

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 alkylamines

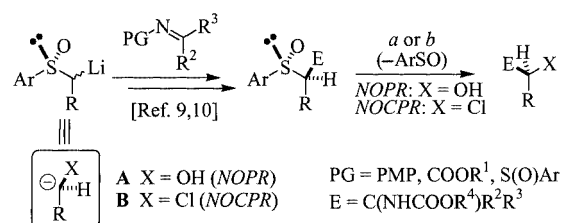
is displaced by a chlorine atom in a one-pot reaction with clean stereoinversion at carbon. Several 1,2-chloroamines produced via NOCPR were transformed into the corresponding aziridines.

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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*-mono-protected 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]



NOPR: “Non-Oxidative” Pummerer Reaction [Ref. 6]

NOCPR: “Non-Oxidative” Chloro-Pummerer Reaction [This work]

Scheme 1. (a) (NOPR): $(\text{CF}_3\text{CO})_2\text{O}$, *sym*-collidine, then $\text{H}_2\text{O}/\text{K}_2\text{CO}_3$, NaBH_4 ; (b) (NOCPR): $(\text{COCl})_2$, *sym*-collidine, then MeOH , NaBH_4

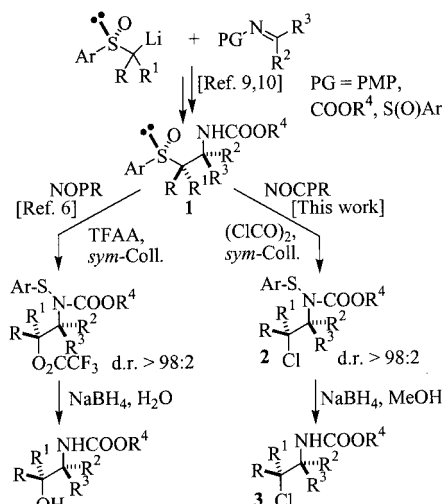
Results and Discussion

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]

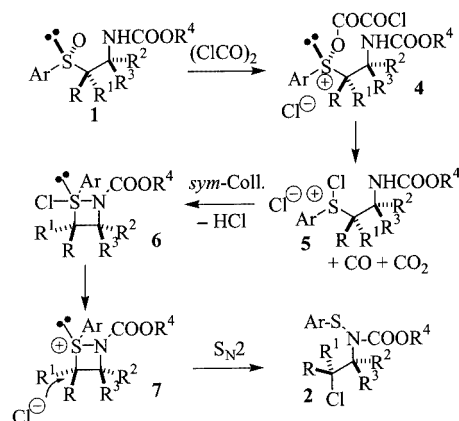
Entry	Prod.	R	R ¹	R ²	R ³	Yield (%)
1	2a	H	H	H	CHF ₂	82
2	3b	H	H	H	CClF ₂	85
3	3c	H	H	H	3-F-C ₆ H ₄	>98
4	3d	H	H	H	PMP ^[b]	>98
5	3e	CH ₃	H	CF ₃	CO ₂ Me	60
6	3f	H	Ph	CF ₃	CF ₃	65
7	3g	Ph	H	CF ₃	CO ₂ Et	72
8	3h	Allyl	H	H	CF ₃	87
9	3j	CH ₃	H	H	C ₂ H ₅	75
10 ^[c]	3k	H	Allyl	<i>i</i> Bu	H	68 ^[d]

^[a] Ar = *p*-Tol except for entry 1, where Ar = 1-Naphthyl; R⁴ = Bn except for entry 5, where R⁴ = Et. ^[b] PMP = 4-MeO-C₆H₄. ^[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., CH₂Cl₂, –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 ¹⁹F 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 NaBH₄ (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 CO₂. 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**.



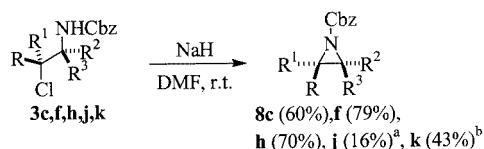
Scheme 3

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 Cl₂ 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 SO₂Cl₂/*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 CF₃ group of **8h** produced 1.5% and 2.0% heteronuclear NOE enhancements of the diastereotopic CH₂ allylic protons in *cis* position (R = allyl), and only 0.5% of the aziridine ring proton (R¹ = H) *trans* to the trifluoromethyl. In the case of **8f**, irradiation of CHCF₃ produced a 3.0% NOE on the *ortho*-phenyl protons in *cis*, but no NOE was observed with the CHPh 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 ¹H 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 F₂₅₄ of 0.25 mm thickness were used. Flash chromatography (FC): silica gel 60 (230–400 ASTM mesh). ¹H, ¹³C and ¹⁹F NMR: Bruker 250 MHz and 500 MHz spectrometers, chemical shifts in ppm (δ), tetramethylsilane (TMS) as internal standard for ¹H and ¹³C nuclei ($\delta_{\text{H/C}} = 0.00$), C₆F₆ external standard ($\delta_{\text{F}} = -162.90$) for ¹⁹F. 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 CaH₂. 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 CH₂Cl₂ 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 NaBH₄ (ca. 5 equiv.) was added portionwise. After consumption of the intermediate sulfenamide **2** (TLC), the reaction was quenched with a saturated aqueous NH₄Cl solution and extracted with CH₂Cl₂. The collected organic layers were dried over anhydrous Na₂SO₄, 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/Et₂O, 80:20). $[\alpha]_{\text{D}}^{25} = +23.4$ (*c* = 0.6, CHCl₃). FTIR (film): $\tilde{\nu}$ = 1718, 1383, 1278 cm⁻¹. ¹H NMR (250 MHz, CDCl₃): 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. ¹³C NMR (62.3 MHz, CDCl₃): 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. ¹⁹F NMR (235.4 MHz, CDCl₃): 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). $[\alpha]_{\text{D}}^{25} = +1.3$ (*c* = 0.8, CHCl₃). M.p. 50–51 °C. FTIR (KBr): $\tilde{\nu}$ = 3310, 1703, 1546, 1279 cm⁻¹. ¹H NMR (250 MHz, CDCl₃): 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. ¹³C NMR (62.3 MHz, CDCl₃): 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. ¹⁹F NMR (235.4 MHz, CDCl₃): 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). $[\alpha]_{\text{D}}^{25} = +13.6$ (*c* = 1.2, CHCl₃). M.p. 49–50 °C. FTIR (KBr): $\tilde{\nu}$ = 3333, 1691, 1535, 1267 cm⁻¹. ¹H NMR (250 MHz, CDCl₃): 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. ¹³C NMR (62.3 MHz, CDCl₃): 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. ¹⁹F NMR (235.4 MHz, CDCl₃): 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).

$[\alpha]_D^{25} = -33.7$ ($c = 0.8$, CHCl_3). M.p. 103–104 °C. FTIR (KBr): $\tilde{\nu} = 3449, 1719, 1509, 1385, 1248 \text{ cm}^{-1}$. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.32$ (m, 5 H), 7.21 (d, $J = 8.5 \text{ Hz}$, 2 H), 6.87 (d, $J = 8.5 \text{ Hz}$, 2 H), 5.39 (br. d, $J = 8.1 \text{ Hz}$, 1 H), 5.12 (d, $J = 12.4 \text{ Hz}$, 1 H), 5.08 (d, $J = 12.4 \text{ Hz}$, 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): $\delta = 159.4, 155.6, 136.2, 128.5, 128.2, 127.7, 125.5, 114.2, 67.1, 55.3, 47.8 \text{ ppm}$. MS (DIS EI, 70 eV): m/z (%) = 322 (9) $[\text{M} + 3]^+$, 320 (9) $[\text{M} + 1]^+$.

Methyl (2*S*,3*S*)-2-Benzoyloxycarbonylamino-3-chloro-2-trifluoromethylbutyrate (3e): Formula mass 291.65. Yield 60%. $R_f = 0.49$ (hexane/Et₂O, 80:20). $[\alpha]_D^{25} = -2.0$ ($c = 0.9$, CHCl_3). FTIR (film): $\tilde{\nu} = 3408, 1741, 1508, 1250, 1199 \text{ cm}^{-1}$. ^1H NMR (250 MHz, CDCl_3): $\delta = 5.75$ (br. s, 1 H), 5.20 (q, $J = 6.9 \text{ Hz}$, 1 H), 4.16 (q, $J = 6.9 \text{ Hz}$, 2 H), 3.92 (s, 3 H), 1.71 (d, $J = 6.9 \text{ Hz}$, 3 H), 1.28 (t, $J = 6.9 \text{ Hz}$, 3 H) ppm. ^{13}C NMR (62.3 MHz, CDCl_3): $\delta = 164.5, 154.1, 123.0$ (q, $J = 289.4 \text{ Hz}$), 69.1 (q, $J = 28.7 \text{ Hz}$), 61.8, 54.2, 54.0, 20.8, 14.3 ppm. ^{19}F NMR (235.4 MHz, CDCl_3): $\delta = -69.2$ (s) ppm. MS (DIS EI, 70 eV): m/z (%) = 292 (2) $[\text{M} + 1]^+$.

Benzyl (1*S*,1'*R*)-[1-(Chlorophenylmethyl)-2,2,2-trifluoroethyl]carbamate (3f): Formula mass 357.75. Yield 65%. $R_f = 0.32$ (hexane/Et₂O, 80:20). $[\alpha]_D^{25} = -81.3$ ($c = 0.8$, CHCl_3). M.p. 112–113 °C. FTIR (KBr): $\tilde{\nu} = 3330, 17802, 1543, 1290, 1254 \text{ cm}^{-1}$. ^1H NMR (250 MHz, CDCl_3): $\delta = 7.35$ (m, 11 H), 5.26 (d, $J = 2.3 \text{ Hz}$, 1 H), 5.14 (s, 2 H), 5.03 (m, 1 H) ppm. ^{13}C NMR (62.3 MHz, CDCl_3): $\delta = 155.6, 135.6, 135.2, 129.4, 128.8, 128.6, 128.5, 128.2, 127.9, 123.6$ (q, $J = 283.0 \text{ Hz}$), 67.9, 58.5 (q, $J = 29.6 \text{ Hz}$), 58.0 ppm. ^{19}F NMR (235.4 MHz, CDCl_3): $\delta = -72.8$ (d, $J = 6.8 \text{ Hz}$) ppm. MS (DIS EI, 70 eV): m/z (%) = 359 (3) $[\text{M} + 2]^+$, 357 (8) $[\text{M}^+]$.

Ethyl (2*R*,3*S*)-2-Benzoyloxycarbonylamino-2-(chlorophenylmethyl)-3,3,3-trifluoropropionate (3g): Formula mass 429.82. Yield 72%. $R_f = 0.33$ (hexane/EtOAc, 80:20). $[\alpha]_D^{25} = -23.7$ ($c = 0.7$, CHCl_3). FTIR (film): $\tilde{\nu} = 3414, 1748, 1496, 1220 \text{ cm}^{-1}$. ^1H NMR (250 MHz, CDCl_3): $\delta = 7.37$ (m, 10 H), 5.80 (br. s, 1 H), 5.76 (s, 1 H), 5.16 (d, $J = 12.4 \text{ Hz}$, 1 H), 5.10 (d, $J = 12.4 \text{ Hz}$, 1 H), 4.02 (m, 2 H), 1.04 (t, $J = 7.0 \text{ Hz}$, 3 H) ppm. ^{13}C NMR (62.3 MHz, CDCl_3): $\delta = 163.3, 154.0, 135.6, 134.6, 129.8, 128.8, 128.6, 128.4, 128.3, 123.2$ (q, $J = 290.4 \text{ Hz}$), 69.4 (q, $J = 27.7 \text{ Hz}$), 67.6, 60.7, 13.4 ppm. ^{19}F NMR (235.4 MHz, CDCl_3): $\delta = -67.7$ (s) ppm. MS (DIS EI, 70 eV): m/z (%) = 432 (1) $[\text{M} + 3]^+$, 430 (3) $[\text{M} + 1]^+$.

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). $[\alpha]_D^{25} = +4.6$ ($c = 0.4$, CHCl_3). FTIR (film): $\tilde{\nu} = 1741, 1271, 1500, 1159 \text{ cm}^{-1}$. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.36$ (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, $J = 5.8 \text{ Hz}$, 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): $\delta = 161.3, 135.2, 132.9, 128.7, 128.6, 128.1, 123.3$ (q, $J = 275.6 \text{ Hz}$), 117.9, 68.9, 41.0, 39.0 (q, $J = 40.7 \text{ Hz}$), 31.7 ppm. ^{19}F NMR (470.6 MHz, CDCl_3): $\delta = -67.1$ (dd, $J = 100.1$ and 6.6 Hz) ppm. MS (DIS EI, 70 eV): m/z (%) = 323 (1) $[\text{M} + 2]^+$, 321 (3) $[\text{M}^+]$.

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). $[\alpha]_D^{25} = -26.3$ ($c = 1.02$, CHCl_3). FTIR (film): $\tilde{\nu} = 3326, 1704, 1513, 1233 \text{ cm}^{-1}$. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.33$ (m, 5 H), 5.11 (m, 2 H), 4.89 (br. d, $J = 6.9 \text{ Hz}$, 1 H), 4.17 (q, $J = 6.9 \text{ Hz}$, 1 H), 3.74 (q, $J = 6.9 \text{ Hz}$, 1 H), 1.59 (quintet, $J = 6.9 \text{ Hz}$, 2 H), 1.49 (d, $J = 6.9 \text{ Hz}$, 3 H), 0.94 (t, $J = 6.9 \text{ Hz}$, 3 H) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): $\delta = 156.5, 136.5, 128.5, 128.1, 128.0, 66.9, 61.0, 57.3, 29.4, 22.4, 10.4 \text{ ppm}$. MS (DIS EI, 70 eV): m/z (%) = 256 (5) $[\text{M} + 1]^+$, 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/Et₂O, 80:20). ^1H NMR (500 MHz, CDCl_3): $\delta = 7.35$ (m, 7 H), 7.05 (d, $J = 7.7 \text{ Hz}$, 2 H), 5.88 (m, 1 H), 5.30 (d, $J = 12.9 \text{ Hz}$, 1 H), 5.27 (d, $J = 12.9 \text{ Hz}$, 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, $J = 11.9 \text{ Hz}$, 1 H), 1.20 (m, 2 H), 0.90 (m, 1 H), 0.79 (d, $J = 5.6 \text{ Hz}$, 3 H), 0.53 (br. d, $J = 4.7 \text{ Hz}$, 3 H) ppm. MS (EI, 70 eV): m/z (%) = 431 (30) $[\text{M}^+]$, 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). $[\alpha]_D^{25} = +40.3$ ($c = 0.52$, CHCl_3). FTIR (film): $\tilde{\nu} = 3328, 1705, 1511, 1248, 1219 \text{ cm}^{-1}$. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.33$ (m, 5 H), 5.85 (m, 1 H), 5.13 (m, 2 H), 5.10 (m, 2 H), 4.90 (d, $J = 6.4 \text{ Hz}$, 1 H), 4.06 (q, $J = 6.4 \text{ Hz}$, 1 H), 3.93 (t, $J = 6.4 \text{ Hz}$, 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, $J = 6.7 \text{ Hz}$, 3 H), 0.91 (d, $J = 6.7 \text{ Hz}$, 3 H) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): $\delta = 156.2, 136.5, 133.9, 128.5, 128.2, 128.0, 118.4, 66.9, 66.4, 52.1, 43.1, 40.1, 24.7, 22.9, 22.3 \text{ ppm}$. MS (EI, 70 eV): m/z (%) = 310 (1) $[\text{M} + 1]^+$, 309 (0.6) $[\text{M}^+]$, 274 (0.5) $[\text{M} - \text{Cl}]^+$, 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). $[\alpha]_D^{25} = +76.9$ ($c = 0.4$, CHCl_3). FTIR (film): $\tilde{\nu} = 1725, 1299, 1196 \text{ cm}^{-1}$. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.32$ (m, 5 H), 6.99 (m, 4 H), 5.18 (d, $J = 11.9 \text{ Hz}$, 1 H), 5.14 (d, $J = 11.9 \text{ Hz}$, 1 H), 3.48 (dd, $J = 6.4$ and 4.7 Hz , 1 H), 2.71 (d, $J = 6.4 \text{ Hz}$, 1 H), 2.26 (d, $J = 4.7 \text{ Hz}$, 1 H) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): $\delta = 163.5$ (d, $J = 153.1 \text{ Hz}$), 162.1, 139.7 (d, $J = 7.6 \text{ Hz}$), 135.6, 131.3, 130.1 (d, $J = 8.4 \text{ Hz}$), 130.0, 128.6, 128.4, 128.3, 122.0, 114.9 (d, $J = 21.1 \text{ Hz}$), 113.1 (d, $J = 22.6 \text{ Hz}$), 68.5, 38.9, 35.3 ppm. ^{19}F NMR (470.6 MHz, CDCl_3): $\delta = -113.3$ (dt, $J = 8.9$ and 5.8 Hz) ppm. MS (EI, 70 eV): m/z (%) = 271 (5) $[\text{M}]^+$.

(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). $[\alpha]_D^{25} = +22.6$ ($c = 0.8$, CHCl_3). FTIR (film): $\tilde{\nu} = 1734, 1282, 1155 \text{ cm}^{-1}$. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.20$ (m, 10 H), 5.05 (d, $J = 11.9 \text{ Hz}$, 1 H), 4.94 (d, $J = 11.9 \text{ Hz}$, 1 H), 3.80 (d, $J = 2.7 \text{ Hz}$, 1 H), 3.50 (m, 1 H) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): $\delta = 158.8, 134.9, 131.5, 129.3, 128.9, 128.5, 128.42, 128.40, 127.2, 122.7$ (q, $J = 275.0 \text{ Hz}$), 68.9, 42.2 (q, $J = 2.8 \text{ Hz}$), 41.3 (q, $J = 40.0 \text{ Hz}$) ppm. ^{19}F NMR (470.6 MHz, CDCl_3): $\delta = -71.4$ (d, $J = 5.0 \text{ Hz}$) ppm. MS (EI, 70 eV): m/z (%) = 322 (2) $[\text{M} + 1]^+$.

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). $[\alpha]_D^{25} = +4.6$ ($c = 0.4$, CHCl_3). FTIR (film): $\tilde{\nu} = 1741, 1271, 1500, 1159 \text{ cm}^{-1}$. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.36$ (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, $J = 5.8 \text{ Hz}$, 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 (2S,3R)-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} . ^1H 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) [$\text{M} + 1$] $^+$, 176 (8), 91 (40).

Benzyl (2S,3R)-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} . ^1H 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) [$\text{M} + 1$] $^+$, 138 (6), 91 (38).

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