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Synthesis of fluorinated allylic amines: Reaction of 2-(trimethylsilyl)ethyl sulfones and sulfoxides with fluorinated imines

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Dedicated to Prof. Kenji Uneyama on the occasion of his winning of the ACS Award.

Abstract

A new synthesis of fluorinated allylamines through the reaction of 2-(trimethylsilyl)ethyl sulfones and sulfoxides (as vinyl anion equivalents) with imines and imino esters has been described. The process includes a TBAF-mediated fragmentation of 2-(trimethylsilyl)ethyl sulfones to afford the desired allylic amines. When the reaction is performed with the corresponding sulfoxides, the fragmentation takes place under the addition conditions, affording the final products in a single step.

Keywords: Fluorinated allylamines; Fluorinated imines; Fluorinated imino esters; 2-(Trimethylsilyl)ethyl sulfones and sulfoxides

1. Introduction

Allylamines are remarkable structural units found in several naturally occurring compounds [1]. This, coupled with the fact that they are also important synthetic intermediates for the preparation of biologically active products, has led to their popularity as starting materials for the synthesis of a range of useful products such as amino acids, alkaloids, and carbohydrate derivatives [2].

Although much has been written on allylamines and their applications, their fluorinated analogs have received far less attention. The methods described to date for the preparation of fluorinated allylamines, for example, take advantage of the two strategies commonly used for generating fluorinated compounds in general, namely the direct introduction of the CF_3 moiety [3] or the use of fluorinated building blocks that can subsequently be transformed into the desired allylic amine skeleton. In this context, fluorinated imines [4], fluorinated β-enamino phosphonates [5], fluorinated allylic mesylates [6], and fluorinated β-aminosulfones [7] have been used to prepare these types of derivatives.

Previous work by our group has demonstrated that anions of methyl sulfones or methyl sulfoxides **2** react with imidoyl chlorides **1** (as fluorinated building blocks) to generate the corresponding β-enamino sulfones or sulfoxides **3**. These, in turn, can be reduced and transformed into the desired allylic amines **4** through a methylenation-desulfonylation reaction sequence of the corresponding β-aminosulfones in a Julia-type process (Scheme 1) [7].

Furthermore, 2-(trimethylsilyl)ethyl sulfones and sulfoxides **6** have been found to be useful synthetic equivalents of vinyl anions [8] for the preparation of different olefins and dienes (Kocienski olefin synthesis). This is due to the fact that the trimethylsilyl group can be easily removed upon treatment with fluoride ions (Fig. 1).

Taking all this into account, we proposed that the use of fluorinated imines instead of imidoyl chlorides would provide the most direct strategy for obtaining the desired allylic amines. Additionally, the use of 2-(trimethylsilyl)ethyl sulfoxides or sulfones in a reaction with fluorinated imines **5** (in a new

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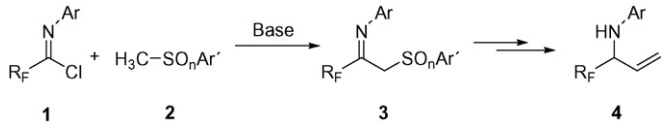


Scheme 1.

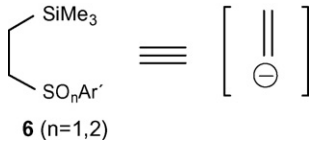
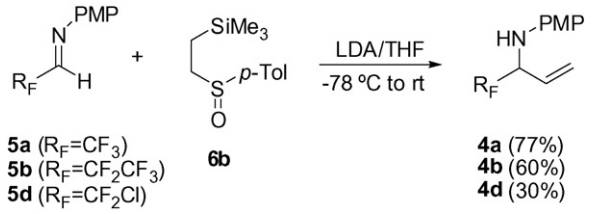


Fig. 1. 2-(TMS)ethyl sulfones and sulfoxides as vinyl anions equivalents.

application of the Kocienski methodology) would be particularly interesting as the trimethylsilyl group suffers fragmentation under mild conditions. As an extension of our previous work, we thus developed a new method for the creation of allylic amines **4** by reacting 2-(trimethylsilyl)ethyl sulfones **6** with fluorinated imines **5** [either with aldimines (R^1=H) or imino esters (R^1=COOR)], followed by a TBAF-mediated fragmentation of the 2-(trimethylsilyl)ethyl derivatives (Scheme 2). It is worth noting that when the reaction was performed with the sulfoxide analogs, the formation of the allylamine was achieved in a single step, with the elimination process taking place spontaneously *in situ*. Our retrosynthetic analysis for the synthesis of the fluorinated allylic amines **4** is presented in Scheme 2.

2. Results and discussion

The first step involved the reaction of the lithium anion of 2-(trimethylsilyl)ethyl-*p*-tolyl sulfone **6a**, which was obtained upon treatment with 2 equiv. of LDA, with fluorinated aldimines **5a–c**. The reaction was performed at −40 °C and, after the aqueous workup, afforded β-aminosulfones **7a–c** as a mixture of diastereoisomers in which the *anti* product was predominant (dr *anti*/*syn* > 10/1). The fragmentation of the trimethylsilyl group was carried out with TBAF at 0 °C in THF

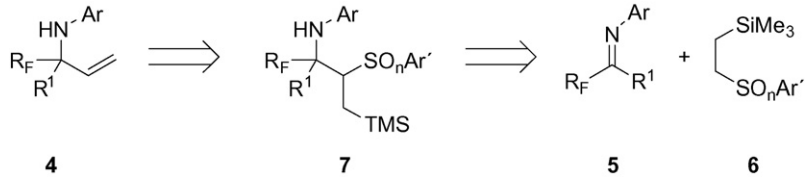


Scheme 4.

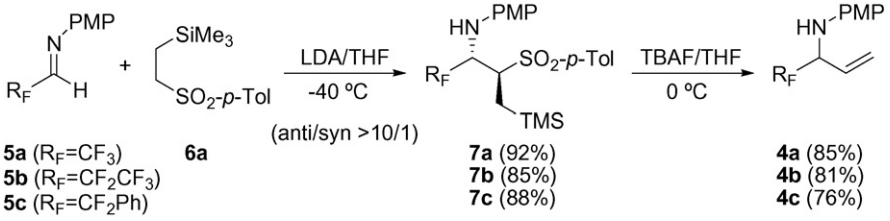
to produce the desired allylic amines **4a–c** in good yields (Method A) after chromatographic purification (Scheme 3).

We then extended this methodology to the corresponding sulfoxides (Scheme 4). When we performed the addition of the fluorinated imine **5a** with the lithium anion of 2-(trimethylsilyl)ethyl-*p*-tolyl sulfoxide **6b**, the crude reaction mixture proved to be a complex one in which it was possible to identify the final allylamine **4a**. After several isolation attempts, we discovered that when the reaction mixture was allowed to reach room temperature and then subjected to acidic treatment, the allylamine could be isolated in 77% yield (Method B). Under these conditions, aldimines **5b** and **5d** thus afforded the corresponding allylic amines in good to moderate yields.

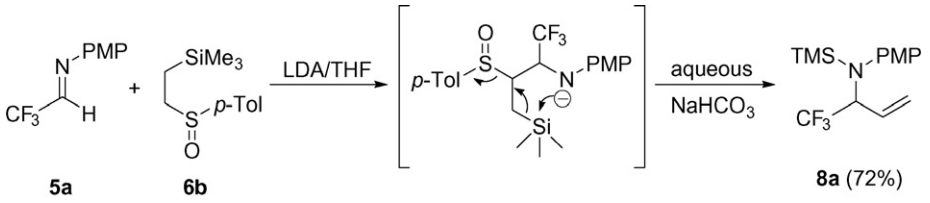
It is worth noting that under these conditions it was possible to perform the two-step, organometallic addition-trimethylsilyl group fragmentation sequence in a single operation, giving rise to the final allylamines **4** directly. Furthermore, when the workup was carried out with sodium bicarbonate instead of acidic medium, the final allylamine was obtained as the *N*-trimethylsilyl derivative **8a**. This finding prompted us to propose the explanation for this tandem process as set out in Scheme 5. Thus, once the addition to the imine takes place, the lithium amide intermediate can attack the silicon, thereby starting the fragmentation process. This would explain why the trimethylsilyl group is attached to the nitrogen after the purification process. Nevertheless, when these conditions were applied to the sulfone in its reaction with imine **5a**, it produced a mixture of the addition product **7a** and the final allylic amine **4a** in a 3:1 ratio and in 48% overall yield. Without further investigation, it is difficult to explain why the fragmentation



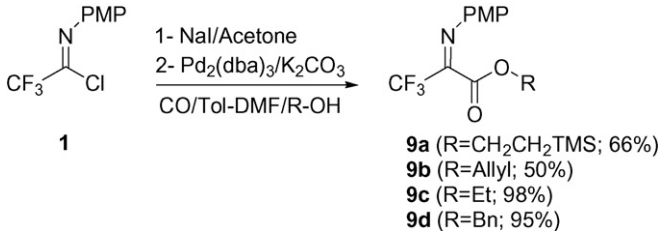
Scheme 2.



Scheme 3.



Scheme 5.



Scheme 6.

process takes place easily with sulfoxides, but with more difficulty when a sulfone is involved.

As an extension of this protocol, we surmised that the application of this tandem process to fluorinated imino esters would convert them into quaternary fluorinated α-amino acids. These types of derivatives are of interest because when they are introduced into peptidic chains, they impose conformational restrictions on the parent peptide. This introduction has thus become a commonly used strategy to improve the biological properties of bioactive peptides. In our work, starting imino esters **9** were synthesized in accordance with Uneyama's methodology [9] by carrying out a palladium catalyzed alcoxycarbonylation reaction with the corresponding imidoyl iodide (which had previously been prepared through reaction of imidoyl chloride **1** with sodium iodide), in the presence of carbon monoxide and the corresponding alcohol (Scheme 6).

The imino esters **9** thus obtained were then were subjected to the tandem protocol through reaction with the lithium sulfinyl anion of **6b**. In light of our previous experience, we subsequently allowed the reaction to reach room temperature; this gave rise to a complex reaction mixture, probably due to the addition of both the iminic and ester functionalities. In order to perform the chemoselective addition to the iminic function of **9**, the reaction conditions were optimized. When the reaction temperature was kept between −50 and −30 °C, the reaction took place in a chemoselective fashion to afford the corresponding amino acids **10a–d** with the trimethylsilyl group attached to the nitrogen; the best results were obtained when lithium bis(trimethylsilyl)amide was used as a base. Unfortunately, because these amines decomposed under purification conditions, only moderate yields of the silylated amino acids **10** were obtained as purified products (Scheme 7). The final fluorinated quaternary α-amino acids **4e–h** were obtained in quantitative yield by removing the TMS group with amberlyst.

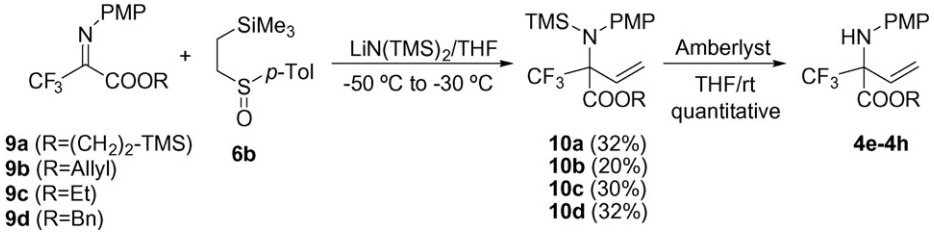
3. Conclusions

In summary, we have developed a new and simple methodology to access fluorinated allylic amines and fluorinated quaternary α-amino acids through addition of 2-(trimethylsilyl)ethyl sulfones and sulfoxides to fluorinated imines and imino esters. The process was more efficient when 2-(trimethylsilyl)ethyl sulfoxides were used as starting materials since a tandem protocol involving an organometallic addition-elimination sequence occurred spontaneously under the normal reaction conditions to afford the final allylamine derivatives **4** and **10** in a single step. An asymmetric version of this protocol is currently underway in our laboratories.

4. Experimental

4.1. General experimental procedures

All reactions were performed with magnetic stirring in flame-dried glassware under an argon atmosphere with dry, distilled solvents. Tetrahydrofuran (THF) was distilled over Na–K alloy. All other commercially obtained solvents or reagents were used as received. All reactions were monitored with thin layer chromatography (TLC) in which precoated 250 micron softlayer silica gel GF uniplates (Merck) were used. TLC plates were visualized with UV light (254 nm), vanillin, or cerium molybdate stains. Flash chromatography was performed with the indicated solvent system on normal phase silica gel (230–400 mesh, particle size 0.040–0.063 mm). In several cases, all of which are clearly identified in the text, the silica gel



Scheme 7.

for column chromatography was deactivated prior to the actual separation through overnight treatment with a 2% solution of triethylamine in hexane, followed by equilibration with the solvent mixture finally employed. Yields refer to chromatographically and spectroscopically pure compounds. All new compounds were determined to be at least 95% pure by means of NMR. All melting points were determined with an open capillary. Chemical shifts were reported in δ values relative to either tetramethylsilane for ^{1}H NMR, fluorotrichloromethane for ^{19}F NMR, or the solvent peak for ^{13}C NMR. The units for coupling constants are Hertz (Hz).

The preparation of **5a**, **b**, **d** [10], **5c** [11], and **9c**, **d** [9] has been described previously.

4.1.1. General procedure for the condensation of 2-(trimethylsilyl)ethyl-p-tolylsulfone *6a* with fluorinated aldimines (*5a–c*): synthesis of β-aminosulfones (*7a–c*)

A solution of 2-(trimethylsilyl)ethyl-*p*-tolylsulfone (**6a**) (1 mmol) in 2 mL of dry THF was added dropwise to a stirred solution of LDA (2.1 mmol) in dry THF (8 mL) under nitrogen at 0 °C. After 15 min at the same temperature, the yellow solution was cooled to −40 °C. A solution of *N*-PMP (fluoroalkyl)imine **5** (2 mmol) in 2 mL of dry THF was then added. After 1 h of stirring at −40 °C, the reaction was quenched with aqueous NH_4Cl and extracted with ethyl acetate; the combined organic phases were washed with brine and dried over anhydrous sodium sulfate. The residue obtained after solvent evaporation was purified by means of column chromatography with hexanes:ethyl acetate as eluent to afford the desired *N*-PMP α-fluoroalkyl-β-sulfonylamines **7**.

4.1.2. N-(4-Methoxyphenyl)-1-trifluoromethyl-3-trimethylsilyl-2-p-tolylsulfonyl-1-propanamine (*7a*)

By means of the general procedure described above, **7a** was obtained from **6a** (128 mg) as a yellow oil (211 mg) in 92% yield after flash chromatography with hexanes:ethyl acetate (5:1) as eluent. *Major isomer*: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.12 (s, 9H), 1.05 (dd, J = 15.6 and 4.2 Hz, 1H), 1.19 (dd, J = 15.6 and 7.8 Hz, 1H), 2.40 (s, 3H), 3.56–3.60 (m, 1H), 3.63 (d, J = 9 Hz, 1H), 4.34–4.44 (m, 1H), 6.58 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): −1.0, 9.7, 21.6, 56.6, (q, $^2J_{CF}$ = 29 Hz), 60.8, 114.7, 115.6, 128.5 (q, $^1J_{CF}$ = 204 Hz), 129.35, 129.7, 133.3, 139.4, 145.2, 153.4. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −59.2 (s, 3F). HRMS Calc. for $C_{21}H_{28}F_3NO_3SSi$: 459.1511. Found: 459.1509.

4.1.3. N-(4-Methoxyphenyl)-1-(1,1,2,2,2-pentafluoroethyl)-3-trimethylsilyl-2-p-tolylsulfonyl-1-propanamine (*7b*)

By means of the general procedure described above, **7b** was obtained from **6a** (110 mg) as a yellow oil (185 mg) in 85% yield after flash chromatography with hexanes:ethyl acetate (5:1) as eluent. *Major isomer*: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.03 (s, 9H), 1.31-1.07 (m, 2H), 2.37 (s, 3H), 3.58–3.61 (m, 1H), 3. 73 (s, 3H), 4.61–4.73 (m, 1H), 6.57 (d, J = 9.0 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): −0.0, 11.8, 21.5, 53.4–54.5, 55.5, 61.05, 115.1, 114.4 (tq, $^1J_{CF}$ = 259 Hz, $^2J_{CF}$ = 36 Hz), 118.8 (qt, $^1J_{CF}$ = 285 Hz, $^2J_{CF}$ = 35 Hz), 128.5, 129.6, 135.5, 138.9, 145.1, 153.4. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −123.27 (d, J = 270 Hz, 1F), −117.8 (d, J = 270 Hz, 1F), −123.27 (s, 3F), HRMS Calc. for $C_{22}H_{28}F_5NO_3SSi$: 509.1479. Found: 509.1471.

4.1.4. N-(4-Methoxyphenyl)-1-difluoro(phenyl)methyl-3-trimethylsilyl-2-p-tolylsulfonyl-1-propanamine (*7c*)

By means of the general procedure described above, **7c** was obtained from **6a** (100 mg) as a yellow oil (177 mg) in 88% yield after flash chromatography with hexanes:ethyl acetate (5:1) as eluent. *Major isomer*: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.05 (s, 9H), 0.8 (dd, J = 15.3 and 3.9 Hz), 0.97 (dd, J = 15.3 and 9.0 Hz), 2.34 (s, 3H), 3.51 (ddd, J = 9.0, 3.9 and 1 Hz, 1H), 3.64 (s, 3H), 4.41–4.52 (m, 1H), 6.34 (d, J = 9.0 Hz, 2H), 6.61 (d, J = 9.0 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.30–7.40 (m, 5H), 7.45 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): −0.3, 10.0, 21.2, 59.1 (q, $^2J_{CF}$ = 28 Hz), 55.6, 61.4, 114.3, 115.7, 121.9 (t, $^1J_{CF}$ = 250 Hz), 125.7, 129.4, 129.7, 128.3, 129.5, 133.8, 134.1 (q, $^2J_{CF}$ = 26 Hz), 140.8, 144.6, 152.7. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −103.3 (dd, J_{FF} = 245 Hz, J_{FH} = 14 Hz, 1F), −101.7 (d, J_{FF} = 245 Hz, 1F). HRMS Calc. for $C_{27}H_{33}F_2NO_3SSi$: 517.1918. Found: 517.1916.

4.2. General procedures for the synthesis of allylamines *4a–d*

4.2.1. Method A: treatment of β-aminosulfones *7a–c* with TBAF

At room temperature, 1.5 equiv. of *n*-tetrabutylammonium fluoride (TBAF) was added to a solution of 0.3 mmol of β-aminosulfone in anhydrous THF (3 mL) under nitrogen. The resulting mixture was stirred for 40 min until the starting material had been totally consumed, as indicated by TLC monitoring. The mixture was then concentrated and the residue was subjected to flash chromatography using hexanes:isopropyl ether (4:1) as eluent.

4.2.2. Method B: condensation of the 2-(trimethylsilyl)ethyl-p-tolylsulfoxide *6b* with fluorinated aldimines *5a*, *5b* and *5d*

A solution of 2-(trimethylsilyl)ethyl-*p*-tolylsulfoxide (**6b**) (1 mmol) in 1 mL of dry THF was added dropwise to a stirred solution of LDA (2.5 mmol) in dry THF (6 mL) under nitrogen at 0 °C. After 15 min at the same temperature, the yellow solution was cooled to −78 °C. A solution of *N*-PMP (fluoroalkyl)imine **5** (1.5 mmol) in 1 mL of dry THF was then added. After three hours, the reaction was warmed to room temperature, quenched with HCl (3 M), and extracted with ethyl acetate. The combined organic extracts were washed with Na_2CO_3 and brine and then dried over Na_2SO_4. Solvent evaporation afforded a yellow oil which was subjected to flash

chromatography to afford the desired α-fluoroalkyl allylic amines **4**.

*4.2.3. 4-Methoxyphenyl[1-trifluoromethylallyl]amine (**4a**)*

Following the general procedures described above, **4a** was obtained as an oil in 85% yield from **7a** (Method A) and in 77% yield from **5a** (Method B).

*4.2.4. 4-Methoxyphenyl[1-(1,1,2,2,2-pentafluoroethyl) allyl]amine (**4b**)*

Following the general procedures described above, **4b** was obtained as an oil in 81% yield from **7b** (Method A) and in 60% yield from **5b** (Method B).

*4.2.5. 4-Methoxyphenyl[1-difluoro(phenyl)methylallyl]amine (**4c**)*

Following the general procedure described above, **4c** was obtained as an oil in 76% yield from **7c** (Method A).

*4.2.6. 4-Methoxyphenyl[1-chlorodifluoromethylallyl]amine (**4d**)*

Following the general procedure described above, **4d** was obtained as an oil in 30% yield from **5d** (Method B).

*4.2.7. (4-Methoxyphenyl)(trimethylsilyl)[1-trifluoromethylallyl]amine (**8a**)*

N-Trimethylsilylamine **8a** was isolated with a slightly modified procedure of Method B. Instead of receiving acidic treatment, the reaction was quenched with sodium bicarbonate. Starting from **5a** (141 mg), *N*-trimethylsilylamine **8a** was obtained as a pale yellow oil (150 mg) in 72% yield.^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.08 (s, 9H), 3.79 (s, 3H), 4.08 (quint, J = 8.4 Hz, 1H), 5.33 (d, J = 9.6 Hz, 1H), 5.37 (d, J = 16.8 Hz, 1H), 5.75 (dd, J = 16.8 and 9.6 Hz, 1H), 6.79 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 0.22, 55.2, 62.8 (q, $^{2}J_{CF}$ = 28 Hz), 113.4, 120.54, 125.8 (q, $^{1}J_{CF}$ = 285 Hz), 131.8, 133.6, 135.76, 157.5. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −71.9 (d, $^{3}J_{HF}$ = 8 Hz, 3F). HRMS Calc. for $C_{14}H_{20}F_3NO_3Si$: 303.1266. Found: 303.1266.

*4.2.8. 2-(Trimethylsilyl)ethyl 3,3,3-trifluoro-2-(4-methoxyphenylimino)propanoate (**9a**)*

Iminoester **9a** was prepared from *N*-PMP trifluoroimidoyl chloride **1** as a yellow oil in 66% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.00 (s, 9H), 0.87–0.93 (m, 2H), 3.81 (s, 3H), 4.25–4.30 (m, 2H), 6.89 (d, J = 9.0 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): −1.7, 17.1, 55.4, 65.4, 114.3, 118.4 (q, $^{1}J_{CF}$ = 276 Hz), 122.4, 139.0, 146.8 (q, $^{2}J_{CF}$ = 36 Hz), 159.4, 160.5. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −70.1 (s, 3F). HRMS Calc. for $C_{15}H_{21}F_3NO_3Si$ (M + 1): 348.1243. Found: 348.1190.

*4.2.9. Allyl 3,3,3-trifluoro-2-(4-methoxyphenylimino)propanoate (**9b**)*

Iminoester **9b** was prepared from *N*-PMP trifluoroimidoyl chloride **1** as a yellow oil in 50% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.82 (s, 3H), 4.67 (d, J = 6.0 Hz, 2H), 5.24 (d, J = 10.2 Hz, 1H), 5.25 (d, J = 17.3 Hz, 1H), 5.75 (tdd, J = 17.3, 10.2 and 6.0 Hz, 1H), 6.89 (d, J = 9.0 Hz, 2H), 7.01 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 55.4, 66.9, 114.3, 118.4 (q, $^{1}J_{CF}$ = 276 Hz), 120.2, 122.2, 130.0, 138.9, 146.2 (q, $^{2}J_{CF}$ = 37 Hz), 159.5, 160.0. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −69.9 (s, 3F). HRMS Calc. for $C_{13}H_{12}F_3NO_3$: 287.0769. Found: 287.0755.

*4.2.10. General procedure for the synthesis of the allyl aminoesters **10a–d***

LHMDS (5 mmol) in hexanes 1 M was added dropwise to a stirred solution of 2-(trimethylsilyl)ethyl-*p*-tolylsulfoxide (**6b**) (1 mmol) in 6 mL dry THF cooled to −10 °C. After 20 min at the same temperature, the yellow solution was cooled to −50 °C. A solution of *N*-PMP(fluoroalkyl)iminoesters **10** (1 mmol) in 6 mL of dry THF was then added. After three hours, the reaction (which had reached −30 °C) was quenched with aqueous NH_4Cl and worked up in the routine fashion. Flash chromatography of the oily residue with mixtures of hexane:ethyl ether as eluent afforded the desired *N*-PMP *N*-trimethylsilyl fluoroalkyl allylamino esters **10**.

*4.2.11. 2-(Trimethylsilyl)ethyl 2-[(4-methoxyphenyl)(trimethylsilyl)amino]-2-(trifluoromethyl)-3-butenoate (**10a**)*

According to the general procedure described above, 86.6 mg of *N*-PMP (fluoroalkyl)iminoester **9a** (0.25 mmol) afforded 36 mg of *N*-PMP *N*-trimethylsilyl aminoester **10a** as a yellow oil in 32% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.03 (s, 9H), 0.08 (s, 9H), 1.05–1.16 (m, 2H), 3.79 (s, 3H), 4.21–4.38 (m, 2H), 5.18 (d, J = 17.4 Hz, 1H), 5.22 (d, J = 10.8 Hz, 1H), 5.47 (dd, J = 17.4 and 10.8 Hz, 1H), 6.75 (d, J = 9.3 Hz, 2H), 7.07 (d, J = 9.3 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): −1.6, 1.5, 17.3, 55.2, 64.4, 73.9 (q, $^{2}J_{CF}$ = 27.7 Hz), 112.5–113.7 (m), 119.1, 124.8 (q, $^{1}J_{CF}$ = 285 Hz), 132.3, 134.3–132.9 (m), 136.2, 157.6, 169.4 (s). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −71.2 (s, 3F). HRMS Calc. for $C_{20}H_{32}F_3NO_3Si_2$: 447.1873. Found: 447.1860.

*4.2.12. Allyl 2-[(4-methoxyphenyl)(trimethylsilyl)amino]-2-(trifluoromethyl)-3-butenoate (**10b**)*

According to the general procedure described above, 71.5 mg of *N*-PMP (fluoroalkyl)iminoester **9b** (0.25 mmol) afforded 19.3 mg of *N*-PMP *N*-trimethylsilyl aminoester **10b** as a yellow oil in 20% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.03 (9H, s), 3.79 (s, 3H), 4.65–4.80 (m, 2H), 5.17 (d, J = 17.4 Hz, 1H), 5.22 (d, J = 10.8 Hz, 1H), 5.33 (dd, J = 10.5, 1.2 Hz, 1H), 5.44 (dd, J = 17.1, and 1.2 Hz, 1H), 5.47 (dd, J = 17.4 and 10.8 Hz, 1H), 5.99 (tdd, J = 17.1, 10.5 and 5.7 Hz, 1H), 6.76 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 1.4, 55.3, 66.4, 73.1 (q, $^{2}J_{CF}$ = 26.2 Hz), 112.6–113.9 (m), 119.5, 120.0, 124.8 (q, $^{1}J_{CF}$ = 286 Hz), 131.0, 132.1, 132.9–134.0 (m), 136.1, 157.6, 169.0. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm):

−71.4 (s, 3F). HRMS Calc. for $C_{18}H_{24}NO_3F_3Si$: 387.1478. Found: 387.1476.

*4.2.13. Ethyl 2-[(4-methoxyphenyl)(trimethylsilyl)amino]-2-(trifluoromethyl)but-3-enoate (**10c**)*

According to the general procedure described above, 68.5 mg of *N*-PMP (fluoroalkyl)iminoester **9c** (0.25 mmol) afforded 28.5 mg of *N*-PMP *N*-trimethylsilyl aminoester **10c** as a yellow oil in 30% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.03 (s, 9H), 1.38 (t, J = 7.2 Hz, 3H), 3.79 (s, 3H), 4.205–4.38 (m, 2H), 5.16 (d, J = 17.7 Hz, 1H), 5.22 (d, J = 10.8 Hz, 1H), 5.46 (dd, J = 17.7 Hz and 10.8 Hz, 1H), 6.76 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 9.0 Hz 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 1.4, 13.9, 55.2, 61.9, 73.1 (q, $^2J_{CF}$ = 25.5 Hz), 112.3–113.6, 119.9, 124.8 (q, $^1J_{CF}$ = 285 Hz), 132.2, 132.9–134.2, 136.2, 157.6, 169.2. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −71.7 (s, 3F). HRMS Calc. for $C_{17}H_{24}F_3NO_3Si$: 375.1477. Found: 375.1493.

*4.2.14. Benzyl 2-[(4-methoxyphenyl)(trimethylsilyl)amino]-2-(trifluoromethyl)-3-butenoate (**10d**)*

According to the general procedure described above, 84 mg of *N*-PMP (fluoroalkyl)iminoester **9c** (0.25 mmol) afforded 35 mg of *N*-PMP *N*-trimethylsilyl aminoester **10c** as a yellow oil in 32% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.00 (9H, s), 3.78 (s, 3H), 5.05 (d, J = 17.7 Hz, 1H), 5.16 (d, J = 11.1 Hz, 1H), 5.23 (d, J = 12.3 Hz, 1H), 5.30 (d, J = 12.3 Hz, 1H), 5.46 (dd, J = 17.7 Hz and 11.1 Hz, 1H), 6.73 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 7.39–7.41 (m, 5H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ (ppm): 1.5, 55.2, 67.6, 73.2 (q, $^2J_{CF}$ = 25 Hz), 112.8- 113.8 (m), 120.1, 124.8 (q, $^1J_{CF}$ = 285 Hz), 128.5, 128.6, 128.6, 132.0, 133.1–133.7 (m), 134.7, 136.2, 157.6, 169.1. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −71.7 (s, 3F). HRMS Calc. for $C_{22}H_{27}F_3NO_3Si$ (M + 1): 438.1712. Found: 438.1723.

*4.2.15. Hydrolysis of silyl aminoesteres **10a–c**: typical procedure for the synthesis of allylaminoesters **4e–h***

A solution of 0.1 mmol of *N*-PMP *N*-trimethylsilyl fluoroalkyl allylamino esters **10** in 2 mL of anhydrous THF was treated with Amberlyst for 15 min at room temperature. After filtration and evaporation of the solvent, *N*-PMP fluoroalkyl allylamino esters **4** were isolated in quantitative yield.

*4.2.16. 2-(Trimethylsilyl)ethyl 2-[(4-methoxyphenyl)amino]-2-(trifluoromethyl)-3-butenoate (**4e**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.02 (s, 9H), 0.92–0.97 (m, 2H), 3.73 (s, 3H), 4.49 (brs, 1H), 4.25–4.29 (m, 2H), 5.57 (d, J = 10.8 Hz, 1H), 5.61 (d, J = 17.2 Hz, 1H), 6.24 (dd, J = 17.2 and 10.8 Hz, 1H), 6.64 (d, J = 9.2 Hz, 2H), 6.73 (d, J = 9.2 Hz, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ (ppm): −1.65, 17.0, 55.5, 65.7, 68.6 (q, $^2J_{CF}$ = 27 Hz), 114.1, 118.6, 122.4, 123.8 (q, $^1J_{CF}$ = 285 Hz), 128.6, 137.0, 153.6, 167.7. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −74.1 (s, 3F). HRMS Calc. for $C_{17}H_{24}F_3NO_3Si_1$: 375.1476. Found: 375.1475.

*4.2.17. Allyl 2-[(4-methoxyphenyl)amino]-2-(trifluoromethyl)-3-butenoate (**4f**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.73 (s, 3H), 4.67 (d, J = 5.6 Hz 2H), 5.22 (dd, J = 10.4, and 1.2 Hz, 1H), 5.27 (d, J = 17.2, and 1.2 Hz, 1H), 5.59 (d, J = 11 Hz, 1H), 5.63 (d, J = 17 Hz, 1H), 5.78 (tdd, J = 17.2, 10.4, and 5.6 Hz), 6.25 (dd, J = 17 Hz, J = 10 Hz, 1H), 6.64 (d, J = 9.2 Hz, 2H), 6.72 (d, J = 9.2 Hz. 2H).^{13}C NMR (100.5 MHz, $CDCl_3$) δ (ppm): 55.5, 67.3, 69.1 (q, $^2J_{CF}$ = 27 Hz), 114.2, 118.7, 119.3, 122.8, 123.7 (q, $^1J_{CF}$ = 285 Hz), 128.4, 130.7, 136.8, 153.8, 167.3. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −74.15 (s, 3F). HRMS Calc. for $C_{15}H_{16}F_3NO_3$: 315.1082. Found: 315.1073.

*4.2.18. Ethyl 2-[(4-methoxyphenyl)amino]-2-(trifluoromethyl)-3-butenoate (**4g**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.19 (t, J = 7.0 Hz, 3H), 3.73 (s, 3H), 3.79 (s, 1H), 4.19–4.30 (m, 2H), 5.58 (d, J = 10.5 Hz, 1H), 5.62 (d, J = 17.4 Hz, 1H), 6.25 (dd, J = 17.4 and 10.5 Hz, 1H), 6.64 (d, J = 9.3 Hz, 2H), 6.73 (d, J = 9.3 Hz. 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ (ppm): 13.7, 55.1, 63.0, 68.9 (q, $^2J_{CF}$ = 27 Hz), 114.1, 118.6, 122.6, 123.7 (q, $^1J_{CF}$ = 285 Hz), 128.5, 137.0, 153.7, 167.6. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −71.6 (s, 3F). HRMS Calc. for $C_{14}H_{16}F_3NO_3$: 303.1082. Found: 310.1089.

*4.2.19. Benzyl 2-[(4-methoxyphenyl)amino]-2-(trifluoromethyl)-3-butenoate (**4h**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.73 (s, 3H), 5.17 (d, J = 12.0 Hz, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.58 (d, J = 10.8 Hz, 1H), 5. 63 (d, J = 17.2 Hz, 1H), 6.43 (dd, J = 17.2 and 10.8 Hz, 1H), 6.59 (d, J = 9.2 Hz, 2H), 6.68 (d, J = 9.2 Hz, 2H), 7.15–7.18 (m, 2H), 7.28–7.32 (m, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ (ppm): 55.5, 68.5, 69.1 (q, $^2J_{CF}$ = 27 Hz), 114.2, 118. 4, 122.8, 123.6 (q, $^1J_{CF}$ = 285 Hz), 128.2, 128,4, 128,5, 128.5, 134.5, 136.9, 153.7, 167.5. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −74.3 (s, 3F). HRMS Calc. for $C_{19}H_{18}F_3NO_3$: 365.1239. Found: 365.1243.

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