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Difluoromethyl and Chlorofluoromethyl Sulfoximines: Synthesis and Evaluation as Electrophilic Perfluoroalkylating Reagents

Bruce Pégot,[a] Céline Urban,[a] Aaron Bourne,[a] Thanh Nghi Le,[a] Sébastien Bouvet,[a] Jérôme Marrot,[a] Patrick Diter,[a] and Emmanuel Magnier*[a]

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An efficient and convenient method is described that allows the synthesis of a set of difluoromethyl sulfoximines, as well as chlorofluoromethyl sulfoxides, sulfones, and sulfoximines. Our procedure does not require metals or nonrecommended freons, and it gives rise to an original route to Hu's reagent. Unprecedented chlorofluoromethyl sulfoximines have been also isolated, and these compounds have been shown to act as an electrophilic source of this original bis-halogenated moiety. The mechanism of the electrophilic chlorofluoromethylation is also discussed.

Introduction

The preparation of organofluorine compounds is a very important challenge in modern chemistry. The progress that has been made in this research field has resulted in major improvements in catalysis, materials science, and energy, and also in life sciences (agrochemistry and medicinal chemistry).[1] The number of publications devoted to the synthesis of new fluoroalkylated compounds or to the invention of new fluorination reagents has recently grown exponentially.[2] In the field of electrophilic perfluoroalkylation, two important recent developments can be noted: i) the number of reagents available is increasing; and ii) they can be used to generate either a radical (by chemical initiation or light irradiation) or a nucleophilic species (with the help of a metal, often copper).[2i,2j,3] Three main families of reagents are now at the disposal of chemists. The first group, based on trifluoromethylsulfonium chemistry, was first proposed by Yagupolskii and then extended in terms of diversity and efficiency by Shreeve, Umemoto, Shibata, Laali, and ourselves.[3c,4] The second family, hypervalent iodine(III)-CF_3 compounds, was introduced by Togni in 2006, and is now widely used for an impressive and exponentially growing number of trifluoromethylation applications.[5] The third family represents a far more recent innovation, and is related to the fascinating chemistry of sulfoximines (Figure 1).[6] Although they are less widely used as electrophilic fluorinating reagents, these molecules are very promising because of the multiple structural variations offered by their skeleton.[7] Two main types of structural variation have been studied: the fluorinated chain and the activating group attached to the nitrogen. Modifications of these groups have a great impact on the reactivity. Indeed, Shibata has demonstrated that with a common nucleophile, a β-keto ester, trifluoromethylated reagent **1** gave only C–C bond formation, whereas compound **2** led only to monofluoromethylation of the oxygen atom, and compound **4** gave a mixture of *C*- and *O*-difluoromethylation.[8] Prakash and Hu independently showed that the reagents **3** and **4**, whose structures differ only in the activating group, showed similar reactivities in the difluoro functionalization of various heteroatoms.[9] Our own experience led us to discover a clear-cut difference between compounds **5**, **6**, and **7**.[10] Compound **5** did not react with an acetylenic carbanion (unlike sulfoximinium **1**), whereas compounds **6** and **7** proved to be efficient for the introduction of a monofluoromethyl or difluoromethyl group onto an sp carbon.

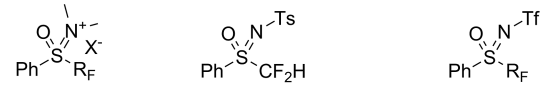

Figure 1. Overview of sulfoximines as electrophilic fluoroalkylating reagents.

One of the major drawbacks of the chemistry of the *S*-perfluoalkylated sulfoximines was their cumbersome synthesis, which often needed very acidic conditions and toxic reagents, or nitrene and copper catalysts (Scheme 1, route a).[11] In 2009, we facilitated access to *S*-aryl *S*-perfluoroalkylated NH-sulfoximines by introducing a three-step procedure (route b).[10,12] Perfluoroalkyl sulfoxides, formerly activated by trifluoromethanesulfonic anhydride,

[a] Institut Lavoisier de Versailles (ILV), UMR CNRS 8180, Université de Versailles,
St Quentin en Yvelines, 45 avenue des Etats-Unis,
78035 Versailles CEDEX, France
E-mail: emmanuel.magnier@uvsq.fr
http://www.ilv.uvsq.fr/research/Echo/echo.htm

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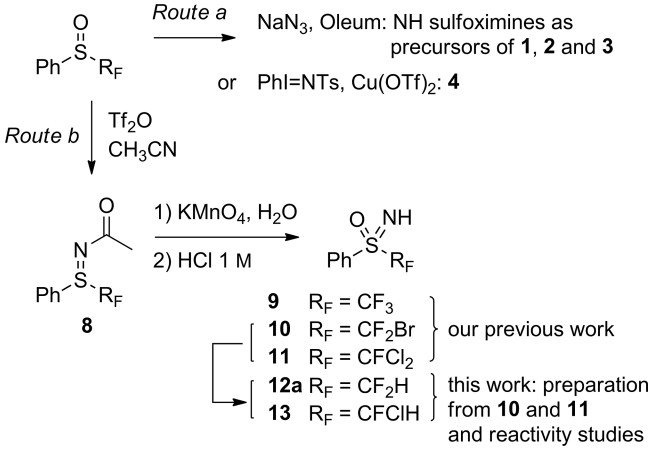
were transformed into sulfilimines **8** through a Ritter-like process. A subsequent oxidation and deprotection sequence delivered a set of sulfoximines **9**–**11**.[13] Unfortunately, we noticed during our previous studies that the difluoromethyl sulfilimines were unstable; this precluded the preparation of the corresponding difluoromethyl sulfoximines **12**. We were then intrigued by the possibility of circumventing this difficulty by exploring the reactivity of sulfoximines **10** and **11**. Their transformation into skeletons **12** and **13**, respectively, as well as studies of their reactivity, are given in this article.

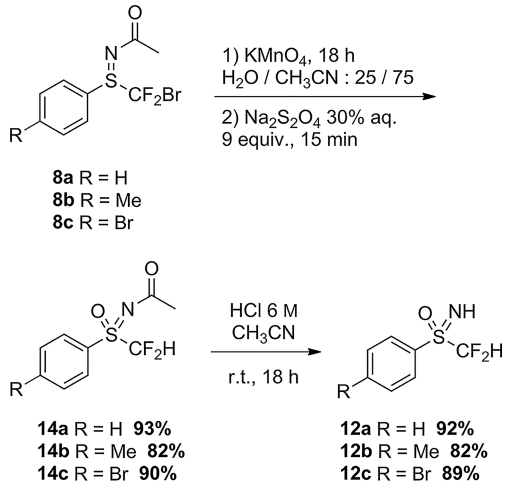


Scheme 1. Preparation of perfluoroalkylated sulfoximines.

Results and Discussion

In our previous work devoted to the synthesis of sulfoximine **10**, we noticed the presence, in the crude product mixture, of traces of compound **12a**.[10] This reaction occurred during the final treatment by sodium dithionite, which was added, as a powder, to reduce the remaining potassium permanganate. We were very pleased to be able to transform this side-reaction into a useful synthetic transformation by modifying the reaction conditions (Scheme 2). First, the oxidation of phenyl bromodifluoromethyl sulfilimine **8a** was carried out overnight in a precise mixture of H_2O and CH_3CN (25:75) to allow complete homogenisation of the reaction medium. Next, a freshly prepared aqueous solution of sodium dithionite was introduced in excess to give, after 15 min, phenyl difluoromethyl sulfoximine **14a** in an almost quantitative yield. This transformation was easily extended to substituted aromatic rings in **8b** and **8c**. Following our previously described method, NH sulfoximines **12a**–**12c** were then synthesized in a second step from precursors **14a**–**14c** in excellent yields.

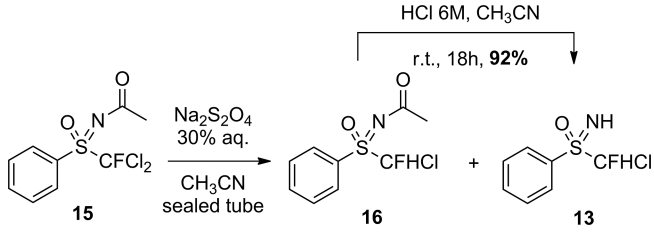
Encouraged by these results, we then decided to extend our dehalogenation process to dichlorofluoromethyl sulfoximine **15**. The previous mild one-pot conditions proved to be inefficient in this case due to the strength of the carbon–chlorine bond, and the starting material (i.e., **15**) was recovered unchanged. However, we were pleased to succeed in the selective cleavage of only one of the carbon–chlorine bonds in sulfoximine **15**. Thermal activation and an excess



Scheme 2. Synthesis of difluoromethyl sulfoximines from sulfilimines.

of sodium dithionite were necessary for the success of the transformation (Table 1). Moreover, the choice of reaction conditions determined whether *N*-acylsulfoximine **16** or NH sulfoximine **13** was formed. With 4.5 equiv. of sodium dithionite at 60 or 80 °C, compound **16** was obtained in good yield, but with an incomplete conversion (Table 1, entries 1 and 2). When the temperature was increased to 100 °C, and the reaction was carried out in a sealed tube, very surprisingly the deprotected sulfoximine (i.e., **13**) was formed (Table 1, entry 3). Compound **13** was isolated quantitatively by doubling the number of equivalents of dithionite (Table 1, entry 4), whereas acyl derivative **16** was the sole product formed when the number of equivalents of the reducing agent was multiplied by three (Table 1, entry 5). We assume that the acyl deprotection was promoted by the HCl produced during the process (Table 1, entry 4). This side-reaction was inhibited by the presence of a large amount of sodium dithionite, which is probably able to neutralize the acidic medium (Table 1, entry 5). The reaction time was dramatically reduced by microwave heating (MW;

Table 1. Preparation of chlorofluoromethyl sulfoximines.



Entry	Temp. [°C]	$Na_2S_2O_4$ [equiv.]	Time [h]	Yield [%] 15	16	13
1	60	4.5	18	40	60	–
2	80	4.5	48	24	76	–
3	100	4.5	48	24	–	76
4	100	9	18	–	–	93
5	100	13.5	18	–	100	–
6	120 (MW)	9	0.5	–	95	–
7	120 (MW)	13.5	0.5	–	86	–

Table 1, entries 6 and 7). Under these conditions, the acyl moiety of the sulfoximines was always preserved, whatever the quantity of sodium dithionite used in the reaction. Finally, it was also possible to deacylate pure product **16** to give **13** in almost quantitative yield by simple treatment with HCl.

We were pleased to succeed in separating, by flash chromatography, the two diastereoisomers of compound **16**. Fortunately, one of the diastereomers was solid. Its structure was solved by X-ray analysis (Figure 2). Interestingly, the S–CFHCl bond lies almost perpendicular to the plane defined by the aromatic ring, whereas the bonds of the "sulfur–nitrogen–acyl functionality" are in the same plane as the aromatic moiety. This conformational behaviour has already been observed with trifluoromethyl sulfilimines and sulfoximines, as well as with the trifluoromethoxy moiety.[12a,14]

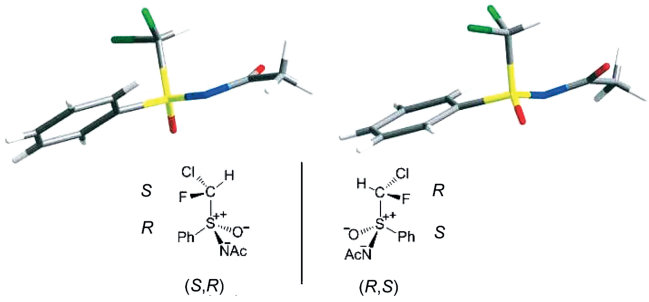
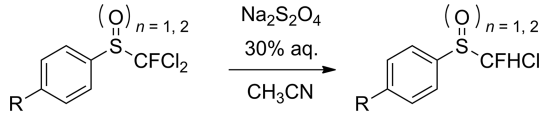


Figure 2. X-ray analysis of *N*-acetyl chlorofluoromethyl phenyl sulfoximine (**16**).

In order to assess our strategy, and to extend it to a wider range of sulfur functionalities, we turned our attention to dichlorofluoromethyl phenyl sulfoxides and sulfones **17a**–**17f** (Table 2). The corresponding chlorofluoromethyl derivatives (i.e., **18a**–**18f**) were either still unknown or had previously been prepared by tedious methods using toxic reagents such as fluorine or ozone-depleting gases.[15] Compared to the sulfoximine series, an increase of the reaction time and greater excess of sodium dithionite were necessary. Sulfoxide **18a** was isolated in a moderate yield, even though total conversion had occurred (Table 2, entries 1–3). As no other fluorinated compounds were recovered, we concluded that degradation phenomena were responsible for this problem of mass balance. Microwave irradiation did not result in a significant improvement of the isolated yield, but did lead to drastic decreases of both the reaction time and the quantity of reducing agent required to form **18a** (Table 2, entry 4). These conditions also proved to be efficient for the preparation of sulfoxides **18b** and **18c**, and sulfones **18d**–**18f**, although in some instances a higher temperature was necessary (Table 2, entries 6–10).

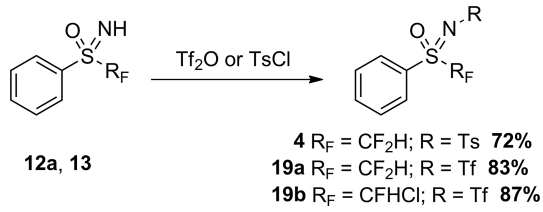
The next part of our study was devoted to the evaluation of the phenyl chlorofluoromethyl sulfoximine moiety as an electrophilic perfluoroalkylating reagent. *N*-Functionalization of the nitrogen with an electron-withdrawing group was a prerequisite. The introduction of tosyl or triflyl groups starting from sulfoximines **12a** and **13** was straightforward (Scheme 3). We were then pleased to be able to describe a new route to Hu reagent **4**, its triflic version **19a**, and a new reagent **19b**.

Table 2. Preparation of chlorofluoromethyl sulfoxides and sulfones.



17a–f **18a–f**

Entry	R	*n*	Temp. [°C]	$Na_2S_2O_4$ [equiv.]	Time [h]	Product	Yield [%]
1	H	1	110	4.5	48	**18a**	9
2	H	1	110	9	48	**18a**	51
3	H	1	110	13.5	48	**18a**	50
4	H	1	110 (MW)	6	0.15	**18a**	53
5	H	1	130 (MW)	6	0.25	**18a**	50
6	Br	1	130 (MW)	6	0.5	**18b**	55
7	Me	1	130 (MW)	6	0.5	**18c**	60
8	H	2	110 (MW)	6	0.5	**18d**	80
9	Br	2	110 (MW)	6	0.5	**18e**	85
10	Me	2	130 (MW)	6	0.5	**18f**	64

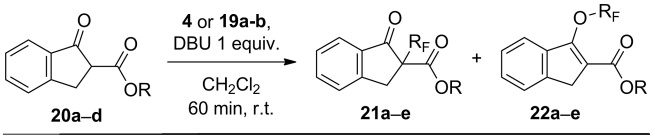


Scheme 3. Synthesis of electrophilic perfluoroalkylating reagents.

In order to compare the electrophilic activity of our new sulfoximines **19a** and **19b** to already existing ones, a set of β-keto esters were chosen as common nucleophiles (Table 3). The reaction conditions used were those previously described by Shibata. When we used the phosphazene base P1-*t*Bu [*tert*-butylimino-tris(dimethylamino)phosphorane], which was reported to give the best yield, we noticed that, in our hands, the quality of this base dramatically decreased with age. This had a negative effect on the reaction yield. For this reason, DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene), a more stable and much less expensive base was used. This resulted in a decrease in the yields, but by a reasonable amount (around 10–15% on average). These conditions allowed us to reproduce a previous result of Shibata (Table 3, entry 1): Hu reagent **4** reacted smoothly with nucleophile **20a** to give a mixture of *C*-alkylated (**21a**) and *O*-alkylated (**22a**) derivatives.[8b] Surprisingly, triflyl analogue **19a** gave exactly the same yield as compound **4** (Table 3, entry 2). The electron-withdrawing properties of the group attached to the nitrogen atom seem to have no influence on the electrophilic properties of these reagents.

Compound **19b** reacted with β-keto ester **20a** to give *C*-alkylated compound **21b** as the sole product (Table 3, entry 3). This reactivity then is different to that of **19b**, which led to a mixture of *C*- and *O*-alkylation. To the best of our knowledge, this represents the first example of the electro-

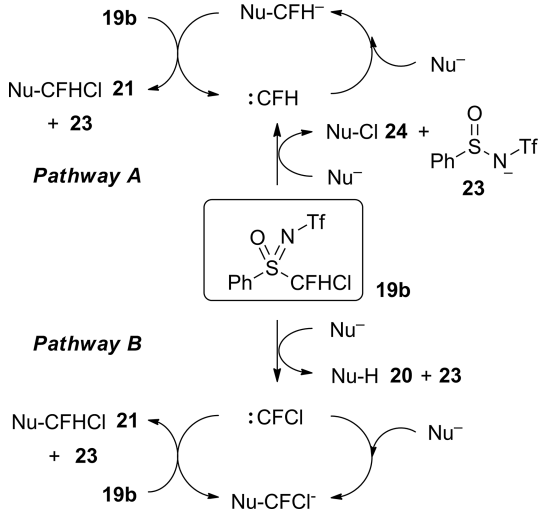
Table 3. Reactivity of sulfoximines **4**, **19a**, and **19b** towards β-keto esters.



Entry	Keto ester	R	Reagent	R_F	Yield of **21** [%]	Yield of **22** [%]
1	**20a**	Me	**4**	CF_2H	**21a** (31)	**22a** (23)
2	**20a**	Me	**19a**	CF_2H	**21a** (31)	**22a** (23)
3	**20a**	Me	**19b**	CFHCl	**21b** (40)	**22b** (0)
4	**20b**	Et	**19b**	CFHCl	**21c** (37)	**22c** (0)
5	**20c**	*i*Pr	**19b**	CFHCl	**21d** (26)	**22d** (0)
6	**20d**	Bn	**19b**	CFHCl	**21e** (36)	**22e** (0)

philic chlorofluoromethylation of a substrate. The scope of this transformation was then studied with three other indanones **20c**–**20e** (Table 3, entries 4–6), yields within the same range were obtained with ethyl and benzyl ester moieties (Table 3, entries 4 and 6), and a slight decrease occurred with an isopropyl ester functionality (Table 3, entry 5).

Previous mechanistic studies from Hu's group and our own allowed us to propose a carbenic pathway for this transformation. Unlike other reagents, two species can come from sulfoximine **19b**, depending on the initiation step. The nucleophile can remove the chlorine atom from **19b** to generate a fluorocarbene (pathway A), or alternatively, it could abstract the hydrogen of **19b** to produce a chlorofluorocarbene species (pathway B; Scheme 4). Both routes can explain the formation of the final ester (i.e., **21**) after independent catalytic cycles involving a reaction between the nucleophilic moiety and the carbene, and completed by the final chlorination (pathway A) or protonation (pathway B).



Scheme 4. Proposed mechanism.

We isolated and characterized derivative **24**, which proves the existence of pathway A. Pathway B can nevertheless not be totally excluded, as the starting material (i.e., **20**) was also recovered at the end of the reaction. The presence of compounds **20** and **24** accounts for the mass balance of this reaction; sulfoximine **19b** is fully consumed. This demonstrates that the initiation step(s) is (are) side-reaction(s) that lower the yields of the fluoroalkylated compounds (i.e., **21**).

Deeper mechanistic discussions are necessary, but they fall outside the scope of this article. The mechanism is currently under investigation in our laboratory, and a fuller discussion will be reported in due course.

Conclusions

We have demonstrated the easy preparation of *S*-difluoromethylated sulfoximines, which allowed use to describe a new route to Hu's reagent, complementary to the seminal one. Our method has also been used for the efficient synthesis of new *S*-chlorofluoromethylated sulfoximines, and the reactivity of these compounds as electrophilic reagents has been demonstrated. This is certainly the first example of the use of sulfoximines for electrophilic chlorofluoromethylation purposes.

Experimental Section

General Procedure for the Preparation of *N*-Acetyl Difluoromethyl Aryl Sulfoximines, Exemplified by the Preparation of *N*-Acetyl *S*-Difluoromethyl *S*-Phenyl Sulfoximine (14a): A mixture of *N*-acetyl bromodifluoromethyl phenyl sulfilimine (100 mg, 0.34 mmol, 1 equiv.) and potassium permanganate (54 mg, 0.34 mmol, 1 equiv.) in water (0.5 mL) and acetonitrile (1.5 mL) was stirred at room temperature overnight. The mixture was made colourless by the addition of a freshly prepared solution (30%) of sodium hydrosulfite (0.53 g, 3.06, mmol, 9.0 equiv.) in water (1.7 mL) over 15 min while stirring. The mixture was then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (pentane/Et_2O, 7:3) to give **14a** (68 mg, 93%) as a colourless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 7.15 (dd, J = 54.7 Hz, 1 H), 7.66 (m, 2 H), 7.81 (m, 1 H), 8.05 (d, J = 7.7 Hz, 2 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –122.6 and –115.5 (AB system, J = 251.1, J = 55.6 Hz, 2 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5, 115.2 (t, J = 289.9 Hz, CF_2), 128.3, 129.5, 130.5, 135.6, 181.0 ppm. MS (ESI): m/z = 234 [M + H]$^+$. HRMS: calcd. for $C_9H_{10}F_2NO_2S$ 234.0400; found 234.0407 (3.0 ppm).

***N*-Acetyl *S*-Difluoromethyl *S*-*p*-Tolyl Sulfoximine (14b):** Colourless oil (82%). ^1H NMR (200 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 2.51 (s, 3 H), 7.14 (dd, J = 53.8 Hz, 1 H), 7.43 (d, J = 8.2 Hz, 2 H), 7.92 (d, J = 8.3 Hz, 2 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –122.9 and –115.7 (AB system, J = 251.1, J = 55.6 Hz, 2 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 26.5, 115.1 (t, J = 289.6 Hz, CF_2), 125.0, 130.3, 130.6, 147.2, 181.1 ppm. MS (ESI): m/z = 248 [M + H]$^+$. HRMS: calcd. for $C_{10}H_{12}F_2NO_2S$ 248.0557; found 248.0541 (–6.5 ppm).

***N*-Acetyl *S*-*p*-Bromophenyl *S*-Difluoromethyl Sulfoximine (14c):** Colourless oil (90%). ^1H NMR (200 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 7.15 (dd, J = 54.7 Hz, 1 H), 7.78–7.92 (m, 4 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –122.3 and –115.2 (AB system, J = 250.5, J = 55.6 Hz, 2 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5, 115.1 (t, J = 290.2 Hz, CF_2), 127.3, 131.7, 132.0, 133.0, 180.9 ppm. MS (ESI), for ^{79}Br: m/z = 312 [M + H]$^+$. HRMS: calcd. for $C_9H_9{}^{79}BrF_2NO_2S$ 311.9505; found 311.9469 (–11.5 ppm).

General Procedure for the Synthesis of *NH*-Sulfoximines under Acidic Conditions, Exemplified by the Preparation of *S*-Difluoromethyl *S*-Phenyl Sulfoximine (12a): HCl (6 M aq.; 4.2 mL) was added to a solution of *N*-acetyl difluoromethyl phenyl sulfoximine (1.3 g, 4.2 mmol, 1 equiv.) in acetonitrile (4.2 mL). The reaction mixture was stirred at room temperature for 18 h, and then water (50 mL) was added. The crude mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were washed with $NaHCO_3$ (10% aq.), dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane/Et_2O, 6:4) to give **12a** (1.05 g, 92%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.21 (br. s, 1 H), 6.16 (t, J = 54.7 Hz, 1 H), 7.61 (m, 2 H), 7.74 (m, 1 H), 8.07 (m, 2 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –122.5 and –119.5 (AB system, J = 258.0, J = 54.2 Hz, 2 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.2 (t, J = 284.7 Hz, CF_2), 129.3, 130.4, 133.0, 134.8 ppm. MS (ESI): m/z = 192 $[M + H]^+$. HRMS: calcd. for $C_7H_8F_2NOS$ 192.0295; found 192.0289 (–3.1 ppm).

***S*-Difluoromethyl *S*-*p*-Tolyl Sulfoximine (12b):** Colourless oil (82%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.48 (s, 3 H), 3.00 (br. s, 1 H), 6.13 (t, J = 54.9 Hz, 1 H), 7.42 (d, J = 8.6 Hz, 2 H), 7.95 (d, J = 8.3 Hz, 2 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –122.6, –119.4 (AB system, J = 258.0, J = 54.9 Hz, 2 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 115.2 (t, J = 285.0 Hz, CF_2), 130.0, 130.1, 130.5, 146.3 ppm. MS (ESI): m/z = 206 $[M + H]^+$. HRMS: calcd. for $C_8H_{10}F_2NOS$ 206.0451; found 206.0468 (8.3 ppm).

***S*-Difluoromethyl *S*-*p*-Bromophenyl Sulfoximine (12c):** Colourless oil (89%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.14 (br. s, 1 H), 6.14 (t, J = 54.6 Hz, 1 H), 7.77 (dt, J = 8.7, J = 2.1 Hz, 2 H), 7.93 (dt, J = 8.7, J = 1.9 Hz, 2 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –122.0 and –118.8 (AB system, J = 258.0, J = 54.9 Hz, 2 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.2 (t, J = 285.8 Hz, CF_2), 130.8, 131.9, 132.2, 132.8 ppm. MS (ESI) for ^{79}Br: m/z = 270 $[M + H]^+$. HRMS: calcd. For $C_7H_7{}^{79}BrF_2NOS$ 269.9400; found 269.9429 (10.7 ppm).

General Procedure for the Synthesis of Chlorofluoromethyl Sulfoximines, Exemplified by the Preparation of *N*-Acetyl *S*-Chlorofluoromethyl *S*-Phenyl Sulfoximine (16): A mixture of *N*-acetyl dichlorofluoromethyl phenyl sulfoximine (1.185 g, 4.17 mmol, 1 equiv.), a freshly prepared solution (30%) of sodium hydrosulfite (9.80 g, 56.3, mmol, 13.5 equiv.) in water (32 mL), and acetonitrile (19 mL) was stirred at 100 °C overnight in a sealed tube. The solution was cooled, then it was diluted with water (10 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were dried with $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on silica gel (pentane/Et_2O, 7:3) gave **16** (0.96 g, 92%) as a colourless oil, two diastereoisomers. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.25 (s, 3 H), 7.50–7.90 (m, 4 H), 8.09 (t, J = 8.4 Hz, 2 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –139.2 (d, J = 50.1 Hz, 1 F), –132.0 (d, J = 48.0 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 26.8, 104.5 (d, J = 286.9 Hz, CF), 105.8 (d, J = 289.1 Hz, CF), 129.2, 129.3, 130.8, 131.2, 135.5, 135.6, 180.6, 180.8 ppm. MS (ESI) for ^{35}Cl: m/z = 250 $[M + H]^+$. HRMS: calcd. for $C_9H_{10}{}^{35}ClFNO_2S$ 250.0105; found 250.0101 (–1.6 ppm).

***S*-Chlorofluoromethyl *S*-Phenyl Sulfoximine (13):** Colourless oil, two diastereoisomers (92%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.35 (s, 2 H), 6.49 (d, J = 50.2 Hz, 1 H), 6.56 (d, J = 51.0 Hz, 1 H), 7.61 (m, 4 H), 7.75 (m, 2 H), 8.09 (d, J = 7.6 Hz, 4 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –131.9 (d, J = 50.1 Hz, 1 F), –130.1 (d, J = 51.4 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 105.8 (d, J = 285.3 Hz, CF), 106.4 (d, J = 288.5 Hz, CF), 129.2, 129.3, 130.2, 130.3, 132.9, 133.0, 134.7, 134.8 ppm. MS (ESI) for ^{35}Cl: m/z = 208 $[M + H]^+$. HRMS: calcd. for $C_7H_8{}^{35}ClFNOS$ 207.9999; found 207.9998 (–0.5 ppm).

General Procedure for the Synthesis of Aryl Chlorofluoromethyl Sulfoxides and Sulfones as Exemplified by the Preparation of Chlorofluoromethyl Phenyl Sulfoxide (18a): A freshly prepared solution (30%) of sodium hydrosulfite (450 mg, 2.64, mmol, 6 equiv.) in water (1.5 mL) was added to a solution of 1-methyl-4-dichlorofluoromethyl phenyl sulfoxide (100 mg, 0.44 mmol, 1 equiv.) in acetonitrile (1.1 mL). The reaction mixture was then stirred at 110 °C for 10 min in a microwave reactor. Dichloromethane (10 mL) and water (10 mL) were added. The aqueous phase was washed with dichloromethane (10 mL), and the organic phase was washed three times with water (3 × 10 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica; pentane/Et_2O, 8:2) to give **18a** (45 mg, 53%) as a colourless liquid, two diastereoisomers. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.48 (d, J = 52.0 Hz, 1 H), 6.50 (d, J = 52.0 Hz, 1 H), 7.61 (m, 3 H), 7.75 (m, 2 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –138.1 (d, J = 50.0 Hz, 1 F), –138.0 (d, J = 50.0 Hz, 1 F) ppm.[16]

Chlorofluoromethyl *p*-Bromo-phenyl Sulfoxide (18b): Colourless liquid, two diastereoisomers (55%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.48 (d, J = 50.6 Hz, 1 H), 6.50 (d, J = 50.2 Hz, 1 H), 7.61 (d, J = 8.5 Hz, 4 H), 7.72 (d, J = 8.5 Hz, 4 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –139.3 (d, J = 50.5 Hz, 1 F), –139.1 (d, J = 50.1 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.8 (d, J = 284.6 Hz, CF), 109.4 (d, J = 291.1 Hz, CF), 127.6, 127.9, 128.1, 128.2, 132.7, 132.8, 136.3, 136.4 ppm. MS (ESI): m/z = 271 $[M + H]^+$. HRMS: calcd. for $C_7H_6{}^{79}BrClFOS$ 270.8997; found 270.8995 (0.7 ppm).

Chlorofluoromethyl *p*-Methylphenyl Sulfoxide (18c): Colourless liquid, two diastereoisomers (60%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.44 (s, 6 H), 6.43 (d, J = 50.7 Hz, 1 H), 6.44 (d, J = 50.5 Hz, 1 H), 7.37 (d, J = 8.1 Hz, 4 H), 7.60–7.66 (m, 4 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –138.9 (d, J = 50.5 Hz, 1 F), –138.4 (d, J = 50.7 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 21.8, 109.2 (d, J = 283.8 Hz, CF), 110.1 (d, J = 289.1 Hz, CF), 126.0, 126.4, 130.2, 130.3, 134.2, 134.3, 144.0, 144.1 ppm. MS (ESI): m/z = 207 $[M + H]^+$. HRMS: calcd. for $C_8H_9{}^{35}ClFOS$ 207.0048; found 207.0047 (0.5 ppm).

Chlorofluoromethyl Phenyl Sulfone (18d): Colourless liquid (80%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.56 (d, J = 48.0 Hz, 1 H), 7.66 (m, 2 H), 7.81 (m, 1 H), 8.02 (m, 2 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –137.0 (d, J = 48.9 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 104.4 (d, J = 284.9 Hz, CF), 129.5, 130.8, 132.0, 135.7 ppm.[16]

Chlorofluoromethyl *p*-Bromophenyl Sulfone (18e): Colourless liquid (85%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.55 (d, J = 48.9 Hz, 1 H), 7.76–7.88 (m, 4 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –136.9 (d, J = 48.8 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 104.5 (d, J = 282.5 Hz, CF), 130.9, 131.9, 132.3, 133.1 ppm. $C_7H_5BrClFO_2S$ (287.53): calcd. C 29.24, H 1.75; found C 29.36, H 1.62.

Chlorofluoromethyl *p*-Methylphenyl Sulfone (18f): Colourless liquid (64%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 6.52 (d, J = 49.1 Hz, 1 H), 7.43 (d, J = 8.1 Hz, 2 H), 7.88 (d, J = 8.2 Hz, 2 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –137.0 (d, J = 49.0 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 104.6 (d, J = 282.2 Hz, CF), 129.0, 130.3, 131.0, 147.4 ppm. $C_8H_8ClFO_2S$ (222.66): calcd. C 43.15, H 3.62; found C 42.91, H 3.87.

***N*-Toluylsulfonyl *S*-Difluoromethyl *S*-Phenyl Sulfoximine (4):** Toluenesulfonyl chloride (0.15 mg, 0.78 mmol, 1.5 equiv.) was added to

a solution of difluoromethyl phenyl sulfoximine (0.1 g, 0.52 mmol, 1 equiv.) and pyridine (0.13 mL, 1.6 mmol, 3 equiv.) in CH_2Cl_2 (1.2 mL) at room temperature. The mixture was heated at reflux overnight. HCl (1 M aq.; 3 mL) was added, and the crude mixture was extracted with CH_2Cl_2 (3× 5 mL). The combined organic extracts were washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on silica gel (pentane/CH_2Cl_2, 5:5) gave **4** (140 mg, 72%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 7.17 (t, J = 54.1 Hz, 1 H), 7.27 (d, J = 8.5 Hz, 2 H), 7.64 (t, J = 7.4 Hz, 2 H), 7.81 (t, J = 7.6 Hz, 1 H), 7.92 (d, J = 8.3 Hz, 2 H), 8.03 (d, J = 7.8 Hz, 2 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –120.9 and –114.7 (AB system, J = 248.3, J = 55.1 Hz, 2 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 115.5 (t, J = 291.5 Hz, CF), 126.8, 127.8, 129.6, 129.8, 130.8, 136.3, 139.5, 143.8 ppm.[16]

General Procedure for the Synthesis of *N*-Triflyl Sulfoximines, Exemplified by the Preparation of *N*-Trifluoromethylsulfonyl *S*-Difluoromethyl *S*-Phenyl Sulfoximine (19a): Trifluoromethanesulfonic anhydride (0.13 mL, 0.78 mmol, 1.5 equiv.) was added to a solution of difluoromethyl phenyl sulfoximine (0.1 g, 0.52 mmol, 1 equiv.) and pyridine (0.13 mL, 1.6 mmol, 3 equiv.) in CH_2Cl_2 (1.2 mL) at 0 °C. The mixture was stirred for 7 h at room temperature. Water (5 mL) was added, and the crude mixture was extracted with CH_2Cl_2 (3× 5 mL). The combined organic extracts were washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on silica gel (pentane/Et_2O, 8:2) gave **19a** (140 mg, 83%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.98 (t, J = 53.8 Hz, 1 H), 7.76 (t, J = 7.7 Hz, 2 H), 7.94 (t, J = 7.4 Hz, 1 H), 8.08 (d, J = 7.7 Hz, 2 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –120.1 and –114.1 (AB system, J = 248, J = 53 Hz, 2 F), –78.7 (d, J = 1.4 Hz, 3 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.5 (t, J = 291.8 Hz, CF_2), 118.9 (q, J = 318.6 Hz, CF_3), 126.7, 130.3, 130.8, 137.4 ppm. MS (ESI): m/z = 324 $[M + H]^+$. HRMS: calcd. for $C_8H_7F_5NO_3S_2$ 323.9788; found 323.9817 (9.0 ppm).

***N*-Trifluoromethylsulfonyl *S*-Chlorofluoromethyl *S*-Phenyl Sulfoximine (19b):** Colourless oil, two diastereoisomers (87%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32 (d, J = 48.7 Hz, 1 H), 7.36 (d, J = 48.2 Hz, 1 H), 7.76 (t, J = 7.7 Hz, 4 H), 7.94 (t, J = 7.4 Hz, 2 H), 8.11 (t, J = 7.3 Hz, 4 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –135.4 (d, J = 48.7 Hz, 1 F), –130.9 (d, J = 48.0 Hz, 1 F), –78.9 (s, 3 F), –78.7 (s, 3 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 106.1 (d, J = 290.7 Hz, CF), 106.8 (d, J = 289.1 Hz, CF), 118.9 (q, J = 318.6 Hz, CF_3), 126.9, 127.0, 130.0, 131.1, 131.3, 137.2, 137.3 ppm. MS (ESI) for ^{35}Cl: m/z = 340 $[M + H]^+$. HRMS: calcd. for $C_8H_7{}^{35}ClF_4NO_3S_2$ 339.9492; found 339.9492 (0 ppm).

General Procedure for Electrophilic Perfluoroalkylation, Exemplified by the Reaction Between β-Keto Ester 20a and Sulfoximine 4: DBU (29 μL, 0.19 mmol, 1.2 equiv.) was added to a stirred solution of methyl 1-indanone-2-carboxylate (30 mg, 0.16 mmol, 1 equiv.) in CH_2Cl_2 (2.3 mL), and the mixture was stirred for 15 min at room temperature. Chlorofluoromethyl phenyl *N*-trifluoromethylsulfonyl sulfoximine (79 mg, 0.24 mmol, 1.5 equiv.) was added, and the mixture was stirred for 1 h at room temperature. The solvent was evaporated, and the residue was purified by preparative TLC (pentane/ethyl acetate, 9:1) to give a mixture of **21a** (12 mg, 31%) and **22a** (9 mg, 23%).

Methyl 2-(Difluoromethyl)-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (21a): Colourless oil (31%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.57 and 3.75 (AB system, J = 17.5 Hz, 2 H), 3.80 (s, 3 H), 6.61 (t, J = 55.2 Hz, 1 H), 7.44 (t, J = 7.5 Hz, 1 H), 7.50–7.75 (m, 2 H), 7.79 (d, J = 7.9 Hz, 1 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –129.4 and –125.9 (AB system, J = 287.7, J = 55.3 Hz, 2 F) ppm.[16]

Methyl 3-(Difluoromethoxy)-1*H*-indene-2-carboxylate (22a): Colourless oil (23%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.73 (s, 2 H), 3.86 (s, 3 H), 7.19 (t, J = 7.9 Hz, 1 H), 7.35–7.72 (m, 4 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –82.2 (d, J = 75.0 Hz, 2 F) ppm.[16]

Methyl 2-(Chlorofluoromethyl)-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (21b): Colourless oil, two diastereoisomers (40%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 3.80 (s, 3 H), 3.56–3.95 (m, 4 H), 7.0 (d, J = 49.0 Hz, 1 H), 7.03 (d, J = 48.6 Hz, 1 H), 7.43 (t, J = 7.4 Hz, 2 H), 7.57–7.81 (m, 6 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –145.6 (d, J = 49.4 Hz, 1 F), –142.1 (d, J = 48.7 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.2, 31.3, 53.5, 53.6, 67.2 (d, J = 91.3 Hz), 67.4 (d, J = 87.8 Hz), 101.6 (d, J = 249.1 Hz, CF), 101.7 (d, J = 247.9 Hz, CF), 125.2, 125.4, 126.4, 128.1, 133.9, 136.1, 136.2, 153.5, 154.0, 165.7, 165.9, 166.6, 195.5, 195.8 ppm. MS (ESI), for ^{35}Cl: m/z = 257 $[M + H]^+$. HRMS: calcd. for $C_{12}H_{11}{}^{35}ClFO_3$ 257.0381; found 257.0381 (0 ppm).

Ethyl 2-(Chlorofluoromethyl)-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (21c): Colourless oil, two diastereoisomers (37%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 6 H), 3.54–3.93 (m, 4 H), 4.17–4.30 (m, 4 H), 6.99 (d, J = 49.1 Hz, 1 H), 7.02 (d, J = 48.6 Hz, 1 H), 7.42 (t, J = 7.2 Hz, 2 H), 7.56–7.79 (m, 6 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –145.3 (d, J = 49.1 Hz, 1 F), –142.1 (d, J = 48.5 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.1, 31.3, 31.5, 62.9, 63.0, 67.3 (d, J = 57.0 Hz), 67.7 (d, J = 60.2 Hz), 101.9 (d, J = 248.9 Hz, CF), 102.1 (d, J = 243.0 Hz, CF), 125.4, 126.5, 126.6, 128.2, 134.2, 136.2, 136.3, 153.8, 154.3, 166.2, 195.8 ppm. MS (ESI), for ^{35}Cl: m/z = 271 $[M + H]^+$. HRMS: calcd. for $C_{13}H_{13}{}^{35}ClFO_3$ 271.0537; found 271.0540 (1.1 ppm).

Isopropyl 2-(Chlorofluoromethyl)-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (21d): Colourless oil, two diastereoisomers (26%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21–1.28 (m, 12 H), 3.52–3.92 (m, 4 H), 5.03–5.11 (m, 2 H), 6.98 (d, J = 49.2 Hz, 1 H), 7.01 (d, J = 48.5 Hz, 1 H), 7.42 (t, J = 7.1 Hz, 2 H), 7.59–7.78 (m, 6 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –145.2 (d, J = 49.2 Hz, 1 F), –142.3 (d, J = 48.4 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 31.3, 67.4 (d, J = 54.8 Hz), 67.8 (d, J = 58.3 Hz), 70.8, 70.9, 101.9 (d, J = 248.7 Hz, CF), 102.0 (d, J = 243.0 Hz, CF), 125.2, 126.4, 126.5, 128.0, 134.1, 136.0, 136.1, 153.7, 154.2, 165.5, 195.9 ppm. MS (ESI), for ^{35}Cl: m/z = 285 $[M + H]^+$. HRMS: calcd. for $C_{14}H_{15}{}^{35}ClFO_3$ 285.0694; found 285.0695 (0.4 ppm).

Benzyl 2-(Chlorofluoromethyl)-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (21e): Colourless oil, two diastereoisomers (36%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.55–3.95 (m, 4 H), 5.20 (m, 4 H), 7.02 (d, J = 49.0 Hz, 1 H), 7.05 (d, J = 48.5 Hz, 1 H), 7.25–7.45 (m, 12 H), 7.55–7.80 (m, 6 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –145.3 (d, J = 48.9 Hz, 1 F), –141.9 (d, J = 48.5 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 67.4 (d, J = 57.0 Hz), 67.8 (d, J = 60.5 Hz), 68.3, 99.4, 99.1, 104.4, 125.4, 125.5, 126.4, 126.5, 127.8, 128.0, 128.5, 128.6, 128.7, 134.0, 134.7, 134.8, 136.1, 136.2, 153.6, 154.1, 165.1, 166.0, 195.4, 195.7 ppm. MS (ESI), for ^{35}Cl: m/z = 355 $[M + H]^+$. HRMS: calcd. for $C_{17}H_{13}{}^{35}ClFO_3$ 355.0518; found 355.0513 (1.4 ppm).

Supporting Information (see footnote on the first page of this article): Copies of the crystallographic data, and NMR spectra of all the compounds.

Acknowledgments

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[16] NMR spectroscopic data are fully consistent with those already published; see the Supporting Information.

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