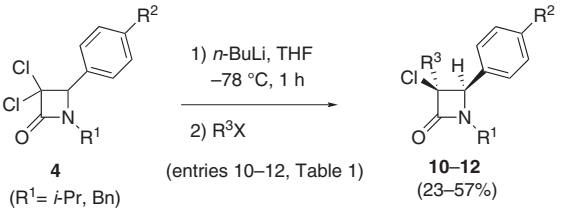
Two experiments were conducted to confirm these assumptions. The first one was the workup of the reaction mixture (from **4a**, R^1 = *i*-Pr, R^2 = H) immediately after addition of water, so as to leave little time for the isomerization to take place, and mainly the *cis*-derivative should be isolated. To conduct this experiment, the same procedure was followed as in the previous cases. After the addition of water to the enolate, the reaction mixture was stirred during only one minute and subsequently poured into 10% citric acid to neutralize lithium hydroxide. This procedure confirmed the above mentioned hypothesis and almost only the *cis*-derivative was observed in the crude reaction mixture (*cis*:*trans* 1:0.06) (Scheme 3).

The second experiment checked the potential of lithium hydroxide to isomerize the *cis*-isomer **6a** to the *trans*-isomer **6b**. Thus, the isolated *cis*-3-chloro-1-isopropyl-4-phenyl-2-azetidinone (**6a**) was reacted with lithium hydroxide in a tetrahydrofuran–water mixture (THF–H_2O, 4:1). After a reaction time of 40 hours, *cis*- and *trans*-3-chloro-1-isopropyl-4-phenyl-2-azetidinone (**6a** and **6b**) were isolated (*cis*:*trans* = 1:2.63). These two experiments are in agreement with the proposed course of the reaction, implying at first only the formation of *cis*-3-chloro-1-isopropyl-4-phenyl-2-azetidinone (**6a**), which, in the presence of a base, isomerizes to the thermodynamically more stable *trans*-derivative **6b** (Scheme 3).



Scheme 3

This was also confirmed when alkyl halides were used as electrophiles (Table 1, entries 10–12 and Scheme 4). In these cases, only the formation of the *cis*-3-alkyl-3-chloro-4-phenylazetidin-2-ones **10a**–**12a** was detected. This relative *cis*-stereochemistry was checked and confirmed by NOE experiments between the 3-alkyl substituent and the C_4-proton of compounds **10** and **11** (Figure 1).



Scheme 4

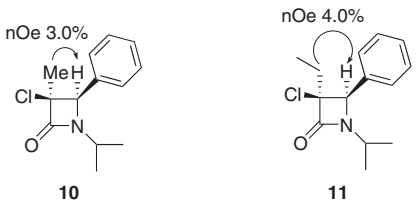


Figure 1 NOE between the 3-alkyl substituent and the C_4-proton of compounds **10** and **11**

From these results, also the influence of steric hindrance during the reaction could be derived. The bulkier the introduced electrophile, the lower the yield of the compound obtained.

Further attempts to extend this reaction to the use of other electrophiles failed. The introduction of a methoxycarbonyl functionality by the use of methyl chloroformate, dimethyl carbonate or methyl cyanoformate did not succeed (entries 14–16). Very complex reaction mixtures were ob-

tained from which only trace amounts of *cis*- and *trans*-3-chloro-1-isopropyl-4-phenyl-2-azetidinones were isolated. Also more sterically and electronically demanding electrophiles, like trimethylsilyl 2-bromoethyl ether (entry 13), did not give an alkylation product. The expected product from this reaction could possibly lead towards the synthesis of spiro-β-lactams. Possibly, the previously observed influence of steric hindrance plays a major role in this negative result.

In conclusion, a straightforward method for the synthesis of new *cis*-4-aryl-3-chloro-2-azetidinones **6a**–**9a** was developed. This methodology was further extended to the use of alkyl halides as electrophiles, while more complex electrophiles could not be introduced.

^{1}H and ^{13}C NMR spectra were recorded at 270 and 68 MHz, respectively. The type of carbon and hydrogen was determined by DEPT ^{13}C-^{1}H and ^{1}H-^{1}H COSY techniques. Mass spectra were performed with a Varian MAT 112 spectrometer at 70 eV using a GC-MS coupling or a direct inlet system. IR spectra were obtained from a Perkin-Elmer 1310, Perkin-Elmer 983G or Perkin-Elmer Spectrum One spectrophotometer. Et_2O and THF were freshly distilled from sodium wire and sodium benzophenone ketyl, respectively. Petroleum ether used had bp 40–60 °C. Melting points were measured with a Büchi 535 or Büchi 540 apparatus and are uncorrected. 2-Aryl-3,3-dichloroazetidinones **4** were synthesized by cycloaddition of dichloroketene, generated in situ from dichloroacetyl chloride, and an appropriate arylideneamine.[1,4]

Halogen–Lithium Exchange Reactions of 4-Aryl-3,3-dichloro-2-azetidinones 4; *cis*-3-Chloro-1-isopropyl-4-phenyl-2-azetidinone (6a); Typical Procedure

A solution of 3,3-dichloro-1-isopropyl-4-phenyl-2-azetidinone (**4a**; R^1 = *i*-Pr, R^2 = H) (1.00 g, 3.9 mmol) in THF (10 mL) was placed under N_2 and kept at –78 °C. With a syringe, a 2.5 M solution of *n*-BuLi in hexanes (1.90 mL, 4.7 mmol) was added through the septum. The resulting mixture was kept at –78 °C for 1 h. Afterwards, *p*-TsOH·H_2O (3.69 g, 19.4 mmol) in THF (10 mL) was added. The reaction mixture was allowed to stir for 20 h, and the temperature was allowed to reach to r.t. The mixture was poured into H_2O and extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried ($MgSO_4$). After filtration and evaporation of the solvent, the crude product **6a** was obtained. Further purification was performed by flash chromatography (petroleum ether–EtOAc, 6:4); R_f 0.38; mp 74.7–75.6 °C.

In the rest of the cases further purification was performed by recrystallization or flash chromatography.

IR (KBr): 1771 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.13 and 1.34 [2 × 3 H, 2 d, *J* = 6.9 Hz, [CH(C*H*$_3$)$_3$], 3.79 (1 H, septet, *J* = 6.9 Hz, C*H*Me$_2$), 4.97 and 5.04 (2 × 1 H, 2 d, *J* = 4.9 Hz, NC*H*C_6H_5 and CHCl), 7.27–7.42 (5 H, m, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 20.22 and 21.13 [CH(*C*H$_3$)$_3$], 45.98 (*C*HMe$_2$), 60.02 and 60.18 (N*C*HC_6H_5 and CHCl), 128.34, 128.41 and 129.09 (C_o, C_m, C_p), 134.30 (C_q), 164.00 (C=O).

MS: *m*/*z* (%) = 223/225 (M^+, 2), 180/182 (20), 139 (15), 114 (21), 109 (15), 107 (14), 99 (100), 86 (12), 83 (18), 81 (15), 67 (19), 56 (11), 55 (23), 45 (16).

Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.44; H, 6.27; N, 6.27. Found: C, 63.99; H, 6.35; N, 6.19.

***trans*-3-Chloro-1-isopropyl-4-phenylazetidin-2-one (6b)**

Flash chromatography: petroleum ether–EtOAc (6:4); R_f 0.64.

IR (KBr): 1765 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.07 and 1.31 [2 × 3 H, 2 d, *J* = 6.9 Hz, CH(C*H*$_3$)$_3$], 3.75 (1 H, septet, *J* = 6.9 Hz, C*H*Me$_2$), 4.46 and 4.53 (2 × 1 H, 2 d, *J* = 1.6 Hz, NCH and CHCl), 7.35–7.47 (5 H, m, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 19.80 and 20.74 [CH(*C*H$_3$)$_3$], 45.63 (*C*HMe$_2$), 62.23 and 64.75 (NCH and CHCl), 126.42, 128.86 and 129.08 (C_o, C_m, C_p), 136.24 (C_q), 163.13 (C=O).

MS: *m*/*z* (%) = M^+ (not detected), 145 (2), 139 (57), 137 (100), 131 (4), 130 (5), 117 (2), 116 (2), 115 (2), 102 (46), 101 (7), 100 (2), 89 (2), 88 (3), 83 (5), 77 (16), 75 (4), 74 (2), 69 (8), 62 (2), 50 (7), 49 (2).

Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.44; H, 6.27; N, 6.27. Found: C, 64.31; H, 7.21; N, 6.20.

***cis*-3-Chloro-1-isopropyl-4-(4-methylphenyl)-2-azetidinone (7a)**

Mp 82.8–84.0 °C (MeOH).

IR (KBr): 1765 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.12 and 1.33 (2 × 3 H, 2 d, *J* = 6.6 Hz, CH(C*H*$_3$)$_3$], 2.39 (3 H, s, C_qCH_3), 3.78 (1 H, septet, *J* = 6.6 Hz, C*H*Me$_2$), 4.94 and 5.02 (2 × 1 H, 2 d, *J* = 4.9 Hz, NC*H*C_6H_4 and CHCl), 7.22–7.26 (4 H_{arom}, m).

^{13}C NMR ($CDCl_3$): δ = 20.20 and 21.17 [CH(*C*H$_3$)$_3$], 21.28 (C_qCH_3), 45.88 (*C*HMe$_2$), 59.84 and 60.22 (N*C*HC_6H_4 and CHCl), 128.35 and 129.05 (C_o and C_m), 131.16 (C_p), 138.99 (C_q), 164.08 (C=O).

MS: *m*/*z* (%) = 237/239 (M^+, 1), 202 (M^+ – Cl, 11), 161 (9), 159 (1), 155 (56), 153 (100), 147 (10), 118 (31), 116 (15), 92 (7).

Anal. Calcd for $C_{13}H_{16}ClNO$: C, 65.70; H, 6.74; N, 5.90. Found: C, 65.99; H, 6.45; N, 5.84.

***trans*-3-Chloro-1-isopropyl-4-(methylphenyl)azetidin-2-one (7b)**

Flash chromatography: petroleum ether–EtOAc (6:4), R_f 0.53.

IR (KBr): 1769 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.06 and 1.30 (2 × 3 H, 2 d, *J* = 6.6 Hz, CH(C*H*$_3$)$_3$], 2.38 (3 H, s, C_qCH_3), 3.74 (1 H, septet, *J* = 6.6 Hz, C*H*Me$_2$), 4.44 and 4.49 (2 × 1 H, 2 d, *J* = 1.6 Hz, NCH and CHCl), 7.23 and 7.25 (2 × 2 H, 2 d, *J* = 9 Hz, C_6H_4).

^{13}C NMR ($CDCl_3$): δ = 20.09, 21.08 and 21.22 [CH(*C*H$_3$)$_3$ and C_qCH_3], 45.80 (*C*HMe$_2$), 62.53 and 64.92 (NCH and CHCl), 126.63 and 129.79 (C_o, C_m), 133.48 and 139.37 (2 C_q), 163.57 (C=O).

MS: *m*/*z* (%) = 236/238 (1, M^+), 152/154 (100), 151 (11), 146 (15), 145 (13), 130 (10), 120 (12), 119 (32), 118 (44), 117 (82), 116 (38), 115 (75), 103 (18), 102 (13), 91 (58), 90 (25), 84 (11), 78 (12), 77 (23), 76 (11), 70 (42), 65 (31), 63 (20), 51 (15).

Anal. Calcd for $C_{13}H_{16}ClNO$: C, 65.70; H, 6.74; N, 5.90. Found: C, 65.80; H, 6.87; N, 5.78.

***cis*-3-Chloro-1-cyclohexyl-4-phenyl-2-azetidinone (8a)**

Yield: 65%; mp 126.4–126.8 °C (MeOH).

IR (KBr): 1744 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 0.99–1.32 and 1.55–1.87 and 2.00–2.05 [10 H, m, $(CH_2)_5$], 3.37–3.47 (1 H, m, NCH), 4.98 and 5.04 (2 × 1 H, 2 d, *J* = 4.9 Hz, NC*H*C_6H_5 and CHCl), 7.27–7.45 (5 H, m, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 24.85, 25.01, 25.09, 30.44 and 31.27 [$(CH_2)_5$], 53.57 (NCH), 60.04 and 60.22 (N*C*HC_6H_5 and CHCl), 128.32, 128.41 and 129.06 (C_o, C_m, C_p), 134.39 (C_q), 164.04 (C=O).

MS: *m/z* (%) = M^+ (not detected), 157 (3), 147 (2), 145 (2), 139/141 (100), 132 (3), 104 (19), 101 (3), 83 (3), 77 (7), 67 (1), 57 (4), 55 (6), 51 (3).

Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.32; H, 6.83; N, 5.31. Found: C, 68.46; H, 6.96; N, 5.24.

***trans*-3-Chloro-1-cyclohexyl-4-phenylazetidin-2-one (8b)**
Flash chromatography: petroleum ether–EtOAc (6:4), R_f 0.65.

IR (KBr): 1769 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 0.96–2.04 [10 H, m, $(CH_2)_5$], 3.33–3.45 (1 H, m, NCH), 4.44 and 4.54 (2 × 1 H, 2 d, *J* = 1.6 Hz, NCH and CHCl), 7.34–7.46 (5 H, m, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 24.95, 25.01, 30.21, 31.15 and 32.80 [$(CH_2)_5$], 53.75 (NCH), 62.85 and 65.15 (NCH and CHCl), 126.95, 129.20 and 129.31 (C_o, C_m, C_p), 136.71 (C_q), 163.82 (C=O).

MS: *m/z* (%) = M^+ (not detected), 175 (2), 153 (3), 151 (4), 138/140 (100), 135 (3), 131 (3), 105 (4), 103 (20), 91 (31), 86 (18), 84 (28), 77 (7), 74 (8), 59 (13), 55 (4), 51 (3), 49 (5), 47 (6).

Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.32; H, 6.83; N, 5.31. Found: C, 68.22; H, 6.94; N, 5.26.

***cis*-1-Benzyl-3-chloro-4-phenyl-2-azetidinone (9a)**
Flash chromatography: petroleum ether–EtOAc (8:2), R_f 0.34.

IR (neat): 1770 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 3.89 [1 H, d, *J* = 15 Hz, C*H*(H)C_6H_5], 4.77 (1 H, d, *J* = 5 Hz, NC*H*C_6H_5), 4.88 [1 H, d, *J* = 15 Hz, CH(*H*)C_6H_5], 5.05 (1 H, d, *J* = 5 Hz, CHCl), 7.13–7.39 (10 H, m, 2 × C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 44.92 (NCH_2), 60.23 (NCH), 61.11 (CHCl), 128.07, 128.19, 128.48, 128.53, 128.86 and 129.04 (2 C_o, 2 C_m, 2 C_p), 132.95 and 134.32 (2 C_q), 163.95 (C=O).

MS: *m/z* (%) = 271/273 (M^+, 0.4), 138/140 (100), 132 (2), 104 (4), 103 (25), 91 (40), 77 (10), 65 (7), 51 (10).

Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.73; H, 5.16; N, 5.16. Found: C, 70.89; H, 5.40; N, 5.11.

***trans*-1-Benzyl-3-chloro-4-phenylazetidin-2-one (9b)**
Flash chromatography: petroleum ether–EtOAc (8:2), R_f 0.36.

IR (neat): 1774 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 3.82 [1 H, d, *J* = 15 Hz, C*H*(H)C_6H_5], 4.38 (1 H, d, *J* = 1.7 Hz, NC*H*C_6H_5), 4.56 (1 H, d, *J* = 1.7 Hz, CHCl), 4.88 [1 H, d, *J* = 15 Hz, CH(*H*)C_6H_5], 7.13–7.38 (10 H, m, 2 × C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 44.90 (NCH_2), 63.18 (NCH), 65.25 (CHCl), 126.61, 128.03, 128.41, 128.88, 129.22 and 129.40 (2 C_o, 2 C_m, 2 C_p), 134.66 and 137.30 (2 C_q), 163.63 (C=O).

MS: *m/z* = M^+ (not detected), 194/196 ($M^+ - C_6H_5$, 2), 103 (20), 91 (21), 77 (7), 65 (5), 51 (3).

Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.73; H, 5.16; N, 5.16. Found: C, 70.50; H, 5.28; N, 5.06.

***cis*-3-Chloro-1-isopropyl-3-methyl-4-phenyl-2-azetidinone (10)**
Yield: 57%; mp 106.6–106.8 °C (MeOH).

IR (KBr): 1747 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 1.14 and 1.35 [2 × 3 H, 2 d, *J* = 6.9 Hz, $CH(CH_3)_3$], 1.87 [3 H, s, $C(O)CH_3$], 3.76 (1 H, septet, *J* = 6.9 Hz, C*H*Me_2), 4.62 (1 H, s, NC*H*C_6H_5), 7.31–7.45 (5 H, m, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 20.22 and 21.02 [$CH(CH_3)_3$], 24.55 [$C(O)CH_3$], 45.59 (*C*HMe_2), 68.01 (N*C*HC_6H_5), 72.69 [C_qCl(CH_3)], 128.05 and 128.28 (C_o, C_m), 128.95 (C_p), 135.27 (C_q), 167.13 (C=O).

MS: *m/z* (%) = 237/239 (M^+, 1), 152 (73), 150 (100), 130 (14), 116 (63), 114 (38), 90 (12).

Anal. Calcd for $C_{13}H_{16}ClNO$: C, 65.70; H, 6.74; N, 5.90. Found: C, 65.80; H, 6.94; H, 5.86.

***cis*-3-Chloro-3-ethyl-1-isopropyl-4-phenyl-2-azetidinone (11)**
Yield: 40%; mp 70.9–71.1 °C (MeOH).

IR (KBr): 1748 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 1.13 and 1.36 (2 × 3 H, 2 d, *J* = 6.6 Hz, $CH(CH_3)_3$], 1.17 (3 H, t, *J* = 7.26 Hz, CH_2CH_3), 2.14 (2 H, m, CH_2CH_3), 3.76 (1 H, septet, *J* = 6.93 Hz, C*H*Me_2), 4.67 (1 H, s, NC*H*C_6H_5), 7.30–7.44 (5 H, m, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 9.07 (CH_2CH_3), 20.31 and 21.06 [$CH(CH_3)_3$], 30.64 (CH_2CH_3), 45.59 (*C*HMe_2), 65.91 (N*C*HC_6H_5), 77.43 [C_qCl(CH_2CH_3)], 128.10 and 128.26 (C_o, C_m), 128.82 (C_p), 135.40 (C_q), 166.95 (C=O).

MS: *m/z* (%) = 251/253 (M^+, 1), 216 (M^+ – Cl, 2), 166/168 (100), 151 (6), 131 (41), 115 (10), 91 (6).

Anal. Calcd for $C_{14}H_{18}ClNO$: C, 66.81; H, 7.16; N, 5.57. Found: C, 66.95; H, 7.32; N, 5.52.

***cis*-1-Benzyl-3-chloro-4-phenyl-3-propyl-2-azetidinone (12)**
Flash chromatography: petroleum ether–EtOAc (8:2); R_f 0.52; yield: 23%.

IR (neat): 1781 cm^{-1} (C = O).

^1H NMR ($CDCl_3$): δ = 0.95 (3 H, t, *J* = 7.6 Hz, CH_3), 1.41–1.72 (2 H, m, CH_2CH_3), 1.89–2.17 (2 H, m, $CH_2CH_2CH_3$), 3.86 [1 H, d, *J* = 14.5 Hz, NC*H*(H)C_6H_5], 4.44 (1 H, s, NC*H*C_6H_5), 4.93 [1 H, d, *J* = 14.5 Hz, NCH(*H*)C_6H_5], 7.10–7.45 (10 H, m, 2 C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 13.93 (CH_2CH_3), 17.99 (CH_2CH_3), 39.21 ($CH_2CH_2CH_3$), 44.49 (NCH_2), 66.38 (N*C*HC_6H_5), 77.99 (C_qCl), 127.57, 127.99, 128.10, 128.34, 128.46 and 128.67 (2 C_o, 2 C_m, 2 C_p), 133.82 and 134.63 (2 C_q), 166.88 (C=O).

MS: *m/z* (%) = 278 (M^+ – Cl, 2), 145 (13), 103 (7), 91 (100), 77 (11), 65 (10), 51 (3).

Anal. Calcd for $C_{19}H_{20}ClNO$: C, 72.74; H, 6.38; N, 4.47. Found: C, 72.94; H, 6.68; N, 4.45.

Halogen–Lithium Exchange Experiments Confirming the Proposed Reaction Mechanism
The first experiment (vide supra) conducted to confirm some mechanistic aspects of the results obtained from the previously described halogen–lithium exchange reactions, was concerned with the isomerization of *cis*-3-chloro-1-isopropyl-4-phenyl-2-azetidinone (**6a**) to the corresponding *trans*-derivative **6b**. *cis*-3-Chloro-1-isopropyl-4-phenyl-2-azetidinone (**6a**; 0.10 g, 0.4 mmol) was dissolved in a H_2O–THF solvent mixture (1:4, 2 mL). Subsequently, $LiOH·H_2O$ (0.06 g, 0.5 mmol) was added and the resulting mixture was stirred during 40 h. Afterwards, H_2O was added and the aqueous layer was extracted with Et_2O. Drying ($MgSO_4$), filtration and evaporation of the solvent yielded the crude reaction product, i.e. a mixture of *cis*- and *trans*-3-chloro-1-isopropyl-4-phenyl-2-azetidinones (**6a** and **6b**), which was used to determine the ratio of both products by ^1H NMR spectroscopy. The *cis*:*trans* ratio obtained turned out to be 1:2.63.

In a second experiment, the conventional procedure was followed. A solution of 3,3-dichloro-1-isopropyl-4-phenyl-2-azetidinone (**4a**; R^1 = *i*-Pr, R^2 = H; 1.00 g, 3.9 mmol) in THF (10 mL) was placed under N_2 and kept at –78 °C. With a syringe, a 2.5 M solution of *n*-BuLi in hexanes (1.90 mL, 4.7 mmol) was added through the septum. The mixture was kept at –78 °C for 1 h. Afterwards, H_2O (0.14 g, 7.8 mmol) in THF (10 mL) was added. The reaction mixture was stirred for only 1 min and subsequently poured into 10% citric acid

to neutralize LiOH. The aqueous layer was extracted with Et_2O. Drying ($MgSO_4$), filtration and evaporation of the solvent yielded the crude reaction product, i.e. a mixture of *cis*- and *trans*-3-chloro-1-isopropyl-4-phenyl-2-azetidinones (**6a** and **6b**), which was used to determine the ratio of both products by ^1H NMR spectroscopy. The *cis*:*trans* ratio obtained turned out to be 1:0.06.

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