The "Non-Oxidative" Chloro-Pummerer Reaction: Novel Stereospecific Entry to Vicinal Chloroamines and Aziridines

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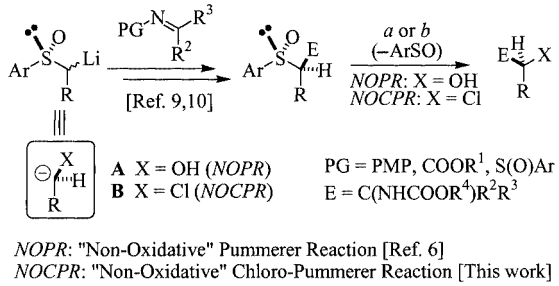
This article describes a new, useful synthetic tool, the "Non-Oxidative" Chloro-Pummerer Reaction (NOCPR), which allows for the use of enantiomerically pure α-Li alkylsulfoxides as chiral α-chloroalkyl carbanions with *N*-protected imines. In this reaction the sulfinyl group of *N*-alkoxycarbonyl-β-sulfinylamines derived from aryl-, fluoroalkyl- and alkylimines is displaced by a chlorine atom in a one-pot reaction with clean stereoinversion at carbon. Several 1,2-chloroamines produced via NOCPR were transformed into the corresponding aziridines.

Introduction

The sulfinyl group is one of the most extensively used auxiliaries in asymmetric synthesis,[1] yet its synthetic potential is underutilised owing to the lack of direct methods for removing this group from a stereogenic centre while preserving the stereochemical information. This represents a serious drawback, because the ability of the sulfinyl auxiliary to give rise to excellent 1,2-induction in C-C bond-forming reactions[2,3] cannot easily be exploited for the creation of new stereodefined sulfur-free stereogenic centres. Recently, we reported a stereospecific intramolecular variant of an "interrupted" Pummerer reaction,[4] which was dubbed by us as the "Non-Oxidative" Pummerer Reaction (NOPR).[5] This reaction allows for a one-pot replacement of a sulfinyl group with hydroxyl in a stereospecific S_N2 fashion (Scheme 1 and 2).[6] This protocol enabled us and others to transform a number of β-sulfinylamines *N*-monoprotected as amides or carbamates, which are nowadays easily accessible intermediates,[7] into the corresponding β-amino alcohols with high yields and total stereocontrol. Taking advantage of the NOPR, α-lithiated sulfoxides could be successfully used as synthetic equivalents of chiral α-hydroxy carbanions **A**[8] (Scheme 1) with enolisable (R^3 = alkyl)[9] as well as with non-enolizable imines (R^3 = aryl, fluoroalkyl).[10] Now we disclose, in full detail, the "Non-Oxidative" *Chloro*-Pummerer Reaction (NOCPR),[11] a new methodology which extends the spectrum of application of α-lithium sulfoxides to synthetic equivalents of chiral α-chloro-carbanions **B** (Scheme 1). The NOCPR allows for a one-pot S_N2 displacement of an arylsulfinyl group by chlorine under Swern-type conditions[12] from *N*-alkoxycarbonyl α-alkyl-, α-fluoroalkyl-, and α-aryl-β-sulfinylamines. The NOCPR provides a general and efficient entry to a wide range of enantiomerically pure vicinal chloroamine derivatives, which are important building blocks in modern organic and medicinal chemistry.[13]



Scheme 1. (a) (NOPR): $(CF_3CO)_2O$, *sym*-collidine, then H_2O/K_2CO_3, $NaBH_4$; (b) (NOCPR): $(COCl)_2$, *sym*-collidine, then MeOH, $NaBH_4$

Results and Discussion

A representative set of *N*-alkoxycarbonyl-β-sulfinylamines **1a**–**k** (Scheme 2 and Table 1), with known stereochemistry,[9,10] was prepared by a C-C bond-forming reaction of enantiomerically pure α-lithium sulfoxides with suitably *N*-protected imines. Substrates **1** were treated with oxalyl

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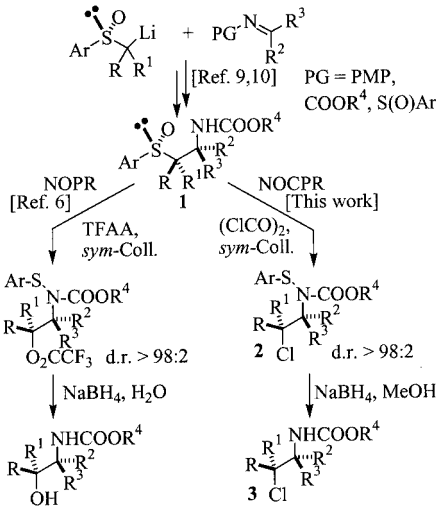


Scheme 2

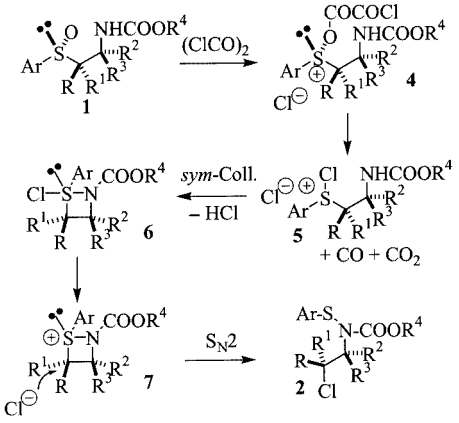
Table 1. Synthesis of β-chloroamines by NOCPR[a]

Entry	Prod.	R	R^1	R^2	R^3	Yield (%)
1	**2a**	H	H	H	CHF_2	82
2	**3b**	H	H	H	$CClF_2$	85
3	**3c**	H	H	H	3-F-C_6H_4	>98
4	**3d**	H	H	H	PMP[b]	>98
5	**3e**	CH_3	H	CF_3	CO_2Me	60
6	**3f**	H	Ph	H	CF_3	65
7	**3g**	Ph	H	CF_3	CO_2Et	72
8	**3h**	Allyl	H	H	CF_3	87
9	**3j**	CH_3	H	H	C_2H_5	75
10[c]	**3k**	H	Allyl	*i*Bu	H	68[d]

[a] Ar = *p*-Tol except for entry 1, where Ar = 1-Naphthyl; R^4 = Bn except for entry 5, where R^4 = Et. [b] PMP = 4-MeO-C_6H_4. [c] A *p*-tolylsulfinyl group having (*S*)-configuration was used. [d] The intermediate sulfenamide **2k** could be isolated in nearly quantitative yield by FC.

chloride (1.5 equiv.) in the presence of *sym*-collidine (3 equiv., CH_2Cl_2, −50 °C), which resulted in a fast and stereoselective rearrangement to the β-chlorosulfenamides **2**. In this process, the sulfinyl group undergoes deoxygenation and migration to the β-nitrogen, while a new C−Cl bond is formed with stereoinversion at carbon. This key issue is demonstrated for the transformations of **1e−k** into **2e−k** (entries 5−10), which took place with a degree of stereoselection greater than 98:2, as shown by the fact that no minor diastereomers of **3** could be detected either by ^1H and ^{19}F NMR analysis of the crude reaction mixtures, or isolated by flash chromatography (FC). Crude intermediates **2**, which can be isolated by FC (see entries 1 and 10), were diluted with methanol, then treated in situ with an excess of $NaBH_4$ (about 5 equiv.), providing the final β-chloroamines **3** as single diastereomers (entries 5−10), isolated in good to excellent overall yields by FC. The NOCPR is generally applicable to β-sulfinylamines **1** *N*-monoprotected as carbamates, including fluoroalkyl, aryl (**1c,d**), alkyl (**1j,k**), and sterically congested structures such as **1e,g**. In the case of highly hindered **1g**, a side-product identified as *N*-Cbz α-methoxy-α-trifluoromethylglycine ethyl ester, presumably arising from retro-Mannich fragmentation of **1g** and nucleophilic attack of methanol on the intermediate *N*-Cbz imine of ethyl trifluoropyruvate, was isolated in 25% yield. It is worth noting that epimerization by double displacement (Cl^- displaces Cl^-), which is a potential side-reaction, was never observed. The addition of $(COCl)_2$ in the presence of *sym*-collidine is crucial to achieve high yields of **3**, because in the absence of a base, oxalyl chloride is able to deoxygenate competitively the sulfoxides **1** to the corresponding sulfides.

The mechanism of the NOCPR is very likely to be as shown in Scheme 3, consistent with the proposed outcome of the Swern reaction,[12] and in analogy with the mechanism of the NOPR, which has recently been investigated in detail.[14] One equivalent of oxalyl chloride acylates the sulfinyl oxygen of **1** providing salt **4**, which decomposes into **5** by loss of CO and CO_2. Then, a molecule of HCl is removed by *sym*-collidine and the sulfur cation is intercepted by the adjacent carbamic nitrogen atom, producing the intermediate cyclic four-membered σ-sulfurane **6**.



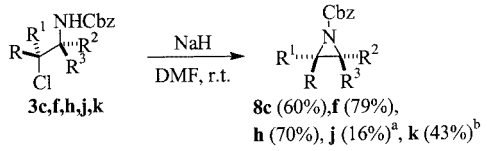
Scheme 3

Dissociation of the latter into an ion-pair **7** triggers its recombination *via* S_N2-type attack of the generated chloride anion to the sulfur-substituted stereogenic carbon, which produces the final β-chlorosulfenamide **2**. Release of the four-membered ring strain in **6** is likely to play a significant role, favouring a fast, stereocontrolled displacement. It is more than likely that deoxygenation of **1** to the corresponding sulfides, a side-reaction observed when oxalyl chloride is used without *sym*-collidine (see above), involves formation of Cl_2 from **5** when it cannot be rapidly transformed into **6** by action of the base.[12b]

Besides the combination $(COCl)_2$/*sym*-collidine, we examined other reagents as possible NOCPR promoters, but the results were disappointing. In fact, treatment of sulfoxide **1h** with thionyl chloride/*sym*-collidine produces deoxygenation to the sulfide, while SO_2Cl_2/*sym*-collidine affords a complex mixture of unidentified products. Also, in the case of an attempted " Non-oxidative" Bromo-Pummerer reaction, the deoxygenation of sulfoxides **1** to the corresponding sulfides took place quantitatively upon treatment

of **1** with oxalyl bromide under the optimized NOCPR conditions.

Among the possible derivatives of vicinal chloroamines, aziridines constitute a valuable class of compounds both for their pharmaceutical properties and for their synthetic versatility.[15] Treatment of **3c,f,h,j,k** with NaH (1.5 equiv.) in DMF (Scheme 4) gives the enantiomerically pure *N*-Cbz aziridines **8c,f,h,j,k** in moderate to good yields, except for **8j** which forms at a very slow rate. In contrast, under the same conditions, the sterically congested β-chloroamine **3g** does not produce the corresponding aziridine.



Scheme 4. [a] Unchanged **3j** recovered in nearly quantitative yield after 48 hours. [b] Unchanged **3k** recovered in 35% yield after 2 hours.

The relative configurations of aziridines **8f,h,k** were unambiguously determined by NOE experiments. For example, irradiation of the CF_3 group of **8h** produced 1.5% and 2.0% heteronuclear NOE enhancements of the diastereotopic CH_2 allylic protons in *cis* position (R = allyl), and only 0.5% of the aziridine ring proton (R^1 = H) *trans* to the trifluoromethyl. In the case of **8f**, irradiation of C*H*CF_3 produced a 3.0% NOE on the *ortho*-phenyl protons in *cis*, but no NOE was observed with the C*H*Ph proton in *trans*. Finally, irradiation of the allylic methylene of **8k** produced a relevant 2.8% NOE on the *cis* isobutyl methylene. The stereochemistry of **8j** was assigned by comparison of its ^{1}H NMR spectrum and polarimetric analyses with those described by García Ruano et al.[7a]

In summary, we have disclosed in full detail the "Non-Oxidative" Chloro-Pummerer reaction (NOCPR), a stereospecific process for replacing a sulfinyl group of *N*-alkoxycarbonyl β-sulfinylamines with chlorine. This reaction opens up a straightforward route to enantiomerically pure, stereodefined β-chloroamines and some important derivatives like aziridines, and extends the scope of sulfoxides in asymmetric synthesis.

Experimental Section

General Details: Melting points (m.p.): uncorrected; capillary apparatus. Polarimetric analyses: PROPOL polarimeter. Analytical TLC: routinely used to monitor reactions, plates precoated with E. Merck silica gel 60 F_{254} of 0.25 mm thickness were used. Flash chromatography (FC): silica gel 60 (230−400 ASTM mesh). ^{1}H, ^{13}C and ^{19}F NMR: Bruker 250 MHz and 500 MHz spectrometers, chemical shifts in ppm (δ), tetramethylsilane (TMS) as internal standard for ^{1}H and ^{13}C nuclei ($\delta_{H/C}$ = 0.00), C_6F_6 external standard (δ_F = −162.90) for ^{19}F. MS: TSQ Finnigan Mat three-stage quadrupole instrument, DIS (Direct Inlet System) used for pure compounds. IR: Perkin−Elmer System 2000 FT-IR (scan range: 15600 cm^{-1}; combined scan direction), with a Perkin−Elmer Multiscope FTIR Microscope. THF was freshly distilled from Na/benzophenone. Diisopropylamine and dichloromethane were freshly distilled from over CaH_2. In all other cases, commercially available reagent-grade solvents were employed without purification. All reactions where anhydrous organic solvents were employed were performed under nitrogen, after flame-drying the glass apparatus. The synthesis of β-sulfinylamines **1** is described in references 9 and 10.

The "Non-oxidative" Chloro-Pummerer reaction. General Procedure: Neat oxalyl chloride (1.5 equiv.) was added dropwise to a solution of *N*-alkoxycarbonyl β-sulfinylamine **1** (1 equiv.) and *sym*-collidine (3 equiv.) in dry CH_2Cl_2 at −50 °C. After complete consumption of the starting material (TLC) the reaction was allowed to reach room temperature. Sulfenamides **2a** and **2k** could be isolated in pure form by FC, otherwise (in the one-pot reaction protocol) the crude mixture was diluted with MeOH, then excess $NaBH_4$ (ca. 5 equiv.) was added portionwise. After consumption of the intermediate sulfenamide **2** (TLC), the reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The collected organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent removed in vacuo. Purification of the crude mixture by FC produced the corresponding β-chloroamine **3**.

Benzyl (*S*)-*N*-(1-Chloromethyl)-2,2-difluoroethyl[(1-naphthyl)thio]-carbamate (2a): Formula mass 421.89. Yield 82%. R_f = 0.69 (hexane/Et_2O, 80:20). $[\alpha]_D^{23}$ = +23.4 (*c* = 0.6, $CHCl_3$). FTIR (film): $\tilde{\nu}$ = 1718, 1383, 1278 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 9.5 Hz, 1 H), 7.86 (d, *J* = 9.5 Hz, 1 H), 7.75 (d, *J* = 7.7 Hz, 1 H), 7.40 (m, 9 H), 5.80 (dt, *J* = 55.9 and 5.2 Hz, 1 H), 5.34 (d, *J* = 12.9 Hz, 1 H), 5.27 (d, *J* = 12.9 Hz, 1 H), 4.89 (m, 1 H), 3.94 (dd, *J* = 11.2 and 10.3 Hz, 1 H), 3.76 (dd, *J* = 11.2 and 4.3 Hz, 1 H) ppm. ^{13}C NMR (62.3 MHz, $CDCl_3$): δ = 157.7, 135.2, 133.6, 129.7, 128.7, 128.6, 128.5, 128.1, 128.0, 126.6, 126.4, 125.7, 124.7, 123.0, 113.6 (t, *J* = 246.0 Hz), 69.6, 64.5 (t, *J* = 25.9 Hz), 39.6 ppm. ^{19}F NMR (235.4 MHz, $CDCl_3$): δ = −122.4 (dd, *J* = 291.9 and 55.9 Hz, 1F), −128.1 (ddd, *J* = 291.9, 55.9 and 9.5 Hz, 1 F) ppm. MS (DIS EI, 70 eV): *m*/*z* (%) = 423 (25) [M + 2]$^+$, 421 (12) [M$^+$].

Benzyl (*R*)-(2-Chloro-1-chloromethyl-2,2-difluoroethyl)carbamate (3b): Formula mass 298.11. Yield 85%. R_f = 0.55 (hexane/EtOAc, 80:20). $[\alpha]_D^{23}$ = +1.3 (*c* = 0.8, $CHCl_3$). M.p. 50−51 °C. FTIR (KBr) : $\tilde{\nu}$ = 3310, 1703, 1546, 1279 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.39 (m, 5 H), 5.31 (br. d, *J* = 9.7 Hz, 1 H), 5.28 (s, 2 H), 4.72 (m, 1 H), 3.85 (dd, *J* = 12.0 and 3.9 Hz, 1 H), 3.70 (dd, *J* = 12.0 and 6.9 Hz, 1 H) ppm. ^{13}C NMR (62.3 MHz, $CDCl_3$): δ = 155.6, 135.6, 128.6, 128.5, 128.2, 127.6 (t, *J* = 297.8 Hz), 67.9, 58.6 (t, *J* = 25.9 Hz), 41.5 ppm. ^{19}F NMR (235.4 MHz, $CDCl_3$): δ = −60.8 (dd, *J* = 166.8 and 9.2 Hz, 1F), −61.6 (dd, *J* = 166.8 and 8.1 Hz, 1F) ppm. MS (DIS EI, 70 eV): *m*/*z* (%) = 300 (2) [M + 3]$^+$, 299 (16) [M + 2]$^+$, 298 (4) [M + 1]$^+$, 297 (22) [M$^+$].

Benzyl (*S*)-[2-Chloro-1-(3-fluorophenyl)ethyl]carbamate (3c): Formula mass 307.75. Yield > 98%. R_f = 0.44 (hexane/EtOAc, 80:20). $[\alpha]_D^{23}$ = +13.6 (*c* = 1.2, $CHCl_3$). M.p. 49−50 °C. FTIR (KBr): $\tilde{\nu}$ = 3333, 1691, 1535, 1267 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34 (m, 5 H), 7.02 (m, 4 H), 5.57 (br. d, *J* = 7.2 Hz, 1 H), 5.14 (d, *J* = 12.1 Hz, 1 H), 5.09 (m, 1 H), 5.07 (d, *J* = 12.1 Hz, 1 H), 3.79 (m, 2 H) ppm. ^{13}C NMR (62.3 MHz, $CDCl_3$): δ = 162.9 (d, *J* = 246.0 Hz), 155.6, 141.3 (d, *J* = 7.4 Hz), 136.0, 130.3 (d, *J* = 9.2 Hz), 128.6, 128.2 (d, *J* = 7.4 Hz), 122.2, 115.0 (d, *J* = 20.3 Hz), 113.6 (d, *J* = 22.2 Hz), 67.2, 55.1, 47.7 ppm. ^{19}F NMR (235.4 MHz, $CDCl_3$): δ = −113.3 (dt, *J* = 9.8 and 6.5 Hz) ppm. MS (DIS EI, 70 eV): *m*/*z* (%) = 309 [[M + 2]$^+$, 4], 307 [(M)$^+$, 13]

Benzyl (*S*)-[2-Chloro-1-(4-methoxyphenyl)ethyl]carbamate (3d): Formula mass 319.78. Yield > 98%. R_f = 0.50 (hexane/EtOAc, 70:30).

$[\alpha]_D^{23} = -33.7$ ($c = 0.8$, $CHCl_3$). M.p. 103−104 °C. FTIR (KBr): $\tilde{\nu}$ = 3449, 1719, 1509, 1385, 1248 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 7.21 (d, J = 8.5 Hz, 2 H), 6.87 (d, J = 8.5 Hz, 2 H), 5.39 (br. d, J = 8.1 Hz, 1 H), 5.12 (d, J = 12.4 Hz, 1 H), 5.08 (d, J = 12.4 Hz, 1 H), 5.00 (m, 1 H), 3.80 (m, 2 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 159.4, 155.6, 136.2, 128.5, 128.2, 127.7, 125.5, 114.2, 67.1, 55.3, 47.8 ppm. MS (DIS EI, 70 eV): m/z (%) = 322 (9) $[M + 3]^+$, 320 (9) $[M + 1]^+$.

Methyl (2*S*,3*S*)-2-Benzyloxycarbonylamino-3-chloro-2-trifluoromethylbutyrate (3e): Formula mass 291.65. Yield 60%. R_f = 0.49 (hexane/Et_2O, 80:20). $[\alpha]_D^{23} = -2.0$ (c = 0.9, $CHCl_3$). FTIR (film): $\tilde{\nu}$ = 3408, 1741, 1508, 1250, 1199 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 5.75 (br. s, 1 H), 5.20 (q, J = 6.9 Hz, 1 H), 4.16 (q, J = 6.9 Hz, 2 H), 3.92 (s, 3 H), 1.71 (d, J = 6.9 Hz, 3 H), 1.28 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (62.3 MHz, $CDCl_3$): δ = 164.5, 154.1, 123.0 (q, J = 289.4 Hz), 69.1 (q, J = 28.7 Hz), 61.8, 54.2, 54.0, 20.8, 14.3 ppm. ^{19}F NMR (235.4 MHz, $CDCl_3$): δ = −69.2 (s) ppm. MS (DIS EI, 70 eV): m/z (%) = 292 (2) $[M + 1]^+$.

Benzyl (1*S*,1′*R*)-[1-(Chlorophenylmethyl)-2,2,2-trifluoroethyl]carbamate (3f): Formula mass 357.75. Yield 65%. R_f = 0.32 (hexane/Et_2O, 80:20). $[\alpha]_D^{23} = -81.3$ (c = 0.8, $CHCl_3$). M.p. 112−113 °C. FTIR (KBr): $\tilde{\nu}$ = 3330, 17802, 1543, 1290, 1254 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35 (m, 11 H), 5.26 (d, J = 2.3 Hz, 1 H), 5.14 (s, 2 H), 5.03 (m, 1 H) ppm. ^{13}C NMR (62.3 MHz, $CDCl_3$): δ = 155.6, 135.6, 135.2, 129.4, 128.8, 128.6, 128.5, 128.2, 127.9, 123.6 (q, J = 283.0 Hz), 67.9, 58.5 (q, J = 29.6 Hz), 58.0 ppm. ^{19}F NMR (235.4 MHz, $CDCl_3$): δ = −72.8 (d, J = 6.8 Hz) ppm. MS (DIS EI, 70 eV): m/z (%) = 359 (3) $[M + 2]^+$, 357 (8) $[M^+]$.

Ethyl (2*R*,3*S*)-2-Benzyloxycarbonylamino-2-(chlorophenylmethyl)-3,3,3-trifluoropropionate (3g): Formula mass 429.82. Yield 72%. R_f = 0.33 (hexane/EtOAc, 80:20). $[\alpha]_D^{23} = -23.7$ (c = 0.7, $CHCl_3$). FTIR (film): $\tilde{\nu}$ = 3414, 1748, 1496, 1220 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.37 (m, 10 H), 5.80 (br. s, 1 H), 5.76 (s, 1 H), 5.16 (d, J = 12.4 Hz, 1 H), 5.10 (d, J = 12.4 Hz, 1 H), 4.02 (m, 2 H), 1.04 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (62.3 MHz, $CDCl_3$): δ = 163.3, 154.0, 135.6, 134.6, 129.8, 128.8, 128.6, 128.4, 128.3, 123.2 (q, J = 290.4 Hz), 69.4 (q, J = 27.7 Hz), 67.6, 60.7, 13.4 ppm. ^{19}F NMR (235.4 MHz, $CDCl_3$): δ = −67.7 (s) ppm. MS (DIS EI, 70 eV): m/z (%) = 432 (1) $[M + 3]^+$, 430 (3) $[M + 1]^+$.

Benzyl (1*S*,2*S*)-(2-Chloro-1-trifluoromethylpent-4-enyl)carbamate (3h): Formula mass 321.72. Yield 87%. R_f = 0.38 (hexane/EtOAc, 80:20). $[\alpha]_D^{23} = +4.6$ (c = 0.4, $CHCl_3$). FTIR (film): $\tilde{\nu}$ = 1741, 1271, 1500, 1159 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36 (m, 5 H), 5.86 (m, 2 H), 5.24 (dq, J = 17.0 and 1.5 Hz, 1 H), 5.16 (s, 2 H), 5.15 (dq, J = 10.0 and 1.5 Hz, 1 H), 3.04 (quintet, J = 5.8 Hz, 1 H), 2.72 (qq, J = 6.2 and 1.5 Hz, 1 H), 2.50 (m, 1 H), 2.39 (m, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 161.3, 135.2, 132.9, 128.7, 128.6, 128.1, 123.3 (q, J = 275.6 Hz), 117.9, 68.9, 41.0, 39.0 (q, J = 40.7 Hz), 31.7 ppm. ^{19}F NMR (470.6 MHz, $CDCl_3$): δ = −67.1 (dd, J = 100.1 and 6.6 Hz) ppm. MS (DIS EI, 70 eV): m/z (%) = 323 (1) $[M + 2]^+$, 321 (3) $[(M)^+]$.

Benzyl (1*S*,2*S*)-(2-Chloro-1-ethylpropyl)carbamate (3j): Formula mass 255.74. Yield 75%. R_f = 0.35 (hexane/EtOAc, 90:10). $[\alpha]_D^{23} = -26.3$ (c = 1.02, $CHCl_3$). FTIR (film): $\tilde{\nu}$ = 3326, 1704, 1513, 1233 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (m, 5 H), 5.11 (m, 2 H), 4.89 (br. d, J = 6.9 Hz, 1 H), 4.17 (q, J = 6.9 Hz, 1 H), 3.74 (q, J = 6.9 Hz, 1 H), 1.59 (quintet, J = 6.9 Hz, 2 H), 1.49 (d, J = 6.9 Hz, 3 H), 0.94 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 156.5, 136.5, 128.5, 128.1, 128.0, 66.9, 61.0, 57.3, 29.4, 22.4, 10.4 ppm. MS (DIS EI, 70 eV): m/z (%) =256 (5) $[M + 1]^+$, 148 (12), 91 (100).

Benzyl (1*R*,2*R*)-*N*-(2-Chloro-1-isobutylpent-4-enyl)-*N*-[(4-methylphenyl)thio]carbamate (2k): Formula mass 432.02. Yield > 98%. R_f = 0.60 (hexane/Et_2O, 80:20). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35 (m, 7 H), 7.05 (d, J = 7.7 Hz, 2 H), 5.88 (m, 1 H), 5.30 (d, J = 12.9 Hz, 1 H), 5.27 (d, J = 12.9 Hz, 1 H), 5.10 (m, 2 H), 4.59 (br. m, 1 H), 4.15 (br. m, 1 H), 2.64 (br. m, 1 H), 2.40 (m, 1 H), 2.31 (s, 3 H), 1.68 (br. t, J = 11.9 Hz, 1 H), 1.20 (m, 2 H), 0.90 (m, 1 H), 0.79 (d, J = 5.6 Hz, 3 H), 0.53 (br. d, J = 4.7 Hz, 3 H) ppm. MS (EI, 70 eV): m/z (%) = 431 (30) $[M^+]$, 123 (15), 91 (100).

Benzyl (1*R*,2*R*)-(2-Chloro-1-isobutylpent-4-enyl)carbamate (3k): Formula mass 309.83. Yield 68%. R_f = 0.30 (hexane/EtOAc, 95:5). $[\alpha]_D^{23} = +40.3$ (c = 0.52, $CHCl_3$). FTIR (film): $\tilde{\nu}$ = 3328, 1705, 1511, 1248, 1219 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (m, 5 H), 5.85 (m, 1 H), 5.13 (m, 2 H), 5.10 (m, 2 H), 4.90 (d, J = 6.4 Hz, 1 H), 4.06 (q, J = 6.4 Hz, 1 H), 3.93 (t, J = 6.4 Hz, 1 H), 2.54 (m, 1 H), 2.56 (m, 1 H) 1.63 (m, 1 H), 1.54 (m, 1 H), 1.34 (m, 1 H), 0.93 (d, J = 6.7 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 156.2, 136.5, 133.9, 128.5, 128.2, 128.0, 118.4, 66.9, 66.4, 52.1, 43.1, 40.1, 24.7, 22.9, 22.3 ppm. MS (EI, 70 eV): m/z (%) = 310 (1) $[M + 1]^+$, 309 (0.6) $[M^{+\cdot}]$, 274 (0.5) $[M - Cl]^+$, 220 (10), 176 (10), 91 (100).

Synthesis of Aziridines 8. General procedure: A dispersion (60% by weight) of NaH (1.5 equiv.) was added portionwise to a cooled solution of the β-chloroamine **3** (1 equiv.) in dry DMF at 0 °C. After complete consumption of the starting material (1−2 hours, except for **3j** and **3k** whose incomplete reactions were quenched after 48 and 2 hours respectively) the reaction was quenched with a saturated solution of NH_4Cl and extracted with EtOAc. The collected organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent removed in vacuo. Purification of the crude reaction mixture by FC afforded pure aziridine **8**.

Benzyl (*S*)-2-(3-Fluorophenyl)aziridine-1-carboxylate (8c): Formula mass 271.29. Yield 60%. R_f = 0.62 (hexane/EtOAc, 80:20). $[\alpha]_D^{23} = +76.9$ (c = 0.4, $CHCl_3$). FTIR (film): $\tilde{\nu}$ = 1725, 1299, 1196 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 6.99 (m, 4 H), 5.18 (d, J = 11.9 Hz, 1 H), 5.14 (d, J = 11.9 Hz, 1 H), 3.48 (dd, J = 6.4 and 4.7 Hz, 1 H), 2.71 (d, J = 6.4 Hz, 1 H), 2.26 (d, J = 4.7 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.5 (d, J = 153.1 Hz), 162.1, 139.7 (d, J = 7.6 Hz), 135.6, 131.3, 130.1 (d, J = 8.4 Hz), 130.0, 128.6, 128.4, 128.3, 122.0, 114.9 (d, J = 21.1 Hz), 113.1 (d, J = 22.6 Hz), 68.5, 38.9, 35.3 ppm. ^{19}F NMR (470.6 MHz, $CDCl_3$): δ = −113.3 (dt, J = 8.9 and 5.8 Hz) ppm. MS (EI, 70 eV): m/z (%) = 271 (5) $[M]^+$.

(2*S*,3*R*)-2-Phenyl-3-trifluoromethyl-aziridine-1-carboxylic acid benzyl ester (8f). Formula mass 321.29. Yield 79%. R_f = 0.54 (hexane/EtOAc, 80:20). $[\alpha]_D^{23} = +22.6$ (c = 0.8, $CHCl_3$). FTIR (film): $\tilde{\nu}$ = 1734, 1282, 1155 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.20 (m, 10 H), 5.05 (d, J = 11.9 Hz, 1 H), 4.94 (d, J = 11.9 Hz, 1 H), 3.80 (d, J = 2.7 Hz, 1 H), 3.50 (m, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 158.8, 134.9, 131.5, 129.3, 128.9, 128.5, 128.42, 128.40, 127.2, 122.7 (q, J = 275.0 Hz), 68.9, 42.2 (q, J = 2.8 Hz), 41.3 (q, J = 40.0 Hz) ppm. ^{19}F NMR (470.6 MHz, $CDCl_3$): δ = −71.4 (d, J = 5.0 Hz) ppm. MS (EI, 70 eV): m/z (%) = 322 (2) $[M + 1]^+$.

Benzyl (2*R*,3*R*)-2-Allyl-3-trifluoromethylaziridine-1-carboxylate (8h): Formula mass 285.26. Yield 70%. R_f = 0.38 (hexane/EtOAc, 80:20). $[\alpha]_D^{23} = +4.6$ (c = 0.4, $CHCl_3$). FTIR (film): $\tilde{\nu}$ = 1741, 1271, 1500, 1159 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36 (m, 5 H), 5.86 (m, 1 H), 5.24 (dq, J = 17.0 and 1.5 Hz, 1 H), 5.16 (s, 2 H), 5.15 (dq, J = 10.0 and 1.5 Hz, 1 H), 3.04 (quintet, J = 5.8 Hz, 1 H), 2.72 (qq, J = 6.2 and 1.5 Hz, 1 H), 2.50 (m, 1 H), 2.39

(m, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 161.3, 135.2, 132.9, 128.7, 128.6, 128.1, 123.3 (q, *J* = 275.6 Hz), 117.9, 68.9, 41.0, 39.0 (q, *J* = 40.7 Hz), 31.7 ppm. ^{19}F NMR (470.6 MHz, $CDCl_3$): δ = −66.5 (d, *J* = 6.6 Hz) ppm. MS (EI, 70 eV): *m*/*z* (%) = 285 (17) [M^+].

Benzyl (2*S*,3*R*)-2-Ethyl-3-methylaziridine-1-carboxylate (8j): Formula mass 219.28. Yield 16%. R_f = 0.35 (hexane/EtOAc, 90:10). $[\alpha]_D^{23}$ = −14.3 (*c* = 0.35, CH_2Cl_2). FTIR (film): $\tilde{\nu}$ = 1723, 1288, 1223 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 5.11 (m, 2 H), 2.55 (quintet, *J* = 6.1 Hz, 1 H), 2.37 (q, *J* = 6.1 Hz, 1 H), 1.55 (m, 1 H), 1.46 (m, 1 H), 1.23 (d, *J* = 6.1 Hz, 3 H), 1.05 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.9, 136.2, 128.5, 128.2, 128.0, 67.8, 44.0, 37.8, 20.8, 12.8, 11.4 ppm. MS (CI, 70 eV): *m*/*z* (%) = 220 (100) [M + 1]$^+$, 176 (8), 91 (40).

Benzyl (2*S*,3*R*)-2-Allyl-3-isobutylaziridine-1-carboxylate (8k): Formula mass 273.37. Yield 43%. R_f = 0.37 (hexane/EtOAc, 95:5). $[\alpha]_D^{23}$ = +11.2 (*c* = 0.4, $CHCl_3$). FTIR (film): $\tilde{\nu}$ = 1723, 1291, 1219 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 5.89 (m, 1 H), 5.19 (d, *J* = 17.2 Hz, 1 H), 5.11 (m, 2 H), 5.08 (d, *J* = 10.4 Hz, 1 H), 2.52 (m, 2 H), 2.32 (m, 1 H), 2.19 (m, 1 H), 1.82 (sept, *J* = 6.7 Hz, 1 H), 1.38 (m, 2 H), 0.99 (d, *J* = 6.7 Hz, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.8, 136.2, 134.6, 128.5, 128.1, 128.0, 116.7, 67.9, 41.4, 41.3, 36.5, 32.2, 29.7, 27.1, 22.7, 22.4 ppm. MS (CI, 70 eV): *m*/*z* (%) = 274 (100) [M + 1]$^+$, 138 (6), 91 (38).

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